# A Longitudinal Analysis of Cognitive and Eye Movement Deficits in Alzheimer's Disease

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# Abstract

The main purpose of this thesis was to investigate longitudinally, cognitive and eye movement deficits in Alzheimer's disease. A key aspect of the work was to examine the potential utility of saccadic eye movements in the diagnosis of Alzheimer's disease. Study I investigated saccadic error rates and error correction in Alzheimer's disease, other dementias and healthy elderly control participants using reflexive and voluntary saccade paradigms, to identify salient findings for further analysis. Study II explored the fixation offset effect in Alzheimer's disease, other dementias and healthy elderly control participants, to study the attention (fixation) disengagement deficit previously reported in Alzheimer's disease. Study III examined the effects of normal aging and disease, comparing Alzheimer's disease patients and other dementia types with healthy young adult control participants, healthy elderly control participants and Parkinson's disease patients. Study IV assessed the potential effects of acetylcholinesterase inhibitors on baseline data to eliminate medication effects. Study V investigated repeated measures data for salient observations from Studies I and II in Alzheimer's disease patients and healthy elderly control participants over an 18 month period. Study VI evaluated salient saccadic eye movement and neuropsychological assessment variables, with a view to generating regression models that could predict dementia. Alzheimer's disease patients were found to commit inhibition errors that increased in proportion according to the demands of the voluntary saccade task. Error-correction analysis, revealed that a high proportion of errors remain uncorrected in the antisaccade task, a finding apparently specific to dementia. The results were found to be consistent with the notion that the voluntary saccade tasks require selective attention, the facilitation of which is dependent on task goals being sufficiently activated in working memory. The magnitude of fixation offset effect was greater for Alzheimer's disease patients than controls and Parkinson's disease patients at baseline, but the longitudinal analysis showed that this magnitude decreased over subsequent test sessions. The large initial magnitude of fixation offset effect is believed to have been caused by over compensation of volitional compensation strategies at baseline, when the Alzheimer's disease patients had mild dementia. Regression models using antisaccade variables and neuropsychological assessment scores as predictors both performed well. It is feasible that models could be developed that would enable a reduced set of neuropsychological assessments to be used and three predictors from one antisaccade task. The results confirm that the antisaccade task is a useful model paradigm for the study of oculomotor dysfunction in dementia.

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# Chapter One

# Introduction to the Study of Eye Movement Research in Alzheimer's Disease

## 1.1 Introduction to the Study of Eye Movements

Eye movement research offers the scientist (and clinician) a valuable tool with which to gather important information regarding activity in oculomotor control systems, brain function and the localisation of disease. Using eye movements as a model system to study the regulation of neural activity provides the researcher with a number of benefits over other motor systems. Leigh and Zee Leigh (1999) outline the following points: i). Choosing from a range of oculographic technologies, it is possible to record accurate measurements of eye movement activity as rotations of the eyes are limited to three planes; ii). Eye movements fall into a number of different categories which correspond with visual activity, physiology and neuroanatomical substrates; iii) As the mechanical load that the eye muscles move against is constant, there is a lack of monosynaptic stretch; iv) Eye movement abnormalities are often characteristic of a particular pathophysiology, anatomical location or pharmacological disturbance.

Eye movements have been used extensively in the study of psychiatric and neurological illness taking advantage of neuropsychological insights, derived from versatile experimental design. Detection of the cortical structures involved in the control of saccadic eye movements revealed by research employing various neuroimaging techniques, animal models and human lesion investigations, has highlighted the crucial role of the prefrontal cortex and the parietal lobes (Cornelissen et al., 2002; Guitton, Buchtel & Douglas, 1985; Kimmig et al., 2001; Law, Svarer, Rostrup & Paulson, 1998; Nieuwenhuis, Ridderinkhof, Blom, Band & Kok, 2001; Paus, Petrides, Evan & Meyer, 1993; Pierrot-Deseilligny, 1991; Pierrot-Deseilligny, Milea &

Müri, 2004; Pierrot-Deseilligny, Rivaud, Gaymard, Müri & Vermersch, 1995; Pierrot-Deseilligny, Ploner, Müri, Gaymard & Rivaud-Pechoux, 2002; Schall, 2004; Schlag & Schlag-Rey, 1987; Sweeney et al., 1996). Thus, a profile of disturbance indicated by performance on specific saccadic eye movement paradigms (saccadic eye movements and paradigms are outlined in Section 1.3) can give a valuable insight of brain dysfunction and oculomotor control.

Neuropsychological research has been employed widely as a means of investigating sensorimotor integration and executive function (see Section 1.1.1), yielding connections with high-level cognition. Planned control of action and cognition is governed by the prefrontal cortex (*dorsolateral prefrontal cortex,* the *frontal eye fields,* the *supplementary eye fields,* and the *anterior cingulate cortex*), linked with sub-cortical areas of the brain via distinct neural pathways (Section 1.4). Neuropsychological enquiry has thus utilized eye movement methodology extensively to probe executive function. The field of eye movement research benefits from a range of accurate recording systems that has the potential to deliver a plethora of measurements and behavioural information.

Behavioural oculomotor paradigms have indicated selective impairments in neurological patients, psychiatric patients and other groups such as dyslexics, highlighting the potential of eye movements to reveal abnormalities. Eye movement research on patients with schizophrenia has revealed deficits in smooth pursuit (see section 1.2.1 gaze shifting) eye movements (Broerse, Crawford & den Boer, 2001; Crawford & Broerse, 2001; Crawford et al., 1998; Diefendorf & Dodge, 1908; Holzman, Proctor & Hughes, 1973) and with saccadic eye movements where patterns of cognitive dysfunction have been elucidated (Crawford & Broerse, 2001), as identified by deficits of inhibitory control (McDowell & Clementz, 1997; Sereno & Holzman, 1995), prolonged latency (Hutton & Kennard, 1998; Klein, Heinks, Andresen, Berg & Moritz, 2000a) and saccadic accuracy (McDowell, Myles-Worsley, Coon, Byerley & Clementz, 1999). Research with Parkinson's disease patients using saccadic

paradigms has also revealed a number of abnormalities including dysmetric responses and a characteristic multi-stepping pattern in the primary response, using a remembered target location paradigm (Crawford, Henderson & Kennard, 1989b). Additionally, abnormalities have been found for antisaccade latency and error rates (Briand, Strallow, Hening, Poizner & Sereno, 1999) and the relationship between antisaccade latency and error rates and clinical symptoms in Parkinson's disease (Briand et al., 1999; Kitagawa, Fukushima & Tashiro, 1994).

A range of saccadic abnormalities have been revealed in dyslexia from erratic saccadic eye movements in visual tracking (Pavlidis, 1981) and reduced centre-of-gravity effect in a double-spot paradigm (Crawford & Higham, 2001), to possible attentional deficits where dyslexic participants produce high frequencies of express saccades (Fischer & Weber, 1990). Additionally, dyslexic participants have been found to have poor fixation control, lower vergence amplitudes and poor smooth pursuit compared with controls (Eden, Stein, Wood & Wood, 1994). A study into patients suffering from human immunodeficiency virus (HIV) discovered that abnormal saccadic accuracy (amplitude) was a sensitive measure between patients and healthy control participants (Merrill, Paige, Abrams, Jacoby & Clifford, 1991).

Huntington's disease (Lasker, Zee, Hain, Folstein & Singer, 1987, 1988) and progressive supranuclear palsy (Pierrot-Deseilligny, Rivaud, Pillon, Fournier & Agid, 1989) are two additional diseases where eye movement abnormalities have been revealed. A further line of enquiry in the study of eye movements has been to conduct research on patients with dementia and of particular importance for this thesis, the study eye movements in Alzheimer's disease (AD). A review of these studies can be found in Section 1.5.

Eye movement research provides a conduit by which researchers can thus understand more thoroughly, the neurocognitive systems underlying oculomotor processes; for example, inhibition of prepotent response and self-monitoring by evaluating error correction. The relative ease by which eye movement data can be collected in the laboratory or clinical setting demonstrates the neuropsychological utility of oculomotor methodology and its capacity to

study both reflexive and complex behaviour (Leigh & Kennard, 2004). This property is particularly useful given the encumbrance of secondary behavioural characteristics that present in certain diseases (e.g. Alzheimer's disease), which can overshadow primary cognitive dysfunction.

This thesis will focus on the investigation of primary horizontal saccadic eye movements and explore saccadic error and correction, self-monitoring, attention and a variety of temporal and spatial measurements in dementia patients of the probable Alzheimer type. The research employs a range of oculographic paradigms, utilising involuntary and voluntary oculomotor methodology.

### *1.1.1 Executive Function and Cognitive Terminology*

The present thesis uses some terminology that is often applied vaguely in the wider literature, including the terms: executive function, working memory, visual attention, and inhibitory control. Therefore, this section aims to clearly define these terms and show how they are related in the context of the saccadic eye movement research described throughout the chapters that follow.

*Executive Function:* The term executive function stems from traditional theories of working memory (Baddeley, 1986) and is used in the present thesis to refer to higher-order cognitive processing for purposeful action such as planning, self-regulation, monitoring, volition and problem solving, i.e. the flexible control of cognition and action. The issue of there being a central control mechanism (such as the central executive in Baddeley's original model of working memory) that controls the various mechanisms of cognitive control (e.g. memory and attention) remains a source of debate. There is a substantial amount of evidence to support the concept of a control mechanism that integrates the various cognitive functions and motor control (see Sections 1.4.2.3 and 3.1). Whereas in the past the *central executive* from Baddeley's working memory model may have been considered for this purpose, in the present thesis Baddeley's model is superseded by Miller and Cohen's *'Integrative theory of*

*prefrontal cortex function'* (Miller & Cohen, 2001). In Miller and Cohen's theory executive function, i.e. cognitive control, is orchestrated by the prefrontal cortex through the "... active maintenance of patterns of activity that represent goals and the means to achieve them" (p. 171) and via the resolution of competitive processes between weak task-relevant information and stronger (automated) task-irrelevant information pathways, to achieve goal-directed behaviour. Furthermore, Miller and Cohen's theory corresponds with Massen's hypothesis for the parallel programming of exogenous (externally stimulated) and endogenous (internally generated) components in volitional saccade tasks (Massen, 2004). Massen's approach exemplifies the notion of task-relevant information (e.g. goal = antisaccade) and task-irrelevant information (e.g. antisaccade error = automated/reflexive saccade) and is therefore useful in explaining the inhibitory mechanisms responsible for successful completion of the antisaccade task and *how* inhibition errors may occur (see Section 1.3, 1.3.1, 1.3.2 & 1.3.2.1). A more detailed account of these theoretical constructs is discussed in Chapter 3, Section 3.1.

*Working Memory:* In the present thesis the term working memory is used to describe an active store which can hold information for short periods of time (i.e. short-term memory) for online processing and manipulation. Thus, working memory is part of executive function where information can be integrated with long-term memory and other cognitive modules e.g. prior to motor action, and can produce dynamic outcomes for example in arithmetic and problem solving by the manipulation of task rules and goals. This definition of working memory is basically the same as in Baddeley's model (1986), except that it is used here to describe executive functioning from within the framework of Miller and Cohen's integrative theory of prefrontal cortex function. Miller and Cohen's theory is useful as a fundamental theoretical construct for executive function, where the prefrontal cortex is viewed as key to the active maintenance of task rules and goals. Allied to this theory the goal activation approach of Nieuwenhuis and colleagues applies the connectionist modelling of Miller and Cohen's theory (and others) in the context of antisaccade task (Nieuwenhuis, Broerse, Nielen & de Jong, 2004). Central to this approach and commensurate with Miller and Cohen's theory, the level by which a given task goal is activated is vital to the success of volitional control.

Although task requirements may be fully understood by participants, goal activation failures result in goal neglect, which Nieuwenhuis et al. consider to be a characteristic of executive dysfunction. Nieuwenhuis et al.'s goal activation approach directly supports Miller and Cohen's theory of prefrontal cortex function, and is a useful framework when attempting to explain *why* failures to consistently focus attention on task requirements may occur (see Chapter 3, Section 3.1). In summary, Miller and Cohen's theory of prefrontal cortex function provides a contemporary framework for understanding working memory function (i.e. executive control) and the goal activation approach of Nieuwenhuis et al. can be conceptualised as a function of working memory.

*Visual Attention and Inhibitory Control:* Visual attention can be externally/exogenously stimulated or internally/endogenously generated. This can result in an overt shift of attention with an eye movement (to salient objects or events of interest) or in covert attention without an eye movement (Humphreys & Bruce, 1995). Furthermore, attention can be broadly categorised into i) selective attention, ii) sustained attention and iii) divided attention. Selective attention is where attention is directed to a particular stimulus whilst ignoring other irrelevant stimuli. Sustained attention is the ability to maintain an attentional focus for a prolonged period e.g. in a visual fixation task. Divided attention can be defined as the ability to share attention over more than one process at a time e.g. during dual task experiments (Perry & Hodges, 1999).

The prefrontal cortex has long been associated with endogenous selective visual attention and inhibitory control (Banich et al., 2000; Chao & Knight, 1997; Doricchi et al., 1997; Fukuyama et al., 1997; Kimberg & Farah, 2000; Lecas, 1995; Mishkin, 1964; Posner & Petersen, 1990). Therefore, in the present thesis visual attention and inhibitory control are viewed from the perspective of Miller and Cohen's integrative theory of prefrontal cortex function (Miller & Cohen, 2001). The theory views attention and inhibition as a reflection of behaviour stemming from a single underlying mechanism of cognitive control, following on from competition between processing pathways that are responsible for task performance. This suggests that selective attention and inhibition are two sides of the same coin. This idea

corresponds with the biased competition model of Desimone and Duncan in which attention is the result of biasing competition in support of task-relevant information, and inhibition is the consequence of the attentional biasing against the irrelevant information (Desimone & Duncan, 1995) i.e. attending to a stimulus automatically results in the inhibition of other stimuli. Chapter 3, Section 3.1 explains (in the context of the present thesis) how attentional processing and working memory are closely related in endogenous tasks and how the success of attentional processing relies on the extent to which a particular goal is activated in working memory.

## 1.2 The Importance of Eye Movements for Foveation

The visual system in humans has evolved to elicit functionally specific, useful and helpful information for the problem solving brain, thereby enhancing fitness and ultimately facilitating continued existence in the natural world. Inextricably linked to the fully operational healthy visual system, various types of eye movements play a crucial role in enabling the eyes to scan a scene, track a moving target and to locate objects of interest through a combination of movements and fixations. Therefore, eye movements perform two vital functions: firstly they serve to *shift* the direction of gaze and secondly, to *stabilise* the position of gaze so that the image, perhaps first detected in peripheral vision, falls onto the fovea (Figure 1.1). Thus, eye movements can actually facilitate foveation independently of head movements in foveate animals (Delgado-Garcia, 2000), but also serves to counter movements of the head that would otherwise disrupt visual processing due to sweeping visual stimulation across the retina.

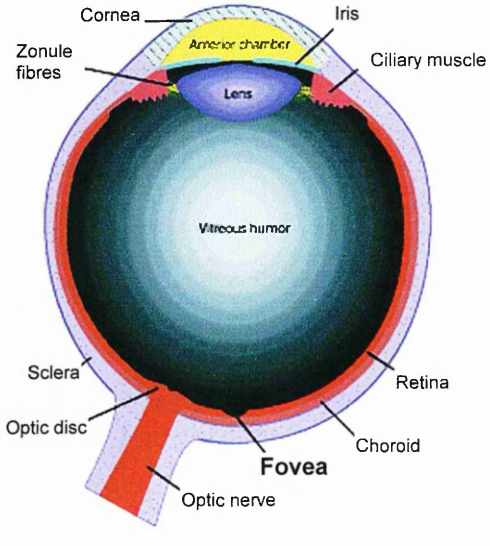



**Figure 1.1** Diagram Illustrating a Cross-section of the Human Eye Highlighting the Location of the Fovea (sagittal section, adapted from Zigmond etal., 1999)

This function is very important for the visual system as the fovea, which is approximately centred on the visual axis serving 1° of visual field (Hughes, 1975), is the point of highest resolution on the retina (Hess, Burgi & Bucher, 1946; Jacobs, 1979; Perry & Cowey, 1985).

The retina is a highly complex part of the central nervous system (CNS), comprising a multifaceted array of photoreceptors (i.e. rods and cones) and three layers of ganglion cells (with five different cell types) that enable temporal, spatial and chromatic aspects of visual processing in the physical world (Figure 1.2). Vitally significant to the present topic, retinal ganglion cells consist of two major categories, M cells and P cells. M cells receive most of their input from rod photoreceptors, whereas P cell input is derived mainly from cone photoreceptors. M cells and P cells form the basis of two morphologically and physiologically distinct visual channels. The channels project from the retina via the optic nerve, through the optic chiasm and on to form the optic tracts. The optic tracts proceed to the dorsal lateral geniculate nuclei (LGN), which are linked to the striate cortex (primary visual cortex) via the optic radiations to form the magnocellular and parvocellular pathways (Leventhal, Rodieck & Dreher, 1981; Perry & Cowey, 1981; Perry, Oehler & Cowey, 1984). Retinotopic mapping is maintained at each level of the retina – geniculate – striate pathway (Figure 1.3).

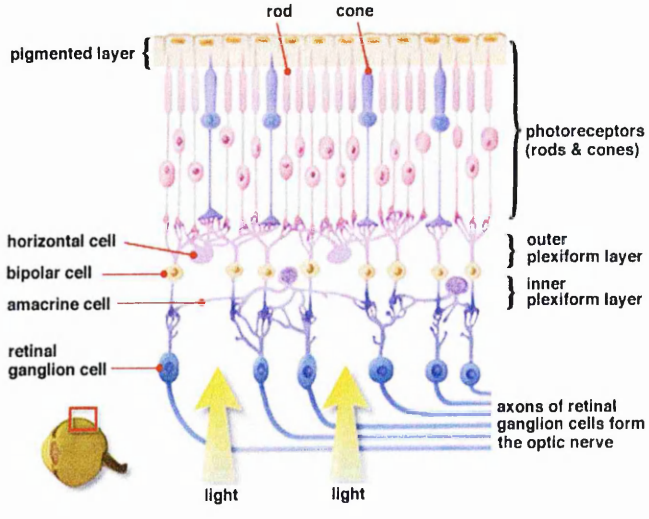



**Figure 1.2** A Diagram to Illustrate the Complex Layers of the Human Retina
(from Hall & Robinson, 1998)

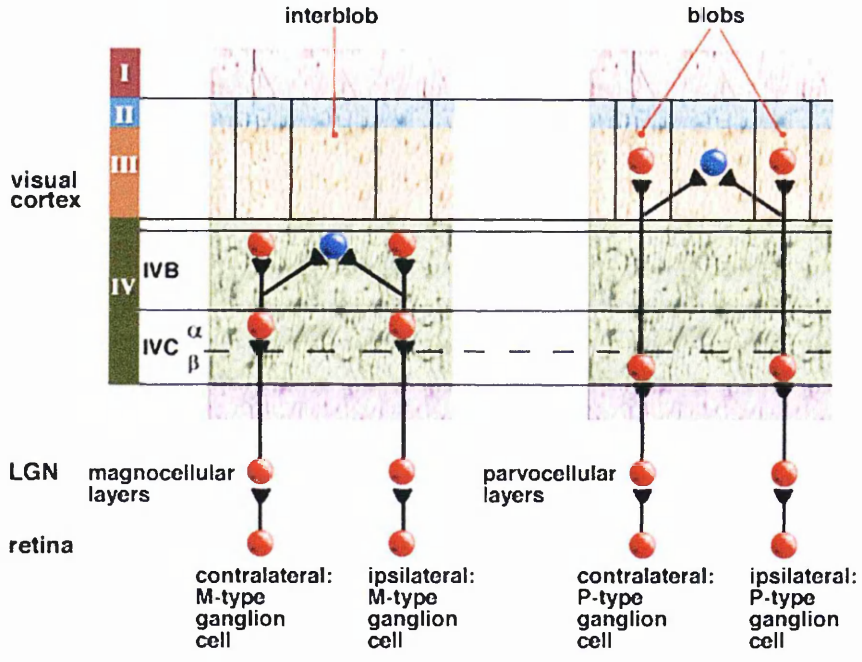



**Figure 1.3** Illustration Representing the M and P Visual Pathways
(from Hall & Robinson, 1998)

The characteristics of a third channel, the koniocellular pathway links with a third category of ganglion cell, W cells which are not relevant to the focus of the present thesis. There is a variation in the quantities of M ganglion cells and P ganglion cells at retinal eccentricity. The fovea and parafoveal areas of the retina contain a higher density of P ganglion cells than M ganglion cells, whereas M ganglion cells are evenly distributed across the retina. P ganglion cells are physiologically more sensitive to images of high contrast and low spatial frequencies and M ganglion cells more sensitive to low contrast and high spatial frequencies (Derrington & Lennie, 1984). Thus, foveation enables visual perception via the area of the retina with highest visual acuity, where the P ganglion cells of the parvocellular system are most prolific. This physiology provides the visual system with mechanics for a parallel dual-processing system, where the high resolution of a foveated image enables detailed analysis and focused attention. Superior sensitivity to high spatial frequencies, motion and low contrast in peripheral areas of the retina - afforded readily by the magnocellular system - permits the visual system to easily detect movement and objects of potential interest for

subsequent eye movements (and head and limb movements). Objects or salient events entering peripheral vision frequently trigger a reflexive ocular movement, known as the visual grasp reflex (VGR; Hess et al., 1946; Ingle, 1973), orienting the eyes so as to foveate an image of the object. The eye movement facilitates foveal fixation to within roughly 0.5° of midpoint on the fovea (Leigh & Zee, 1999). Essentially, the combined physiological characteristics of foveal and peripheral vision have evolved to provide an efficient system for survival in nature.

### *1.2.1 Stabilising and Shifting Gaze*

Fundamentally important to the visual system, there are two versatile groups of eye movements that facilitate efficient foveation, *gaze-stabilising* and *gaze-shifting* mechanisms. By definition, *gaze-stabilisation* mechanisms serve to *maintain* a given visual input on the fovea, whereas *gaze-shifting* mechanisms provide the capacity for *conveying* an image onto the fovea (Leigh & Zee, 1999). There are numerous classes of gaze-stabilisation eye movements, which include the vestibulo-ocular system, the optokinetic system, smooth pursuit, visual fixation and vergence, where the eyes are able to binocularly converge or diverge disconjugately, as a target moves towards or away from the eyes. Stabilisation of gaze is activated automatically as a reflexive compensatory strategy (the vestibulo-ocular reflex; VOR) during head movements and thus retains foveation. The labyrinthine semicircular canals possess angular acceleration sensors that mediate the VOR. A combination of the VOR and supplementary optokinetic system correction, achieves accurate stabilisation across a range of head movements and postures (Robinson, 1977). The optokinetic system provides visually mediated saccades, as a result of sustained rotation when the VOR signal declines.

Mechanisms for gaze-shifting include quick-phase nystagmus, which resets the eyes to their normal working range so as to view objects and subsequent scenes during regular bodily rotations. Part of the vergence system also falls into this category of eye movement, enabling the eyes to move disconjugately in certain situations, for example, locating an object at close

range. A further type of gaze-shifting mechanism is the saccadic system. Leigh and Zee (1999) provide the a useful summary for the functional classification of eye movements in Table 1.1.

**Table 1.1** The Classification of Eye Movements (adapted from Leigh & Zee 1999)

| Eye movement | Role of the system |
|---|---|
| Saccade | Rapid conjugate eye movements to convey an image to the fovea to enable fixation |
| Smooth pursuit | The ability to track a moving object and maintain the image on the fovea |
| Vestibular | The vestibulo-ocular reflex can maintain an image on the fovea during rotations of the head |
| Optokinetic | The optokinetic system maintains the image on the fovea through constant rotations of the head (following the VOR) |
| Visual fixation | Visual fixation maintains foveation of stationary objects |
| Quick-phase nystagmus | Resets the eyes to normal working range when self-rotating |
| Vergence | Disconjugate eye movements facilitating foveation of objects moving towards or away from the eyes i.e. target depth |

### *1.2.1.1 Moving the Eye*

The eye is positioned in the orbit, a socket-type recess in the front of the skull. It is held in position by three pairs of extraocular muscles, which are able to move the eye with synergistic action through horizontal, vertical and oblique directions (Figure 1.4).

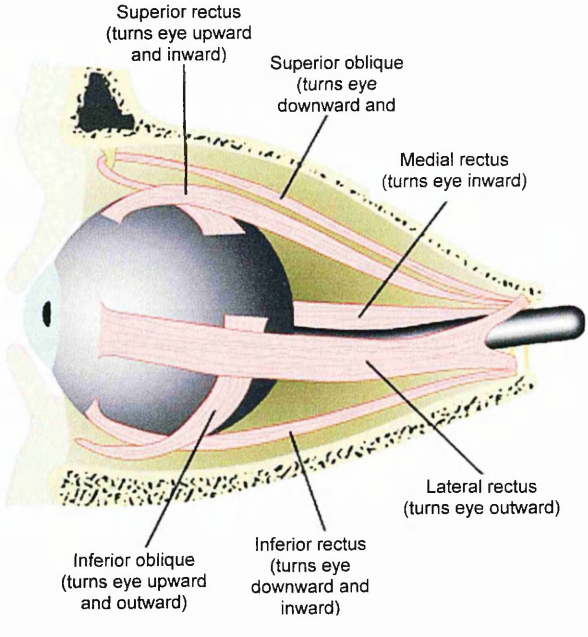



**Figure 1.4** The Extraocular Muscles
(adapted from Zigmond etal., 1999)

Horizontal eye movements (from side-to-side) are implemented by the *lateral* and *medial recti* muscles. Vertical eye movements (up and down) are facilitated by the *superior* and *inferior recti muscles*, whereas rotational eye movements are enabled by the *superior* and *inferior oblique* muscles. Brainstem motor neurons innervate the extraocular muscles. Specifically, this involves in the third (*oculomotor*), fourth (*trochlear*) and sixth (*abducens*) cranial nerve nuclei (Sparks, 2002). The functions of the cranial nerves involved in eye movements are displayed in Table 1.2 below.

**Table 1.2** Brainstem Innervation of Extraocular Muscles

| Cranial Nerve | Extraocular Muscles |
|---|---|
| Oculomotor (III) | Ipsilateral medial and inferior rectus, contralateral superior rectus and inferior oblique |
| Trochlear (IV) | Contra-lateral superior oblique |
| Abducens (VI) | Inpsilateral lateral rectus |

The primary area of investigation for this thesis is the saccadic eye movement, which is discussed in Section 1.3 below. Further discussion detailing the neurological control of saccadic eye movements can be found in Section 1.3.1.

## 1.3 Saccadic Eye Movements

Fundamental to day-to-day vision saccadic eye movements are generated for example, when we read text and thus serve to shift gaze direction and minimize drift of retinal image between fixations. The word saccade can be defined as '*jump*' and saccades may occur as a series of rapid conjugate jerks of the eyes, which can be horizontal, vertical or oblique. When a saccade is executed direction cannot be altered, thus, the saccade is a ballistic movement of the eyes facilitating efficient foveation for a given fixation point. The saccadic system enables the eyes to make rapid shifts of gaze from one point to another, with a peak velocity of up to $700^{\circ}s^{-1}$ for large amplitude saccades (Becker, 1991). There is a consistent saturating relationship between saccade velocity and amplitude, i.e. the size of movement (saccade

duration and amplitude are also related linearly). As saccade size increases the faster the speed of the movement. The relationship between saccade velocity and amplitude is often termed the main sequence (Bahill, Clark & Stark, 1975), and the main sequence is also found in microsaccades and quick-phase nystagmus.

Saccadic behaviour manifests as two main categories, comprising involuntary and voluntary eye movements. Classification of these two categories is discussed in the following sections (1.3.1 & 1.3.2).

### *1.3.1 Involuntary Saccadic Eye Movements*

Involuntary saccadic eye movements can be classified by a number of behavioural characteristics. The most basic form is quick phases of vestibular nystagmus, resulting from stimulation of the vestibular or optokinetic system to realign the eyes as a consequence of drift (Leigh & Zee, 1999). Involuntary saccades may appear spontaneously, without stimulation of the visual system by internal or external cues. The rapid eye movement activity that takes place whilst sleeping, is also involuntary. The end of Section 1.2 outlined the VGR, which is a saccadic response that occurs as a result of the sudden appearance of an external stimulus (visual, auditory or tactile). These saccades are frequently called *reflexive* saccades and involve *bottom-up* processing (the term *prosaccade* is often used interchangeably with reflexive saccade). However, the VGR is not a fully formed primary reflex as it can be inhibited, for example, during the antisaccade task. Despite the fact that visually-guided saccades involve an accurate motor system, they do not require response inhibition and working memory. Therefore, the cognitive system is placed under a relatively low load, the demand perhaps comparable with that required by visual attention (Broerse et al., 2001) where there is focussed awareness by the visual system. Reflexive saccades (*horizontal*) are included in the experimental design for the present study and a representation of the spatial

characteristics for this type of saccade, are illustrated in Figure 1.5 (A) (a detailed account of the experimental paradigm can be found in Chapter 2, Section 2.3.3.1 & Figure 2.5(A)).

### *1.3.2 Voluntary Saccadic Eye Movements*

Voluntary saccades are under volitional control and may be generated towards a known stimulus location in a prosaccade fashion, in response to a command or during purposeful activity. Volitional saccades can also be made to remembered locations. Additionally, voluntary responses include anticipatory and predictive behaviour, for example, in searching for a target a saccade may be initiated ahead of appearance of the stimulus, due to a prediction of the target location or temporal characteristics. Thus, voluntary saccadic eye movements invoke a higher load on the cognitive system, utilizing multiple cognitive centres including high-level executive functions, that include planning, visual attention, anticipation, memory, inhibition of prepotent response (to the VGR) and sensory-motor integration. Voluntary saccades are therefore a product of top-down cognitive processing and can be considered as *concept-driven* (see Section 1.4). One such volitional task is the antisaccade first used by Hallett (1978).

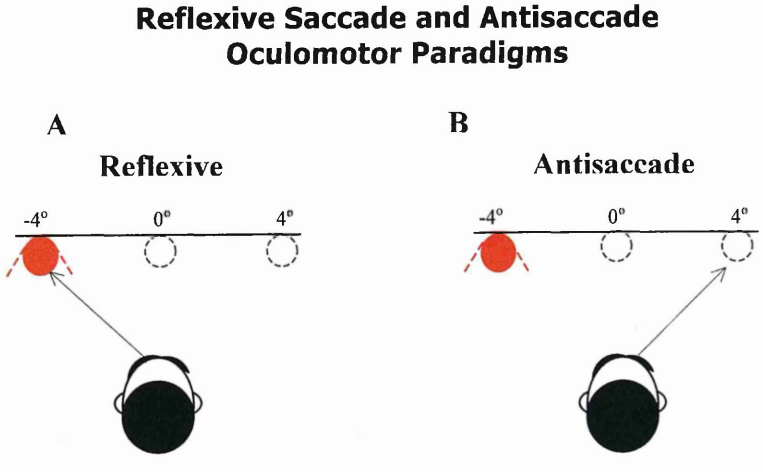



**Figure 1.5** The diagram above illustrates the basic concept of reflexive saccade (A) and antisaccade (B) paradigms. In the reflexive saccade paradigm a saccade is produced directly towards the target. Conversely for the antisaccade paradigm a voluntary saccade is generated to the opposite hemifield, from that of the target.

### 1.3.2.1 The Antisaccade Task

The antisaccade task is one of the most widely used paradigms in the study of voluntary saccades and the inhibition of inappropriate action (Amador, Schlag-Rey & Schlag, 2004; Dorris & Munoz, 1995; Everling, Dorris & Munoz, 1998a; Fischer, Gezeck & Hartnegg, 2000; Mockler & Fischer, 1999; Roberts, Ralph, Hager & Heron, 1994), and places a high level of demand on the cognitive system. During the task the eyes have to move to an equidistant location in space, in the opposite hemifield (the mirror location) from where the target is (Figure 1.5 (B) & 2.5 (B)). To achieve this the visual system must first avoid overt capture of visual attention by the stimulus, which is presented randomly in the left or right visual field. This is done by volitionally maintaining attention and visual fixation on the central fixation point, thereby inhibiting the prepotent response created by the newly presented visual target appearing in peripheral vision (*note*, the VGR would normally result in a prosaccade towards the target). Concurrently, the top-down processing must also generate a representation of an *imaginary target location* in the opposite hemifield from that of the actual target. This endogenous process must to be initiated with sufficient time to spare so that the competing saccade programme of the VGR can be overridden. Attending to the coordinates of the imaginery target location, a volitional saccade must be generated immediately to the imagined spatial location. Therefore, compared with involuntary reflexive saccades antisaccades incur additional reprocessing time. This is due to the fact that attentional mechanisms inhibit saccadic response and attention must shift to the opposite hemifield from that where the visual stimulus is actually located (provided that attention was allocated in the first place).

### 1.3.2.2 Inhibition of Response Tasks

Alternative experimental paradigms can be designed to probe other aspects of volitional and inhibitory control. By manipulating the rules, saccadic inhibition tasks can be conducted to exert higher levels of cognitive load thereby taxing the executive system. Due to the

instructional set of the paradigm - requiring response inhibition/response selection (where response is required to a certain target but not to others) and attention for action (self-monitoring of response) - these tasks draw on higher-order executive function and motor-related processing (Braver, Barch, Gray, Molfese & Snyder, 2001; Isomura, Ito, Akazawa, Nambu & Takada, 2003). The *Go / No-Go* task is an example of this type of task.

In eye movement tasks that employ *Go/No-Go* methodology the rule for example, may be that a voluntary prosaccade is commissioned towards a certain visual stimulus for the *Go* component of the test, however, for the *No-Go* component, a particular visual stimulus must be ignored by inhibiting the prepotent response to peripheral stimuli. Thus, these types of task require intact capacity for inhibitory and volitional control (Kiehl, Liddle & Hopfinger, 2000; Menon, Adleman, White, Glover & Reiss, 2001) (see Chapter 2, Section 2.3.3.3).

#### *1.3.2.3 Cognitive Considerations for Inhibition of Prepotent Response*

In order to carry out the antisaccade and Go/No-Go tasks the voluntary saccade system is integrated with higher-centres of cognition that facilitate working memory, problem solving, and error-monitoring. To perform the tasks correctly and efficiently the brain manipulates the problem forming an instructional set in accord with task instructions. The brain accomplishes this organization and manages the heavy demands inherent with the tasks by processing information via functionally integrated cognitive systems (Weber, Schwarz, Kneifel, Treyer & Buck, 2000), distributed in parallel (Selemon & Goldman-Rakic, 1988) for what are in essence frontal lobe tasks. Examination of variables derived from prosaccade and antisaccade paradigms has enabled the study of fundamental cognitive operations involved in the generation of eye movements. In particular, with voluntary saccades, the error correction rate provides a 'window' with which to observe the ability for self-monitoring, inhibitory control and the level of understanding that a participant has for a given task.

#### 1.3.2.3.1 Functional Basis of Voluntary Saccade Error

The precise functional basis of erroneous saccades in the antisaccade task, which requires inhibition of the prepotent response (suppression of reflexive gaze towards the target) and the generation of a voluntary saccade away from the target, is still a source of debate. Hallet & Adams (1980) postulated that reflexive errors towards the target in the antisaccade task result when a cancellation signal is issued too late to interrupt the automatic programming which executes the VGR. Referring to frontal lobe lesion patients Guitton and colleagues took a related approach and postulated that high error rates in the antisaccade task may be a consequence of frontal lobe damage, which slows down programming of the stop signal that is necessary to interrupt programming of the reflexive saccade and thus inhibit the VGR (Guitton et al., 1985). Roberts and colleagues proposed another account of inhibition errors in the antisaccade task (Roberts et al., 1994). Roberts et al. suggested that the systems of working memory and inhibitory control of prepotent response interact to enable on-line suppression of the VGR in healthy individuals (see Section 1.3.2.3.2). Roberts et al. (1994) reported that tasks such as the antisaccade (Hallett, 1978), Wisconsin Card Sorting Test (Milner, 1963) and the Stroop test (Stroop, 1935) all require suppression of a prepotent response and are also sensitive to frontal lobe function. The present thesis supports the notion that from a functional perspective the mechanisms of *working memory* and *attention* are strongly implicated in the antisaccade task, Wisconsin Card Sorting Test and Stroop test (Roberts et al., 1994), competing endogenous and exogenous programming systems that facilitate volitional control and counteract the impulsivity of compelling prepotent response.

#### 1.3.2.3.2 The Working Memory Perspective for Erroneous Saccades

Roberts et al. (1994) demonstrated how working memory (see Chapter 3, Section 3.1) resources are depleted during the antisaccade paradigm by introducing an arithmetic task to run simultaneously with the antisaccade task. Interestingly, when the cognitive load was increased

by the mathematical task to a level that left little or no surplus working memory capacity, error rates in the antisaccade task also increased. However, the secondary mathematical task did not increase error rates in the reflexive saccade task. Roberts et al. reported that the errors produced when the antisaccade task was performed simultaneously with a secondary task resembled those produced by patients with prefrontal dysfunction. From a working memory perspective, the results from Roberts et al. correspond with the working memory model of on-line processing for plans and goals (Baddeley, 1986; Daneman & Carpenter, 1980; Roberts et al., 1994). Furthermore, the results also demonstrate that as task complexity increases demands on cognitive capacity also increase and consequently resources of available working memory are diminished causing under activation of the task goal.

Failure to inhibit the VGR in the antisaccade task results in error, which may or may not be corrected. Applying the concept of working memory this will depend on the level of working memory resources available, according to cognitive load of a given task (Stuyven, Van der Goten, Vandierendonck, Claeys & Crevits, 2000) and the extent to which a task is activated in working memory. Therefore, if working memory function is compromised or weakened to some degree (for example due to lesion in the frontal lobe), then this may be observed as a lack of ability to inhibit the prepotent response (as working memory and attention/inhibitory control are working as functionally integrated systems), lack of suppression of the VGR and consequently the generation of erroneous prosaccades (Roberts et al., 1994). Therefore, the resulting proportion of prosaccade errors in the antisaccade task denotes the inhibition function (Pierrot-Deseilligny et al., 2004). Contemporary approaches to the working memory perspective are considered in greater detail in Chapter 3, Section 3.1.

Healthy adults show improved performance over time on the antisaccade task, as evidenced by reduced error rates and improved saccade accuracy (Ettinger et al., 2003). This may verify somewhat that successful execution of the antisaccade paradigm (and other voluntary tasks) in healthy individuals is reliant on efficient executive control over motor

function and attention, through the level of task activation in working memory. Improvement on the antisaccade task represents that a learning process has taken place and that volitional control over prepotent response mechanisms has been reinforced by the executive system.

#### *1.3.2.3.3 Inhibition and Prefrontal Cortex*

The antisaccade task was termed a measure of frontal lobe integrity in early lesion studies by Guitton and colleagues (Guitton et al., 1985), and the prefrontal cortex considered fundamental for inhibitory control of prepotent response and the suppression of reflexive saccades (Roberts et al., 1994) and working memory (Goldman-Rakic, 1999; Sawaguchi & Goldman-Rakic, 1994). Section 1.4.5 highlights the important role of the dorsolateral prefrontal cortex in the antisaccade task. Past research has reported disinhibition in patients with frontal lobe lesions during neuropsychological assessment with tests that require working memory and frontal lobe function. Luria referred to the problems of perseveration (that patients are often aware that they have made a repetitive *incorrect* response) and lack of inhibition in finger tapping tests ("conflict" command and other tests such as "Go/No-Go"; and "alternating commands") with frontal lobe lesion patients; this behaviour in the frontal lobe lesion patient being consistently distinct from the problems encountered by nonfrontal lesion patients (Luria, 1966, 1973). Drewe also used the Go/No-Go paradigm with finger tapping rules and found similar results, reporting that when patients with frontal lobe lesions have correctly mimicked the experimenter in a control condition they have great difficulty inhibiting the previously correct response in the experimental condition. Following training, patients were supposed to tap the table twice in response to a single tap by the experimenter and not at all to a double tap (Drewe, 1975). Furthermore, patients with frontal lobe lesions have been found to produce the same type of perseverative behaviour when using the Wisconsin Card Sorting Test (Drewe, 1976; Milner, 1963).

These findings help to demonstrate the rationale that underpins a working memory explanation of the error component in the antisaccade task. The above studies emphasise deficits by patients with damage to frontal cortex and are believed to utilize working memory. Performance in the antisaccade task by frontal lobe lesion patients (Guitton et al., 1985; Walker, Husain, Hodgson, Harrison & Kennard, 1998), primate studies (Goldman-Rakic, 1987) and neuroimaging with PET in humans (Owen, Doyon, Petrides & Evans, 1996a) has revealed correlates that are consistent with working memory function. Thus, there appears to be a strong relationship between frontal lobe function in working memory and the role that this plays in manipulating task instructions on-line, for inhibitory control and the ability to perform the antisaccade and Go/No-Go tasks efficiently. Subsequent sections of this thesis will highlight the importance of the prefrontal cortex and the vital role of this area in the production of voluntary eye movements.

### 1.3.3 *Saccadic Measures*

The methodology adopted for the research in this thesis will be discussed in Chapter 2, and will outline the available techniques for recording eye movements and the reasons for the approach utilized in this study. The present investigation used infrared oculography and produced a range of saccadic variables. The saccadic outcome measures include the following:

- *Latency*: which is measured as the time (recorded in milliseconds) from when a visual stimulus is presented in the visual field to the movement of the eyes, i.e. the time taken to generate a saccadic eye movement from target presentation.
- *Amplitude*: the distance that the eye travels, giving a measure of accuracy at locating a given target. Due to the fact that the eyes are virtually spherical and move with a rotating motion, measurement is made using the unit of degrees.
- *Duration*: how long the saccade lasts measured in milliseconds

- *Maximum velocity*: the maximum velocity attained by the saccadic eye movement measured in degrees per second.

For the present study the above measurements are reported across a number of paradigms, which are outlined in Chapter 2. The principal area of enquiry is the recording of measurements for the variables of the initial (primary) saccade, generated after the visual target is presented. However, when directional errors are generated, a spontaneous corrective saccade in the correct direction is often produced to compensate. These corrected error saccades are also monitored to provide important information regarding error correction and self-monitoring. Secondary corrective saccades following inaccurate primary saccades, commonly caused by undershooting the target (and also any dynamic overshoot), are not assessed in the present thesis. A range of computer spreadsheet templates were designed and used to manipulate and summarise saccade data resultant from analysis of analogue saccade signal data. The templates proved to be an invaluable time-saving tool, and aided the creation of further primary outcomes and secondary information from the initial saccadic output (across paradigms). The parameters generated include:

- Proportion of correctly directed primary saccades [1].
- Proportion of uncorrected primary saccade errors.
- Proportion of corrected errors (incorrectly directed primary saccade followed by a corrective saccade).
- Corrected error primary and secondary latency and also the intersaccadic interval (turn-around time) measured in milliseconds.
- Corrected error primary and secondary saccade amplitudes and also the final eye position (FEP) measured in degrees.

[1] Percentages are calculated as the proportion of the total valid trials.

- Proportion of anticipatory saccades, defined as all responses with latencies of <80 milliseconds.
- Proportion of omissions (no saccade generated).

## 1.4 Overview of the Neurological Control of Saccades

### *1.4.1 The Brainstem and Saccade Control*

Whereas commands for *vertical* saccades derive from premotor neurons in the rostral midbrain (Büttner, Büttner-Ennever & Henn, 1977; Büttner-Ennever & Büttner, 1978; Sparks, 2002), for *horizontal* reflexive saccades[2], motoneurons innervating the extraocular muscles (Section 1.2.1.1) receive their inputs from saccade-generating neural mechanisms in the brainstem (the pons and medulla). Saccade burst neurons (*long-lead burst* neurons LLBNs and *excitatory burst* neurons - EBNs) found in the paramedian pontine reticular formation (PPRF) (Fuchs, Kaneko & Scudder, 1985; Moschovakis & Highstein, 1994) operate at high frequency for the generation of saccades, but are at rest during fixation (Figure 1.6).

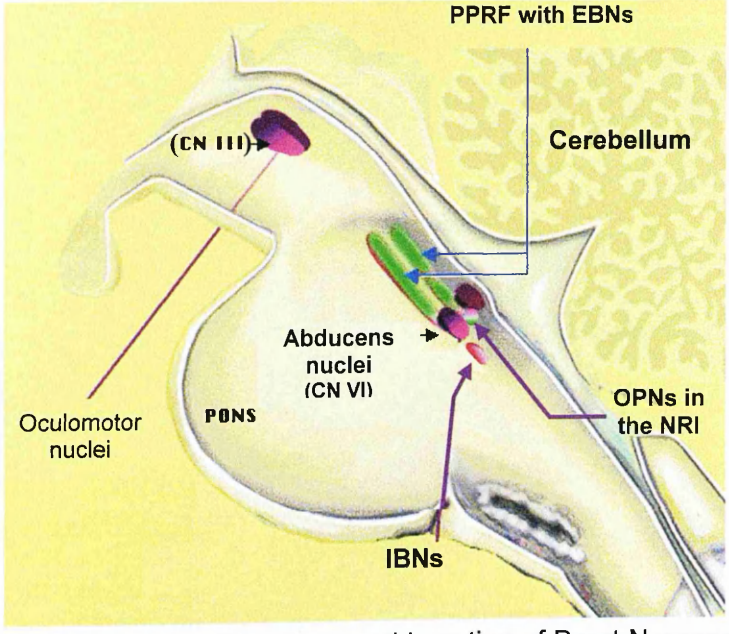



**Figure 1.6** Illustration of the Brainstem and Location of Burst Neurons (PPRF, Parmedian Pontine Reticular Formation; EBNs, Excitatory Burst Neurons; IBNs, Inhibitory Burst Neurons; OPNs, Omnipause Neurons; NRI, Nucleus Raphe Interpositus) adapted from Peyronnard and Charron (1997).

[2] This account will discuss horizontal saccade control *only*, the focus of the present thesis.

*Inhibitory burst neurons* (IBNs), located in the dorsomedial rostral medulla (Horn, Büttner-Ennever & Büttner, 1996; Scudder, Fuchs & Langer, 1988; Strausmann, Highstein & McCrea, 1986), project across the midline to inhibit contralateral abducens motor neurons and interneurons throughout ipsilateral saccade activity (Strausmann et al., 1986). It is assumed that the role of the IBNs is to suppress antagonist muscle activity, as axons also project to parts of the pontine reticular formation, the nucleus prepositus and the vestibular nucleus.

The PPRF is the horizontal saccade burst generator (Büttner-Ennever & Büttner, 1988; Strausmann et al., 1986), activity in this area having been found to be exclusive to horizontal saccades, as identified by microstimulation and lesion studies (Cohen & Komatsuzaki, 1972; Henn, Lang, Hepp & Reisine, 1984). Located in the nucleus reticularis pontis, the PPRF is found bilaterally of the midline, ventral and rostral in relation to the abducens nucleus. Pathways derived from the contralateral cerebral cortex and superior colliculus conduct input to the PPRF (Büttner-Ennever & Büttner, 1988). The ipsilateral abducens nucleus receives input from the PPRF and innervates motor neurons to the ipsilateral lateral rectus muscle. Interneurons from the abducens nucleus to the inferior pons lead to the medial longitudinal fasciculus (MLF) and the contralateral medial rectus extraocular muscle subnucleus of the oculomotor nucleus (Sparks, 2002) (see Table 1.2 relating cranial nerves to extraocular muscles).

Omnipause neurons (OPNs), located towards the midline of the caudal reticular pontine formation in the nucleus raphe interpositus (NRI) (Büttner-Ennever, Cohen, Pause & Fries, 1988) produce tonic activity between saccades, but pause fully just preceding and throughout saccades (Cohen & Henn, 1972; Keller, 1974; Luschei & Fuchs, 1972). The omnipause neurons are connected widely to burst neurons (Büttner-Ennever & Büttner, 1978; Horn, Büttner-Ennever, Wahle & Reichenberger, 1994; Strausmann, Evinger, McCrea, Baker & Highstein, 1987). As omnipause neurons must cease inhibition of burst neurons before a saccade can commence (Everling, Paré, Dorris & Munoz, 1998b; Horn et al., 1994) they act as

a gating mechanism assisting with the synchronisation of premotor saccade burst neuron operation, and facilitating efficient fixation and saccade production (Fuchs et al., 1985; Munoz, 2002).

The generation of a saccade involves precise neural activity in the form of *pulse* and *step* commands. The EBNs are largely responsible for initiation of the saccadic pulse command for motor neuron operation, with the level of activation integral to the dynamics of saccade amplitude, duration and velocity (Munoz, 2002; Robinson, 1975). The step command for motor neuron operation is generated by excitatory activity in the nucleus prepositus hypoglossi (NPH) and medial vestibular nucleus (MVN); tonic activity in the NPH and MVN is proportional to eye position (Scudder, Kaneko & Fuchs, 2002; Sparks, 2002). It is believed that the LLBNs may provide an important link in a feedback loop, that enables resetting and integration of saccades (Kustov & Robinson, 1995; Leigh & Zee, 1999). As the LLBNs are situated in the PPRF, connect with omnipause neurons (Hepp & Henn, 1983; Scudder, Moschovakis, Karabelas & Highstein, 1996a, 1996b) and also project to the central mesencephalic reticular formation (which is linked to the superior colliculus), Leigh and Zee (1999) postulate that the LLBNs may fulfil their role by two functions: i). Spatial-to-temporal transformation of saccadic commands; and ii). Synchronisation of onset and end of saccades.

#### *1.4.1.1 Functions of the Superior Colliculus in Saccade Control*

The superior colliculus (SC), located in the midbrain, is a vital component for the interaction of cortical areas and the central reticular formation. The SC consists of seven complex topographically mapped layers. These layers can be grouped into dorsal (*superficial*), and ventral sections, by their functional characteristics. The dorsal layers seem to be involved in visual processing and attention and have been shown to receive direct afferent projections from the retina (with retinotopographical mapping) and the striate (visual) cortex (Cynader & Berman, 1972), and send efferents to the lateral geniculate nuclei (LGN), pulvinar and

pretectal nuclei (Leigh & Zee, 1999). Ventral layers of the SC have retinotopic *motor mapping* and generate premotor commands for saccades (Ma, Graybiel & Wurtz, 1991) with many efferent connections to brainstem nuclei that contribute to the production of saccadic eye movements (e.g. PPRF and MLF). There are also projections to the thalamus.

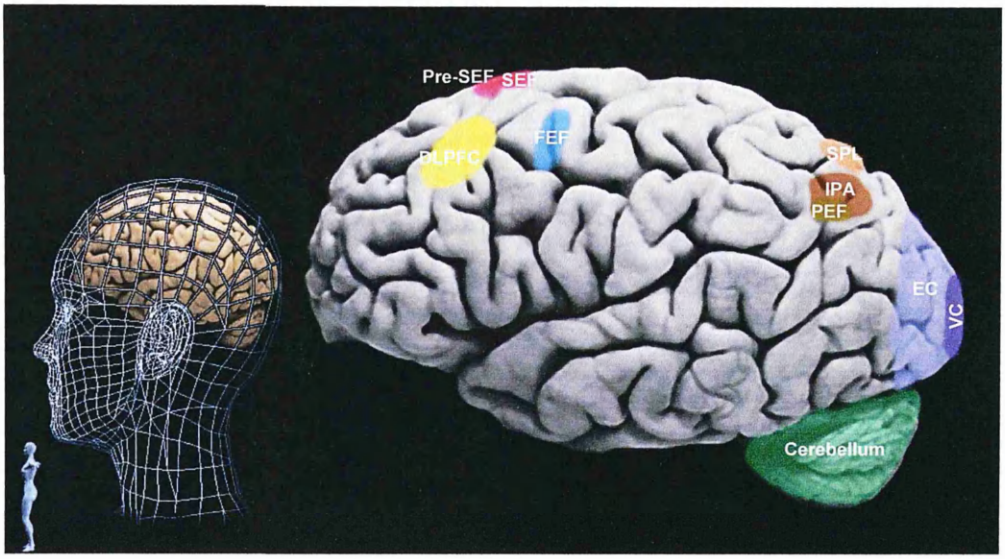



**Figure 1.7** An Illustration of the Main Cortical Areas Involved with the Control and Generation of Saccadic Eye Movements

Dorsolateral Prefrontal Cortex (DLPFC); Frontal Eye Field (FEF); Supplementary Eye Field (SEF); Pre-Supplementary Eye Field (Pre SEF); Intraparietal areas (IPA); Parietal Eye Field (PEF); Superior Parietal Lobule (SPL); Primary (Striate) Visual Cortex VC; Extrastriate Cortex (EC); Cerebellum (adapted from Pierrot-Deseilligny et al., 2004; and Rosenzwieg, Leiman & Breedlove, 1999)

The ventral layers of the SC also receive important projections from areas of the frontal cortex, including the frontal eye fields (FEF), supplementary eye fields (SEF), and dorsolateral prefrontal cortex (DLPFC); some of which link via the basal ganglia (Moschovakis, Karabelas & Highstein, 1988; Segraves, 1992; Shook, Shlag-Rey & Schlag, 1990). In addition, the SC also receives input via projections from the posterior parietal cortex (PPC), specifically, the parietal eye fields (PEF) and the cerebellum (cortical areas and cerebellum can be seen in Figure 1.7).

Given the characteristics of these structures, it is postulated that the ventral layers of the SC are imperative for sensory-motor integration, mediating and interfacing information between the many structures. Recent primate antidromic and orthodromic stimulation studies

(Sommer & Wurtz, 2004a, 2004b) have revealed further insight into the feedback pathway provided by the ascending projections from the SC to the mediodorsal thalamus and onto the FEF. Topographically organised presaccadic activity was found to travel unchanged from SC to FEF and this activity is believed to provide *vector* signals for imminent saccades.

Reflexive saccadic eye movements (*prosaccades*) move toward objects of interest and maintain fixation as a result of opponent neural processes (Büttner-Ennever & Horn, 1997) that make it possible for high-speed interchange between saccade and fixation. The opponent processes that activate and inhibit the VGR brainstem activity are situated in the ventral layers of the SC. Thus, the *pulse-step* command system in the pontine and midbrain areas of the brainstem receives inputs largely from the SC.

Two sorts of cells in the SC - fixation and movement - are responsible for managing when and where the eyes move (Rafal, Machado, Ro & Ingle, 2000). Throughout fixation, neurons in the rostral pole of the SC generate tonic discharge, their function being augmented by stimulation when an object is fixated, thereby holding the eyes in position (fixation cells); these cells are able to inhibit movement cells. Movement cells are located caudally to the rostral pole neurons and these cells assist the eyes when moving to a new location; they are also inhibited by fixation cells (Machado & Rafal, 2000b; Munoz & Wurtz, 1993a, 1993b; Wurtz & Munoz, 1995). The SC, PPRF, and ocular motor nuclei are the final common pathway for all types of saccade.

### *1.4.2 Saccade Control by the Cerebral Cortices*

The cerebral cortices play a crucial role in the generation eye movements, including both reflexive and voluntary saccades. In the first instance, visual input is transmitted via the retina – geniculate – striate pathway (Section 1.2) to the parietal lobes (PPC, parietal eye field (PEF) and superior parietal lobule (SPL)), where sensory-motor transformations and attentional processes take place (Section 1.4.1.3)(Andersen, Snyder, Bradley & Xing, 1997; Anderson &

Mountcastle, 1983; Colby & Goldberg, 1999; Thier & Andersen, 1996). Saccadic and fixation activity is then distributed throughout a network that includes the cerebellum, frontal lobes and sub-cortical brainstem structures (Sections 1.4.1 & 1.4.1.2) with complex projections that are linked at numerous levels (Hikosaka, Takikawa & Kawagoe, 2000; Schall & Thompson, 1999; Tinsley & Everling, 2002). Two main pathways seem to perform important functions in mediating reflexive and volitional saccades. Reflexive saccades are largely controlled by a posterior pathway involving projections from the PPC to the SC which mediates reflexive saccades via the SC. Volitional saccades rely on anterior pathways that are mainly involved in mediating saccades via the FEF, SEF and DLPFC.

#### *1.4.2.1 The Frontal Eye Fields*

The FEF (Figure 1.7) have been identified by PET, fMRI and cortical stimulation studies (Fox, Fox, Raichle & Burde, 1985; Kleineschmidt, Merboldt, Requardt, Hänicke & Frahm, 1994; Sweeney et al., 1996). They are located around the lateral precentral sulcus leading superiorly to the intersection with the superior frontal sulcus, and involve the precentral gyrus and middle frontal gyrus (Leigh & Zee, 1999; Paus, 1996; Pierrot-Deseilligny et al., 1995). However, in another study by Luna and colleages (Luna et al., 1998) using fMRI, the frontal eye field was found to be limited to the precentral sulcus only for visually-guided saccades and not reaching into Brodmann's area 8 (An illustration of Brodmann's areas is shown in Appendix 23). A recent high resolution fMRI investigation confirmed the localised saccade area of the FEF to be in the upper portion of the antrerior wall of the precentral sulcus (Rosano, Krisky & Welling, 2002).

Many areas of the cortex and sub-cortex are involved in an array of intricate neural pathways that facilitate parallel processing and thus the integration of numerous sensory-motor systems in the production of cognitive and behavioural operations and the FEF is no exception to this. *Primate* studies have revealed high-level interactivity with inputs from many areas,

including the visual cortex and inferior parietal lobule (IPL specifically the PEF). Inputs from *contralateral* regions are also found to include the FEF, SEF, DLPFC, thalamic nuclei, cerebellum, SC and substantia nigra pars reticulata (SNPr) (Huerta, Krubitzer & Kaas, 1987; Leigh & Zee, 1999; Sommer & Wurtz, 2004a; Stanton, Goldberg & Bruce, 1988a, 1988b, 1995). Primate studies have also shown that the FEF not only sends reciprocal projections to these centres, but in addition, sends projections to the SC, caudate nucleus, SNPr, NRI and the nucleus reticularis tegmenti pontis (Huerta, Krubitzer & Kaas, 1986; Leichnetz, Smith & Spencer, 1984; Stanton et al., 1988b).

Neurons found in the FEF have been shown to discharge prior to the commencement of visually-guided saccades and memory-guided saccades (Bruce & Goldberg, 1985). Recent fMRI studies have revealed that during reflexive saccades, the FEF discharge prior to onset of saccades and that the PEF is also highly activated (Connolly, Goodale, Menon & Munoz, 2002; De Souza, Menon & Everling, 2003). However, in the antisaccade task, the FEF was activated prior to antisaccade generation, but not the PEF, which indicates that the FEF field is involved in the preparation of the antisaccade. It is postulated by Pierrot-Deseilligny et al. (2004) that the lesion studies (Rivaud, Müri, Gaymard, Vermersch & Pierrot-Deseilligny, 1994) and fMRI investigations (Pierrot-Deseilligny et al., 2003a; Pierrot-Deseilligny, Rivaud, Gaymard & Agid, 1991b) demonstrate that the FEF triggers correct antisaccades, whereas the DLPFC exercises inhibitory control over the reflexive saccade system via the FEF.

As mentioned in Section 1.4.1.2, recent findings from primate studies (Sommer & Wurtz, 2004a, 2004b) have emphasised the crucial presaccadic topographically mapped vector signalling information that the SC projects to the FEF via the mediodorsal thalamus. Sommer and Wurtz conclude that the information is important for the coordination of saccade sequences and the stabilisation of vision from one saccade to the next. Previous research has noted that lesions of the FEF cause prolonged reflexive saccades on a fixation-target overlap task (Sharpe, 1986), whereas tasks with fixation point offset prior to target onset cause little

problem; i.e. employing a temporal gap between fixation point offset and target onset[3] (Pierrot-Deseilligny et al., 1991b). The delay reported for fixation disengagement in the overlap task possibly relates functionally to the reciprocal pathways between the FEF and SC, as discussed in Section 1.4.1.2, where two types of cell in the SC - fixation and movement - are responsible for managing when and where the eyes move (Rafal et al., 2000; Segraves & Goldberg, 1987; Segraves, 1992).

### *1.4.2.2 The Parietal Eye Field and Saccade Generation*

The discussion in Sections 1.4.1 & 1.4.1.2 highlights that the basis of involuntary saccadic eye movement generation is largely the result of activity in the brainstem and midbrain, further to sensory integration, via relevant cortical areas. Interestingly however, involuntary saccades can also be triggered by various cortical areas, including the parietal lobe, namely the PEF (Pierrot-Deseilligny et al., 1995); the parietal lobes being crucially involved in gaze control and attention (Leigh & Zee, 1999).

The location of the PEF in humans (Figure 1.7) was shown by fMRI to be around the interparietal sulcus (Müri, Ploner, Iba-Zizen, Derosier & Pierrot-Deseilligny, 1996) which is in the superior area of the angular gyrus and supramarginal gyrus (lying in Brodmann's areas 39 & 40, Appendix 23). Luna and colleagues (Luna et al., 1998) found that during visually-guided saccades, fMRI revealed activity in the parietal lobes in the precuneus, through the intraparietal sulcus and also reaching into the SPL and the IPL.

Brain lesion studies have shown that patients with lesions to the posterior parietal cortex (PPC), specifically the PEF, produce visually-guided saccades with significantly prolonged latencies (Heide & Kompf, 1998; Pierrot-Deseilligny et al., 1991b). Moreover, bilateral lesions of the PPC and the FEF in the human brain result in severe disruption for the triggering of both reflexive and volitional saccades (Pierrot-Deseilligny, Gautier & Loron,

[3] The 'gap' or 'fixation offset paradigm' - terms used interchangeably - is employed in Chapter 4 of this thesis.

1988), whereas damage to the FEF alone prolongs reflexive saccade latency for targets in the contralateral hemifield (Pierrot-Deseilligny, Rivaud, Penet & Rigolet, 1987). Electrical microstimulation studies in the lateral intraparietal area (LIP) of the intraparietal sulcus - the PEF in rhesus monkeys - have shown that stimulation of the *lateral wall* results in saccades that travel in a similar direction, regardless of initial position; whereas stimulation of the intraparietal sulcus *floor* and sub-ranging *white matter*, produces eye movements in directions that are dependent on initial eye position (Thier & Andersen, 1996). The LIP in humans, is known to project directly to the FEF and SEF (Schall, 1997; Schall & Thompson, 1999), thus demonstrating an important interface between visual input, brainstem and frontal regions.

In the gap/overlap paradigm (see Chapter 4), unilateral lesion studies have revealed saccade latency to be increased bilaterally in the gap task and additionally to be significantly worse in the overlap task (with a tendency for patients with right-sided lesions to have the largest latencies in the overlap task) (Pierrot-Deseilligny et al., 1995; Pierrot-Deseilligny et al., 1991b). Therefore, given these findings, it is plausible to suggest that the PEF is involved in coding for particular objects of interest in spatial coordinates, and in the generation and triggering of saccades.

Further evidence that demonstrates the importance of the role of the parietal lobes in saccadic control was revealed in an EEG study by Wauschkuhn and colleagues (Wauschkuhn et al., 1998), who found that for voluntary saccades, presaccadic activity contralateral to saccade direction began about 100 msecs. prior to saccade initiation and was greatest in mesial parietal sites with involvement of some fronto-central test-oriented activity. This group of researchers interpreted this finding as the triggering signal for saccade execution. They also reported contralateral activation of lateral parietal areas optimal at 250 msecs. subsequent to stimulus onset, irrespective of saccade direction. Further activity was found at 330-480 msecs. contralateral to the stimulus if the stimulus was the target of the saccade. They postulated that these findings are an indication of parietal lobe involvement in both independent and

interdependent processing of saccade preparation and shifts of visual attention. A recent primate study demonstrated that projections from the PEF to the FEF are more involved in processing visual information, whereas the PEF projection to the SC is more involved in saccade generation (Ferraina, Paré & Wurz, 2002). This again reinforces the evidence that the PEF provides the trigger for execution of reflexive saccades, via the parieto-collicular pathway.

In summary, the parietal lobes seem to be vitally important for the control of saccades in a number of ways, which include high-level processing of spatial head position and sensory-motor transformations, shifts (disengagement) of attention (both overt and covert)(Andersen et al., 1997; Colby & Goldberg, 1999; Corbetta, Miezin, Shulman & Petersen, 1993), the triggering of visually-guided saccades and a clear role in the programming of environment/visually-guided saccades, via the PEF.

#### *1.4.2.3 The Dorsolateral Prefrontal Cortex*

The DLPFC is located in Brodmann's areas 9 and 46 (Appendix 23) on the dorsolateral area of the frontal lobe, in the middle third of the middle frontal gyrus (Figure 1.7) (Leigh & Zee, 1999; Rajkowska & Goldman-Rakic, 1995). There are reciprocal cortico-cortical connections with the FEF, SEF, PPC, hippocampus, parhippocampal cortex, cingulate cortex and nuclei of the thalamus; and descending projections to the PPRF, SC, caudate and putamen (Cavada & Goldman-Rakic, 1989; Huerta & Kaas, 1990; Selemon & Goldman-Rakic, 1988).

The DLPFC is active during voluntary saccade generation, for example, with saccades to remembered target locations and in antisaccade tasks (Matsuda et al., 2000; Müri et al., 1998; O'Driscoll et al., 1995; Sweeney et al., 1996). Patients with lesions of the DLPFC have been shown to have impairment on these tasks (Guitton et al., 1985; Pierrot-Deseilligny et al., 2003b; Pierrot-Deseilligny, Rivaud, Gaymard & Agid, 1991b), Pierrot-Deseilligny et al. (2003), showing that a lesion localised to the DLPFC caused impairment of ability to inhibit the VGR in the antisaccade task. Furthermore, in a primate study of working memory,

pharmacological demobilisation of the DLPFC with D1 dopamine antagonists found that contralateral saccades were inaccurate in a remembered target location task (Sawaguchi & Goldman-Rakic, 1994). A further primate study recently investigated neuronal activity in the DLPFC during a directional-delay task for both memory-guided and visually-guided saccades. The results showed that most of the DLPFC neurons that were active during the delay period, were also active when the sensory stimulus remained on (Tsujimoto & Sawaguchi, 2004). Tsujimoto & Sawaguchi postulated that this sustained representation of information in the DLPFC should have potential utility in flexible cognitive controls of behaviour. Pierrot-Deseilligny et al. (2004) postulated that the DLPFC can exert inhibitory control over the SC directly via the prefronto-collicular tract, revealed by a human anatomical study (Gaymard, Francois, Ploner, Condy & Rivaud-Pechoux, 2003). Additionally, using fMRI, Matsuda et al. found that the DLPFC was only active during voluntary (antisaccade) saccades in humans and not in reflexive saccade tasks (Matsuda et al., 2000). They postulated that the DLPFC plays an important role in the inhibition of reflexive saccades. Moreover, Pierrot-Deseilligny et al. (2004) also speculated that the DLPFC is involved in the decisional processing of saccadic eye movements, by modulating inhibitory control of the reflexive saccade system and memorised information on-line in accord with task instructions. Additionally Pierrot- Deseilligny et al. (2004) refer to an fMRI study (in preparation by Milea et al. at the time of writing) that has found evidence of significant activation of the DLPFC during the selection period, prior to saccade generation in a self-selection saccadic task with healthy participants. It seems that this evidence supports the notion that the DLPFC is considerably involved in working memory processing and that this contributes to the processing of information, for voluntary saccade generation.

The interconnections between the DLPFC and the anterior cingulate cortex (ACC) have been identified during antisaccade and remembered saccade tasks by PET and EEG studies (Anderson et al., 1994; Nieuwenhuis et al., 2001; Sweeney et al., 1996). Investigation of the

posterior cingulate cortex (PCC) in primates has also shown that there is neuronal discharge before and after saccadic eye movements (Olson, Musil & Goldberg, 1996). A more recent study has refined this position somewhat using fMRI, and discovered that the PCC is active during reflexive saccades, but not during endogenous saccades (Mort et al., 2003).

Research has also discovered that the ACC, more specifically, the area referred to as the cingulate eye field (CEF), probably regulates activity in the DLPFC. Evidence from lesion studies of the CEF found dysfunction of inhibitory control for reflexive prosaccades in the antisaccade task (Milea et al., 2003) and impairment of memory guided saccades (Gaymard et al., 1998b).

Another study conducted event-related fMRI of the ACC during an erroneous response task and discovered that the ACC is active during both correct and incorrect responses (Carter et al., 1998). Carter and colleagues postulated that this finding possibly reflects the capacity of the ACC to detect conditions under which errors are likely to occur. Further fMRI study of error related activity has revealed that the ACC's role in executive function is an evaluative one, providing on-line detection of processing conflicts, perhaps associated with deteriorating performance (Carter, Botvinick & Cohen, 1999; Kiehl et al., 2000). Furthermore, a recent study of primates using single unit recording of neural activity in a saccade countermanding task revealed dissociation of activity for error, reinforcement and conflict in the ACC. This finding supports the hypothesis that the ACC monitors for the consequences of actions (Ito, Stuphorn, Brown & Schall, 2003). The significance of this role can be emphasised from an oculomotor perspective. Pierrot-Deseilligny et al. (2004) suggest that the CEF perhaps governs endogenous saccade preparation, whereas the PCC interacts with attentional signals from the PPC, thus preparing the PEF for reflexive response.

Given the reciprocal cortico-cortical interconnectivty of the DLPFC with the FEF, SEF, PPC and descending pathways to sub-cortical nuclei (particularly the hippocampus and SC), the above findings appear to reflect that the relationship between the DLPFC and the anterior

cingulate cortex is multi-functional, forming part of a distributed parallel processing system, serving spatial working memory, inhibitory/suppressive control of reflexive response, and error processing and self-monitoring, which are all conducive to an efficient and correctional working memory.

#### *1.4.2.4 The Supplementary Eye Fields*

The SEF was first termed an eye field when neurons were found to fire prior to and during reflexive and spontaneous saccades (Schlag & Schlag-Rey, 1985, 1987). The SEF corresponds with the location of Brodman's area 6 (Appendix 23) and is thus situated on the dorsomedial surface of the frontal lobe; on the superior frontal gyrus, superior to the FEF and anterior to the supplementary motor area (SMA) (Fox et al., 1985; Petit et al., 1996; Petit et al., 1993; Sweeney et al., 1996). An additional area of interest is the pre-supplementary eye field (Pre-SEF), which is located just anterior to the SEF (Figure 1.7).

The SEF has many afferent and efferent pathways and is reciprocally connected with the FEF, cingulate cortex, DLPFC, caudate nucleus, interparietal sulcus (PEF), superior temporal sulcus and thalamic nuclei (Bates & Goldman-Rakic, 1993; Luppino, Rozzi, Calzavara & Matelli, 2003; Shook, Shlag-Rey & Schlag, 1988; Shook, Shlag-Rey & Schlag, 1991). However, the is SEF in primates has been found to have a higher proportion of connections with prefrontal and skeletomotor areas and fewer connections with the visual cortex compared to the FEF, for example, which has greater connectivity with extrastriate areas (Huerta & Kaas, 1990). Additional investigation with primates has also demonstrated a convergence of FEF and SEF projections in the caudate nucleus and the striatum (Parthasarathy, Schall & Graybiel, 1992). The SEF has also been found to project to the OPNs in the NRI, caudate nucleus , putamen, SC, pontine nuclei (Huerta & Kaas, 1990; Shook et al., 1988; Shook et al., 1990).

Characteristics of saccade related activity have been revealed with neuroimaging techniques, and have shown that the SEF is active during the antisaccade task (Kimmig et al., 2001; O'Driscoll et al., 1995; Sweeney et al., 1996), remembered saccades (Anderson et al., 1994; O'Sullivan, Jenkins, Henderson & Kennard, 1995) and sequences of saccades (O'Sullivan et al., 1995; Petit et al., 1996).

The complex status of the SEF in saccadic control was also emphasised in primate studies, where different populations of SEF neurons have been identified that appear to relate to novel and familiar stimuli on a saccadic learning task (Chen & Wise, 1995). Activation of these populations of cells changes significantly according to task learning, via stimulus-saccade association. These neurons are more common in the SEF, than comparable cells found in the FEF and has led to the notion that the SEF may perform the role of an adaptable system that can integrate sensory input and motor response (Chen & Wise, 1996). Furthermore, a recent electrophysiological study of the SEF in the rhesus monkey (Olson & Gettner, 2002), has confirmed that activity is enhanced when difficult and complex rules are involved in a task or were conflict arises. Interestingly, recent TMS and fMRI investigations have highlighted that the Pre-SEF is activated during the presentation of a visual sequence and the SEF is active prior to activation of a programmed sequence (Pierrot-Deseilligny, Müri, Ploner, Gaymard & Rivaud-Pechoux, 2003b). It appears that the SEF plays an important role in presaccadic activity and saccade control, mediating the programming of saccades. The SEF seems to be highly implicated where saccades are incorporated into complex behaviour such as remembering a target location or performing other voluntary learned tasks, as in antisaccade paradigms.

### *1.4.3 The Cerebellum and Saccade Control*

The cerebellum (Figure 1.7) is a vital component for eye movements (Hayakawa, Nakajima, Takagi, Fukuhara & Abe, 2002) providing a calibration function that facilitates

optimal eyesight. There are two essential sub-divisions i). The vestibulocerebellum (important for the dynamics of the VOR); and ii). The dorsal vermis and fastigial nucleus (Leigh & Zee, 1999). Quaia and colleagues (Quaia, Lefevre & Optican, 1999) emphasise the indispensable role of the cerebellum in playing three key roles in the control of saccadic eye movements i). The cerebellum provides further activation, to improve acceleration of the eyes; ii). Monitors the advancement of a saccade towards the target; and iii). Chokes off drive from the SC to end the saccade.

The dorsal vermis and fastigial nucleus are key sub-structures for the initiation of saccadic eye movements. These nuclei are concerned with the accuracy of saccades and control the size of the pulse component. Lesions of these areas have been shown to result in saccadic pulse dysmetria, with undershoot and overshoot of the target (Siebold, Glonti, Kleine & Büttner, 1997; Takagi, Zee & Tamargo, 1996), and recently, structural MRI has confirmed the role of the vermis in saccade gain (Ettinger et al., 2002).

### *1.4.4 Control of Voluntary Eye Movements*

Voluntary eye movements are regulated by the cerebral cortices, namely the visual cortex, dorsolateral prefrontal cortex (DLPFC, important for programming memory-guided saccades and providing inhibition of prepotent responses), frontal eye fields (FEF is involved in the disengagement of the fixation system and is able to initiate visually guided saccades and locate remembered or predicted positions for saccades), the supplementary eye fields (SEF, vital for the arrangement of multiple saccades and also, the integration of saccades with head and body movements) and the inferior parietal lobule (see PEF Figure 1.7) (concerned with visuospatial integration)(Corbetta et al., 1993; Pierrot-Deseilligny, Israel, Berthoz, Rivaud & Gaymard, 1993; Pierrot-Deseilligny et al., 1995). Sub-cortical structures are also involved in the generation of voluntary saccades, including the superior colliculus and basal ganglia (substantia nigra pars reticulata). Endogenous control of the fronto-nigral-collicular circuitry

enables inhibition of the VGR and fixation reflexes, and thereby the production of voluntary saccades (Burman & Bruce, 1997; Everling et al., 1998). Voluntary control of saccadic eye movements may be disturbed if these circuits are damaged, as exemplified by the findings of research involving adults with damage to the frontal cortex that has been found to impede suppression of the VGR (Guitton et al., 1985; Pierrot-Deseilligny, 1991; Rafal et al., 2000). Lesions of the FEF result in little disruption to reflexive saccades, however, the dynamics (prolonged latency and lowered peak velocity) of voluntary (and remembered) saccades were found to be significantly impeded (Gaymard, Ploner, Rivaud, Vermersch & Pierrot-Deseilligny, 1998a; Gaymard, Ploner, Rivaud-Pechoux & Pierrot-Deseilligny, 1999).

### *1.4.5 Neural Control in the Antisaccade Task*

There appear to be a range of brain regions that form the neural substrates of antisaccade eye movements and the specific location of these areas is still a matter for deliberation (Everling & Fischer, 1998). Research involving neuroimaging techniques has produced inconsistent results, which could be due to a number of reasons. It is probable that the differences lie in a combination of different methodologies and the lack of good temporal resolution with brain imaging methods, despite having good spatial resolution.

As discussed in Sections 1.4.1.2, 1.4.2.1 – 1.4.2.5 & 1.4.4, there is substantial overlap in the neural basis for exogenously (reflexive) and endogenously (voluntary) generated saccades, with the prerequisite that the production of the volitional antisaccade will incur a higher proportion of top-down processing as compared with the simpler and less cognitively demanding reflexive tasks. Therefore, it is suggested that antisaccades utilise the same circuitry, fundamental to reflexive saccadic eye movements which includes the FEF (Section 1.4.2.1), PEF (Section 1.4.2.2), cerebellum (Section 1.4.3) and brainstem structures (Sections 1.4.1 & 1.4.1.1; PPRF & SC). For antisaccade paradigms, the task involves a number of additional cognitive operations, which require higher-level processing and thus additional

cortical areas for successful completion of the task: i). Inhibition of the VGR, i.e. suppression of the reflexive response; ii). Representation of an imaginary target, created in the opposite hemifield, from that of the target; iii). Coordinating the coordinates of the imaginary target, a volitional saccade is generated to the imagined spatial location.

Many studies have discovered neural correlates that have helped provide insight into the precise location of the areas involved during the generation of antisaccades. Initially, clinical studies investigating lesion sites, suggested that difficulties in suppressing reflexive glances during goal-directed saccades (antisaccade task) concerned the FEF, DLPFC (Section 1.4.2.3) and SMA (SEF) (Guitton et al., 1985) and later, lesions of the FEF were implicated in prolonged antisaccade latency (Rivaud et al., 1994). Further lesion studies have highlighted a significant role for the DLPFC, demonstrating higher error rates for this lesion site (Fukushima, Fukushima, Miyasaka & Yamashita, 1994; Gaymard et al., 1999; Gaymard et al., 1998b; Pierrot-Deseilligny et al., 1991b). As discussed in Section 1.4.2.3, the cingulate cortex is highly interconnected with the DLPFC and interestingly, lesions to ACC also result in higher antisaccade error rates (Gaymard et al., 1998b), perhaps emphasising the putative self-monitoring and error processing role of the ACC (Carter et al., 1999; Carter et al., 1998; Kiehl et al., 2000).

Brain imaging studies using fMRI and PET have also found variously, that the FEF, SEF ACC, DLPFC and sub-cortical areas are active during antisaccade tasks. For example, two studies, Müri et al., using fMRI (Müri et al., 1998) and Sweeney et al., using PET (Sweeney et al., 1996) found the DLPFC to be significantly active in the antisaccade task. Paus and colleagues (Paus et al., 1993) compared activation of brain regions using PET during reflexive and antisaccade tasks and discovered that the ACC and PPC were significantly more active than other areas of the brain during the antisaccade task. Whereas, O'Driscoll and colleagues (O'Driscoll et al., 1995), also using PET, found a different pattern of increased activation during the antisaccade task that included the FEF, SMA, striate cortex, superior

parietal lobe and sub-cortical areas (putamen and thalamus). O'Driscoll et al. (1995) postulated that the FEF was responsible for inhibition of the reflexive saccade component of the antisaccade task. This notion was reinforced by Cornelissen and colleagues (Cornelissen et al., 2002) using fMRI to study antisaccade and prosaccade tasks and discovered that the FEF was active prior to the execution of correct antisaccades, whereas this did not occur for errors of inhibition. The similarity between the findings of O'Driscoll et al. and Cornelissen et al. further supports the idea that the FEF is involved in presaccadic inhibitory processes. This notion has been reinforced by recent neuroanatomical studies (pharmacological inactivation) of these regions of the brain in the monkey (Sommer & Wurtz, 2004a) which have found prominent presaccadic activity travelling unchanged from the SC to the FEF.

EEG has also been used to elucidate which areas of the brain are active during the antisaccade task. The shift of attention from the target stimulus (found to be in the contralateral hemisphere from the target) to the imaginary representation of a target (in the ipsilateral hemisphere with the target) was observed to be in the parietal cortex by Everling and colleagues (Everling, Spantekow, Krappmann & Flohr, 1998c). Additionally, Evdokimidis and colleagues (Evdokimidis, Liakopoulos, Constantinidis & Papageorgiou, 1996) postulated that a reduction in neural activity noted to occur 100 msec. prior to the initiation of a saccade (Everling, Krappmann & Flohr, 1997) was related to the frontal mechanism for reflexive saccade inhibition.

In summary, it appears that a distributed network, involving both cortical and sub-cortical structures of the brain is involved in the successful execution of antisaccades. The demands of the antisaccade task involve complex neural programming of both spatial and temporal task parameters. In order to achieve the goal of the task the mind not only utilizes brainstem circuitry involved in the production of reflexive saccadic responses, but also integrates this circuitry with higher-cortical pathways involving the FEF, PPC, SEF, DLPFC and ACC to bring about efficient volitional control.

## 1.5 The Dementias

The term dementia covers a broad range of disorders which are characterised by various cognitive deficits and differentiated by etiology (American Psychiatric Association, 1994). In the United Kingdom prevalence rates show that there are in excess of 700,000 people suffering from dementia, and in the region of 18,500 of these people are below age 65 years. One person in twenty over the age of 65 years and one person in five over the age of 80 years are afflicted with dementia. Estimates put the figure for people with dementia worldwide, at approximately 18 million (source: Alzheimer's Society U.K., 2003). The incidence of dementia cases is progressively growing, as the proportion of older people steadily increases. In North America and Europe, approximately 4% of the population reached 65 years of age in the year 1900, whereas by 1980, the proportion of the population over 65 years had increased to roughly 10% of the overall expanding population (Kolb & Whishaw, 1996). Therefore, dementia is associated largely with old age, revealed by improved health and survival into old age (Whitehouse, Lerner & Hedera, 1993).

The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) published by the American Psychiatric Association (APA) (1994) lists the following types of dementia according to etiology: Dementia of the Alzheimer's Type (AD); Vascular Dementia; Or due to HIV Disease; Head Trauma; Parkinson's Disease; Huntington's Disease; Pick's Disease; Creutzfeld-Jakob Disease; and Dementia Due to Other General Medical Conditions; Substance-Induced Persisting Dementia; Dementia Due to Multiple Etiologies; Dementia Not Otherwise Specified.

Multiple cognitive deficits are central to the diagnosis of dementia and include memory impairment as the pivotal factor, along with one or more disturbances, which comprise a deficit of executive function, agnosia, apraxia or aphasia. For a diagnosis of dementia, disturbance in cognitive performance should have interfered with everyday life to the extent that social activities or employment are impeded, with cognition having deteriorated to a lower degree

than that prior to onset of symptoms. Needless to say, it is useful to have a reliable and close informant of the patient (with a good working knowledge of the patient) along at interview, as patients often have difficulty in presenting a full and reliable account of their history.

### 1.5.1 Alzheimer's Disease

Alzheimer's Disease (AD) is defined by the National Institute on Aging as progressive, irreversible declines in memory, performance of routine tasks, time and space orientation, language and communication skills, abstract thinking, and the ability to learn and carry out mathematical calculations – executive function. Other symptoms include personality changes and impaired judgement. The most widespread of the dementias, Alzheimer's disease constitutes up to 55% of the total cases of dementia (source: Alzheimer's Society, U.K., 2003).

#### 1.5.1.1 Pathological Characteristics of Alzheimer's Disease

It is possible to distinguish between the healthy aging brain and the AD brain by comparison of neuronal degeneration (only observable post-mortem), the healthy aging brain showing significantly less cell loss and considerably fewer neurofibrillary tangles (Morrison & Hof, 1997; Price, Davis, Morris & White, 1991). The AD brain is found to be affected by two types of lesion, i) neuritic plaques, a dense build-up of cellular debris, consisting extracellularly, of the protein β–amyloid; and ii) twisted strands (neurofibrillary tangles) of a protein called tau inside cells, in particular, pyramidal cells and the hippocampus (Clarke & Goate, 1993; Goedert, 1993). There is substantial synaptic loss in many areas of the brain that are vital to: Memory - the hippocampus; Emotion and personality – the amygdala; Impairment of sense of smell - olfactory areas. Cell loss in the entorhinal limbic system leads to disconnection of the hippocampus.

In addition to sub-cortical damage, areas of the cerebral cortex and temporal cortex suffer increasing cell loss as the disease progresses (Terry, Peck, De Theresa, Schecter &

Horoupian, 1981; Wilcock, Esiri, Bowen & Hughes, 1988): The frontal cortex – resulting in executive, strategic and social self-monitoring problems; the temporal cortex – which results in agnosia, aphasia and problems with memory (Hodges & Patterson, 1995); Degeneration of the parietal cortex causing spatial orientation and attention difficulties and anosognosia (Jones & Richardson, 1990; Zola-Morgan & Squire, 1993). Concomitant with neuronal loss, are lower levels of the neurotransmitter acetylcholine (see Chapter 6) (Beach et al., 2000; Coyle, Price & DeLong, 1983; Davies & Maloney, 1976; Giacobini, 1990), primarily due a high degree of cell loss in the basal forebrain region, i.e. the nucleus basalis of Meynert and the nucleus of the diagonal band complex (Arendt, Bigl, Arendt & Tennstedt, 1983; Francis, Palmer, Snape & Wilcock, 1999; Whitehouse, Price, Clark, Coyle & DeLong, 1981). These nuclei are responsible for supplying the hippocampus and many areas of the cortex with modulatory and activating cholinergic input. Other modulatory neurotransmitters affected include, noradrenalin, serotonin and dopamine (Moore, 1990) which are crucial for efficient frontal lobe function and inhibitory control (see Section 1.4.2.1). As the disease advances, there is extensive cortical atrophy and ventricular enlargement (Figure 1.8 shows an MRI scan illustrating extensive neural degeneration in a patient with advanced Alzheimer's disease).

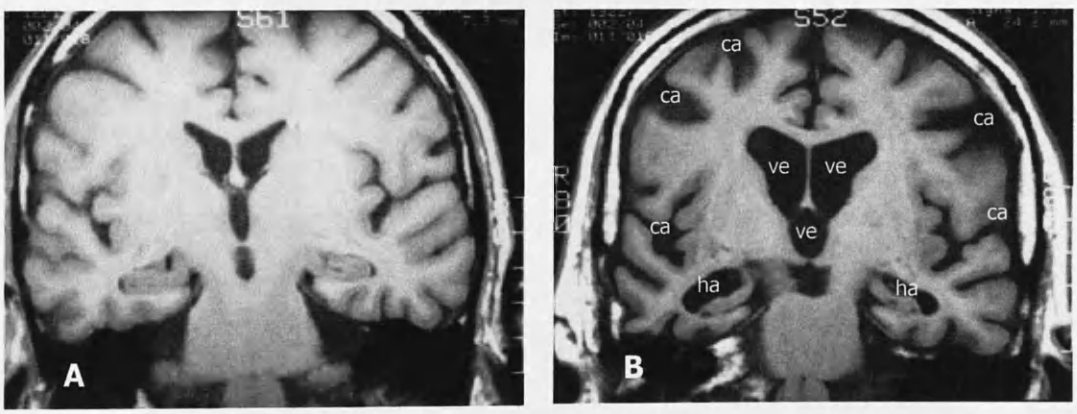



**Figure 1.8** Magnetic Resonance Image of Alzheimer Diseased Brain

Comparative coronal sections of a healthy (normal) brain from a 78 year-old (A) and the brain of a 74 year-old patient with AD/MMSE score of 15 (B). Note: Cerebral (ca) and hippocampal atrophy (ha); and ventricular enlargement (ve), compared with normal brain on left (adapted from Detoledo-Morrell et al. 1997).

The diagnosis of AD relies on the presence of a recognizable clinical syndrome and the exclusion of other possible causes of dementia. There are to date no specific biological or pathophysiological markers available in the diagnosis of AD (Kennard, 1998). Although some promising advances have been made in preclinical neuropsychological assessment (Visser et al., 2002) and the development of neuroimaging and cerebrospinal fluid analysis (Okamura et al., 2002).

### *1.5.1.2 Clinical and Cognitive Features of Alzheimer's Disease*

The symptoms and pathology of Alzheimer's disease, as defined on the previous two pages, originated from the work on a case study by the German physician, Alois Alzheimer in 1906. The clinical features of AD present with an insidious slow onset and progressive deterioration of cognition. The following criteria extracted from DSM-IV, assist with a clinical perspective on the symptoms for the diagnosis of AD.

**Diagnostic criteria for Dementia of the Alzheimer's Type**

A. The development of multiple cognitive deficits manifested by both

   (1) memory impairment (impaired ability to learn new information or to recall previously learned information)
   (2) One (or more) of the following cognitive disturbances:
      (a) aphasia (language disturbance)
      (b) apraxia (impaired ability to carry out motor activities despite intact motor function)
      (c) agnosia (failure to recognise or identify objects despite intact sensory function)
      (d) disturbance in executive functioning (i.e. planning, organising , sequencing, abstracting)

B. The cognitive deficits in Criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.

C. The course is characterised by gradual onset and continuing cognitive decline.

D. The cognitive deficits in Criteria A1 and A2 are not due to any of the following:

   (1) other central nervous system conditions that cause progressive deficits in memory and cognition (e.g. cerebrovascular disease, Parkinson's disease, Huntington's disease, subdural haematoma, normal-pressure hydrocephalus, brain tumor)
   (2) systemic conditions that are known to cause dementia (e.g. hypothyroidism, vitamin $B_{12}$ or folic acid deficiency, niacin deficiency, hypercalcaemia, neurosyphilis, HIV infection)
   (3) substance induced conditions

E. The deficits do not occur exclusively during the course of a delirium.

F. The disturbance is not better accounted for by another Axis I disorder (e.g. Major Depressive Disorder, Schizophrenia).

(American Psychiatric Association, 1994)

#### 1.5.1.2.1 Memory Impairment in Alzheimer's Disease

The disease process seems to initially affect anterograde memory (memory from the time of disease onset) involving episodic memory (Lishman, 1986) and recent memory. For example, prospective memory becomes a major problem for the AD patient, often forcing adoption of memory aid strategies to remember appointments. The diary of an AD patient early on in the disease is cluttered with things to do, often to no avail as they forget to use the aid particularly as time moves on in their daily schedule, and this problem simply becomes worse as the disease progresses. This is exemplified by experiences during the course of the research for the present thesis, when many appointments were missed and rebooked as a result of AD patients failing to attend the hospital.

Recall memory is immensely impaired for the AD sufferer where even after only a short retention period, low scores result on tests of immediate recall for word lists. However, AD performance on tasks that do not induce a high working memory load, for example the Digit Span *forwards* test (Wechsler, 1997a) are found, is found to be relatively unimpaired in the early stage of the disease (Cherry, Buckwalter & Henderson, 2002) but deteriorates with severity. Importantly, tasks that cause a high working memory load such as the Digit Span *reverse* (Wechsler, 1997a) and Spatial Span *reverse* (Wechsler, 1997b), are found to result in lower scores for AD patients, even in the early stages of disease. This confirms a common finding in AD patients, that early on in the disease, executive function and in particular working memory are deteriorating and therefore tests with a high cognitive load (see Section 1.3.2.3.2) requiring mental manipulation, planning and purposeful thought are more cognitively taxing for the AD patient than simpler tasks (Baddeley, Logie, Bressi, Della Sala & Spinnler, 1986; Becker, 1988; Cherry et al., 2002; Collette, Linden, Bechet & Salmon, 1999; Grossman & Rhee, 2001; Kensinger, Anderson, Growdon & Corkin, 2004). From a neuropsychological perspective, this denotes the reliance of working memory on the frontal

lobes, temporal and hippocampal regions of the brain and the obvious difficulties that AD patients have compared with healthy elderly controls.

Semantic memory, autobiographical and remote/retrograde memory (memory prior to onset) or implicit memory are affected as the disease becomes more severe. The lack of capacity to learn and use new material and strategies, and the ability to form new memories are thus curtailed in AD, resulting in impairment of acquisition. AD patients, often in the initial stages the disease, fail to recognize groups (form associations) or categories when presented with items at a higher level (superordinate category), during semantic or verbal fluency tests. Typically, mild to moderate AD patients make perseverative statements, perhaps only minutes apart. A further compounding problem that is frequently present as a component of executive dysfunction for the AD patient, is the lack of ability to monitor response performance and error correction (Mathalon et al., 2003; Perry & Hodges, 1999), something which is normally a routine part of daily life (Perry & Hodges, 1999).

#### *1.5.1.2.2 Language Difficulties in Alzheimer's Disease*

Language problems present early on in AD, usually following on from memory difficulties (Nebes, 1990). Word finding difficulties, during conversation, become more severe as the disease advances, with frequent circumlocution, often causing frustration. In the early stages, deficits are more semantically based. However, as the disease progresses, grammatical – syntactic aspects of conversation become more impaired following the moderate stage of the disease with the gradual breakdown of semantic context and comprehension leading to aphasia with eventual loss of speech in the profound stage of disease.

#### *1.5.1.2.3 The Moderate Stage of Alzheimer's Disease*

As AD advances into the moderate stage, visuospatial, constructional, ideomotor and ideational praxis impairments appear (McKhann et al., 1984; Welsh, Butters, Hughes, Mohs &

Heyman, 1992). Therefore AD patients present with problems of face recognition (prosopagnosia), object identification, disorientation when finding their way about previously known areas (but not necessarily around the home), problems carrying out automated (over-learned) tasks and confusion, for example, over what they are doing during the day or what they have done. For instance, the AD patient may believe that they need to change into alternative clothing a number of times through the day. Later in the disease, patients may present with a Parkinson's type gait, poor ambulation and motility of limbs with the face progressively appearing more vacant. Eventually at the profound stage, the AD patient requires permanent nursing care, but may still be able to sit in an easy chair throughout the day. In the final stage of AD and worst scenario for the patient and family, the patient will pass through their final days in a bed (which can last a considerable length of time) with cot sides raised for their safety to ensure they do not fall out.

#### *1.5.1.2.4 Neuropsychiatric and Behavioural Disturbance in Alzheimer's*

The manifestation of neuropsychiatric symptoms and behavioural problems may vary widely between individual cases, which can complicate diagnosis. However, these attributes help to predict the likely burden to the caregiver and also indicate how difficult a given piece of research may be with a particular case. The spouse, close friend or relative is often a very good informant of the changes that are presenting with the patient.

For AD, a common symptom is a change in personality. A particular problem recognised in many patients, is that they may seem to be less inhibited in the social context, perhaps presenting with inappropriate touching and speech; or for example, a disinhibition of sexual behaviour. Patients may also become apathetic or alternatively, present with what is apparently an extreme caricature (or amplification) of previous character trait. Delusion is also common, the patient perhaps believing that they are in the wrong house; suspect infidelity in their partner; have feelings of abandonment; 'capgras', where the patient believes that the

spouse has been replaced by someone else (which could be more of a cognitive problem); or not recognize themselves in the mirror (which could also be a cognitive problem) (O'Neill & Carr, 1999). Some patients suffer from hallucination, the most common type being visual hallucination but other types do exist, including auditory, olfactory and haptic. Interestingly, recent research has indicated that disturbance of the olfactory system may be a common early dysfunction in AD (Schiffman, Graham, Sattely-Miller, Zervakis & Welsh-Bohmer, 2002).

Low mood is also common in AD (Kopelman, 1986; Lishman, 1986), however, there are also cases of mania, anxiety, anger and agitation (Ballard & Eastwood, 1999). Other non-cognitive behavioural problems that are common in AD include irregularity in eating patterns, sexual dysfunction, wandering, shouting and screaming, psychomotor restlessness, disturbed sleep/wake patterns rage and violence (Rapp, Flint, Herrmann & Proulx, 1992).

## 1.6 Eye Movement Research in Alzheimer's Disease

Research investigating eye movements in AD has explored a range of techniques, including smooth pursuit eye tracking (see Table 1.1), visual tracking (for example *exploratory* behaviour) and saccadic eye movements. However, compared to other strands of psychiatric investigation using eye movement methodology, such as for example schizophrenia, there is a relative lack of research in the area possibly due to the formidable challenge that the dementia patient presents.

Saccadic eye movement dysfunction in AD has been reported for a number of parameters, including prolonged latency, reduced peak velocity, hypometric amplitude and increased antisaccade error rates.

### *1.6.1 Smooth Pursuit Studies in Alzheimer's Disease*

Findings from smooth pursuit studies have shown that performance for AD patients is different to that of healthy control participants, although there appears to be some

inconsistency in the findings. Zaccara and colleagues (Zaccara et al., 1992) showed that peak velocity during smooth pursuit was significantly lower for AD patients than controls, as was the percent target matching index. AD patients were found to produce significantly more anticipatory saccades than control participants. Zaccara et al. (1992) also found that AD patients produced more catch-up saccades than controls, a finding supported by other studies (Fletcher & Sharpe, 1988; Gangemi et al., 1990; Hutton, Nagel & Loewenson, 1984; Kuskowski, Malone, Mortimer & Dysken, 1989; Müller, Richter, Weisbrod & Klingberg, 1991). Using discriminant function analysis, Zaccara et al. (1992) produced an equation using oculographic variables, that they believe could possibly create an index of disease severity and thus predict clinical condition. Multivariable discriminant scores were found to be significantly correlated with Mini Mental State Examination scores, and thereby related to cognitive decline in AD patients. Zaccara et al. (1992) also suggested that AD patients may be impaired in determining target speed, as demonstrated by the number of dysmetric catch-up saccades produced by AD patients, which may be due to degeneration of the middle temporal visual area (MT) as indicated by lesion studies (Duersteler, Wurtz & Newsome, 1987). However, a study by Moser et al. (Moser, Kömpf & Olschinka, 1995) found no significant difference for smooth pursuit gain between AD patients and controls (although gain was *reduced* for patients), although the target was restricted to $15^{\circ}s^{-1}$ and moving with constant ramps with a triangular trajectory. In contrast, the smooth pursuit stimulus used in the study by Zaccara et al. (1992), employed an unpredictable velocity that ranged from $5^{\circ}s^{-1}$ to $100^{\circ}s^{-1}$. Therefore, it is plausible to suggest that the stimulus used by Moser and colleagues (1995) was more predictable than the Zaccara et al., (1992) stimulus, thus enabling participants to more easily anticipate stimulus activity. Therefore, the unpredictability of the spatial and temporal stimulus characteristics incorporated within the Zaccara et al. (1992) experiment perhaps revealed the vulnerability of the visuospatial attention system and inhibitory control (as indicated by the significant number of anticipatory saccades) in AD patients. In another study

of smooth pursuit eye movements, that tested a small group of AD patients (*seven*) on four occasions over a twelve month period (Hutton, 1985), a progressive impairment of pursuit tracking was reported. Cross-correlations showed that there was a decline in eye to target accuracy over time. However, it was not clear whether the changes in pursuit eye movement performance correlated with the changes in cognitive ability over time. A number of studies have reported that AD patients produce large inappropriate saccadic intrusions during smooth pursuit tasks(Fletcher & Sharpe, 1988; Gangemi et al., 1990; Jones, Friedland, Kos, Stark & Thompkins-Ober, 1983; Kuskowski et al., 1989). Therefore, this finding supports the notion that AD patients have dysfunctional inhibitory control.

### *1.6.2 Eye Tracking and Exploratory Ability in Alzheimer's Disease*

A number of studies have recently revealed dysfunction in eye tracking or scanning ability in AD patients. Lueck and colleagues revealed disorganised visual scanning during reading (Lueck, Mendez & Perryman, 2000) and Mosimann et al. (Mosimann, Felblinger, Ballinari, Hess & Müri, 2004) discovered that visual exploration was less focused and delayed on normalised regions of interest when scanning a clock face. An investigation of exploratory eye movements in AD found AD patients to have diminished curiosity (Daffner, Scinto, Weintraub, Guinessey & Mesulam, 1992) and another study of visual search strategy in AD demonstrated that planning of search strategy was inefficient and initiation of saccadic movements delayed (Rösler et al., 2000).

### *1.6.3 Saccadic Eye Movement Abnormalities in Alzheimer's Disease*

Abnormalities revealed in the investigation of saccadic eye movements in AD suggest impairment of neurocognitive processes that are responsible for attention, visual fixation, inhibitory control and self-monitoring with corrective action.

### 1.6.3.1 Reflexive Saccadic Eye Movements in Alzheimer's Disease

Saccade latency was reported to be related to dementia severity in an early study of reflexive saccades (Pirozzolo & Haunsch, 1981), however, in another study Hershey and colleagues did not substantiate this finding; although they did highlight that saccade latency was prolonged for AD patients and other dementia type patients compared to age-matched control participants (Hershey et al., 1983); a finding further corroborated by recent studies (Bylsma et al., 1995; Shafiq-Antonacci, Maruff, Masters & Currie, 2003). More recently, Schewe and colleagues examined AD patients using an involuntary saccade paradigm and discovered that the Mini Mental State Examination (MMSE) scores of AD patients were significantly correlated with abnormal levels of various parameters, including saccadic intrusions during fixation (gaze impersistence), amplitude and latency (Schewe, Uebelhack & Vohs, 1999).

Fletcher and Sharpe (Fletcher & Sharpe, 1986) discovered that whilst attempting to fixate a central point, prior to peripheral target onset using a predictable prosaccade task, AD patients showed impersistence of gaze and also presented with large amplitude saccadic intrusions in the opposite direction to that required (a finding supported by Bylsma (1995) who also detected saccadic intrusions). In a task where targets appeared at unpredictable locations, AD patients generated saccades with significantly longer latencies than those of control participants, compared with the predictable target task where no significant difference was found between groups. Findings from an involuntary reflexive saccade task by Moser et al. (1995) revealed further support for the common finding that AD patients generate saccades with prolonged saccadic latency, compared with controls, but the same study did not reveal any significant differences between groups for saccadic amplitude and maximum velocity. However, in the study by Fletcher and Sharpe (1986) peak velocity was shown to be significantly lower for AD patients, compared with controls in the unpredictable involuntary saccade task and saccade latency was significantly prolonged, whereas no difference was

demonstrated between groups in the predictable target task. In contrast to Moser et al. (1995), who found no difference between-groups for peak velocity but did find a corresponding significant prolongation of latency for unpredictable target locations. A further study by Scinto et al. reported no difference between ADs and elderly controls for saccade latency (Scinto et al., 1994). However, in this study Scinto et al. used double-steps of the target to induce saccades and the instructions may have been somewhat confusing for patients, which seems to have been reflected in the incredibly high error rate of 40%. Generally (when reported), the mean for group error for AD patients on random reflexive saccade tasks is very much lower (e.g. Shafiq-Antonacci et al. 2% and the present study also approximately 2%). Therefore, the nature of the Scinto et al. task provides a plausible argument for excluding the study from any further comparison with other studies mentioned at this point.

The present thesis will employ reflexive saccade tasks that exert low cognitive demand, with the targets directionally randomised in presentation, at locations with near eccentricity that borders parafoveal and peripheral vision. A single $4^{\circ}$ target was employed as target location uncertainty is a major stimulus factor that determines saccadic reaction times (Walker, Deubel, Schneider & Findlay, 1997). In reducing this uncertainty and using of a near target location together with a salient target the aim was to facilitate the task as much as possible for the AD and elderly participants

It is also important to consider, that there is only a limited amount of time available when conducting laboratory eye movement tests - in view of the clinical group involved, AD patients and elderly persons - before fatigue and data quality may be compromised and also, patient/participant care is of paramount concern in this elderly experimental population. Therefore, in reducing the complexity of experimental conditions by restricting the number of levels, potential confounding factors are modulated and data output focused in relatively few trials for each test. Exploration of inhibitory and attentional aspects will be achieved by the introducing of gap and overlap paradigms (Section 1.3.1 & Chapter 2, Section 2.3.3.1).

Analysis of saccadic amplitude to unpredictable target locations (randomised target eccentricity and direction) and predictable targets by Fletcher and Sharpe (1986) revealed an impairment in accuracy for AD patients, demonstrated by significantly smaller amplitudes for AD patients, resulting in frequent large corrective secondary saccades. Nakano and colleagues also found significant differences between groups for predictable stimulus amplitude, but this task involved eye and head coordination (Nakano et al., 1999). However, the study by Moser et al. (1995) found no difference between groups in amplitude for unpredictably timed targets. In contrast, another recent study found significant differences between-groups for both predictable and unpredictable target presentation, AD patients producing hypometric saccades compared with controls (Shafiq-Antonacci et al., 2003), supporting the findings of Fletcher and Sharpe (1986). The study by Shafiq-Antonacci et al. used a greater number of target amplitudes for the unpredictable target experiment, similar to Fletcher and Sharpe (1986) and also included more AD patients (N = 32) than the Moser et al. (1995) study (N = 10) resulting in more robust findings. The present thesis will attempt to build on previous investigations of AD and will include 30 dementia patients (Section 2.1.1) investigated across paradigms longitudinally in Chapter 7, and in Chapter 5 disease and age effects will be examined more closely, by comparing the data from the dementia patient group, with the data from a group of 25 Parkinson's disease patients (examining disease effects) and 17 young controls participants (examining age effects).

The study by Bylsma et al. (1995) found no significant differences between groups of AD patients and controls at baseline on a gaze fixation task, whereas on a predictable saccade task the AD group were found to have significantly prolonged saccade latency compared with controls (but no difference was observed for saccadic amplitude or peak velocity). On repeated measures of the study following after a nine-month inter-test interval to plot change, no deterioration was observed in the saccade task, the AD group still was found to have prolonged saccadic latency compared with controls. However, fixation stability appeared to have

significantly deteriorated over time. Bylsma et al. (1995) thus suggest that fixation is a more sensitive marker than saccades for indicating the progression of AD. However, Bylsma et al. (1995) used electro-oculography (EOG) for the study and as mentioned in Chapter 2 (Section 2.3.1), EOG has been found to produce artefacts in the eye movement trace and is vulnerable to other interference (Doig & Boylan, 1989; Iacono & Lykken, 1981; Linsday, Holzman, Haberman & Yasillo, 1987; Ong & Harmen, 1979). Although Bylsma et al. (1995) took care to make adjustments to the data, in an attempt to compensate for irregularities, it remains conceivable that an unreliable level of error was present in the data. Furthermore, the saccadic task involved the use of a predictable stimulus only, which may indicate that the neural pathways involved for a task of this nature are less vulnerable to change over time than, for example an unpredictable stimulus. Additionally, unpredictable stimuli have revealed the more consistent abnormalities between studies. If Bylsma et al. (1995) had included an unpredictable condition (for test-retest) then potentially a more balanced picture may have been found. A further criticism of Bylsma et al. (1995) is the apparent lack of any practice trials in the saccade condition. A study by Abel et al. (2002) also used EOG (as *magnetic search coil* was not tolerated by participants in general) and this study found no significant differences between ADs and controls for reflexive saccade latency in predictable and unpredictable tasks. As to whether the lack of reflexive saccade group differences was due to the EOG method is a matter for debate. However, Abel and colleagues do explain, that calibration was less precise than that required to record amplitude and velocity (which were not to be recorded in the study) and that the EOG signal was relatively poor in the elderly participant study population. Therefore, EOG may be less reliable method for recording eye movements in elderly participant samples. The present thesis will use the infrared scleral reflection method (Chapter 2, Sections 2.3 & 2.5.2) of recording eye movements, due to the systems reliability and ease of application.

### 1.6.3.2 Antisaccade Eye Movements in Alzheimer's Disease

Fletcher and Sharpe (1986) included the antisaccade task in their study and found that AD patients failed to inhibit the VGR on 74% of trials when asked to look in the opposite direction away from the target. A further finding was an omission of response on 22% of trials (however Fletcher and Sharpe (1986) do not report antisaccade latency). In another study that used both clinical (bedside manual type task) and laboratory oculographic antisaccade tasks, Currie et al. (Currie, Ramsden, McArther & Maruff, 1991) also found saccadic errors, again confirming that AD patients display dysfunction in the ability to generate saccades away from a visual target, which would seem to demonstrate poor inhibition of the VGR. Additionally, Currie et al. (1991) reported correlations between antisaccade error rates and disease severity, as indicated by Mini Mental State Examination (MMSE) (Folstein, Folstein & McHugh, 1975) scores. Furthermore, Currie et al. found correlations between antisaccade error rates and tests of frontal lobe function. Conversely, Mulligan and colleagues (Mulligan, Mackinnon, Jorm, Giannakopoulos & Michel, 1996) did not replicate the finding of a relationship between the clinical antisaccade test error rates and MMSE scores. However, strangely Mulligan et al. (1996) fail to give any account of a method for the specific way in which the clinical (*hand*) test was administered to participants (although they do claim to follow the procedures of the test developers) and furthermore, do not conduct any laboratory based oculography tests for the antisaccade task. The number of AD patients (N = 15) included by Mulligan et al. (1996) was only half of the number (N = 30) included in the study by Currie et al. (1991) and the mean age was considerably older in the Mulligan et al study (Mulligan et al. (1996) AD mean age 81.8 years; SD 7.8 years / Currie et al. (1991) mean age 67.0 years; SD 8.0 years). Also, many of the MMSE scores for AD patients in the Mulligan et al. (1996) study appear to cluster highly around 25, whereas in the Currie et al. (1990) study, AD MMSE scores are far more evenly dispersed producing a better representation of severity in the experimental group. Therefore, it is a plausible argument, that the finding by Mulligan et al. (1996) that indicates a lack of

relationship between MMSE scores and antisaccade error rates, may be due to the methodological differences employed between the two studies.

Recent laboratory studies employing the antisaccade task (Abel, Unverzagt & Yee, 2002; Shafiq-Antonacci et al., 2003) have supported the findings of Fletcher and Sharpe (1986) and Currie and colleagues (1991), showing significantly higher error rates for AD patients compared with elderly controls and furthermore, confirming antisaccade error rates to be significantly correlated with MMSE scores (the study by Shafic-Antonacci et al. (2003) also reported that antisaccade latency was observed to be significantly prolonged compared with controls). The present thesis will utilise the simplified temporal and spatial parameters from the reflexive tasks discussed earlier in this Section, and administer these with antisaccade instructions (Section 1.3.2.1 & Chapter 2, Section 2.3.3.2), maintaining the cognitive load induced by the tasks to a minimum. Further voluntary tasks requiring inhibitory control: No-Go and Go / No-Go tasks (Section 1.3.2.1 & Chapter 2, Section 2.3.3.3) will also use the same simple stimulus characteristics. Whilst the No-Go task purely requires inhibition of prepotent response with minimal working memory requirement, the Go/No-Go task is expected to make higher demands on working memory resources, above that required for the antisaccade tasks. Moreover, the present thesis will investigate AD antisaccade performance and performance on each of the other saccadic eye movement paradigms over time – longitudinally, from baseline with repeated measures over three further 6 month inter-test intervals, i.e. in total four experimental sessions will be conducted for each test. This procedure will therefore attempt to plot the trajectory of disease progression, using an extensive range of saccadic eye movement tests (as compared with the Bylsma et al. (1995) study, which simply used a predictable reflexive saccade paradigm on test-retest[4]).

Taken together, the results outlined in this Section highlight a link between saccadic eye movements and cognitive performance, and the possibility that eye movements may be a

[4] Bylsma et al. (1995) did however conduct an additional fixation task also using EOG.

biological indicator of AD. It has been demonstrated that AD patients appear to have difficulties in the suppression of inappropriate action, but the implementation of corrective action has not been fully investigated. Only one study appears to have investigated corrected and uncorrected errors in AD, the study by Abel et al. (2002), which found that AD patients produced a significantly higher proportion of uncorrected errors compared with controls (whereas no significant difference was found between groups for corrected errors). The degree to which ADs have problems with ability for self-monitoring their actions in voluntary saccade tasks requires further investigation, a line of enquiry that will be pursued in this thesis on a longitudinal basis.

In summary, smooth pursuit eye movement results from studies of AD patients are somewhat inconsistent and less extensively studied than saccadic eye movements. This may at least in part be a reflection of AD patient ability to comply with task demands. However, saccadic eye movements would appear 'potentially', to be a more reliable marker for the prediction of disease, particularly with voluntary paradigms such as the antisaccade task and its relationship with cognitive test scores. AD patients consistently show impairment on a number of different saccadic variables, in particular saccade latency (and often amplitude/accuracy and velocity) although this finding is more often observed when targets are unpredictable. Various studies have reported that AD patients produce saccadic intrusions during attempted fixation, indicating impersistence of gaze (probably as a result of anticipatory action and due to impaired inhibitory control). Impairment of inhibitory control appears to be the most clearly consistent finding among studies of AD patients, a deficit that frequently results in unsuccessful suppression of the VGR in antisaccade tasks.

### *1.6.4 Inconsistent Saccadic Eye Movement Research Findings in Alzheimer's*

Although, antisaccade findings using a variety of standard laboratory oculographic techniques are generally in agreement, there appear to be some inconsistencies in the findings

discussed above for reflexive saccade tasks. The differences noted between some of the studies are highly likely to be due to the methodological issues already discussed above, such as differences in spatial and temporal parameters for stimulus presentation, eye movement recording techniques (e.g. recordings from EOG contain noise and artefacts, and are thus unreliable, requiring adjustments to the signal data) mentor differences between studies in the rating (analysis) of analogue signal eye movement data.

Whilst piloting the equipment and setting test parameters for the paradigms included in the present thesis (for paradigms see Chapter 2, Section 2.3.3), it was found that test parameters for healthy elderly volunteer pilot participants had to be reset several times, in order to find satisfactory temporal settings for randomised target presentation. The parameters that were found to be particularly important, although they may not be immediately obvious, were the inter-trial interval, central fixation point duration and target duration. If by varying degrees, the duration of these components was set too short, elderly people ranging from 75 – 85 years were found to have difficulty in performing reflexive saccade tasks, with performance on antisaccade tasks found to be further disrupted. It was also observed that fatigue, caused through extended test sessions, could pose a major problem for this study, therefore the number of trials was set at a low number for each experimental condition (Section 2.3.3) to counteract this potential confound. The studies of reflexive saccadic eye movements in AD, reviewed in Section 1.6.3.1 involved an array of different temporal and spatial stimulus characteristics. Stimulus properties in experimental conditions sometimes comprised fully predictable targets; and/or temporally unpredictable targets; and/or directionally unpredictable targets. The target amplitude in directionally unpredictable conditions, often included a range of eccentricities, which could be responsible for variation in response. For example, in the study by Fletcher and Sharpe (1986) the targets ranged from ±5°, 10°, 20° & 40° (with regular timing), whereas in the Shafiq-Antonacci et al. (2003) study the targets were at eccentricities of ±5°, 7.5°, 10° 12.5° & 15° (with regular timing). Both of these studies showed that AD patients produced

hypometric saccades compared with controls. Interestingly, whereas Fletcher and Sharpe (1986) found no significant difference between AD patients and controls for saccadic latency, Shafiq-Antonacci et al. (2003) did. This difference may be due to inconsistency between the AD patient groups as it appears that AD patients in the Fletcher and Sharpe (1986) study may have been less severely impaired than the AD patients in the analysis conducted by Shafiq-Antonacci et al. (2003), who had a MMSE 17.1, with a large SD of 7.4 (lowest score reported was 4). This draws attention to the putative notion that saccade latency may be related to dementia severity. The mildly impaired patients in the Fletcher and Sharpe (1986) study were found to have significantly prolonged latency for targets with unpredictable *temporal* characteristics only, whereas the more severely impaired patients in the Shafiq-Antonacci et al. (2003) study generated saccades that were prolonged in latency in both predictable and unpredictable (with variable *temporal* and *spatial* properties) experimental conditions.

Therefore, an important consideration for all research involving elderly participants and a further possible explanation for the inconsistent findings between studies, is that there could be variation in the diagnosis or characteristics between different groups of AD patients (from the different studies), although this should be minimal, given that studies usually follow fairly standard diagnostic selection/exclusion criteria, such as DSM-IV criteria, NINCDS-ADRDA criteria and exclusion of other factors that could be responsible for illness.

An additional explanation for inconsistent findings, are possible differences in the characteristics of Alzheimer's disease in different countries. Moreover, it is also feasible that some elderly control participants in the studies above have mild cognitive impairment (MCI), as the cognitive scores of MCI sufferers can be deceptively close to the scores of healthy controls, aside from specific isolated memory deficits such as short-term recall, with deterioration over time and informant reports of memory difficulties (Dubois & Albert, 2004; Grundman et al., 2004). Additionally, prevalence models estimate the likelihood of conversion to MCI from healthy non-affected to range from 1% at age 60 years to as high as 42% at age

85 years (Yesavage et al., 2002). Furthermore, it has also been reported that MCI could possibly be prodromal AD (Dubois & Albert, 2004; Flicker, Ferris & Reisberg, 1991) a transitional state between the changes in cognition that come about through normal aging and those of early dementia. Evidence suggests that approximately 50% of patients diagnosed with MCI develop AD or another form of dementia within five years (Petersen, 2000; Petersen et al., 1999). Therefore, if some cases of undiagnosed MCI were mixed in with various elderly control groups, then the difference between group scores and effects would potentially be reduced. The present study in this thesis, will carefully monitor the performance of individual elderly control participants over time, in an attempt to ensure that participants who show signs of MCI are excluded.

### *1.6.5 Saccadic Eye Movements as a Possible Marker of Alzheimer's Disease*

Customarily, Alzheimer's disease type dementia has been recognised as a degenerative disorder with global neurocognitive deficits. As mentioned in section 1.5, different forms of dementia have now been qualified, as a result of differentiating aetiology and identifying the pathology of brain structures. Accordingly, different profiles of cognitive abnormality correspond to the various forms of dementia (Snowden, 1994). Localization of neurocognitive impairment using neuropsychological assessment batteries to measure a range of cognitive functions, have been adopted with a good deal of success (Perry & Hodges, 1999), although the conventional tests that measure episodic memory, executive function, attention and visuospatial function and language do not have good temporal resolution, specificity and a direct relation to regional functional activity in the brain.

Studying sensorimotor integration using saccadic eye movements may provide an index of neurocognitive function in AD. Various lines of enquiry may inform a greater understanding of the relationships between saccadic eye movements in AD and cognition. For example, is intellectual function associated with saccadic variables? Can a reliable distinction

between AD patients and control participants be facilitated by the analysis of any saccadic variables? Is there a relationship between saccadic factors and severity of AD? The antisaccade eye movement task has been used extensively in psychiatric and behavioural research and provides a means of probing endogenous and exogenous behavioural control (Monsell & Driver, 2000). As outlined in Section 1.1, performance deficits in the antisaccade paradigm have been shown to be present in various psychiatric and neurodegenerative diseases and thus, the antisaccade paradigm is a potential biological marker of such disease (Broerse et al., 2001).

An area of increasing interest to health care professionals and the reason for extensive research in the treatment of dementia, is early diagnosis (Ferrarese & Di Luca, 2003; Foster, 1998; Saunders, Hulette, Welsh-Bohmer & al., 1996). The advantage of early detection of AD by a relatively simple diagnostic test, would be an extremely attractive option for health service providers, as the relative cost and complexity of potential biochemical diagnostic marker systems and logistics (perhaps involving the extraction of cerebrospinal fluid) is extremely higher, than the cost of simple oculomotor test systems.

The advent of an early sensitive easy to administer diagnostic marker for AD would potentially therefore, have vital diagnostic benefits and implications for the primary approach to treatment, quality of life maintenance and prescribing of modern anti-dementia medications, with possible cost saving for the NHS from delayed requirement for nursing home care with the delay in disease progression. Moreover, should a treatment or cure be discovered for Alzheimer's disease it is vital that diagnosis is made at the earliest opportunity before significant neurodegeneration takes place in the brain.

## 1.7 Chapter Summary

This chapter has introduced this thesis and commenced by demonstrating the importance and efficacy of eye movements in both the clinical and research fields,

emphasizing how eye movements have been used extensively as a line of neuropsychological enquiry and in neurological and psychiatric illness. Reliable measurement of eye movements can be made relatively easily in the modern laboratory, and there are advantages in studying movements that the eyes make. Compared to other systems: the eyes only move in three planes; the neuroanatomical substrates have been extensively studied; the mechanical load for the eye muscles is constant, therefore there is a lack of monosynaptic stretch; and eye movement disturbances are often characteristic of certain pathophysiology, anatomical location or pharmacological disturbance.

Saccadic eye movements were discussed as the basis for the present thesis and the utility that they provide in psychiatric and neurological research. The distinction was made between involuntary – reflexive saccadic eye movements and voluntary saccadic eye movements. It was explained that horizontal reflexive saccadic eye movements are largely the result of bottom-up processing triggered by descending pathways from the PEF and generated by the SC in the midbrain, the extraocular muscles receiving input from crucial motor neuron activation structures in the brainstem (the pons and medulla). However, voluntary saccadic eye movements are saccades made in response to specific task instructions or according to internal goals and are largely the product of top-down processing which involves various cognitive systems such as inhibitory control, attention and working memory. The generation of voluntary saccadic eye movements involves many cortical areas, including the FEF, PEF, DLPFC and SEF. There are reciprocal pathways between both the FEF and the PEF with the SC in the midbrain, but the extraocular motor neurons are innervated by the same brainstem structures as for reflexive saccade generation.

Alzheimer's disease is the most prevalent of the dementias, forming approximately 55% of all types and at present diagnosis can only be confirmed postmortem. The neuropathology of the disease extends in particular, through pyramidal cells of the cortex (temporal, parietal and later frontal) and sub-cortically mainly in limbic structures - the hippocampus and amygdala, in

the form of neuritic plaques and neurofibrillary tangles. The disease presents as a progressive and insidious onset of memory dysfunction primarily and problems with executive function, which can be concomitant with deteriorating elements of apraxia, aphasia and agnosia.

Saccadic eye movement research in AD has revealed a range of dysfunction, including relationships between errors on the antisaccade task and clinical rating scales, prolonged saccade latency and hypometric saccade accuracy. A common finding is the generation of errors in the antisaccade task that are believed to be due to a disturbance of inhibitory control, which results in a lack of suppression of the VGR causing inappropriate reflexive saccades towards the target.

# Chapter Two

# Methodology

## 2.1 Participants

Participants for the experimental groups in the studies of the present thesis comprised dementia patients and healthy elderly control participants. All volunteering participants received an information sheet (Appendix 1) outlining the study and written informed consent (Appendix 2) was obtained from each participant. Demographics and brief history records (sample history sheet Appendix 3) were gathered from all participants at test, with detailed additional information extracted from medical records for the dementia patient group. All information, including longitudinal test scores, range of demographics, medical history and prescribed medications, was treated with the strictest confidence, registered under the Data Protection Act (1984) and stored on an extensive secured computerised relational database (Microsoft Access 2000$^{TM}$). Hard copies of all data were also filed for back-up reference and stored in a secure environment. All volunteers to the study were monitored for medications and health problems to ensure that confounding factors, such as mental disorder (e.g. depression), chronic hypertension, major heart disease, alcoholism, neurological disease, morbid conditions of the eye (e.g. congenital nystagmus, strabismus, cataracts), poor eye sight, drug abuse, alcoholism or lack of mobility (e.g. due to old age or chronic arthritis) could be excluded. Visual acuity was assessed for all participants using the Snellen's test (Appendix 4) and participants were also screened for visual neglect using a line bisection test (Appendix 5) (Schenkenberg, Bradford & Ajax, 1980). The Geriatric Depression Scale (GDS – short form, Appendix 22) (Shiekh & Yesavage, 1986; Yesavage et al., 1983) was utilised to test for

depression and revealed that scores for 3 Dementia patients fell within the early mild range of clinical depression at the first stage of testing in the longitudinal program (however, it is not uncommon to find low mood or negativity in dementia patients, Lishman, 1986). All participants were right-hand dominant.

### *2.1.1 Dementia Patients*

Dementia patients with a diagnosis of probable Alzheimer's disease were recruited from the Memory Clinic in the Department of Old Age Psychiatry, Lytham Hospital, National Health Service (NHS), England, U.K., via consultant psychiatrist referral. Assessment and diagnosis of patients adopted the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders 4th ed. (DSM IV) and the National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) diagnostic criteria (McKhann et al., 1984), in an attempt to eliminate individuals with dementia (or alternative illness) of aetiology caused by other than AD. Additionally, a range of clinical investigations were conducted by a physician on the Dementia Patient group (Table 2.1) to exclude other possible causes for illness.

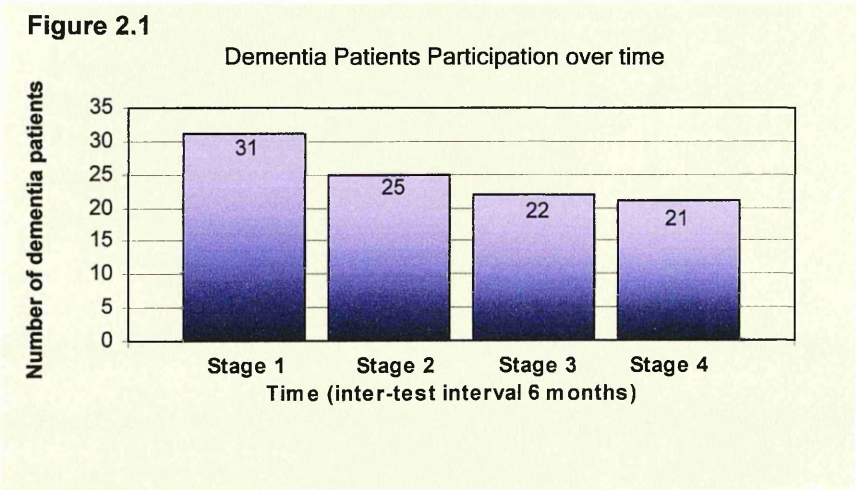
**Table 2.1** Clinical Investigations

| |
|---|
| Clinical interview |
| Physical examination |
| Haemoglobin and full blood count |
| Erythrocyte sedimentation rate |
| Urea and electrolytes |
| Liver function tests |
| Blood glucose |
| Serum vitamin $B_{12}$ and folate |
| Serology for syphilis |
| Urinalysis |
| Electrocardiogram |
| Neurological examination |

A total of sixty-seven patients were invited to join the study. Of the invited patients, twenty indicated that they did not wish to take part, however, forty-seven patients expressed a positive interest with regard to participation (70.1% patient recruitment net success rate). Of the forty-seven dementia patients interested in taking part, four dropped-out prior to testing and eleven were excluded further to screening for one or more of the following: poor eye sight, hemi-neglect, prescribed medication or ill health. The balance of thirty-one candidates were recruited to the study, initially volunteering to join the research project on a longitudinal basis (46.3% longitudinal patient recruitment net success rate).

Attrition of dementia patient numbers over the longitudinal spread of the study can be seen in Figure 2.1. Overall, 67.7% of patients remained for the full duration of the longitudinal period; Retention of dementia patients appeared to correspond with health, thus dementia patients were most obliging in their efforts to continue with the project, if it was in their capacity to participate.

**Figure 2.1**




Reduction of numbers participating on consecutive test stages was due mainly to deterioration of cognition with the progression of dementia disease severity (symptoms ranging from severe loss of memory [e.g. no recollection of the researcher or previous visits], circumlocution, agnosia, confusion and disorientation; fear of participation) and also as a result of general illness. Sadly one patient passed away.

Impairment in the patient group was initially classed as probable Alzheimer's type dementia, consisting of patients with mild to moderate severity, further to assessment using the Standardised Mini Mental State Examination (SMMSE, Appendix 13 and 13.1) (Folstein et al., 1975; Molloy, Alemayehu & Roberts, 1991) and the cognitive sub-scale of the Alzheimer's Diseases Assessment Scale (European version; EADAS-cog. Appendix 14 and14.1; Dahalke et al., 1992; Rosen, Mohs & Davis, 1984). A further as rating of severity was made at stage 1 only utilizing the Clinical Dementia Rating Scale (CDR; Appendix 6) (Hughes, Berg, Danziger, Coben, and Martin, 1982) (Section 2.5 discusses these tests and the range of neuropsychological assessments that were employed for the study). However, subsequent follow-up testing during the longitudinal stages of the research, investigation of clinical notes and collaboration with consultant psychiatrists, revealed the dementia patient group to comprise a range of probable dementia types as displayed in Table 2.2.

**Table 2.2** Composition of Dementia Patient Candidates

| Dementia Type | Number in group |
|---|---|
| Alzheimer's disease | 17 |
| Vascular dementia | 4 |
| Mixed dementia | 4 |
| Transient ischaemic attack | 1 |
| Mild cognitive | 3 |
| No dementia | 2 |

Therefore, in the final analyses the two patients classed as no dementia and a patient who had a recent transient ischaemic attack (TIA) and did not appear to have fully recovered were excluded.

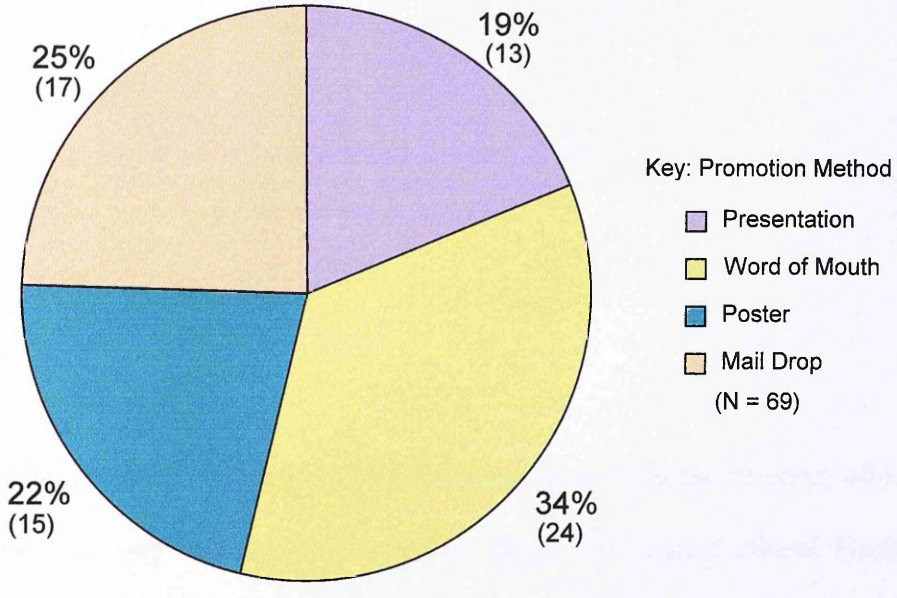
### *2.1.2 Elderly Control Participants*

A Control group, consisting of healthy non-demented elderly control participants was also required for inclusion in the experimental population. In order to recruit sufficient Elderly Control participants (ECs), the research project was promoted, via a number of means to

generate awareness. The range of methods employed to promote the research project, included word of mouth, mail drop information/application pack, presentations to various groups in the locale, including Social Services carer groups and the Lancashire Dementia Research Interest Group (LADRIG). Posters were also designed to promote the study and these were erected in Lytham Hospital, GP surgeries, churches, residential homes and also in a variety of locations at Lancaster University.

Satisfactory response rates (presented in Figure 2.2 below) were generated by each promotional method.

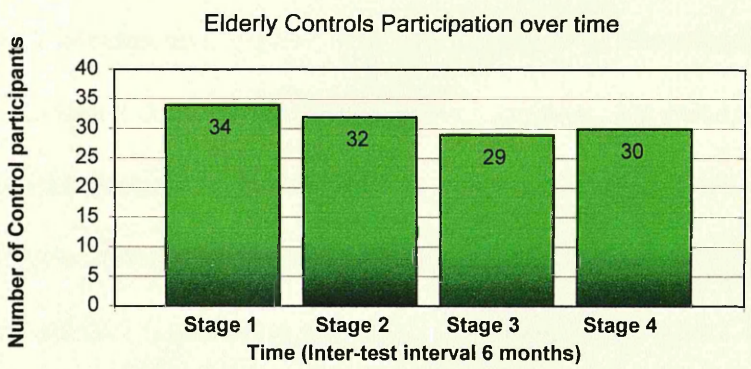
**Figure 2.2** **Control Participant Recruitment Response Rates for the Range of Promotional Methods**




The total number of candidates that applied to be ECs was sixty-nine. Therefore, the recruitment methods employed in the research project awareness campaign as a whole were successful in generating a total of one hundred and sixteen positive responses with combined applications across groups. Forty-six candidates were initially included as ECs for the longitudinal project. However, during the course of the study a further number ECs were excluded, due to exclusionary criteria surfacing that inadvertently had not previously been revealed (e.g. clinical depression; colour blindness; congenital nystagmus; poor mobility;

cataracts). Therefore, the total number of ECs involved in the final analysis and incorporated in subsequent Chapters of this thesis, was reduced to thirty-four. Retention of ECs for the longitudinal duration of the project was good, with 88.2% of ECs remaining throughout the study. Attrition rates for ECs were low and can be seen in Figure 2.3 below. The four ECs that left the study did so for personal reasons or commitments and not due to a lack of interest in the study.

**Figure 2.3**




The research ethics proposal for the project was approved by both the research ethics committee at Lancaster University and by the Blackpool, Wyre and Fylde National Health Service, Local Research Ethics Committee (Approval granted January 2001; Reference number 611).

## 2.2 Health Status of Participants

Sections 2.1.1 and 2.1.2 outlined screening criteria that were applied to volunteers so as to exclude candidates whose performance on saccadic eye movement paradigms may be impeded by confounding illness, impairment or medication. The population of participants included for testing and final analysis in this study - selected from diverse backgrounds - were

elderly people and in view of this fact it is inevitable that a range of non-significant illnesses (from the perspective of this research non-neurological illness) may afflict some of the study population at the time of testing. The focus of this section is to delineate details of the health status for the elderly experimental groups.

### *2.2.1 Effects of Pharmacological Agents on Saccades*

Previous research has indicated that certain drugs exert effects on the CNS that influence brain function and saccadic processes. Many drugs have been found to reduce the state of alertness in humans and thereby alter the dynamics of prosaccadic eye movements, namely reducing the speed, accuracy and variability of saccades, for example, diazepam (Drug group: Benzodiazepine anxiolytic; anticonvulsant; muscle relaxant (BMA, 2001)) (Gentles & Thomas, 1971; Jürgens, Becker & Kornhuber, 1981; Roy-Byrne, Cowley, Radant, Hommer & Greenblatt, 1993), alcohol (Blekher et al., 2002; Lehtinen, Lang, Jäntti & Keskinen, 1979; Wilkinson, Kime & Purnell, 1974) and other various other compounds (Griffiths, Marshall & Richens, 1984). The benzodiazepine group of drugs, has also been found to interfere with antisaccade task performance; Various studies have revealed reduced maximum velocity and prolonged latency (Green & King, 1998; Green, King & Trimble, 2000). The antipsychotic drug chlopromazine, has been found to produce increased error rates (McCarten et al., 2001). Medication was closely monitored when recruiting participants, as part of the exclusionary criteria (Sections 2.1.1 & 2.1.2), taking care not to include those taking drugs that fall into the aforementioned categories.

Given the diminution of alertness and saccadic control that is caused due to the effects of certain drugs, the following Section outlines the medications that were taken by the some members of the elderly experimental population. The descriptions attempt to demonstrate that drugs (or ailments) reported in the subsequent Sub-Sections (2.2.2 & 2.2.3) covering within-group health status , do not effect the CNS in a manner that would impede performance on the

study tasks; more specifically, it is argued that the medications are not detrimental to CNS performance, when used in the correct/adjusted/monitored dosage rate (BMA, 2001); Nor is performance enhanced on the saccadic or neuropsychological tasks. Emphasis should be placed on the continuity of regular prescribed and monitored dosage of medication. Participants in the research population who were taking medication for the various ailments reported were tolerating their medication well, and reported no side effects. A further point of note, is that the action of some drugs is also limited, only lasting for a short time e.g. glyceryl trinitrate 20 – 30 minutes (BMA, 2001). It can therefore be argued, that even if this drug was taken incorrectly or by a person with low tolerance, it is unlikely that any adverse effects such as, for example, dizziness, leg weakness or nausea would still be present at test. The well-being participants was of primary importance throughout the duration of this research. In respect of this, participant welfare was monitored prior to commencement and during experimentation. Participants were asked several times throughout the test sessions, as to their well-being and, therefore, testing would not proceed should a patient feel unwell (fortunately, only two test sessions were terminated – both Elderly Control participants: one with a head cold; the second grieving over the death of a close friend).

#### *2.2.1.1 Experimental Population Medications*

To aid interpretation of the group health status sub-sections, Table 2.3 describes the main generic substances taken by some of the experimental population. Simple medications such as, for example, skin creams, antacids and laxatives have been eliminated from the following account.

**Table 2.3** Generic Medications

| Medication | Common drug | Action |
|---|---|---|
| **Vasodilator** | **Amlodipine** | Act to relax and smooth the muscles surrounding blood vessels, so as to widen the vessel and allow blood to flow more easily. |
| **Diuretic** | **Bendrofluazide** | Affect the filtration process of the kidneys, thereby reducing the level of water and sodium that is returned to the bloodstream; thus due to less water being present in the blood, excess water is removed from tissues and passed in the urine. |
| **Statins** | **Atorvastatin** | Lipid-lowering drugs, that reduce the level of blood cholesterol by acting on the processes of the liver. |
| **Corticosteroid inhaler** | **Budesonide** | Used to treat asthma and act on the respiratory system by reducing airway inflammation. |
| **Bronchodilator** | **Terbutaline** | Act on the autonomic nervous system to relax the muscles around the bronchioles of the lungs, thereby preventing bronchospasm. |

Source: BMA 2001

### *2.2.2 Dementia Patients – Health Status*

Analysis of Dementia Patients' brief history records (Appendix 3) and medical records revealed that eleven patients had an unremarkable medical history, with virtually no medical problems i.e. up to onset of dementia. However, there were some exceptions, including two patients that were found to have a history of ischaemic heart disease some years ago. In both cases, treatment was successful, one of the patients takes Aspirin 75 mg per day and the other case is still receiving long-term daily medication of Aspirin 150 mg; glyceryl trinitrate (Nitrolingual cfc-free pump spray) 400 micrograms; Co-amilofruse 2.5/20 tablet (diuretic); amlodipine 5 mg (anti-angina - blood vessel dilator); and atorvastatin 20 mg (tablet)

(cholesterol lowering drug). Raised blood pressure levels were found in three Dementia Patients (one patient taking daily medication of bendrofluazide 2.5 mg (diuretic), another amlodipine 10 mg (anti-angina - blood vessel dilator) and the other patient losartan 10 mg (antihypertensive).

It was established that a further three patients had age-related diet-controlled diabetes; An additional patient was insulin dependent, taking daily medication of Mixtard 30/70 (insulin), 22 units am, 12 units nocte. Head injury at some stage in the past was reported by eight patients; five of these having resulted in loss of consciousness at the time the injury was sustained. Full recovery from head injury was noted by all patients.

Records signified that one patient had a TIA on two occasions, the most recent six years prior to testing at stage one of the longitudinal study and appeared to have made a full recovery (taking daily medication of Aspirin 75 mg). Severe migraine was reported by one patient, whose spouse indicated that the problem had been present throughout the life-span, particularly in childhood and adolescence, the complaint presenting so regularly at that time that it resulted in the patient losing study time at school. The migraine is now less frequent and less intense.

A number of patients had a medical history which included one or more of the following conditions: skin cancer (full recovery), stomach cancer (full recovery), mastectomy (due to breast cancer – full recovery), appendectomy, hip replacement, knee replacement, eczema, haemorrhoids and arthritis. Chronic Obstructive Airways Disease (COAD) was present in two patients, although medication provided alleviation of symptoms (one patient taking daily medication of beclometasone inhaler, fenoterol with ipratropium bromide (Duovent) inhaler (bronchodilator) and one theophylline tablet (bronchodilator) at night; the other patient on medication of terbutaline (Bricanyl PRN) (bronchodilator); budesonide (Pulmicort turbohaler) (corticosteroid).

Computerised tomographic scanning (CT scans) was carried out on seventeen of the patients, to exclude focal lesion, tumor and subdural haematoma. The CT scans for thirteen of the patients were found to be unremarkable and normal for people of this age group (with regard to sulci size/cerebral atrophy, ventricle dilation and absence of focal lesions). In four patients the CT scans displayed some prominent widening of sulci consistent with limited cerebral atrophy, two of these patients were also found to have moderate ventricular dilation[5].

As discussed in section 2.1, three Dementia Patients may potentially have some mild depression or low mood as indicated by slightly elevated scores on the GDS.

#### *2.2.2.1 Acetylcholinesterase Inhibitors*

The group of twenty-eight Dementia Patients consisted of thirteen patients taking daily medication of acetylcholinesterase inhibitors (AChEI; anti-dementia outlined in Chapter 6) and fifteen patients who were not taking any anti-dementia drugs. Three different AChEI drugs comprised the with-medication group and included the following numbers of patients: Donepezil, N=5; Galantamine, N=3; and Rivastigmine, N=5.

### *2.2.3 Elderly Control Participants – Health Status*

Examination of the history records (Appendix 3) for the thirty-four Elderly Controls indicated that nineteen Elderly Controls had an unremarkable medical history and were in good health. Mild angina was reported for two Elderly Controls, however no medication was prescribed or being taken, in accord with the status of the complaint. Slightly raised blood pressure was present in four Elderly Controls, one of which was not prescribed or taking any medication. The other three Elderly Controls were currently taking prescribed daily medication of one of the following drugs Co-Amilozide 10 mg (diuretic), amlodipine 10 mg (blood vessel dilator) or warfarin (anticoagulant). An Elderly Control participant was taking daily medication of perindopril tert 2 mg (Butylamin) (vasodilator); indapamide 2.5 mg (diuretic) and

[5] One of these patients suffered severe migraine throughout life as discussed in the previous paragraph.

pravastatin 40 mg (cholesterol lowering drug), due to a TIA within 12 months prior to testing, but had made a full recovery when he volunteered for the study (as evidenced by high test performance throughout the study).

Head injury with loss of consciousness was reported to have occurred at some stage in the lives of five Elderly Control participants, all noting that they had made a full recovery. A medical history of deep vein thrombosis (DVT) was found for one Elderly Control, who takes medication of warfarin (anticoagulant) on a daily basis. Mild migraine was recorded for two Elderly Control participants, but no medication was prescribed or being taken due to the status of the complaint. A further two participants were taking daily medication for asthma, one of them using the following inhalers: actuations per day – salbutamol (Ventalin) (bronchodilator) 2 x 2; oxitropium (Oxivent) (bronchodilator) 2 x 2; fluticasone (Flixatide) (corticosteroid) 1 x 2; and the other asthma sufferer was taking a budesonide (Pulmicort) inhaler twice daily.

Two Elderly Control participants recorded a history of prostate cancer and one Elderly Control indicated having had skin cancer in the past. Arthritis was found to be present in the hands of one Elderly Control and three of the Elderly Controls also recorded having had an apendicectomy at some stage in the past. GDS scores for the Elderly Controls included in the study indicated that one person may have very mild depression or low mood, but the level of this score did not raise concern.

## 2.3 Saccadic Eye Movement Recording

### *2.3.1 Apparatus and Equipment*

Horizontal saccadic eye movement measurements were recorded monocularly (left eye) in a dimmed (ambient infrared light eliminated from the room for optimal recording conditions) and quiet room, using an 'Express Eye' (Optom$^{TM}$ Laboratory, Germany) infrared scleral reflection system (the headset can be seen in Figure 2.7, Section 2.4.2). The system has a spatial resolution of 0.1 degree and permits $\pm 15^{o}$ field of view. The temporal resolution of

the equipment is 1 millisecond (operating at a sample rate of 1000 Hz), with a minimum bandwidth of 0 – 250 Hz and 10 bit digitisation rate. This specification falls well within the recommendations of Leigh and Zee for the reliable recording of saccades (Leigh & Zee, 1999). The system infrared amplifier was set at 75.0% throughout the study and analogue eye signal data was recorded on the hard drive of a Dell Inspiron 3800 laptop computer for analysis offline.

Infrared reflection equipment was chosen precisely for its temporal resolution properties and its non-invasive application. Alternatives, such as electro-oculography (EOG), and the search coil technique were avoided for a number of reasons. Firstly, EOG has been found to produce artefacts in the eye movement trace, when a saccade is generated, as a consequence of the neural activity (muscle action potential spike)(Iacono & Lykken, 1981; Linsday et al., 1987), eyelid movement and interference from the other eye (Doig & Boylan, 1989; Ong & Harmen, 1979). Second, the search coil technique was thought to be too invasive for this study, particularly in view of the experimental patient (and elderly) groups involved. Third, the reliability, ease of use and speed with which the system could be set up, was advantageous in enabling experimental procedures to flow rapidly, given the potential for fatigue and problems with task compliance in dementia patients (Perry & Hodges, 1999).

### *2.3.2 Visual Stimulus Properties*

Visual stimuli (targets and central fixation point) were generated by mini lasers mounted on the system headset thereby, largely compensating for possible changes in head position and viewing distance, although a chin rest was used to restrain the head (see Appendix 9). The lasers projected a spot of light subtending approximately 0.2° of visual angle, onto a white tangential screen (Appendix 10) set to eye level, fixed at a distance of 57 cm from the eyes of the participant, a distance common to other studies (Levin, Jones, Stark, Merrin &

Holzman, 1982; O'Driscoll, Lenzenweger & Holzman, 1998). This distance facilitates simple calculation of target amplitude, derived from the formula:

$$\tan(\alpha) = a/b.$$

In this formula $a$ is equal to the distance between the central fixation point and the target; $b$ is the distance of the eye from the target; and the amplitude ($\alpha$ in Figure 2.4 below) is equal to the angle (degrees) produced by $a$ and $b$. In this study, $a = 4$ cm, therefore, $\alpha = 4^{\circ}$.

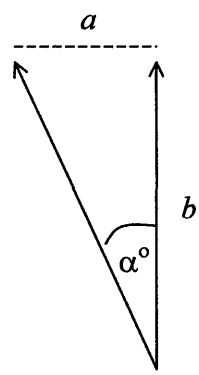



**Figure 2.4** Calculating the Visual Angle of the Stimulus
When $b = 57$ cm, $a$ is approximately equal to $\alpha$.

The stimulus array for each experiment consisted of a central fixation point at $0^{\circ}$ that appeared within a $0.75^{\circ}$ x $0.75^{\circ}$ central square and peripheral targets with eccentricities of $\pm 4^{\circ}$ in the horizontal plane, as depicted in Figures 2.5 and 2.6. The light output from the lasers was bright red in colour, with a wavelength of 635 nanometers and luminance of 66.4 cd/m$^2$ at a distance of 57 cm. Luminance was measured using a Minolta luminance meter, Model LS – 100. The lasers were of class 2 specification, with power of only 0.2 milliwatts. The normal reflex to close the eye lid in bright light, is adequate protection in the case of accidental exposure to lasers of less than one milliwatt power (Fischer, 1998). However, procedures were adopted to avoid directly gazing into the laser beams, as this may cause permanent damage to the retina.

### *2.3.3 Experimental Design*

Oculomotor paradigms included for this study were incorporated into 7 test blocks that were administered at each longitudinal testing session of the project. Experiments began with two blocks utilising prosaccade (*reflexive*) paradigms with i). a gap condition followed by ii). an overlap condition, each consisting of 24 trials. The next three blocks comprised A) a NO-GO condition, followed by two B) & C) GO/NO-GO conditions, each block of 10 trials in length. Two antisaccade tasks followed, using i). a gap condition then ii). an overlap paradigm, each consisting of 24 trials. The reflexive conditions were administered first, to avoid the potential for carry-over effects from the voluntary saccade paradigms (Roberts et al., 1994), and to ensure that prepotent response was optimal, in readiness for the voluntary saccade paradigms. This is particularly important as previous research has highlighted that dementia patients are more accommodative at test, when the least cognitively demanding task i.e. the prosaccade condition is conducted first (Perry & Hodges, 1999).

#### 2.3.3.1 Prosaccade Tasks

##### *2.3.3.1.1 Prosaccade Gap Task*

In the prosaccade gap condition (Figure 2.5, Ai), each trial commenced with the appearance of a central fixation spot displayed for 1000ms within a 0.75° x 0.75° central square. When the central fixation point was extinguished, a temporal gap of 200ms elapsed, prior to illumination of a peripheral target that was presented for 1798 ms. During the presentation of all visual stimuli, targets were randomised in the left and right (50:50) hemifields to avoid predictive behaviour. The inter-trial interval was 1200 ms. The instructions to participants were to:

"*...**look at the lights as quickly and accurately as possible.***"

### 2.3.3.1.2 *Prosaccade Overlap Task*

For the prosaccade overlap condition (Figure 2.5, Aii), each trial commenced with the appearance of a central fixation spot that remained illuminated for 2998 ms within a 0.75° x 0.75° central square, the duration of the whole trial. After the central fixation spot had been displayed for 1200 ms, a peripheral target was illuminated for a period of 1798 ms, overlapping in time with the central fixation point, until the end of the trial at 2998 ms. The presentation of targets were randomised in the left and right (50:50) hemifields, to prevent prediction of target location. The inter-trial interval was 1200 ms. The instructions to participants were as in the gap (previous) task (Section 2.3.3.1.1) where they were asked to look at the lights as quickly and accurately as possible.

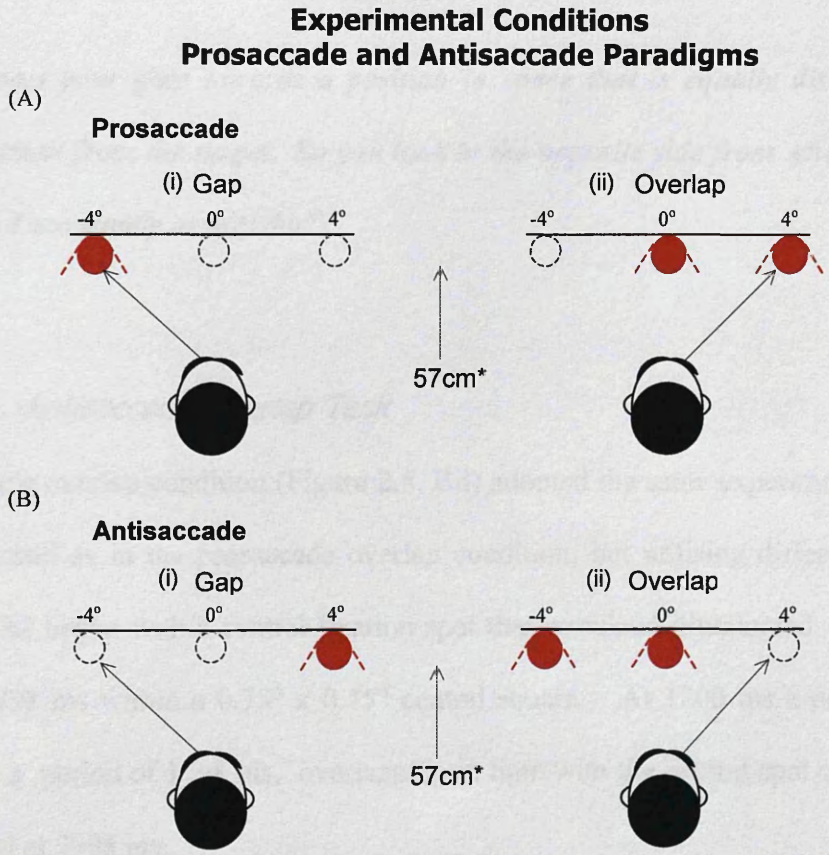



**Figure 2.5** Prosaccade and antisaccade paradigms. In prosaccade tasks, a reflexive saccade is generated directly to the location of the target at onset. For the antisaccade tasks, a voluntary saccade is generated to an equidistant location to that of the target from the central point, but in the opposite hemifield i.e. away from the target. Diagrams A(i) and B(i) illustrate the Gap condition, where the central fixation point is extinguished 200 msec. prior to target onset. In overlap conditions A(ii) and B(ii), the central fixation point remains on throughout the tasks, overlapping with target onset.

* Target screen 57cm from participant at eye level centred on the midline (measured from the point between the evebrows

### 2.3.3.2 Antisaccade Tasks

#### *2.3.3.2.1 Antisaccade Gap Task*

The temporal and spatial characteristics of the visual stimuli for the antisaccade gap condition (Figure 2.5, Bi), were the same as those employed for the prosaccade gap condition, however, different instructions were given. Therefore, each trial commenced with a central fixation point within a 0.75° x 0.75° central square, which was extinguished after 1000 ms had elapsed. Following a temporal gap of 200 ms, a peripheral target was presented for 1798 ms. Again, targets were randomised in the left and right (50:50) hemifields, to avoid predictive behaviour. The inter-trial interval was 1200 ms. The instructions to participants were as follows:

"*...direct your gaze towards a position in space that is equally distant, but in the opposite direction from the target. So you look to the opposite side from where the target is, as quickly and accurately as possible*".

#### *2.3.3.2.2 Antisaccade Overlap Task*

The antisaccade overlap condition (Figure 2.5, Bii) adopted the same experimental settings for the visual stimuli as in the prosaccade overlap condition, but utilising different instructions. Thus, each trial began with a central fixation spot that remained illuminated throughout the trial for 2998 ms within a 0.75° x 0.75° central square. At 1200 ms a peripheral target appeared for a period of 1798 ms, overlapping in time with the central spot of light, until the end of the trial at 2998 ms.

Target presentation was randomised in the left and right (50:50) hemifields, to reduce the chance of prediction of target position. The inter-trial interval was set at 1200 ms. Instructions were the same as in the gap (previous) condition (Section 2.3.3.2.1), participants

were asked to direct their gaze towards a position in space, equally distant but in the opposite direction from the target as quickly and accurately as possible.

### 2.3.3.3 Saccade Inhibition Tasks

#### *2.3.3.3.1 NO-GO Inhibition Task*

The NO-GO inhibition task (Figure 2.6, A), trials started with the presentation of a central fixation point displayed for 1000 ms within a 0.75° x 0.75° central square, followed by a temporal gap of 200 ms. Following the gap period, a peripheral target appeared randomly in either the right or left (50:50) hemifield, for a duration of 700 ms. There was an inter-trial interval of 1000ms. Participants were instructed to:

"***look at the central point*** (*maintaining fixation*) ***and ignore targets that appear to the left or the right of this point*** (*inhibition of response*)".

#### *2.3.3.3.2 GO-Left / NO-GO-Right Inhibition Task*

In the GO-Left / NO-GO-Right task (Figure 2.6, B), the timing set-up of visual stimuli was the same as that used in the NO-Go task. Thus, a central fixation spot was displayed for 1000 ms within a 0.75° x 0.75° central square, followed by a gap of 200 ms. Next, a target was presented randomly in either the right or left (50:50) hemifield and illuminated for 700 ms, to the end of the trial, at which point there was an inter-trial interval of 1000 ms. Participants were told to adhere to the following rule:

"***If a target appears on the right-hand side, ignore it and keep looking straight ahead at the central point. However, if the target appears on the left-hand side, then look at it as quickly and accurately as possible***".

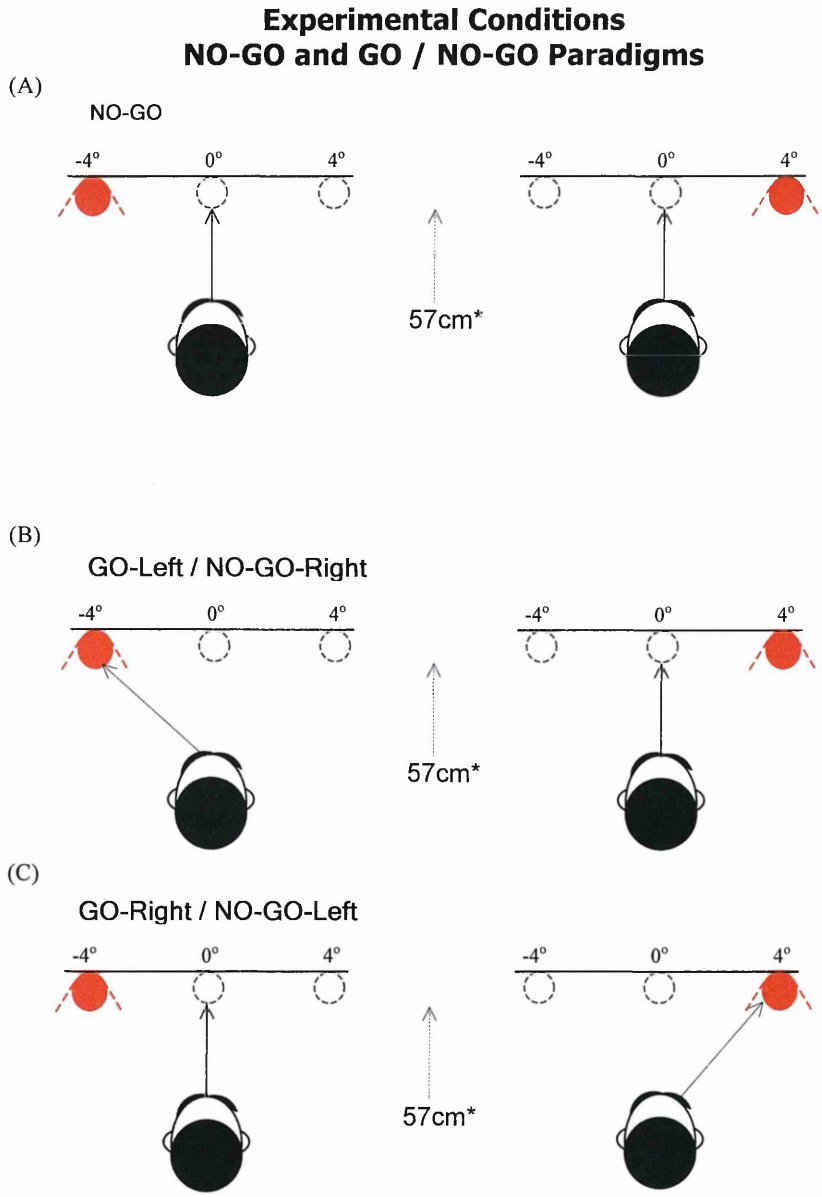



**Figure 2.6** Figure A illustrates the NO-GO task, in which the central fixation spot is fixated and targets, presented randomly in either the right or left hemifield, are ignored. In Figure B, targets appear randomly in the right or left hemifield. On trials where the target is presented in the left hemifield (GO-Left), a saccade is generated towards the target. For trials where the target is presented in the right hemifield (NO-GO – Right) the stimulus is ignored and fixation of the central fixation point maintained. For Figure C (GO-Right / NO-GO-Left) the task instruction is the opposite of that for Figure B. A, B and C all have a temporal gap of 200 msec. from the fixation point offset to target onset.

* Target screen 57cm from participant at eye level centred on the midline i.e.point between the eyebrows

#### 2.3.3.3.3 GO-Right / NO-GO-Left Inhibition Task

For the GO-Right / NO-GO-Left task (Figure 2.6, C), the stimulus array characteristics were the same as in the GO-Left / No-GO-Right task, however, the instruction were the opposite. Therefore, Participants were told to adhere to the following rule:

***"If a target appears on the left-hand side, ignore it and keep looking straight ahead at the central point. However, if the target appears on the right-hand side, then look at it as quickly and accurately as possible".***

## 2.4 Procedures

### 2.4.1 The Clinical Saccadic Eye Movement Task

The first part of the testing procedure was to train participants for the saccadic eye movement tasks. To facilitate a firm grasp of the requirements for the paradigms, a clinical saccadic eye movement task - adapted from (Currie et al., 1991) - was conducted with participants, emulating basic aspects of the infrared oculographic procedures from the main experiments. The training phase of the study facilitated the chance to observe reflexive prosaccade and antisaccade eye movements face-to-face with each participant. In administering the clinical test, the researcher's hands (clenched fist) were held adjacent to the ears and bilaterally equidistant at shoulder width, in the same horizontal plane as the nose. The target was a vertically flexed index finger on the right or left hand. Participants were advised to keep the head in a fixed position looking forwards, moving the eyes only and not the head. As the aim of the clinical test was primarily to train participants, they were also instructed to try to remain alert throughout the tasks, only responding at the appearance of targets and that if they made an error, to continue with the task. Participants were also asked to try to refrain from blinking during trials. An advantage of the clinical saccade test, is that the researcher is

able to modulate the speed of stimulus presentation and should mistakes occur, participants can be informed and advised accordingly.

For the prosaccade task, participants were asked to look straight ahead at the researcher's nose ($0^{o}$ central fixation) and to look at the index finger that moves, as quickly and accurately as possible. When the finger was lowered, the instruction was to look at the nose again, ready for the next trial. A trial only commenced when the researcher was satisfied that the nose was fixated again for the start of a trial. When participants understood the reflexive prosaccade task (The general finding was that an understanding was gained within two or three trials), twelve trials were administered. For the antisaccade task, participants were told that the task had changed and instructed that when the index finger moved, they should look immediately as quickly and accurately as possible, to the opposite direction, at the position of the finger that did not move. Training in the antisaccade task was always found to take a little longer than for reflexive prosaccade saccade training. When participants understood the antisaccade task, twelve trials were conducted and responses (correct, corrected error or uncorrected error) recorded on clinical antisaccade test sheets for analysis (The clinical antisaccade test recording sheet can be found in Appendix 8).

The clinical saccadic eye movement test was found to be extremely helpful and a useful procedure, efficacious for both training and gathering informative data from patients. The test made it possible to ensure that participants thoroughly understood each condition. The procedure facilitates the ability of participants to understand that targets are randomly presented in either hemifield, to minimize anticipation and to reduce the training required during experimental trials with infrared oculography. For the present research project, minimizing the duration of saccadic eye movement test sessions was of particular importance, in view of the fact that the experimental groups comprised elderly people. Extended experimental procedures may cause fatigue for elderly people, particularly dementia patients who exhibit a level of neuropsychiatric disturbance.

### 2.4.2 Infrared Oculography

The comfort of the elderly people taking part in this study was of paramount importance during all testing sessions, therefore, care was taken to ensure that volunteers were as comfortable as possible at all times. For the saccadic eye movement tasks, participants were seated on a comfortable armchair in front of a large desk with their head maintained in position using a chin rest (Appendix 9). The chin rest was fully adjustable (through three dimensions) and manoeuvred to suit each participant according to individual feedback, so as to attain the most comfortable position. Once the chin rest was set to the required custom height, the target projection screen was also adjusted to eye level. The participant was then told to sit back and relax in the chair, whilst the scleral reflection headset was fitted.

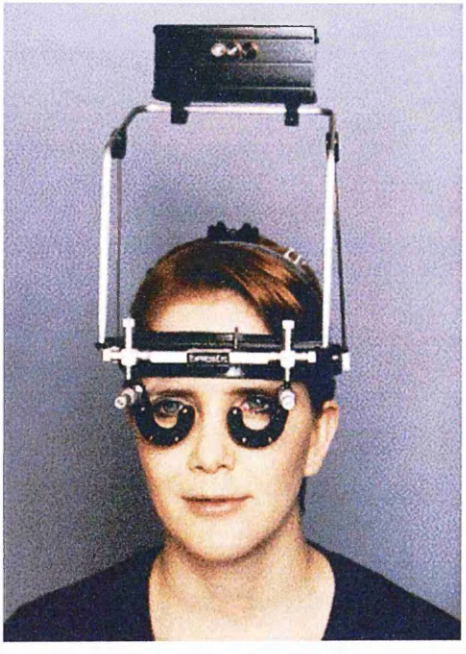


**Figure 2.7** The Express Eye Headset (Optom Lab, Germany).

During this period, the room light was dimmed and participants were adapted to this environment for 5 minutes. The Express Eye system was placed on the participant's head (Figure 2.7) and adjusted as appropriate for individual needs. Participants were then asked to place their chin on the chin-rest, whilst the system was calibrated.

Taking care that the infrared emitter/sensor unit was in the up position (i.e. away from the face) the Express Eye headset was carefully placed on the head of the participant, and adjusted for comfort. Once the headset is in position on the head it is important to work quickly and efficiently, to minimise the experimental session length and thereby maintain the quality of data by reducing the chance of causing fatigue in participants, which can have the effect of reducing alertness (Becker, 1991) and can also increase postsaccadic drift (Bahill & Stark, 1975); small eye movements referred to as glissades (Weber & Daroff, 1972). With the headset in position, participants were instructed to close their eyes, whilst the emitter/sensor unit was positioned approximately 15 – 20 mm in front of the eye, tilted slightly up towards the eye, which reduces disturbance from the upper eyelid. The infrared emitter/sensor unit is capable of fine adjustment by micro screws through three degrees of freedom and can also be tilted, to accommodate custom fitting of the device with individual participants (Figure 2.8).

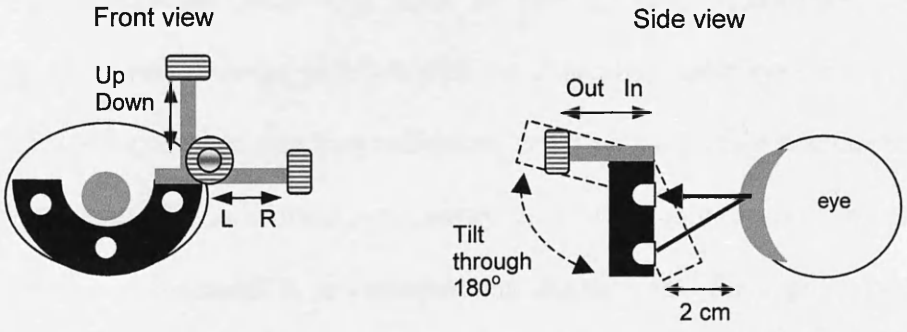



**Figure 2.8** Mechanical adjustment of infrared emitter/sensor apparatus

The fine adjustment of the emitter/sensor unit enables rapid calibration of the eye movement system. It is important that the emitter/sensor unit is positioned correctly in front of the eye as in Figure 2.8, and the infrared amplifier set at a approximately 75%. High amplifier settings and poor positioning of the emitter/sensor mechanism should be avoided, so as to reduce *noise* and non-linear signals (Fischer, 1998).

In the first instance, all three spots of light were illuminated synchronously and participants were asked to identify both the number of lights and stimulus location. With all three points remaining on display participants' responses were reinforced by pointing out each point of light with the statement:

***"Yes, this is the central fixation point, and here is the target on the right and this is the target on the left".***

Calibration of the eye movement recording system was conducted prior to running the block of trials for each experimental condition. During calibration each individual point of light was presented in turn, the three point sequence commencing with the central fixation point followed by the peripheral target in the left hemifield and then the right hemifield. Participants were instructed to:

***"concentrate on the spots of light that appear on the screen in front of you."***

Experimental instructions were read prior to running each oculomotor condition Firstly, the test was explained, drawing parallels with the clinical saccadic eye movement test, the eye movement recording system was then calibrated, followed by the five practice trials for the experimental condition and the instructions repeated prior to running the experimental test. Experimental trials then commenced in accordance with the relevant for a given paradigm, provided that the participant understood the task and that the experimenter was satisfied with the calibration pre-programmed into the Express Eye system (Section 2.3.2; the paradigm specific experimental protocol can be found in Appendix 11). Attendance by participants at eye movement recording sessions was noted on participation log sheets (Appendix 7) for each longitudinal test stage in order to keep track of complete/incomplete sessions, particularly in view of the extensive neuropsychological assessment battery.

### 2.4.3 Saccadic Eye Movement Signal Data Analysis

As the principal focus for the present investigation was a clinical group i.e. Dementia Patients, the researcher was interested in two areas of enquiry, namely behavioural response characteristics and psychophysical recording parameters. Therefore, a number of dependent variables were decided upon, in accordance with the hypotheses set out in section 2.7.

During interactive analysis of analogue saccadic eye movement signal data, primary saccades were excluded according to the following criteria: i). a blink post target onset but prior to the primary saccade; ii). when a saccade occurred early i.e. prior to target onset, or iii). if saccade latency was <80 milliseconds, i.e. an anticipatory saccade. The minimum velocity for a saccade to be included in the analysis was $25^{o}s^{-1}$ and the minimum amplitude 0.5 degrees.

Dependent variables generated from analysis of primary saccades, included latency, amplitude, maximum velocity and duration. From a behavioural perspective, the dependent variables comprised error rates: total errors, corrected errors, uncorrected errors, omissions and anticipatory saccades.

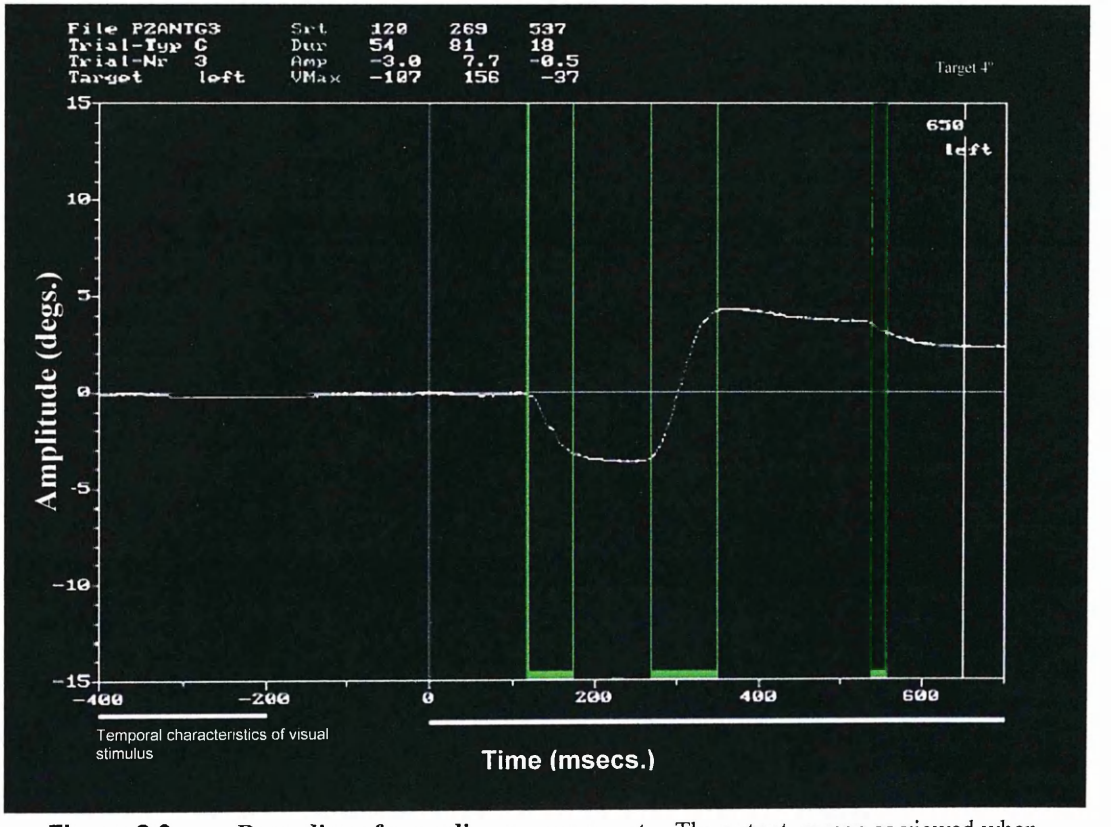



**Figure 2.9** **Recording of saccadic eye movements.** The output screen as viewed when running the interactive saccade analysis program, during the antisaccade gap task. Alzheimer's disease patient making a corrected error.

Additionally, error correction - secondary saccadic measures were taken for secondary saccade latency, inter-saccadic interval (turn around time) and amplitude. Figure 2.9 above, shows a representation of the computer screen output whilst running the Express Eye saccade analysis program.

Figures 2.10A, B and C, illustrate analogue eye movement signal data during analysis, using the interactive analysis program. In Figure 2.10A (adapted from the computer software output screen), the signal trace is displayed for a correct saccade in the antisaccade Gap paradigm. The trace, representing the eye position in time and space, is shown moving away to the opposite hemifield from the target position providing an illustration of a correct antisaccade.

Figure 2.10B shows a typical corrected error response in the antisaccade Gap paradigm, where in the primary reaction the eye looks toward the target (prosaccade), but is corrected by a secondary movement, a corrective saccade that locates the eye to the opposite hemifield to that of the target. An example of uncorrected error in the antisaccade Gap paradigm is presented in Figure 2.10C. The signal trace of the eye is observed to locate the target (prosaccade), which is of course an incorrect response, as the eye should have located a position at an equidistant location in the opposite hemifield to the target position.

For corrected errors, the primary saccade latency and amplitude of the error, were reported dependent variables and the corrective saccade latency, inter-saccade interval, amplitude and final eye position (i.e. final eye position for corrected errors) were also derived from the analyses. For uncorrected errors, primary latencies and amplitudes were monitored and also entered as dependent variables. Resultant measures from the analysis of analogue saccade signal are generated in the form of an output file from the Express Eye analysis program. Furthermore, these files can only be read when transposed onto computer spreadsheets. However, the large amounts of data are arranged in columns with no identification, filtering or sorting and moreover, contain columns of unwanted system numbers.

Therefore, a range of time saving devices were custom produced by the author, in the form of paradigm specific data analysis spreadsheet templates, using Microsoft Excel Spreadsheet ™.

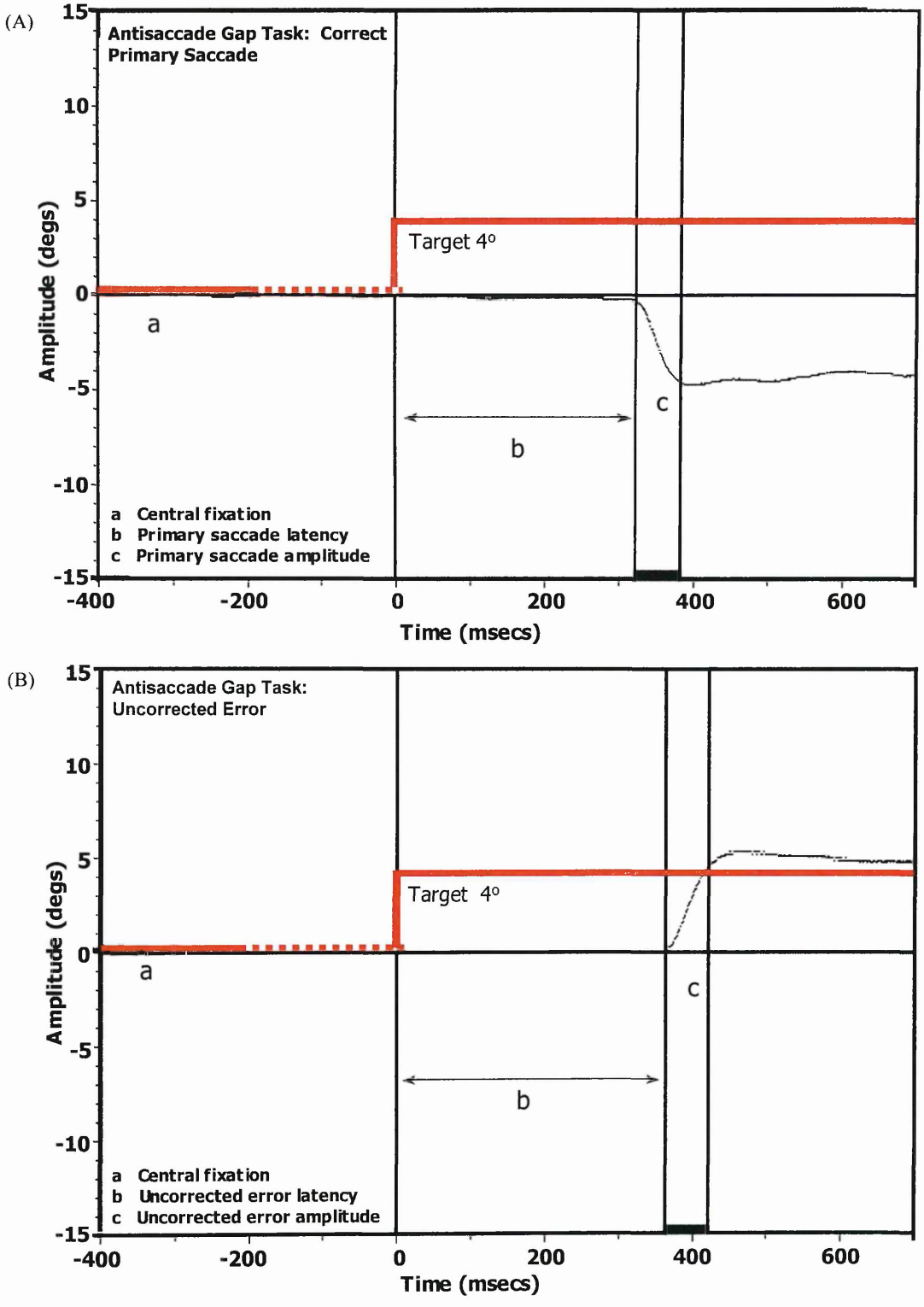



**Figure 2.10** In the figure above the target is indicated by the red line and the task is the antisaccade gap paradigm. Figure A shows a correct primary saccade, the eye moving to an equidistant location in the opposite hemifield to that of the target. Figure B illustrates an uncorrected error, were the eye has moved to locate the target, instead of looking to the opposite hemifield.

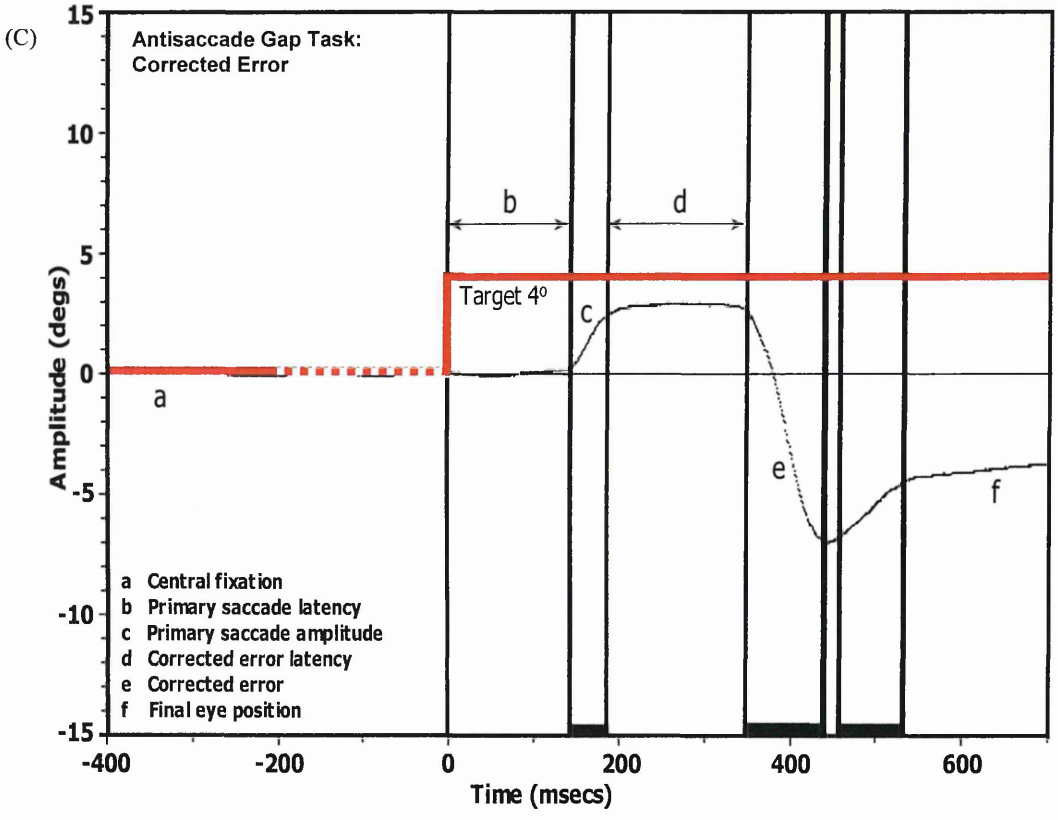



**Figure 2.10 (continued)** Figure C illustrates a corrected error in the antisaccade gap paradigm. The trace shows that the primary response was to look in the same hemifield as the target. However, a corrective saccade quickly relocates the eye to a location in the opposite hemifield to that of the target.

The templates included a sorting tool that utilised macros to remove unwanted functional and system items from the data sheet and to sort the remaining data into meaningful groups. Paradigm specific input templates were produced, in order to sort and filter the data imported from the sorting template. To exemplify a typical data input template, a section from a completed data input template for the antisaccade gap task, is shown in Appendix 12. The data input templates exploit the capacity of a range of formulae, arguments and conditional formats, to facilitate identification and quantification of saccade characteristics and dependent variables, from individual eye movement data output files. Each paradigm specific template also generated a summary (average) of the whole output for (across the bottom of the sheet – not displayed in Appendix 12 due to sheet size) that was incorporated, via a cell pathway linkage, to overall experimental group paradigm specific data summary sheets. These

summary sheets provided the platform from which selected dependent variables for final analysis, were extracted and exported to SPSS version 11.5 (SPSS Inc., Chicago Ill) for statistical manipulation. Further to recording saccadic eye movements, each participant was tested with a battery of screening tests and neuropsychological assessments to provided a range of cognitive measures and correlates for statistical evaluation.

## 2.5 Screening Tests and Neuropsychological Assessment

As discussed in Chapter 1, AD progresses insidiously with a decline in various aspects of cognition and global function, discernible by the following characteristics which are extracted from DSM IV:-

The development of multiple cognitive deficits manifested by both:

1. Memory deficit – lack of capacity to acquire new information or recall previously learned information.
2. Dysfunction by one or more of the following:
    - Aphasia (language disorder)
    - Apraxia (impairment of motor skills, although motor function is intact)
    - Agnosia (failure to recognise or identify objects despite intact sensory function)
    - Disturbance in executive functioning (i.e. planning, organising, sequencing, abstracting).

(American Psychiatric Association, 1994)

Given the span of cognitive impairments intrinsic to AD, a battery of screening tests and neuropsychological assessments were selected and administered to all elderly participants, in order to gauge dementia severity and derive quantitative measures for a range of cognitive function including the components of memory, language, praxis, psychomotor performance, orientation, and various frontal lobe tasks. It has been argued (Perry & Hodges, 1999), that

basic conventional cognitive assessments lack temporal resolution, specificity and thus the capacity to determine the locality brain function. The tests have been found to be limited in their ability to detect early dementia (Feldman & O'Brien, 1999; Filley et al., 1989; Galasko et al., 1990), and may be affected by mood, age, fatigue or low motivation (Shafiq-Antonacci et al., 2003); hence the desire to find tests which are more sensitive or that are capable of detecting underlying pathological disturbance. To this end, the neuropsychological assessments are important for this research, as they provide a range of correlates for comparison with the saccadic eye movement measures and can therefore be used to investigate association between tests and in models of prediction and discrimination.

AD is often characterised by the onset of memory dysfunction, although attentional deficits have been found to feature prominently in the profile of impairment (Parasuraman & Haxby, 1993). A number of previous studies of cognitive impairment in AD have revealed attentional deficits (Spinnler, 1991), using a variety of conventional pencil and paper test methods (Della Sala, Laiacona, Spinnler & Ubezio, 1992; McKhann et al., 1984; Solfrizzi et al., 2002; Stuart-Hamilton, Rabbit & Huddy, 1988). However, Parasuraman and colleagues highlighted the inherent problems of monitoring the dynamics and specificity of attentional deficits in AD, due to the lack of the temporal resolution in conventional pencil and paper type tests (Parasuraman, Greenwood, Haxby & Grady, 1992; Parasuraman & Haxby, 1993).

Measures recorded from the saccadic eye movement paradigms may reveal a signature of underlying impairment, due to disturbance in the oculomotor system, dysfunction of visuospatial cognition (analogous to previous research), working memory leading to problems of inhibitory control and perseveration. If saccadic eye movement paradigms can identify a neurological or behavioural marker in AD, it is feasible to suggest that sensitive tests, designed to measure the specific dynamics characteristic of the impairment, may hold some early diagnostic utility.

### 2.5.1 The Mini Mental State Examination

The Mini Mental State Examination (MMSE) (Folstein et al., 1975) is likely to be the most commonly used brief screening tool for dementia. It is widely used throughout the Western world and in the United Kingdom, a standardised version (Molloy et al., 1991) has been adopted by many NHS authorities so that the same form is used with standardised procedures, facilitating correspondence across service and research (Patel & Renvoize, 2000). Thus, the standardised MMSE (SMMSE; Appendix 13 and 13.1) was utilised in the present study.

When applied to dementia patients the MMSE has been found to perform most successfully in distinguishing between control participants and patients with moderate and severe impairment (Folstein et al., 1975), and it was also demonstrated that the test is sufficiently receptive to detect cognitive decline over time (Teng, Chui, Schneider & Metzger, 1987). However, the test is less able to discern differences between patients with mild dementia and control participants (Knight, 1992), emphasising the necessity for more sensitive diagnostic tests. The test is also prone to 'floor' and 'ceiling' effects and is largely based on language-verbal type sub-tests. Therefore, test performance of patients with damage mainly in the right hemisphere, may surpass that of patients with left hemisphere damage (Adair, 1998).

The MMSE comprises a number of elements that provide rapid assessment for a range of cognitive characteristics, which include items to test:- orientation in time and space; memory (registration and recall); attention; language (object naming, sentence repetition, following commands, reading and writing); constructional praxis (copying a geometric shape - intersecting pentagons). Points are awarded for successful trials (max. score 30) according to the test component. Severity ratings for dementia are as follows: NICE guidelines MMSE and Alzheimer's disease (NICE, 2001):-

- Mild AD: usually associated with scores of 21 to 26
- Moderate AD: usually score of 10 to 20

- Severe AD: usually score of less than 10.

Participants were tested at each stage of the study and the total score recorded for analysis.

### *2.5.2 Alzheimer's Disease Assessment Scale - Cognitive Sub-Scale*

The Alzheimer's Disease Assessment Scale - cognitive sub-scale (ADAScog) (Rosen et al., 1984) was designed with the explicit purpose of assessing the severity of cognitive dysfunction characteristic of AD (Rosen et al., 1984). The test has also been shown to be sensitive to the progression of cognitive dysfunction on a longitudinal basis (Rosen et al., 1984; Rosen, Mohs & Davis, 1986). A European version of the ADAS-cog (EADAS-cog) was adapted from the original test by Dahalke and colleagues (1992) and it is this version that is used by the Memory Clinic (Department of Old Age Psychiatry) at Lytham Hospital in the U.K. and employed by the this research project, as a rating instrument for AD (see Appendix 14 and 14.1).

The ADAS-cog consists of a series of cognitive behaviour tests. The tests examine memory (word list recall and recognition; recall of instructions); language (speech – including word finding difficulty and circumlocution and comprehension); constructional praxis (copying a variety of geometric shapes); orientation (in space and time) and ideational praxis (ability to perform an over-learned task – sending a letter to oneself). The scoring of this test is based on the number of errors made in relation to a points scoring system, i.e. high number of errors equals a higher score (max. score 70). Overall scores of 0-11 indicate that the patient may be normal. However, a score of 12 in conjunction with scores from other tests may signify dementia. Higher scores from 13 through 70 are indicative of dementia and require further investigation into the areas of impairment. Therefore, the test can be a useful instrument alongside other assessments. The EADAS-cog was conducted on all participants at each stage of the longitudinal study, to obtain a total score and a score from two of the sub-tests: recall memory and recognition memory.

### 2.5.3 Clinical Dementia Rating Scale

The CDR (Hughes et al, 1982) is a rating scale to assess dementia severity (Appendix 6). The assessment is completed by the physician, in the clinical setting, by applying detailed knowledge of the patient in six domains: memory; orientation; judgement and problem solving; community affairs; home and hobbies; and personal care. The scale generates a severity rating that places the patient in one of the following categories: healthy (score 0); questionable dementia (score 0.5); mild dementia (score 1); moderate (score 2); and severe dementia (score 3). Fulfilling the role of a global staging measure, the CDR is covers a wide range of function, but has been found to be less susceptible to 'floor' and 'ceiling' effects (Morris, 1997). CDR ratings were conducted by psychiatrist at consultation however, this assessment was only available for stage 1 of the study.

### 2.5.4 National Adult Reading Test

An important consideration for many research projects involving the investigation of psychological and psychophysical factors, is that all extraneous variables have be managed e.g. confounding variables are controlled. This is vital for interpretation of results, so that findings can be reported reliably in view of theoretical rationale. None of the participants involved in this research project had been assessed using psychometric intelligence assessments prior to the study. Therefore, there was no measure of pre-morbid intelligence levels available for any of the dementia patients (and no intelligence measures were in existence for Elderly Controls).

Research in the past described how dementia patients appeared to be able to read surprisingly well, during routine assessments (Nelson & McKenna, 1975). Word reading ability was found to be highly correlated with WAIS Full-Scale IQ scores for adults and also maintained for dementia sufferers (Nelson & O'Connell, 1978). Nelson (Nelson, 1982) produced a test, referred to as the National Adult Reading Test (NART; Appendix 15), that relies on the orthographic characteristics of the English language, namely, the test was found to

be a sensitive measure for previous familiarity of irregular words and thereby purported to predict pre-morbid IQ.

The basic rationale for the test is based on the idea, that in order to read an irregular word in the English language (words where the normal grapheme-to-phoneme correspondences do not apply), the reader must have prior knowledge of the word. Therefore, as the word cannot be read by sounding-out the phonemes (letter sounds) within the word, the word must be recognised (even if the definition is not remembered) so as to pronounce it.

The test is made-up of fifty irregular words of increasing difficulty (Appendix 15), which the participant has to read out aloud. Error scores accumulate for each incorrect answer. A *predicted* pre-morbid IQ score is generated by matching error scores with corresponding NART normative data and applying this to an IQ scale that was derived from regression analyses on the Weschler Adult Intelligence Scale.

The NART is of course well established as a standardised test, however, given the level of word finding difficulty and circumlocution that many dementia patients experience, it is open to question as to whether in some individual dementia cases there may be a subtle level of language impairment that is difficult to detect and that may adversely affect scores and as previous research has found thus underestimate pre-morbid IQ (Stebbins, Gilley, Wilson, Bernard & Fox, 1990).

Disturbance of this nature may perhaps be integral with pathways of the brain that are responsible for reading, difficult words, requiring interaction between the temporal and frontal lobes, namely the anterior cingulate and anterior inferior prefrontal areas (Peterson, Fox, Posner, Mintun & Raichle, 1989), areas of the brain that are also known to be implicated in the pathology of AD (as discussed in Chapter 1). Therefore ultimately, results from the test will depend on the specific nature of cognitive impairment for a given case of dementia, with the consideration that previous research has found that using the NART specifically to estimate pre-morbid ability in dementia patients with language impairment will underestimate pre-

morbid IQ (Stebbins, Wilson, Gilley, Bernard & Fox, 1990). In addition to this, another study reported that the NART is sensitive to decline of language in AD and that the test may even be useful as a predictor of dementia (Schlosser & Ivison, 1989). Despite these findings, the NART is still widely used as a predictor of pre-morbid IQ.

In view of the fore-mentioned problems with the NART, scores in the present study are seen as a tentative guide towards prediction of pre-morbid IQ and thus, interpreted with some caution. Observations are made as to whether scores on this test fluctuate and/or deteriorate during the course of longitudinal investigation.

### *2.5.5 Verbal Fluency*

Verbal fluency is a useful measure of frontal lobe function (Parks et al., 1988; Zangwill, 1966) utilizing the capacity for speed and spontaneity of verbal production. Research of patients with frontal lobe lesions has shown that deficits in verbal fluency appear to be associated with lesions of the orbital-frontal area (often in the left hemisphere, but not exclusively!) of the brain (Milner & Petrides, 1984; Raimer & Hécaen, 1970).

Functional imaging of the brain using positron emission tomography (PET) has revealed that more specifically, both the frontal and temporal lobes show the highest level of cortical activation (indicated by bilateral increase in cerebral glucose metabolic rate) compared with other parts of the brain (Parks, Loewenstein, Dodrill, Barker, Yoshii, Chang, Emran, Apicella, Sheramata and Duara, 1988).

The test employed for the present study (Appendix 16), required participants to name as many words as possible beginning with a specified letter (first trial letter 'S' and the second trial letter 'P') in a 60 second timed trial period (Storandt, Botwinick, Danziger, Berg & Hughes, 1984).

Participants were instructed not to use numbers or the names of people and places and encouraged to carry out the task as quickly as possible. The score was taken as the number of

words spoken out loud and the score for each of the letters was added together, to make a total score (the mean was also calculated). Intrusions (words beginning with the wrong letter) non-words, proper nouns, numbers, words with a different suffix and repetitions were excluded from the final score.

### *2.5.6 Trail Making Test*

The trail making test (Appendix 17) is essentially a test of visual conceptual and visuomotor tracking (Lezak, 1995) and originates from the Army Individual Test Battery (1944). The test consists of two parts: Form A, primarily a measure of psychomotor speed and psychomotor coordination and Form B, requires the concurrent manipulation of information and measures visual sequencing, visuospatial working memory and shift strategy.

Form A, given first, by definition is the easier of the two tests and requires participants to draw a line as quickly as possible, that joins a sequence numbered circles from 1 through 25. Form B is more difficult, as participants have to draw a line (as quickly as possible) that alternates between a sequence of consecutive numbers and letters i.e. 1 – A – 2 – B – 3 – C ... and so on (1 through 13 alternating with A through L). Therefore, psychomotor and sequenced cognition are the vital cognitive capacities that facilitate participation on the task, as the participant has to manipulate two streams of information alternating between the alphabetical letter sequence and number sequence correctly whilst searching for each item on the test sheet. In view of this, close attention is required when administering the assessment, to monitor performance, given that if an error is committed participants are informed of the fault and instructed to return to the circle preceding the mistake and continue with the correct sequence. Mistakes by dementia patients occur frequently on Form B of the test, where patients often perseverate by jumping to the next number or letter instead of alternating from number to letter to number and so on, hence the demands on executive function and working memory. Research

using electrophysiological recordings suggest that frontothalamic regions of the brain are activated during both Forms of the test (Segalowitz, Unsal & Dywan, 1992).

The instructions and scoring methods employed for the present study were designed by Ralph Reitan, who used the test in a study that involved an experimental group with organic damage to the brain (Reitan, 1958). Reitan found that the test was able to discriminate between the experimental group (brain damaged) and controls (without evidence of brain damage), and used the test completion time to devise an ordinal credit system (Appendix 17.1). Therefore, the present study will examine this standardised credit system and the basic task completion time will also be used as a variable. An additional score is also investigated that basically removes the time factor, in order to explore Forms A and B. This is achieved by taking the difference between Forms B and A (i.e. Time B – A). It is postulated that this score correlates with mental capacity and severity of cognitive impairment (Corrigan & Hinkeldey, 1987).

### *2.5.7 Digit Span Test*

The Digit Span test from the Wechsler Adult Intelligence Scale III (Wechsler, 1997a) was also included in the test battery. This test is essentially an assessment of executive function, measuring short-term auditory memory. However, it is important to bear in mind when interpreting results, that test performance also involves attention and concentration and therefore, these attributes may be reflected in the scores (Kaufman, McLean & Reynolds, 1991).

The Digit Span Test consists of two separate sub-tests, Digits Forward and Digits Reverse, both of which are included in the present study (Appendix 18). When administering Digits Forward, a sequence of numbers are read out aloud at a rate of one per second. When the examiner has finished calling out the sequence, the participant responds by recalling the number sequence and calling the sequence out aloud, in the same exact order as the examiner.

For Digits Reverse, a number sequence is called out by the examiner, however, the participant has to recall the sequence in the reverse order, to the number sequence that was called out by the examiner. The tests starts with number sequences of very short length (2 digits), but becomes progressively more difficult, as each sequence grows longer by adding 1 digit after two trials at each sequence length (Digits Forward: max. 9 digits; Digits Reverse: max. 8 digits). One point is awarded for each correct sequence recalled. Both trials are conducted at a given sequence length, regardless of whether there is failure on the first trial of that sequence. The test is terminated if there is failure to recall the two trials of a given sequence length.

Both Digit Span Forward and Digits Span Reverse require working memory and are largely believed to involve the frontal and temporal lobes. Brain scanning with PET has shown that for the Digit Span Forward task, metabolism of glucose occurs bilaterally, although mainly in anterior dorsal areas (Chase et al., 1984). Studies of patients with brain damage, indicate that performance on both Digit Span Forward and Digit Span Reverse is predominantly affected by left hemisphere damage (Black, 1986; Weinberg, Diller, Gerstman & Schulman, 1972). A recent PET study on healthy young adults by Gerton and colleagues, found that Digit Span Forward and Reverse recruit largely overlapping functional neuroanatomy, which is associated with working memory. Most interestingly, the right DLPFC, bilateral IPL and ACC were metabolised during both tasks and the degree of activation shown to increase linearly with increasing task difficulty in the Digit Span Forwards task. During the Digit Span Reverse task, additional areas were prominently recruited, notably the DLPFC was activated bilaterally, with the left IPL and Broca's area. The medial occipital cortex was also found to be strongly activated, which the authors suggest may be the result of participants employing visual imagery strategy – which was supported by the experimental paradigms employed (Gerton et al., 2004). Performance on Digit Span Reverse typically falls approximately 0.6 – 2 digits below recall for Digits Forward (Black & Strub, 1978; Kaplan, Fein, Morris & Delis, 1991), The Digit Span Reverse test requires a higher level of mental-tracking (than the relatively

simple repetition operation for Digit Span Forward) with the increased cognitive load due to simultaneously holding the forward string in memory and generating the reversal procedure.

### 2.5.8 Day/Night Response Inhibition Test

The Day/Night response inhibition test was adapted from an assessment used in a study of frontal lobe function, involving children between 6 and 12 years of age (Gerstadt, Homg & Diamond, 1994). The rationale for the test is based on research that suggests that frontal lobe lesions of the dorsolateral frontal cortex, generally in the left (but not exclusively) hemisphere of the brain (Grafman, Jonas & Salazar, 1990; Milner, 1963; Nelson, 1976) result in problems with response inhibition and rule breaking (Kolb & Whishaw, 1996). Thus, patients with left frontal lesions will present with perseveration on tasks requiring inhibition of a pre-potent response, especially where task demands change.

When administering the test, two A4 cards were placed on the bench in front of participants. One of the cards was white, with a sun in the upper right quarter, the "Day" card (Figure 2.11A) and the other card grey, with a crescent moon and stars in the upper right quarter, the "Night" card (Figure 2.11B).

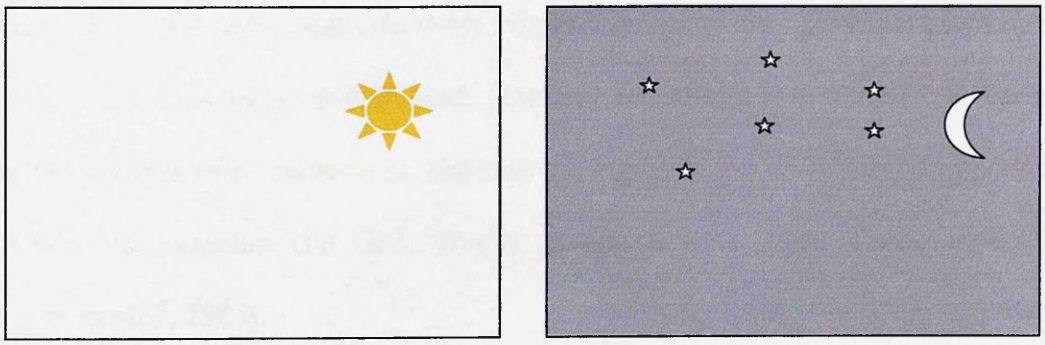



**Figure 2.11** The Day/Night Test. The Day/Night Test is a simple test of inhibitory control. In the control condition the participant identifies the Day card (A) and the Night card (B) directly, by pointing the hand. In the inhibition task, the participant has to point to the opposite card i.e. Day = Night and Night = Day.

In the control condition, participants were instructed to point to the "Day" card, when they heard the word day and the "Night" card, when they heard the word night. Conversely, in the inhibition task participants were required to point to the opposite card, i.e. if day was called out, the instruction was to point to the "Night" card and vice versa, if night is called out to point to the "Day" card. Participants were firstly given 20 trials in the control task followed by 20 trials in the inhibition task, each block of trials comprising 50:50 day and night conditions pseudo-randomly presented. Responses were recorded on Day/Night Inhibition Test response sheets (Appendix 19).

### *2.5.9 Motor Perseveration Test*

This present study used the motor perseveration test designed by A. R. Luria (Luria, 1966, 1973) and can be found in The Middlesex Elderly Assessment of Mental Scale (MEAMS) test battery (Golding, 1989). This assessment is essentially an examination of executive control and frontal lobe function and investigates ability to modify motor response, impairment of which leads to perseveration. The test assesses motor regulation by requiring the participant to generate an opposite response to the signal made by the examiner. For the present assessment, the examiner gives the participant a table tapping rule as follows: Examiner taps once - participant taps twice / Examiner taps twice - participant taps once (see Appendix 19.1 for test and response sheet). Research on patients with frontal lobe damage, has shown that patients often perseverate, copying the signal of the examiner, as opposed to the correct converse response (Le Gall, Truelle, Joseph & etal., 1990; Luria, 1966; Malloy, Webster & Russell, 1985).

### *2.5.10 Gibson Spiral Maze Test*

The Gibson Spiral Maze test (GSM) (Gibson, 1965, 1977) is used to assess psychomotor ability and therefore involves a considerable visuomotor tracking component. In

a sense, the GSM (Appendix 20) has similar motor characteristics to Form A of the trail making test (Section 2.5.7), although it is somewhat easier, requiring relatively minimal sequencing control to draw a pencil line round the track of the spiral outwards until reaching the end, whilst avoiding small circular obstacles. There are two scores recorded, these are time to complete the spiral and the number of errors committed. The present research project adopted to utilize the scoring system from the Clifton assessment procedures for the elderly (CAPE) (Pattie & Gilleard, 1987), however, the present thesis will only use the time to complete the test in seconds as the measure for statistical manipulation. For the CAPE system, the scoring elements (time and errors) are applied to a credit scoring system on an ordinal rating scale as in Table 2.3 (below); The score falls as the error rate increases. The final score may also be awarded extra points, according to the bonus system for speed of performance.

Under CAPE scoring rules, the time limit is 4 minutes for the test to be concluded and errors are scored as 1 error for every obstacle or black line that the pencil comes into contact with; 2 errors for every inch of extended contact or penetration of a black line. Participants are scored as N/C (not completed) if only the first circle of the maze is fulfilled and gives-up subsequent to three prompts. The outcome of the test is N/A (not attempted) is if the participant fails to complete any of the maze and gives-up subsequent to three prompts.

**Table 2.4** CAPE Scoring System for the Gibson Spiral Maze

| **Errors** | 0-12 | 13-24 | 25-36 | 37-48 | 49-60 | 61-72 | 73-84 | 85-96 | 96+ | N/C | N/A |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Score** | 10 | 9 | 8 | 7 | 6 | 5 | 4 | 3 | 2 | 1 | 0 |
| ***Add* Bonus to score** | 2 if Time < or = to 60 secs.<br>1 if Time < or = to 120 secs. | | | | | | | | | | |

N/C = not completed; N/A = not attempted.

### 2.5.11 *Spatial Span Test*

The Spatial Span Test from the Wechsler Memory Scale III (Wechsler, 1997b) measures visuospatial attention and visual memory. The test for Spatial Span involves the use of a block tapping board, as illustrated below in Figure 2.12 (The sequence and responses sheet can be found in Appendix 21). The test is very similar to the block-tapping test designed by P. Corsi, as outlined by Milner (Milner, 1971) except there are 10 blocks, rather than nine as in the Corsi version. The test requires efficient executive function and for a correct response, the ability to hold a sequence of visual-spatial events in working memory. The procedure for administration of this assessment, follows along the same lines as the Digit Span test (Section 2.4.7) but in this, test a sequence of blocks are tapped by the examiner instead of calling out a string of digits.

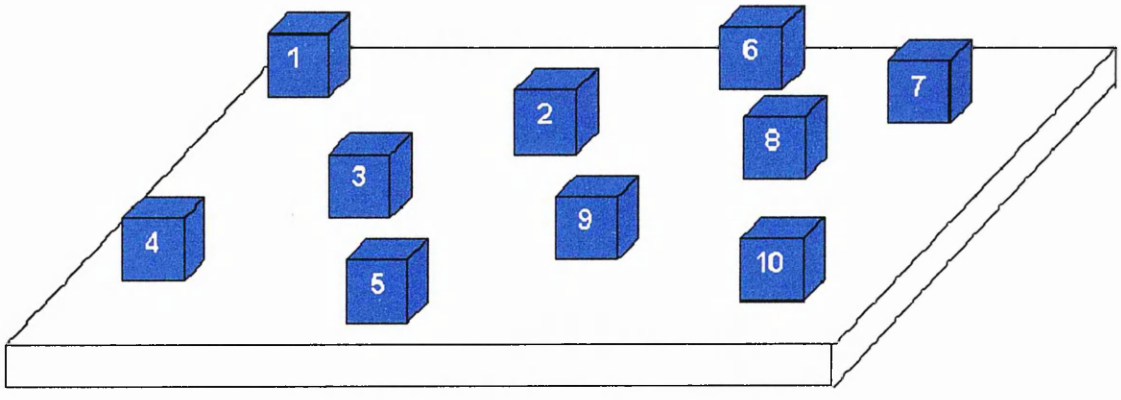



**Figure 2.12** Spatial Span Test Block Tapping Board

As with the Digit Span Test, the Spatial Span Test consists of two separate sub-tests, Spatial Span Forward and Spatial Span Reverse and both of these tests were included in the present study. For Spatial Span Forward, a pre-arranged sequence of blocks, are tapped by the examiner at a rate of one per second. When the examiner has finished tapping the sequence of blocks, the participant is required to tap the exact same sequence of blocks as the examiner. The procedural demands for the Spatial Span Reverse task, involve the examiner tapping a string of blocks on the board and the participant responding by reversing the sequence and

tapping the same blocks, but in reverse. The tests starts with block sequences of very short length (2 blocks), however, the test grows more difficult after two trials at each sequence length, as 1 more block is added onto the chain length (Spatial Span Forward: max. 9 blocks; Spatial Span Reverse: max. 9 blocks). One point is awarded for each correct sequence of blocks tapped. Both trials are administered at a given sequence length, even if there is failure of the first trial at that sequence. The test is terminated after failure of both trials at a given sequence.

The Spatial Span Test has been found to be most sensitive at discriminating between patients with frontal lobe lesions and patients with temporal lobectomy (right or left) or controls (Canavan et al., 1989); Temporal lobe patients performing equal to controls. Test performance is also susceptible in patients with visual field deficit following stroke (regardless of hemisphere), research highlighting poorer spatial memory scores than patients that do not have visual field deficit (De Renzi, Faglioni & Previdi, 1977). Mild to moderately impaired AD patients were found to produce scores only slightly poorer than those of controls, severe AD patients generating scores that were markedly inferior (Corkin, 1982; Sullivan, Corkin & Growdon, 1986).

Clearly, lower scores on this test may reflect attentional deficits, such as poor volitional control or distractibility. Disturbance of attention will thus impair concentration and the capacity for mental tracking.

## 2.6 Observations from Saccadic Eye Movement Research in Alzheimer's Disease

The review in Chapter 1 highlighted how neuropsychological investigation can gain useful insight from saccadic eye movement research. The characteristics of various oculomotor tasks may be manipulated to provide tests that can probe the nature of neurological conditions and cognitive disturbance in psychiatric illness. The antisaccade task (along with

other voluntary saccade paradigms) could prove to be effective in the detection of early AD, as this model paradigm has proved efficacious in other areas of research (Broerse et al., 2001; Monsell & Driver, 2000).

The main conclusions from Chapter 1 concerning the potential predictive capacity of saccadic eye movements for AD can be summarized as follows:

- ✧ It appears that from an early stage in the disease process, saccade latency becomes prolonged for antisaccades as the severity of AD progresses. Whereas reflexive saccade latency may remain relatively unimpaired, until the moderate to severe stage of the disease.

- ✧ Saccade accuracy often seems to be hypometric for reflexive saccades but has been little studied in the antisaccade task.

- ✧ Inhibition errors occur frequently during antisaccade tasks, apparently due to failure in suppression of the VGR. This is evident in AD patients of mild severity.

- ✧ Understanding of the antisaccade task is demonstrated readily in mild AD by the generation of corrected errors. However, a large proportion of errors remain unorrected error, therefore, corrected error performance can be construed as a measure of self-monitoring capacity.

- ✧ Corrected error (secondary corrective saccade) saccade latency is found to be prolonged in AD indicating greater processing cost, as measured by the inter-saccadic interval (turn around time).

- ✧ AD severity seems to be related to working memory function.

- ✧ AD is associated with attentional deficits early on in the course of the disease.

## 2.7 Plan of Research Investigations, Rationale and Hypotheses

As mentioned in Section 1.5.2.2.1, deficits of working memory, attention, inhibitory control and other components of executive function, such as response-monitoring (the ability to self-monitor actions and error correction), planning and carry out dual concurrent tasks, occur early in the course of AD. The primary area of interest for this thesis was to investigate these aspects of cognition by using horizontal saccadic eye movement paradigms and neuropsychological assessment. Furthermore, the main aim was to evaluate measures derived from these methods for their diagnostic utility. The study monitored patients with mild dementia in an attempt to plot the trajectory of disease progression over-time and therefore, includes a longitudinal chapter. In addition to this, the thesis endeavours to provide theoretically important contributions to the understanding of cognitive and eye movement deficits in AD based on the fundamental theoretical constructs. The study explored the performance of AD patients in reflexive (involuntary) saccadic eye movement tasks that are exogenously stimulated, requiring motor initiation of the VGR only, compared with endogenously generated saccades during volitional antisaccade and Go/No-Go tasks that require reprocessing time (due to cognitive load of the task) in addition to motor initiation time.

The *first* area of study focused on inhibitory control of prepotent response in AD. For the antisaccade and Go/No-Go tasks intact inhibitory control is believed to be fundamental to efficient function during the tasks. In Study I (Chapter 3), error and latency analyses were conducted on the experimental population and compared with neuropsychological assessments, in an attempt to ascertain the role of the components of inhibition, volition and working memory resources. Various studies in the past have found antisaccade error rates to be correlated with MMSE scores and somewhat less consistently, reflexive saccade latency to be correlated with cognitive measures. The present study also examined relationships between inhibitory errors and clinical rating scale scores (MMSE and ADAS cog. scores) and

additionally, looked at relationships between antisaccade errors and tests that have a working memory component (in particular: Trail Making; Digit Span *reverse*; Spatial Span *reverse*). The specific hypothesis for this study was that AD patients will demonstrate significant antisaccade (error rate) and Go/No-Go (error rate) impairments, compared with relatively intact reflexive saccade performance.

The *second* study (Chapter 4) investigates an area that has received little attention in AD eye movement research, the fixation offset effect (FOE). AD patients were tested on both reflexive and antisaccade eye movement paradigms, with the aim of investigating the putative attentional disengagement deficit in AD. The FOE for reflexive saccades, is believed to be largely the result of activity in the superior colliculus, which is supposed to be unaffected by AD. However, AD patients have been found to present with a disengagement deficit from an attended stimulus, when required to disengage the attended stimulus and attend an alternative stimulus. Therefore, the main hypothesis for Study II was that whilst saccade latency for AD patients may be prolonged, AD patients should present with an FOE of greater magnitude than that of controls. For the antisaccade paradigm, it was expected that the FOE for AD patients would be significantly attenuated due to the reprocessing costs involved for the antisaccade paradigm, causing any benefit derived from the gap task to be lost.

The analyses in Study III (Chapter 5) encompassed age and disease effects by including data sets from young controls (YC) and Parkinson's disease (PD) patients. The investigations conducted in Studies I and II were analysed in the light of findings from the YCs and PD patients. ADs should produce more uncorrected errors in voluntary saccade tasks than all other groups. The main hypothesis for this study was that AD patients would produce significantly higher uncorrected error rates on the antisaccade and Go/No-Go tasks compared to YCs, ECs and PD patients. The crucial factor here is the ability to self-monitor (and produce a corrective saccade when the VGR is activated in error). An important question was whether the VGR

would be suppressed in the first instance significantly more by PD patients than AD patients, as the results from previous studies are somewhat inconsistent.

No study to date has examined the effects of acetylcholinesterase medication on saccadic eye movements in AD[6]. In the dementia groups under study in the present thesis, a small number of patients were not taking medication of AChEIs at the time of testing. Therefore, although somewhat limited, medicated and non-medicated performance on the aforementioned factors primarily inhibitory control and also attentional disengagement can be assessed and related to clinical rating scale scores. The main hypothesis for Study IV (Chapter 6) was that AD patients taking medication of the new generation of AChEIs would produce significantly better performance than the AD patient group who were not taking AChEIs.

Study V (Chapter 7) examined longitudinal data gathered from AD patients who were able to return over four experimental sessions, with an inter-test interval of six months. Review evidence suggests that only one previous study has examined AD over time, the study discussed in Chapter 1, Section 1.6.3.1 by Bylsma et al. (1995). In this study Bylsma et al. (1995) found that saccadic eye movements were significantly prolonged compared with controls at baseline, but did not deteriorate significantly more than controls over time (as compared with performance on a fixation task which was found to deteriorate over time). However, Bylsma et al. (1995) used a predictable visual stimulus for their study and as discussed in Chapter 1, it is unpredictable reflexive saccade paradigms that have been found to produce the most consistent results revealing saccadic impairment in AD, most prominently so for latency and amplitude. Moreover, no study to date has investigated inhibitory control, using voluntary saccade tasks (antisaccade and Go/No-Go), over time. Therefore, Study V investigated these areas over longitudinal repeated measures, to include factors that include saccade latency, amplitude and error measurement, in an attempt to find a measure that plots the progression of disease over time. Of particular interest, is the analysis of self-monitoring

[6] Abel et al. (2002) tested AD patients who were taking medication of tacrine an acetylcholinesterase inhibitor (anti-dementia drug), but this study did not include comparison group of AD patients without medication.

capacity over time for AD patients compared with normal ageing. For this study the main hypothesis was that inhibitory control, indicated by the number of errors generated in the antisaccade task would be found to deteriorate significantly over time, compared with controls. It was hypothesised that uncorrected errors would increase over time as inhibitory control becomes further impaired and that the ability to correct errors would be reduced over time (as to whether the clinical rating scales detect the same change over time was also examined). Furthermore, investigation of Go/No-Go tasks compared with antisaccade tasks should show significantly more errors in Go/No-Go tasks both within-groups and between-groups over time, as the Go/No-Go task is more demanding of cognitive resources. Additionally, as the attentional disengagement deficit becomes more pronounced in the AD patients over time, then magnitude of the FOE should become significantly greater for AD patients in the reflexive saccade paradigm. A further hypothesis, was that the additional reprocessing time cost induced by the antisaccade tasks (in addition to motor initiation time costs), as opposed to the motor initiation time for reflexive saccade tasks, should become prolonged over time compared to controls, demonstrating a processing deficit for AD over time.

In Study VI (Chapter 8), the neuropsychological assessments outlined in Section 2.5 were compared with saccadic eye movement data, to investigate specific relationships, attempting to highlight certain elements of cognition, in particular attention, working memory and inhibitory control. Analyses were conducted to examine closely, the predictive capacity of both the neuropsychological assessments compared with the saccadic eye movement measures.

The overall theme of the thesis across each of the studies was to attempt to reveal a sensitive indicator for early dementia, more specifically AD, using oculomotor markers and comparing these with cognitive abnormalities. This was done using the antisaccade task (in particular the error rate) and other inhibition task (error rate) measures, against reflexive saccade tasks which are generally viewed as control conditions requiring only motor initiation for the task (given the obvious attentional/perceptual components also involved). Thus,

reflexive tasks are hypothesised to cause few saccadic errors, whereas previous research investigating saccadic latency and amplitude in these tasks has produced inconsistent findings. It may be that any impairment of reflexive saccades, relative to voluntary saccade tasks is found to be only marginal or to deteriorate at a slower rate.

## 2.8 Chapter Summary

This chapter has introduced the methodology that is used for the thesis. Firstly, the recruitment methods and criteria for the participant population was discussed, emphasising that dementia patients with very mild dementia were selected, according to DSM IV and NINCDS-ADRDA criteria and that good response rates were found for each method employed to recruit participants. Attrition rates from the longitudinal study were also discussed and the importance of the working relationship and rapport between researcher and participants emphasised. The health status of participants was also evaluated, indicating that any illnesses or medications presently being taken by participants were not likely to impede performance of the oculomotor system on the saccadic eye movement tasks.

The saccadic eye movement recording technique and reasons for selection of the infrared scleral reflection system was outlined with the preference for this equipment lying in its reliability and non-invasive application. Of paramount concern was the comfort of participants during testing, given the nature of the clinical group and the age of participants involved in the study. The experimental design involved antisaccade and reflexive saccade paradigms (comprising gap and overlap conditions), so as to explore inhibitory control, attention disengagement deficit and the FOE, and basic saccadic measures of saccadic latency, amplitude, velocity and duration. A range of clinical rating scales and neuropsychological assessments were utilised for the study so as to assess dementia severity and cognitive performance (frontal lobe function, working memory, psychomotor ability, attention and orientation), also providing correlational and comparative measures for evaluation with saccadic eye movement measures.

# Chapter Three

## Study I: Dysfunction of Inhibitory Control and Cognitive Impairment in Alzheimer's Disease

### 3.1 Introduction

AD patients have been found to present with a range of cognitive dysfunction, as discussed in Chapter 1, Section 1.5.2. A feature that becomes prominent early on in the disease process, is an impoverishment of inhibitory control and thus the initiation of inappropriate behaviour (see Section 1.5.2.2.4) (O'Neill & Carr, 1999; Rapp et al., 1992). Along with the deficit of inhibition, there is a progressive decline in working memory, (Baddeley et al., 1986; Belleville, Peretz & Malenfant, 1996; Morris, 1994; Morris & Kopelman, 1986) and attention (Parasuraman et al., 1992; Parasuraman & Haxby, 1993; Perry & Hodges, 1999; Perry, Watson & Hodges, 2000).

Various studies of eye movements in AD have also detected a dysfunction of inhibitory control[7]. This problem is readily indicated by a deficit in the ability to inhibit the VGR during the antisaccade task (see Chapter 1, Section 1.3.2.3.1 & 1.3.2.3.2), compared with healthy controls who are able to inhibit the VGR much more efficiently (Abel et al., 2002; Currie et al., 1991; Fletcher & Sharpe, 1986; Maruff & Currie, 1995; Shafiq-Antonacci et al., 2003). Often, this inappropriate activation of the VGR is followed by a spontaneous corrective (secondary) saccade that quickly rotates the eye to the opposite hemifield, thereby correcting the error (Abel et al., 2002; Everling & Fischer, 1998; Mathalon et al., 2003). Antisaccade error rate in AD has been shown by some studies to be related to disease severity (Abel et al., 2002; Currie et al., 1991; Mulligan et al., 1996; Shafiq-Antonacci et al., 2003).

[7] Although it is unclear as to whether or not the various modes of inhibition (and deficits) in behavioural control are related.

Error correction relies on the capacity for self-monitoring behaviour. The ability to monitor ongoing behaviour, predict the consequence of action and correct error when appropriate are abilities that healthy humans are able to carry out as a matter of routine (Blakemore, Rees & Frith, 1998; Menon et al., 2001). Of course, the ability to correct error depends on a number of things, including the level of prior knowledge for a given task, task complexity, ability to generate an appropriate alternative response to error and being able to decide on whether this response is deemed a suitable outcome. For example when problem solving, a number of attempts may be necessary before a correct solution is obtained and in some tasks error correction may become automated, as rules are developed or learning occurs. These abilities are considered by psychological theories which take the view that healthy humans maintain an internal representation of the world and that this knowledge base is evaluated with intentions for action and corresponding external events (Decety, 1996; Jeannerod, 1988). This notion fits very well with the definition of working memory as defined in Section 1.1.1.

The ability for error correction during the antisaccade task in AD, specifically the investigation of corrected and uncorrected error types has received little attention in eye movement research, to date only one study having evaluated this behaviour, revealing the proportion of uncorrected errors to be related to dementia severity (Abel et al., 2002). Is the ability for self-monitoring and error correction dependent on working memory? How closely are these functions related? Given the neural substrates that are believed to be involved in the facilitation of working memory (Inoue, Mikami, Ando & Tsukada, 2004; Nyberg et al., 2003; Owen et al., 1996a; Petrides, 1994; Rushworth, Hadland, Gaffan & Passingham, 2003) and executive control (primarily, the DLPFC and ACC), it can be argued that the cognitive components of error response (initial error/correction), selection and decision making are inextricably linked with working memory capacity. The antisaccade, Go/No-Go and No-Go paradigms, require participants to apply task instructions that invoke higher-order processing

under executive control, so as to facilitate attentional processing and generate prosaccades accordingly. Interference with this behavioural control system through neurodegeneration or by doing tasks with a high cognitive load results in error. Therefore, the saccadic variables derived from these tasks, referred to in Chapters 1 & 2 (Sections 1.3.3, 2.4.1 & 2.4.2, i.e. proportions of: correct saccades, uncorrected errors and corrected errors [as a proportion of total valid trials]; see Figure 3.1), provide behavioural measures of inhibitory control and ability to self-monitor response.

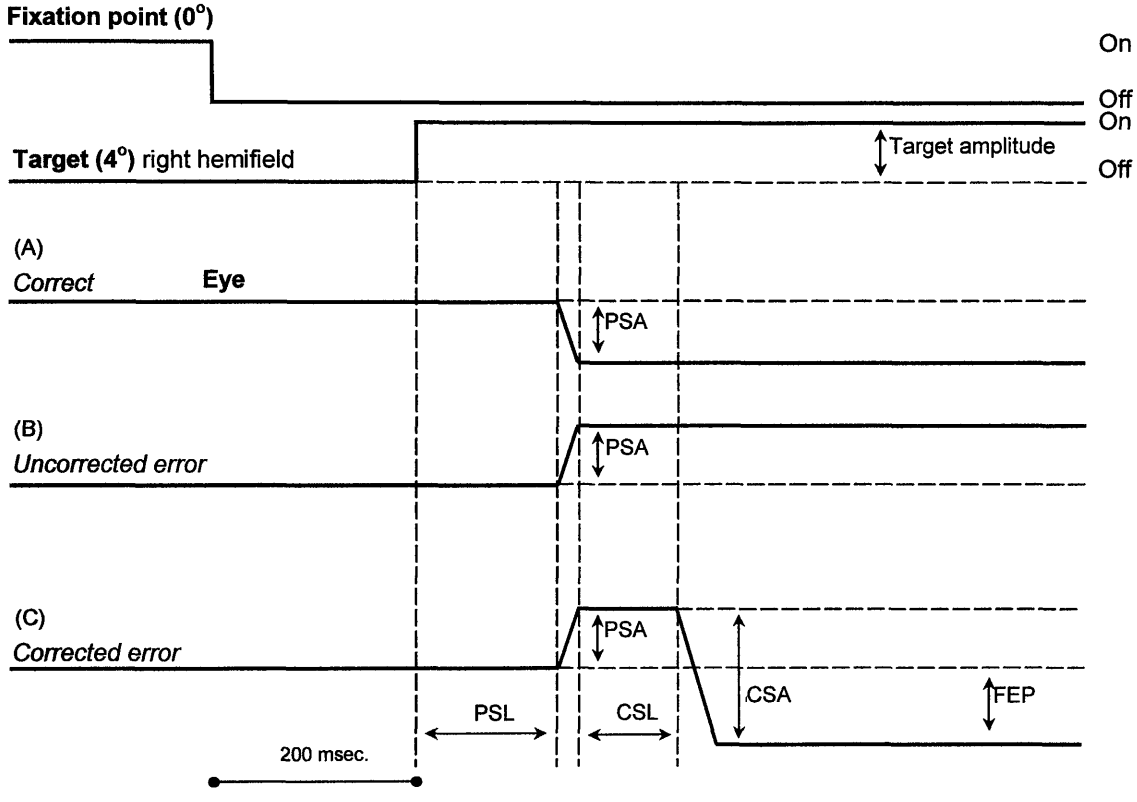



**Figure 3.1** An Illustrative Representation of Responses in the Antisaccade '*Gap*' Task Displaying Temporal and Spatial Characteristics of the Visual Stimulus

(A) ***Correct***: Anti-saccade that was correctly directed into the opposite i.e. left hemifield.

(B) ***Uncorrected error***: A 'reflexive' movement takes the eye incorrectly towards the visual angle of the target. No corrective saccade is generated to correct this error.

(C) ***Corrected error*** : The primary movement takes the eye incorrectly towards the target. This error is subsequently followed by a corrective movement to the opposite hemifield.

PSA = Primary saccade amplitude; CSA = Corrective saccade amplitude; FEP = Final eye position amplitude;
PSL = Primary saccade latency; CSL = Corrective saccade latency.

By S. Higham - adapted from figure drawn for Crawford, Higham & et al. (2005)

Chapter 1 argued that the cognitive processes involved in working memory, attention and inhibitory control are closely related functionally. The fundamental cognitive basis of attentional dysfunction in AD is still disputed and the debate surrounding inhibitory control generally rests with trying to understand the principal mechanism by which inhibition is delivered. For example, in the antisaccade task can the processes simply be thought of in terms of signal processing and the timing demands of the task? Are errors the result of inhibitory control and self-monitoring deficit, and inhibition a separable component of cognition? Or, is inhibition part of attentional control and working memory? Additionally, do inhibition errors in the antisaccade task reflect a disturbance of volitional control and thus a dysfunction in the ability to endogenously generate saccades?

Several hypotheses have been postulated to account for errors of inhibition in the antisaccade task. An early explanation postulated that in order to interrupt the reflexive response (VGR) during the antisaccade task, a stop signal was required (Hallett & Adams, 1980). Hallet and Adams suggested that inhibitory errors occur in healthy human participants, when a cancellation signal arrives too late to cancel the reflexive saccade programme and thus, prosaccade errors are related to saccade programming time compared with the time taken to generate a stop signal. In another study, Reuter and Kathman examined executive function in schizophrenia (schizophrenic patients have also been found to have impaired performance - error rate - on the antisaccade task) and proposed that errors in the antisaccade task were not the result of poor inhibitory control, but due to a deficit in the initiation of antisaccades i.e. impairment of volitional control (Reuter & Kathmann, 2004). They suggest that the exogenous signal for reflexive saccade generation is strong, whereas the endogenous transformation of task instructions into an oculomotor signal to generate an antisaccade, if too weak causes error. Furthermore, Reuter & Kathmann (2004) posit that the exogenous and endogenous signals thus compete (in strength), often ending with the stronger exogenous signal winning, resulting in directional errors in the antisaccade task. In summary, Reuter & Kathmann (2004) concluded

that errors of inhibition on the antisaccade task arise from a deficient volitional control system, and not an isolated inhibitory mechanism. This model is not unlike the working memory framework (see below), where prepotent response would be the strong exogenous signal and the weak endogenous signal the result of insufficiently activated working memory.

Many studies has found evidence to suggest that the error rate in the antisaccade task is a reflection of the efficiency by which working memory is activated (Hutton, Joyce, Barnes & Kennard, 2002; Kimberg & Farah, 1993, 2000; Mitchell, Macrae & Gilchrist, 2002; Petrides, 1994, 1996; Roberts et al., 1994; Stuyven et al., 2000; Walker et al., 1998).

Kimberg and Farah designed a computational model based on the efficiency of working memory function (Kimberg & Farah, 1993, 2000). In the traditional model of working memory by Baddeley (see Figure 2) the central executive (which Baddeley referred to as an *attentional controller*; Baddeley, 1986) was responsible for the manipulation of information

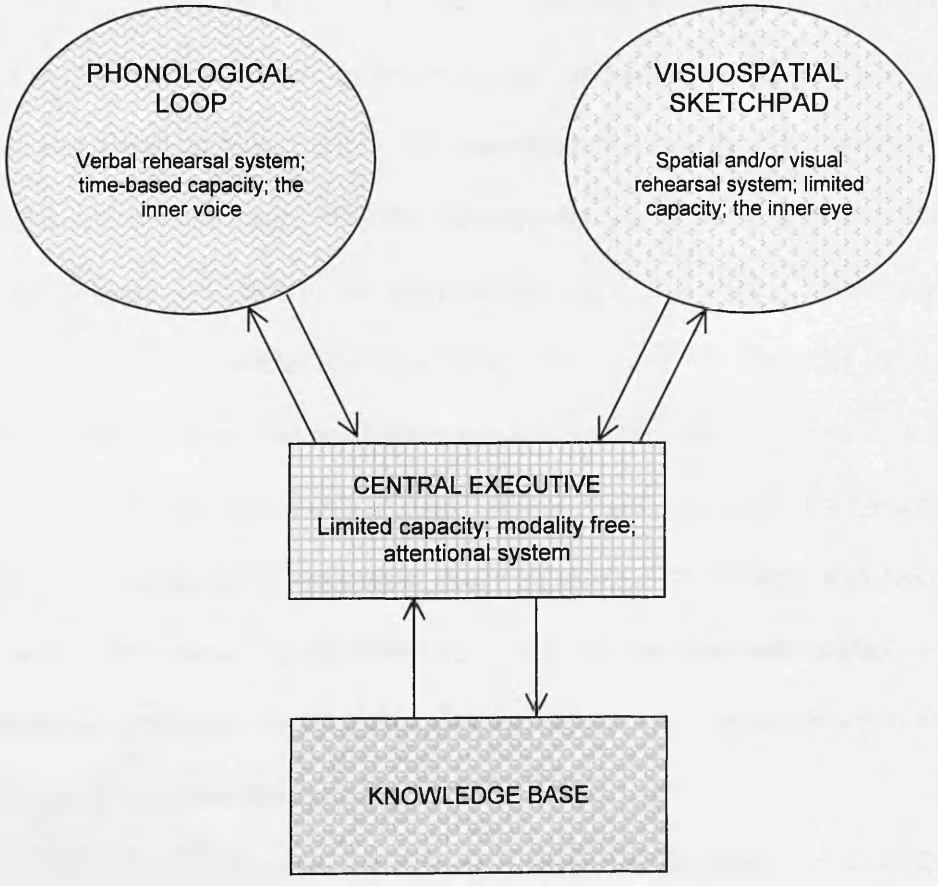



**Figure 3.2** An Illustration of the Working Memory Model
[simplified adaptation from Baddeley & Hitch (1974)]

(i.e. the execution of control) and a storage component responsible for maintaining information online in an activated state. According to Baddeley's model, loss of central executive control is demonstrated, for example, in dual tasks when concurrent loads are placed on working memory. However, the model provided by Kimberg and Farah emphasises a *weakened influence* of working memory rather than the diminution of a central executive.

Kimberg and Farah's model used production-rules systems to model performance on the antisaccade task. The level of production rule activation corresponds with competing responses in a task, determining response selection. There are four sources of activation in the model: 1) working memory activation, 2) priming activation, 3) baseline activation, and 4) noise activation. The simulation model run by Kimberg and Farah gave reflexive saccades (prosaccades) higher baseline activation than antisaccades and simulated working memory to function at sub-optimal level, as would be the case in a dual task scenario (where working memory load is increased by concurrent tasks). Crucially, the reduction in working memory capacity was achieved by decreasing the amount of activation available to working memory. The model was found to have the effect of significantly increasing the number of direction errors in the antisaccade task, whereas virtually no errors were found in the reflexive (prosaccade) saccade task, due to the high baseline activation setting. Kimberg and Farah implicated human lesion studies (Guitton et al., 1985) and the study of infant behaviour (Diamond, 1990), which link the prefrontal cortex to working memory function and inhibitory control. They concluded that poor inhibitory control is not the result of a specific inhibitory mechanism, but is a function of working memory efficiency. Importantly, they suggest that the model simulates the weakening of connections between the prefrontal cortex and posterior areas of the brain, which results in disinhibited behaviour and antisaccade errors (as observed in patients with frontal lobe damage).

Roberts et al. (1994) presented a complimentary explanation to that of Kimberg and Farah, for the involvement of working memory in the inhibition of prepotent response and

ultimately, successful completion of the antisaccade task. Roberts et al. observed that tasks such as the Wisconsin Card Sorting Task, Tower of Hanoi Task, Stroop task and antisaccade task all require executive function and suppression of a prepotent response. The prepotent response can be either incorporated into the task or acquired during the task. In order to carry out the task correctly, a participant must be able to retain information for a short period of time, avoid commission of the prepotent response and initiate the volitional action required by the task instruction. Roberts et al. (1994) argued that working memory processes have to be appropriately activated and maintained in order to enable the inhibition of prepotent responses by default, i.e. if the antisaccade response is actively maintained in working memory then a reflexive saccade to the target will be automatically inhibited. In summary, Roberts et al. hypothesised that if a task goal is insufficiently activated in working memory, due the demands on working memory induced by a secondary task (i.e. a task that requires working memory resources to run online concurrently with the antisaccade task), then errors of prepotent response (reflexive responding) will be increased due to a difficulty in preparing the correct response.

Roberts et al. conducted a dual task antisaccade/arithmetic experiment where the level of working memory load was varied during different arithmetic task conditions. Increasing working memory load by a more demanding secondary arithmetic task was found to result in directional errors (lack of inhibition of the prepotent response) in the antisaccade task, similar to the directional errors reported by Guitton and colleagues in patients with lesions of the frontal lobes (Guitton et al., 1985). Thus, Roberts et al. (1994) concluded that inhibition errors increase on the antisaccade task (and other tasks involving inhibition of prepotent response) if working memory load is increased to a point where the antisaccade task goal is insufficiently activated in working memory and thus unable to intervene in response preparation. The Roberts et al. (1994) approach is appealing as it accounts for varying levels of both pre-potency and working memory load and because of responses that have been found to be

correlates of working memory demonstrated in humans and primates (Goldman-Rakic, 1987; Owen et al., 1996a; Petrides, Alivisatos, Evans & Meyer, 1993). Additionally, as already mentioned lesion evidence also supports the working memory hypothesis (Owen, Morris, Sahakian, Polkey & Robbins, 1996b; Walker et al., 1998). Thus, there is general agreement that prefrontal tasks gauge response inhibition and working memory, but the nature of the principal processes underlying this cognitive system are a source of debate. What is the relationship between working memory and inhibition? Do they interact or do they operate as autonomous systems? According to the interactive framework by Roberts et al. (1994), inhibition of prepotent response occurs as a by-product of successful activation of task goals in working memory. Thus when working memory is at functioning efficiently, inhibition of prepotent response occurs automatically. Increasing demands on working memory decreases inhibitory control.

The concept of working memory is a helpful theoretical construct as it emphasizes an active store which can hold information (i.e. in short-term memory) for online processing and manipulation. Thus, working memory can be seen as a centre of consciousness, where the planning of action, such as that required in voluntary saccade tasks (e.g. antisaccade and Go/No-Go tasks) and error correction in problem solving, is coordinated. However, in the present thesis the traditional model of working memory by Baddeley (Baddeley, 1986, 1990; Baddeley, 1998; Baddeley & Hitch, 1974) is superseded by a contemporary connectionist theory of cognitive control that attempts to explain the mechanisms that facilitate executive control via prefrontal cortex function.

Miller and Cohen's integrative theory of prefrontal cortex function is useful as it aims to unify previous models of attentional control and working memory, and stresses the significance of prefrontal cortex function in these processes. Crucially, the theory emphasises the importance of the prefrontal cortex in the active maintenance of task goals for successful cognitive control over intervening distractions (Miller & Cohen, 2001). Miller and Cohen

highlight the importance of reciprocal projections between the prefrontal cortex and many (posterior) areas of the brain, including sensory and motor systems at both a cortical and sub-cortical level, and the implications these have in the differentiation of top-down and bottom-up processing. In brief, the prefrontal cortex is associated with the top-down processing when behaviour must be guided by internal states to achieve goals (e.g. the antisaccade task and preparation of the correct response). On the other hand the bottom-up control of behaviour is enabled by "hardwired" pathways that rapidly facilitate well known behaviours automatically; for example in response to external events, such as the random appearance of peripheral visual stimuli in the reflexive saccade task.

Fundamental to the theory is the notion that goal-directed behaviour relies on the capacity to select a weak task-relevant response, against a competing stronger task-irrelevant (prepotent) response. This can be exemplified by the Stroop task (Stroop, 1935), especially when participants are required to name the colour of a written word with conflicting stimulus components (e.g. the word BLUE presented in the colour red). Healthy participants generally produce longer response times and higher errors in this condition, and patients with frontal lobe lesions have great difficulty with the task (Cohen & Servan-Schreiber, 1992). This is due to the strong prepotency to automatically read the word (e.g. BLUE), which competes with the weaker task goal of naming the colour in which the word is written (e.g. red). Miller and Cohen suggest that the functions of goal-directed behaviour, selective attention, behavioural inhibition and working memory (implicated in the Stroop task) all rely on the active representation of task goals and rules which are enabled by patterns of activity in the prefrontal cortex. The maintenance of this prefrontal cortex activity orchestrates processing in task relevant pathways in more posterior and/or sub-cortical areas of the brain, according to the demands of a given task. This top-down signalling favours weak task-relevant stimulus response mappings when they are in competition with stronger task-irrelevant mappings. Therefore, behaviour is manifest as a result of competitive processing between different neural

pathways carrying different sources of information, the winning behaviours being those with the strongest activity. For the representation of a task goal to have a biasing influence over automated behaviours (e.g. reflexive saccades), it must remain activated throughout a task. Previous research with primates on a visual working memory task revealed that the prefrontal cortex has the ability to sustain activity during a delay task whilst visual distractors are presented (Miller, Erickson & Desimone, 1996).

Miller and Cohen's integrative theory of prefrontal cortex function also addresses the control of attention and inhibition. Drawing on the biased competition model of Desimone and Duncan (1995), selective attention and inhibition are viewed as two sides of the same coin. Thus, Miller and Cohen propose that selective attention and inhibition are part of a single basic mechanism of cognitive control, commanded by the biasing effects prefrontal cortex activity on task-relevant pathways. Therefore, if task rules are sufficiently activated, representations in the prefrontal cortex will select for the desired task goal and attention will be successfully allocated as a result of inhibition by local competition of conflicting representations (i.e. via areas other than prefrontal cortex). In summary, attention results from biasing competition in support of task-relevant information, and inhibition is the consequence of the attentional biasing against the irrelevant information.

A related view of executive function which is openly supportive of Miller and Cohen's theory is offered by the goal activation approach of Nieuwenhuis and colleagues, with direct reference to the antisaccade task (Nieuwenhuis et al., 2004). As discussed in the previous paragraphs, evidence suggests that goal activation is central to executive function and that the prefrontal cortex maintains a representation of task goals. Nieuwenhuis et al. noted that inconsistent performance on tasks that measure executive function may be the result of a failure to focus attention appropriately. They presented evidence from previous research, suggesting that many psychological tasks share a common reliance on goal activation, a process where task requirements are manipulated into suitable goals and sustained over time

whilst competing with alternative (prepotent) response tendencies. Central to their approach, they adopted the concept of goal neglect which has been used previously to explain failures on tasks purported to require executive function (De Jong, Berendsen & Cools, 1999; Duncan, 1995). Goal neglect occurs when control over behaviour is apparently lost, and has been observed predominantly in tasks that involve conflict or prospective memory. Although task instructions are understood and remembered, there is a failure to translate these requirements into actively maintained goals. Importantly, Nieuwenhuis et al. suggested that failures are most likely when attention is required to perform multiple task demands. Nieuwenhuis et al. argued that the antisaccade task is a conflict task due to the competition between the prepotent reflexive saccade response and the endogenously generated saccade. In summary, experimentation was carried out on healthy young and elderly participants and with reference to two versions of the antisaccade task[8] (one of these cited from an earlier study), both of which required a non-speeded two-choice target response to a stimulus (a face: happy or sad) which appeared in a location opposite (antisaccade) to an initial cue and with a range of stimulus onset asynchronies (SOA; from 100 – 1500 msecs.) randomised across trials. In one of the versions of the task the instructions included an explicit request to make a saccade away from the initial cue (Nieuwenhuis, Ridderinkhof, de Jong, Kok & van der Molen, 2000), whereas in the other form of the task no saccade was specifically requested, instead subjects being instructed to make full use of the cue to improve performance on the target response (Nieuwenhuis et al., 2004). Importantly, in the latter version of the task the need to generate a saccade was implicit, simply induced as a consequence of the (impending) non-speeded two-choice target face (and due to having seen a visual animation of the task requirements prior to practice) and therefore, the generation of a saccade was subordinate to the target discrimination component. Interestingly, the main findings from these experiments were that when no explicit instruction was given to generate an antisaccade, elderly participants required more time at

[8] A prosaccade task was also conducted and used as a control condition.

each SOA than young control participants to suppress the prepotent response created by the cue[9]. A significant proportion of elderly participants' trials remained uncorrected, which demonstrated a regular failure to anticipate target appearance, despite the longer SOAs. In contrast, this was not found to be the case for the version of task (from a previously published study) in which an explicit instruction to make an antisaccade was given. In this version of the task, 'prompting' participants to make saccades appeared to improve elderly control antisaccade performance. Interestingly, the speed with which elderly controls were able to initiate saccades (latency) was unaffected by saccade prompting. These results led Nieuwenhuis et al. to conclude that healthy elderly participants (and also first-episode schizophrenic patients, but not patients with obsessive compulsive disorder) are prone to goal neglect in the antisaccade task and they note that multiple task demands can increase goal neglect, manifesting as increased error rate. Furthermore, they suggest that task instructions, task features and concurrent task demands mediate the goal activation process and conclude that these three key factors modulate attention.

The above approaches to inhibition in the antisaccade task (Kimberg and Farah, 1993, 2000; Roberts et al., 1994; Reuter and Kathmann, 2004; and Nieuwenhuis et al. 2004) all have one main feature in common and that is the level of goal activation allied to a concept of working memory function. This is important as it is directly related to the ability to focus attention on task demands, particularly when concurrent manipulation of tasks is required. Therefore, it is plausible to suggest that these accounts are useful in addressing '*why*' inhibition errors may occur in the antisaccade task. Additionally, Massen (2004) examined a hypothesis that is arguably useful in explaining '*how*' inhibition errors occur in the antisaccade task. Massen tested a hypothesis for the parallel programming of exogenous and endogenous components in the antisaccade task. The main idea behind Massen's '*race*' hypothesis is that reflexive saccades – the exogenous component – are automatically programmed in response to

[9] Repeated with schizophrenic patients the effect was found to be even more pronounced, but this was not the case for patients with obsessive compulsive disorder who were found not to differ from healthy young participants.

the appearance of a peripheral stimulus. This 'hardwired' response corresponds with the bottom-up processing discussed earlier in the account of Miller and Cohen's (2001) theory of prefrontal cortex function. An endogenous component is also concurrently generated – the voluntary antisaccade – which competes with the exogenous saccade programme. Massen manipulated the processing rate for the two components to test the prediction that slowing the exogenous component would result in less inhibition errors, whereas a slowing of the endogenous component should increase the inhibition error rate. In summary, the most relevant findings (e.g. Experiment 1: modulating the probability reflexive saccade and antisaccade trials) were that increased antisaccade errors occurred when endogenous saccade generation was slowed because antisaccade trials were unexpected, when mixed with a high probability for reflexive saccade trials, whereas reflexive saccade generation remained unaffected. In contrast, antisaccade errors were significantly lower when the probability of antisaccade and reflexive saccade trials was equivalent. Furthermore, Massen also found that corrected error saccades, which are often found to follow inappropriate reflexive saccades spontaneously in the antisaccade task, were of short latency (mean 124.3 msecs.), i.e. they were very fast. In fact Massen found that a proportion of the corrective saccades (35%) were less than 80 msecs. These findings support the idea that the reflexive saccade programme and the endogenous antisaccade programme are generated in parallel, as the correction time is simply too short to be the result of a sequential process of saccade generation.

Can the aforementioned models and hypotheses be reconciled? It is plausible to suggest that the parallel '*race*' between exogenous and endogenous components in the antisaccade task is the basic mechanism for inhibition in the antisaccade task and can explain how, antisaccade errors occur at a fundamental level. This fits very neatly with why antisaccade errors may occur when goals are insufficiently activated in working memory, resulting in a lack of attentional processing. Thus, an error occurs when the exogenous parallel saccade programme wins the race against the endogenous saccade programme, which can

happen when demand on working memory resources is high, as when taxed by a secondary task (i.e. the dual task paradigm), causing the task goal to be insufficiently activated and consequently poor attentional processing – multiple task demands ultimately result in a failure of attention.

It is possible to test the Roberts et al. (1994) theory by applying it to a clinical sample that have dysfunctional inhibitory control. Given that one of the main cognitive features of AD is working memory impairment, the voluntary saccade tasks mentioned earlier may reflect this deficit via the varying degrees of task complexity across the voluntary saccade tasks i.e. that oculomotor tasks make specific demands on working memory processes. Table 3.1 applies the approach used by Roberts et al. (1994) to the present study, rating voluntary saccade tasks and psychometric tasks that require working memory as to their pre-potency and working memory demand. The voluntary saccade tasks were preceded by blocks of reflexive trials (see Chapter 2, Section 2.3.3.1 and Appendix 11), so as to optimise the pre-potency of the voluntary tasks that followed.

**Table 3.1** Prepotent Responses, Alternative Responses and Working Memory Demands for the Voluntary Saccade Tasks and Working Memory Tasks in the Study I, Following the Roberts, Hager and Heron Framework

| Task | Prepotent response | Alternate Response | Working Memory demand | Prepotent/ Working memory |
|---|---|---|---|---|
| No-Go | Saccade to target | Ignore Target | Keep instruction active | Working memory: Low<br>Pre-potency: High |
| Antisaccade | Saccade to target | Saccade to opposite side | Keep instruction active apply current context | Working memory: moderate<br>Pre-potency: High |
| Go/No-Go | Saccade to target | Go: Prosaccade<br>No-Go: Inhibit | Keep instruction active apply current context | Working memory: High<br>Pre-potency: High |
| Trail Making B | Don't alternate sequence | Alternate number/letter sequence | Keep last item active and apply current context, alternate sequence | Working memory: High<br>Pre-potency: Moderate |
| Digits Span Reverse | Repeat forward sequence | Reverse sequence | Keep forward sequence active, reverse the sequence | Working memory: High<br>Pre-potency: Moderate |
| Spatial Span Reverse | Repeat forward sequence | Reverse sequence | Keep forward sequence active, reverse the sequence | Working memory: High<br>Pre-potency: Moderate |

Adapted and modified from Roberts, Hager & Heron (1994)

The instructions for the No-Go task are to maintain gaze at the central target location and ignore peripheral targets. The simple instructional set for the No-Go task (relative to the antisaccade and Go/No-Go tasks) is reflected in Table 3.1 as a low demand on working memory, although pre-potency is high due to the unpredictable characteristics of the peripheral targets. Therefore, as this simple fixation task places less demand on working memory (as suggested by Walker et al., 1998) AD patients should perform quite well, but make some level of inhibitory error due to the high pre-potency of the task.

The working memory demand of the antisaccade task is classed as moderate, as the participant has to maintain inhibitory set throughout the trial and produce a single response type to the stimulus. Pre-potency is again high therefore, AD patients should find this task somewhat more difficult as it is postulated that they have working memory deficit thus there ability to carry out the task should be depleted. Thus, executive control of attention may be compromised, resulting in the production of erroneous VGR responses.

For the Go/No-Go task working memory demand is high and as can be seen by the *alternate response* column the task instruction is more complex than that of the antisaccade task. In this task the response is contingent upon the direction of the stimulus and the task requires the constant switching of set, between inhibition and activation, functions that are very demanding of attentional resources and working memory. Additionally, pre-potency is high for the Go/No-Go task which could result in very high inhibitory error rates, as executive function (which is dysfunctional in AD patients) is taxed to such a high level that working memory can no longer intervene to facilitate efficient attentional control. As the task is insufficiently activated in working, this results in failure to inhibit the VGR. Referring to Table 3.1 again, the tasks that require manipulation by working memory (i.e. Trail Making Form B; Digit Span Reverse; and Spatial Span Reverse) are allocated a high working memory component and only moderate pre-potency. Therefore, performance on these tasks that require prefrontal activation for working memory and attention may be correlated with

performance on the voluntary saccade tasks that require higher levels of working memory. Other researchers have employed oculomotor tasks that varied in cognitive demand, so as to examine possible links between inhibitory control and working memory (Hutton et al., 2002; Walker et al., 1998). Hutton et al. (2002)[10] examined inhibitory control in schizophrenic patients, and revealed that inhibitory errors increased as cognitive demands increased, placing higher cognitive load on working memory resources. However, the study did not conduct any psychometric tests that require working memory, as a method of investigating hypothesized links between inhibitory control and working memory. Walker et al. (1998) conducted a case study on a patient with prefrontal cortex damage, also using a range of tasks that varied in working memory demand. This study also found that inhibitory errors increased, as cognitive demand of the oculomotor tasks increased, and attributed this to a spatial working memory deficit due to the nature of the patient's lesion in the prefrontal cortex.

For the present study, in addition to examining inhibition errors as a whole, the investigation of self-monitoring ability in AD patients was examined by analyzing corrected errors and uncorrected error rates (the component parts of inhibitory error) and relating these to working memory tasks. Of particular interest here, is the uncorrected error rate, which a previous study reported as being high for AD patients (Abel et al., 2002). There are a number of possible arguments that could possibly explain the high rate of uncorrected errors for AD patients. Firstly, uncorrected errors may result from a disturbance of pathways in the frontal lobes of the brain, that are responsible for self-monitoring and error correction. A second explanation could be that due depletion of working memory resources the task goal is insufficiently activated in working memory resulting in goal neglect. Thirdly, AD patients may have great difficulty in generating a saccade to an empty location, when a visual stimulus is already fixated, due to a fixation disengagement deficit.

[10] Hutton et al. (2002) used three tests that were used in the Walker et al. (1998) study.

Therefore, the purpose of this study was to examine the underlying cause of inhibitory impairment in AD, by investigating working memory as the principal cause of this deficit and also exploring the capacity for error correction.

### 3.1.1 Aims

The aims of the present study were, to investigate deficits of inhibitory control and self-monitoring in dementia of the Alzheimer's type (AD) at stage one (baseline) in the longitudinal project and establish which measures or analyses are most sensitive in the detection of dementia. The study involved a range of saccadic eye movement paradigms varying in the degree of difficulty (Table 3.1), thus placing different demands on working memory resources. Therefore, the first analysis generated the factor: *voluntary saccade task* to compare the proportions of inhibition errors committed for each voluntary saccade task (No-Go; antisaccade and Go/No-Go) between and within-groups. Relationships between the saccadic (and behavioural) measures on these tasks and cognitive test scores, primarily clinical rating scales (SMMSE and ADAS cog.; see Sections 2.5.1 and 2.5.2 respectively) and neuropsychological assessments (Trail Making; Digit Span; and Spatial Span; see Sections 2.5.6, 2.5.7 & 2.5.11 respectively) that require working memory and frontal lobe function (executive control) were also investigated, in an attempt to link working memory deficit in AD, with inhibition errors. This study also aimed to replicate previous research, that has examined corrected and uncorrected errors in AD (Abel et al., 2002) and this was done by generating the factor: *correctness of performance*. The overall theme of this study was to describe the nature of inhibitory control in AD, its relationship to dementia severity and to establish whether the underlying cause of inhibitory error in AD is due to a working memory deficit.

A notable problem with the study by Abel et al. (2002) was that the AD group were on medication of acetylcholinesterase inhibitors. Thus, drug effects could potentially have affected the outcome. Additionally, the study did not compare the inhibitory errors in the

antisaccade task, to any tasks without an inhibitory component. The present thesis examines drug effects in a later chapter (Study IV, Chapter 6) and as mentioned above, includes a range of different saccadic conditions.

### 3.1.2 Hypotheses

The specific hypotheses for this study were: 1) Due to inhibitory deficit brought about by working memory dysfunction, AD patients will demonstrate significant antisaccade, No-Go and Go/No-Go impairments (error rate), in contrast with relatively intact reflexive saccade performance and compared with healthy controls. 2) Inhibitory error will be significantly related to dementia severity, as working memory deficit advances with disease progression. 3) Moreover, inhibitory errors from the saccadic tasks which have a higher cognitive load, therefore, using more working memory resources, will be significantly greater than for those tasks which carry less cognitive load both between-groups and within the patient group. Alternatively, in a task where prepotent response is very high (No-Go task), placing relatively low demands on working memory, errors should also be significantly higher in the dementia group but reduced compared to saccadic tasks that require more working memory resources. 4) These significant cognitive loadings will be significantly correlated in the AD group, with the neuropsychological assessments that require working memory, due to working memory deficits in AD.

A further line of inquiry for this chapter was to examine the ability of dementia patients to self-monitor performance during the antisaccade task. Therefore, comparisons were made between-groups, on the level of correct antisaccade commissioning and in the capacity for correction in the event of inhibitory error on the factor correctness of performance. 5) The specific hypothesis for this section was that AD patients would commit significantly more uncorrected errors of inhibition than the EC group and furthermore, that uncorrected error will be correlated with dementia severity and related to performance on neuropsychological

assessments that also place high demands on working memory resources. 6) However, as the AD group were in the early stages of dementia it was also hypothesised that a significantly higher proportion of corrected errors (inhibition error corrections) would be evident for this group (demonstrating task understanding), as compared with the EC group who should have less need for error correction due to a lower error rate in the first place. Trend analysis should substantiate these profiles. 7) The inter-saccadic interval for corrected errors (secondary saccade) should be significantly prolonged for the AD group, compared with the EC group, due to a disturbance in error processing which relies on executive function, the operation of which is compromised with working memory deficit.

## 3.2 Methods

### 3.2.1 Participants

The dementia patients for this study were volunteers from the AD Research Project at Lytham Hospital Memory Clinic, United Kingdom. Elderly Control (EC) participants were volunteers from the local community of Lytham. The methods for recruitment, dementia diagnosis criteria, exclusion criteria and health status for the experimental population, were discussed in Chapter 2, Section 2.1. All participants were right-handed.

The Dementia Patient group (N=28; age range = 68–88 years; mean = 76.5; SD = 4.7; male, n=19; female n=9) comprised two sub-groups, AD patients (N=17; age range = 70-88; mean = 76.9; SD = 4.9; male n=12; female n=5) and Dementia of other types [DOT] (N=11; age range = 68-81years; mean = 75.8; SD = 4.4; male n=7; female n=4). The composition of the EC group (N=33; age range = 58–85 years ; mean = 70.5; SD = 6.0; male n=13; female n=20). Clinical rating scale and neuropsychological assessment scores for the groups and sub-groups are shown overleaf in Table 3.2.

**Table 3.2** Clinical Rating Scale and Neuropsychological Assessment Scores

| | Groups | | | | | | Dementia sub-groups | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Elderly control | | | Dementia Patients | | | Alzheimer's disease | | | Other dementia | | |
| | Mean | SD | N | Mean | SD | N | Mean | SD | N | Mean | SD | N |
| **SMMSE** | 29.09 | 1.13 | 33 | 22.39 | 5.78 | 28 | 21.35 | 4.72 | 17 | 24.00 | 7.06 | 11 |
| **EADAS** | 7.79 | 2.46 | 33 | 21.39 | 12.06 | 28 | 22.76 | 9.35 | 17 | 19.27 | 15.65 | 11 |
| **Trails A** | 41.50 | 12.59 | 33 | 73.92 | 34.94 | 26 | 77.67 | 33.16 | 16 | 67.91 | 38.64 | 10 |
| **Trails B** | 80.36 | 26.77 | 33 | 142.18 | 62.25 | 19 | 150.34 | 63.44 | 11 | 130.98 | 62.97 | 8 |
| **DSF** | 10.30 | 2.28 | 33 | 8.75 | 2.20 | 28 | 8.65 | 2.23 | 17 | 8.91 | 2.26 | 11 |
| **DSR** | 7.39 | 2.36 | 33 | 5.39 | 2.79 | 28 | 5.06 | 2.46 | 17 | 5.91 | 3.30 | 11 |
| **SSF** | 7.45 | 1.80 | 33 | 5.36 | 2.08 | 28 | 5.53 | 2.07 | 17 | 5.09 | 2.17 | 11 |
| **SSR** | 6.73 | 1.18 | 33 | 4.32 | 2.06 | 28 | 4.24 | 2.11 | 17 | 4.45 | 2.07 | 11 |

DSF=Digit Span Forward; DSR = Digit Span Reverse; SSF=Spatial Span Forwards; SSR=Spatial Span Reverse
Trails score = time measured in seconds

### 3.2.2 Assessment of Saccadic Eye Movements

All participants used the equipment, task protocol and experimental procedures described in Chapter 2 (Section 2.3), which involved the reflexive saccade gap task; No-Go and Go/No-Go paradigms; and antisaccade gap task with a central fixation point displayed at $0^{o}$ and target at $\pm 4^{o}$ in the horizontal plane, presented randomly by direction.

The reflexive task were presented first, in order to enhance or maximize the prepotent response and also to avoid potential carry-over effects from voluntary saccade paradigms (Roberts et al., 1994). Additionally, as discussed earlier, dementia patients have been found to be more compliant when tasks which are less cognitively taxing are presented first (Perry & Hodges, 1999). However, as so few errors were made by each group in the reflexive saccade gap task (see Table 3.3) they were not included in any of the analyses.

### 3.2.3 Statistical Analysis

Statistical analyses were carried out using SPSS version 11.5 (SPSS Inc., Chicago Ill). Firstly, Dementia Patients (DP) were assessed as a group compared with ECs and then the analysis extended to examine the dementia sub-groups (i.e. ADs and Dementia of other types). No laterality effects were found for any variables therefore data from left and right hemifield

were collapsed. Normality of oculomotor variables was assessed using the skewness index, and variables transformed using square root or square, for positive (>1) or negative (<-1) skewness respectively (Tabachnick & Fidell, 1996). Analyses were conducted using univariate analysis of variance (ANOVA), analysis of covariance (ANCOVA) or repeated measures mixed between-within ANOVA, trend analysis, Scheffe multiple comparisons (noted for a conservative level of correction (Keppel, 1991), p.173) and pair-wise comparisons (t-test), as applicable. For analyses using repeated measures ANOVA, Mauchly's test was conducted on each variable to assess assumptions of sphericity. If assumptions of sphericity were violated, the Greenhouse-Geisser epsilon correction of degrees of freedom were used (Jennings, 1987). Correlational relationships were investigated using Spearman's rank order correlation coefficient.

#### *3.2.3.1 Effects of Age and Education*

The effects of age and education were assessed using Spearman's rank correlation coefficient for age with oculomotor variables. Comparison of age and education between-groups was examined using ANCOVA.

#### *3.2.3.2 Group Comparisons of Saccadic Error Rates and Other Analyses*

The analysis of group differences on saccadic variable was carried out using a two-factor repeated measures ANOVA (factor levels = oculomotor variables; between -groups factor = group). Additionally, univariate ANCOVAs were conducted for each oculomotor variable, with group as the independent variable (patients versus controls) and oculomotor variable as the dependent variable (age was included as a covariate). Trend analyses were utilized to investigate possible trends in specific error types. Multiple comparisons using the Scheffe test and within-groups pair-wise comparisons, employing the t-test where used where applicable.

Effect sizes for oculomotor variables were calculated by applying Cohen's *d* statistic (Cohen, 1988), using the following formula for between-groups designs:

$$\frac{(\mu_1 - \mu_2)}{SD_{(pooled)}}$$

$u_1$ = the mean of group 1and $u_2$ = the mean of group 2. $SD_{(pooled)}$ = the pooled standard deviation of the two groups calculated as follows:

$$\sqrt{\frac{(N_a - 1)SD_a^{\,2} + (N_b - 1)SD_b^{\,2}}{N_a + N_b - 2}}$$

In the above formula, $N_a$ is the sample size of group A, along with standard deviation; and $N_b$ is the sample size of group B, with standard deviation. Cohen used values of *d* to divide the scale of effect size into three intervals as follows:- Values of *d*/effect size: .2 = small; .5 = medium; .8 = large.

Relationships between clinical rating scales, neuropsychological assessments and oculomotor variables were assessed using Spearman's rank correlation coefficients (two-tailed) where applicable.

## 3.3 Results

Skewness (positive) was found to be present for some variables, which was transformed to normalise the skewness of distribution. Statistical analysis of transformed variables generated virtually identical output to untransformed scores, therefore for clarity of interpretation and descriptive statistics, the results given below use untransformed versions (were possible non-parametric analyses of all variables conducted simultaneously for thoroughness, also revealed the same results as ANOVA but are omitted from these sections).

### 3.3.1 Effects of Age and Education

ANOVA revealed a significant difference for age between DPs and ECs ($F[1,59]=18.19$, $p<0.0001$). However, age was not found to be correlated with the majority of oculomotor variables for either group (all correlations: $r<0.09$, $p>0.6$); parametric and non-parametric tests where applicable, respectively). This was with the exception of two variables for DPs and three for ECs, each found to be significant at the 5% level: DPs antisaccade gap task omissions ($r= 0.38$, $n=27$, $p<0.05$) and No-Go task inhibition errors ($r= 0.40$, $n=28$, $p<0.05$); reflexive saccade gap task proportion of correct saccades ($r= 0.38$, $n=32$, $p<0.05$) and reflexive saccade gap task proportion of omissions ($r= 0.45$, $n=32$, $p<0.05$). As a precaution, age was included as a covariate in later analyses.

An ANOVA investigating differences in years of education, revealed no significant difference between DP (mean [years]= 12.2; SD = 2.4) and EC (mean [years] = 12.0; SD = 2.6) groups ($F[1,59]=0.11$, $p>0.7$). All other oculomotor variables (for each group) were found not to correlate with years in education ($r_s<0.25$, $p>0.1$).

### 3.3.2 Group Comparisons of Saccadic Error Rates

#### 3.3.2.1 Comparing Inhibitory Errors Across Voluntary Saccade Tasks

Inhibitory errors were analysed in the No-Go, antisaccade gap and the Go/No-Go tasks (Table 3.3). The order of inhibitory errors across tasks showed that the No-Go task resulted in the least number of inhibitory errors for each group, the antisaccade gap task produced a moderate proportion and the Go/No-Go task was found to result in the highest proportion of inhibitory errors for each group. The DP group were found consistently to produce a higher proportion of inhibitory errors for each task.

A two-factor repeated measures mixed AVOVA was used to evaluate *voluntary saccade task* (with three levels of task) and group (DP and EC groups). The interaction between group and voluntary saccade task did not reach significance. However, trend analysis

**Table 3.3** Descriptive Statistics for Error Analysis

| | | | Groups | | | | | | Dementia sub-groups | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Elderly Controls | | | Dementia Patients | | | Alzheimer's disease | | | Other dementia | | |
| | | | Mean | SD | N | Mean | SD | N | Mean | SD | N | Mean | SD | N |
| Antisaccade | Gap | Correct saccades (%) | 78.34 | 14.77 | 32 | 39.34 | 28.44 | 27 | 33.75 | 27.40 | 17 | 48.84 | 29.03 | 10 |
| | | Inhibition errors (%) | 16.30 | 12.82 | 32 | 48.45 | 26.60 | 27 | 50.66 | 27.49 | 17 | 44.70 | 25.99 | 10 |
| | | Uncorrected errors (%) | 2.09 | 5.50 | 32 | 19.87 | 22.36 | 27 | 23.47 | 23.25 | 17 | 13.76 | 20.42 | 10 |
| | | Corrected errors (%) | 14.21 | 11.88 | 32 | 28.58 | 22.51 | 27 | 27.19 | 21.74 | 17 | 30.94 | 24.76 | 10 |
| Go/No-Go | Gap | Inhibition errors (%) | 35.78 | 27.70 | 32 | 56.87 | 30.22 | 27 | 63.39 | 32.32 | 17 | 45.79 | 23.78 | 10 |
| No-Go | Gap | Inhibition errors (%) | 10.31 | 13.32 | 32 | 33.73 | 29.26 | 28 | 28.49 | 27.35 | 17 | 41.82 | 31.57 | 11 |
| Reflexive saccade | Gap | Correct saccades (%) | 90.98 | 9.87 | 32 | 90.58 | 11.95 | 28 | 89.88 | 12.10 | 17 | 91.67 | 12.22 | 11 |
| | | Directional errors (%) | 0.92 | 2.06 | 32 | 2.10 | 2.90 | 28 | 2.22 | 2.99 | 17 | 1.91 | 2.89 | 11 |
| | | Uncorrected errors (%) | 0.13 | 0.74 | 32 | 0.60 | 1.50 | 28 | 0.49 | 1.39 | 17 | 0.76 | 1.70 | 11 |
| | | Corrected errors (%) | 0.79 | 1.67 | 32 | 1.50 | 2.59 | 28 | 1.72 | 2.97 | 17 | 1.15 | 1.96 | 11 |



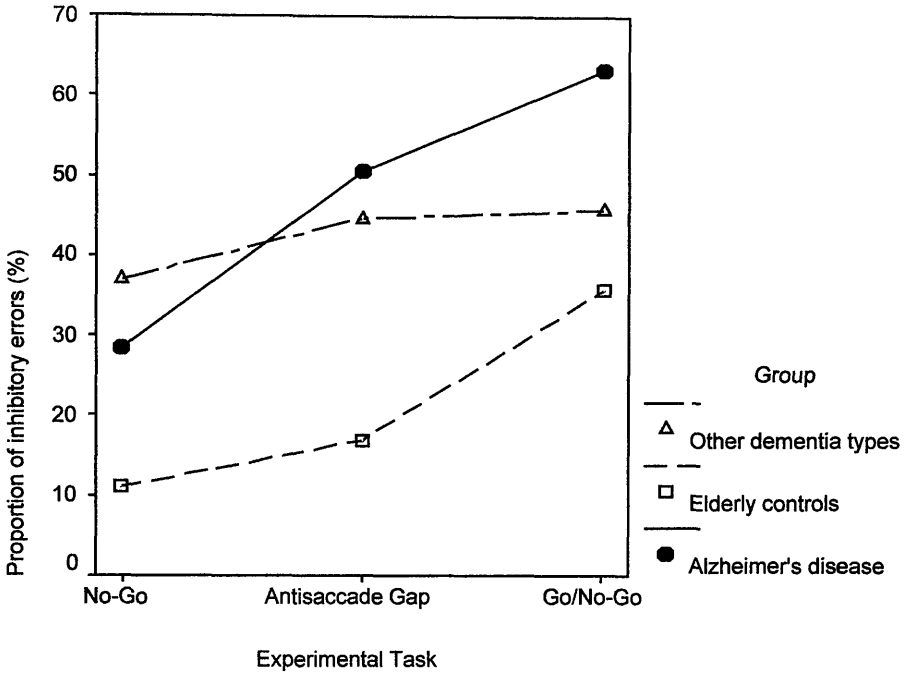
3 Dysfunction of Inhibitory Control

revealed a significant *linear* trend component to the interaction ($F[1,57]=26.29$, $p<0.0001$), demonstrating that there was a significant increase in inhibition errors across saccadic tasks. The main effect of voluntary saccade task was also significant ($F[1.76, 100.48]=28.69$, $p<0.0001$; Greenhouse-Geisser correction), showing that there were overall differences between tasks, both groups generating most errors in the Go/No-Go Task and least in the No-Go task. Additionally, the main effect of group ($F[1, 57]=26.29$, $p<0.0001$) was found to be significant, highlighting that there were overall differences between the groups on the tasks, the DP group producing more inhibitory errors than the EC group.

Univariate ANCOVAs were carried out to analyse differences between-groups (controlling for age as a covariate) for the proportion of inhibitory errors on the No-Go, antisaccade gap and Go/No-Go tasks. The DP group was found to produce significantly more inhibitory errors than the EC group, in all three tasks, No-Go ($F[1,57]=20.23$, $p<0.0001$; $d = 1.1$), antisaccade gap ($F[1,56]=26.0$, $p<0.0001$; $d = 1.6$) and the Go/No-Go task ($F[1,56]=4.41$, $p<0.048$; $d = .7$); therefore showing a significant deficit in performance with large and medium effect sizes, compared with the EC group of, +23.42% for the No-Go task, +32.15% for the antisaccade gap task, and +21.09% for the Go/No-Go task (see Table 3.3). Taken together these findings confirm that the DP group committed significantly more inhibitory errors in each task, compared with the EC group.

The mixed factorial ANOVA was repeated to include the sub-groups. This analysis showed that there was a significant interaction (Figure 3.3) between voluntary saccade task and the between-groups factor of sub-group ($F[3.58, 100.29]=2.26$, $p<0.04$; Greenhouse-Geisser correction) which indicates that there was a significant difference across the task error rates between the sub-groups. The main effect of voluntary saccade task was also significant ($F[1.79, 100.29]=19.94$, $p<0.0001$; Greenhouse-Geisser correction), showing that overall there were differences between the proportions of inhibitory error produced on the saccadic tasks;

**Figure 3.3** Inhibitory Errors for Alzheimer's Disease Compared with Dementia of other types and Elderly Controls in Voluntary Saccade Tasks




Most highly in the Go/No-Go task and least in the No-Go task. The main effect of group was found to be significant, showing that there were overall differences between the groups on proportion of inhibitory errors committed in the tasks ($F[2, 56]=13.29$, $p<0.0001$).

Univariate ANOVA extended to the sub-groups, revealed significant differences in the proportion of inhibition errors committed between-groups for each task (No-Go, $F[2,56]=11.42$, $p<0.0001$; antisaccade gap, $F[2,55]=13.153$, $p<0.0001$ and Go/No-Go, $F[2,55]=3.26$, $p<0.046$). Post-hoc comparisons (Scheffe) showed that the AD group produced significantly more inhibitory errors than the EC group, on all three saccadic tasks, with large effect size (No-Go, $p<0.01$, $d = .9$; antisaccade gap, $p<0.01$, $d = 1.8$; and Go/No-Go, $p<0.01$, $d = 1.0$). Thus, compared with EC group performance, the AD group presented with an inhibitory error rate increase across the tasks of 18.18% for the No-Go task, 34.36% for the antisaccade task and 27.61% for the Go/No-Go task. This finding confirms the hypothesis that inhibitory errors would be significantly greater in each voluntary saccade task for the AD group, compared with inhibitory error rates generated in the EC group. The DOT group also

produced a significantly greater proportion of inhibitory errors compared with the EC group, on the No-Go and the antisaccade gap tasks (both $p<0.01$; $d = 1.5$ and $d = 1.7$ respectively), however, although the DOT group produced more inhibitory errors than the EC group on the Go/No-Go task, this effect did not reach significance which perhaps indicates that the DOT group have better preserved working memory. AD patients produced a greater proportion of inhibitory errors on both the antisaccade gap task and Go/No-Go task compared with patients in the DOT group although these differences were not found to be significant. Conversely, AD patients were found to generate marginally *less* inhibitory errors on the No-Go task, than the DOT group, but this result was also non-significant (Figure 3.3). Taken together, these results suggest that in general, the DOT group showed *less* impairment of attentional control in tasks that require high working memory demand, compared with the AD group. However, the DOT appear to perform more poorly than other groups on the No-Go task, which requires motor preparation for fixation in order to fixate a blank space in the presence of a peripheral target. In summary, these results support the hypothesis that AD patients would produce significantly more inhibitory errors than the EC group in each task.

Within-groups repeated measures analysis of sub-groups of voluntary saccade task, revealed that the main effect of voluntary saccade task was significant for the AD group ($F[2,32]=12.89$, $p<0.0001$) and EC group ($F[1.59,49.14]=20.22$, $p<0.0001$; (Greenhouse-Geisser correction), whereas this factor was not significant for the DOT group ($F[2,18]= 0.86$, $p>0.4$). Trend analysis for the sub-groups revealed a significant linear trend for the AD group (Figure 3.3) across the range of voluntary saccade tasks ($F[1,16]= 18.28$, $p<0.001$), which supports the hypothesis that there would be a significant increase (linearly) in inhibitory errors, across tasks which increase in cognitive load and thus the degree of working memory required to carry out the task. A significant linear trend was also present for the EC group ($F[1,31]= 28.12$, $p<0.0001$), which also supports the hypothesis of an increase in error rate, according to the working memory requirement of the task; The EC group producing significantly less

inhibitory errors on each task, compared with the AD group. No significant trends (i.e. linear, quadratic or cubic) were found for the DOT ($F[1,9] = 1.67$, $p>0.2$), which indicates that although the DOT group produced significantly more errors than the EC group in the No-Go and antisaccade gap tasks, they did not differ significantly in the performance on each of the tasks, whereas the AD group did differ significantly on each task. The reader may recall from Table 3.1 and from the analysis of voluntary saccade task in the present analyses that the order of voluntary tasks is important for the hypotheses set out in Section 3.1.2, which postulate that the tasks vary as to the degree of working memory required to complete a given task, i.e. the No-Go task was considered least demanding; antisaccade gap task – moderate and the Go/No-Go task – high demand. Therefore, the performance of the EC group represents working memory performance during normal healthy aging, whereas the AD scores represent a clinical group with working memory deficit and corresponding inhibitory impairment, which should be reflected in performance across the range of voluntary saccade tasks (which vary in degree of working memory demand). The present analyses supported these hypotheses.

A supplementary set of within-group analyses were conducted to isolate performance across tasks and to substantiate the differences highlighted by trend analysis which showed a linear trend for the AD and EC groups. Pair-wise comparisons were conducted for each group to examine the simple effects between different levels of voluntary saccade task, for the proportion of inhibitory errors committed.

This analysis was firstly conducted on the EC and DP group data. A significant difference was found between the No-Go task and antisaccade gap condition for both groups, producing significantly more errors in the antisaccade gap task (DP group, $t[26]=3.42$, $p< 0.002$; EC group, $t[31]=2.04$, $p<0.05$). The antisaccade gap task was also compared with the Go/No-Go task, which revealed that more inhibitory errors were produced in the Go/No-Go task for both groups; However, this difference was only significant for the EC group ($t[31]=-4.26$, $p<0.0001$). The No-Go and Go/No-Go tasks were separated by the largest difference in

the commission of inhibitory errors, as a function of voluntary saccade task and for each group (as illustrated in Figures 3.3). Not surprisingly, paired samples analysis within-groups for this comparison, revealed a highly significant difference for each group (DP group, t[26]=-4.12, $p<0.0001$; EC group, t[31]=-5.3, $p<0.0001$). These findings confirm that the errors do increase across the sequence of tasks presented in Figure 3.3. No-Go and Go/No-Go tasks were separated by the largest estimated degree of working memory demand (No-Go/low; Go/No-Go/high), which was reflected in significant differences in inhibition errors between these tasks for both groups. The No-Go and antisaccade gap task were also significantly different (antisaccade gap/moderate working memory requirement) for both groups, with more inhibition errors created in the antisaccade gap task, which posed a more difficult challenge for the DP group. The DP group generated a large proportion of errors in both the antisaccade gap task and the Go/No-Go task, which resulted in no significant difference between the two tasks, which indicates that the cognitive load of these tasks was high for the DP group.

Paired samples t-tests for the sub-group analyses of simple effects within-groups can be found in Table 3.4 below. An important observation from this analysis was that there are no significant comparisons between any of the voluntary saccade tasks by the DOT group, which corresponds with the finding that there was no trend present in the data for this group.

**Table 3.4** Pair-wise Within-Group Comparisons of Voluntary Saccade Task Inhibitory Errors Corresponding to Figure 3.3

| | Voluntary saccade task pairwise t-test p-value | | |
|---|---|---|---|
| Subgroup | **No-Go** | **Anti Gap** | **Go/No-Go** |
| AD | p< 0.002 | | p< 0.073 |
| DOT | NS | | NS |
| EC | p< 0.05 | | p< 0.0001 |
| AD | p< 0.001 | | |
| DOT | NS | | |
| EC | p< 0.0001 | | |

**Instruction**: Each pairwise comparison corresponds to the extreme ends of the cell and the above heading

The significant paired comparisons for both the AD group and the EC group, are for the No-Go task with significantly more inhibitory errors generated in the antisaccade gap task. At the other side of Table 3.4, less inhibitory errors were generated in the antisaccade gap task than the Go/No-Go task in both groups, this difference was significant within the EC group but only approaching significance for the AD group. The highest significant difference for the proportion of inhibitory errors generated between voluntary saccade tasks within the sub-groups, was at the extreme ends of the graph (Figure 3.3), for the No-Go and Go/No-Go tasks, which were found to be highly significant within-groups for the AD group and the EC group.

#### *3.3.2.2 Relationships Between Voluntary Saccade Performance and Tasks Involving Working Memory*

Spearman's rank correlation coefficients were calculated to assess the hypothesised relationships. Specifically, that 1) Inhibitory errors would be correlated with dementia severity; 2) That AD group performance on voluntary saccade tasks with a high working memory component (i.e. cognitive load), thus requiring more working memory resources, would be correlated with neuropsychological assessments that require working memory due to AD working memory deficit. Therefore, correlations were conducted between inhibitory errors committed during voluntary saccade tasks (i.e. No-Go; Antisaccade Gap; Go/No-Go) clinical rating scales and neuropsychological assessments (scores in Table 3.2).

The correlations for the AD group and the EC group are displayed in Table 3.5 overleaf (the DOT group were omitted from the table for clarity, and will be reported at the end of this section). For the AD group, the EADAS cog clinical rating scale correlated significantly with the No-Go task ($r= 0.492$, $n=17$, $p<0.05$). However, the correlations between AD group EADAS cog scores and the proportion of inhibitory errors on the other two voluntary saccade tasks were found to decrease with voluntary saccade task difficulty. The fact that these correlations were not significant and reduced proportionately according to task difficulty may be an important observation in itself.

**Table 3.5** An Analysis of Relationships Between Voluntary Saccade Task Inhibitory Error and Psychometric Test Scores

| | Elderly controls | | | Alzheimer's disease | | |
|---|---|---|---|---|---|---|
| | No-Go | Anti Gap | Go/No-Go | No-Go | Anti Gap | Go/No-Go |
| **SMMSE** | -0.345 | -0.256 | 0.164 | -0.216 | -0.241 | 0.081 |
| **EADAS** | 0.014 | -0.003 | -0.135 | **0.492*** | 0.388 | 0.234 |
| **Trails A** | 0.337 | 0.12 | 0.323 | 0.148 ‡ | **0.540* ‡** | 0.248 ‡ |
| **Trails B** | **0.410*** | 0.176 | 0.195 | -0.106 § | 0.154 § | -0.109 § |
| **DSF** | -0.114 | 0.033 | -0.016 | -0.313 | -0.344 | -0.049 |
| **DSR** | 0.010 | -0.195 | 0.113 | -0.014 | **-0.625**** | -0.130 |
| **SSF** | 0.297 | 0.122 | -0.136 | -0.170 | -0.296 | -0.285 |
| **SSR** | 0.084 | 0.143 | -0.103 | -0.182 | **-0.571*** | -0.268 |
| **N** | 32 | 32 | 32 | 17 | 17 | 17 |

**Spearman's rank correlation coefficient * Correlation significant at the 0.05 level/ ** Correlation significant at the 0.01level (2-tailed)**

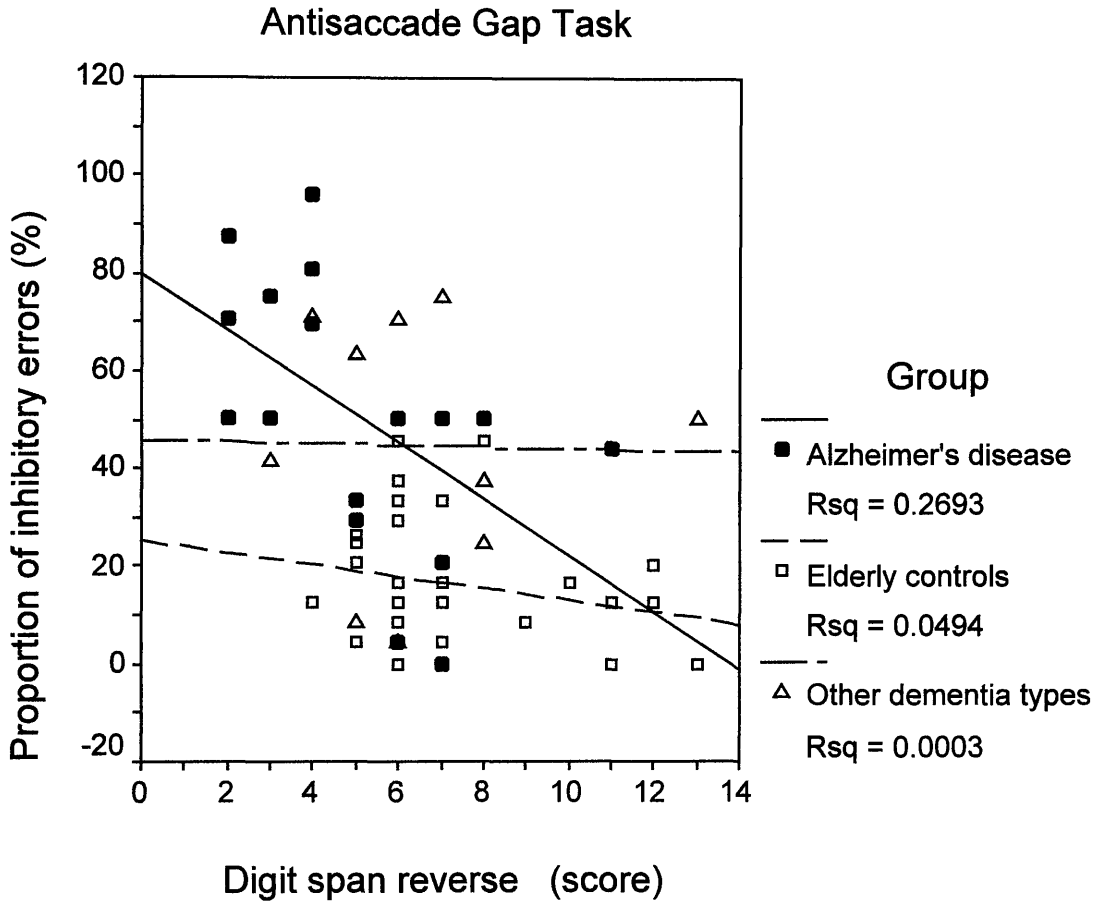
N=16‡; N=11§; N=8†; DSF= Digit Span Forward; DSR = Digit Span Reverse; SSF = Spatial Span Forward; SSR = Spatial Span Reverse

Dementias of other types not included , only significant correlation SSR vs No-Go task (r= .710, n=11, $p< 0.05$).

This finding could indicate that as task difficulty increases, errors increase to a level where *any* relationship with this measure of global cognitive function breaks down, i.e. in the Go/No-Go task, errors were committed whether patients had a high or low EADAS cog score. Digit Span Forwards, which is generally considered to be a test of short-term auditory memory and also attention and concentration was correlated weakly with the No-Go task and the antisaccade gap task (but they failed to reach significance). These results show that focused attention and short-term memory performance do not appear to be related to inhibitory control performance in AD patients. AD group performance on the Trail Making Form A task was found to be significantly correlated with the antisaccade gap task (r= 0.540, n=17, $p<0.05$), which may be due to a dysfunction of attention-shifting and visual search.

A strong significant correlation was also found between the Digit Span Reverse task (scatter plot Figure 3.4) and antisaccade gap task (r= -0.625, n=17, $p<0.01$), and the Spatial

**Figure 3.4** A Scatter Plot Illustrating the Relationship between Alzheimer's Disease Patients' Inhibitory Error During the Antisaccade Gap Task and Digit Span Reverse Test Scores




Span Reverse task was also significantly correlated with the antisaccade gap task (r=-0.571, n=17, $p<0.05$). The Digit Span Reverse and Spatial Span Reverse tasks both load highly on working memory resources and so this finding supports the hypothesis, that in the AD group, performance of neuropsychological assessment tests that require high working memory resources will be related to voluntary saccade tasks that weight highly on working memory resources; due to working memory deficit in the AD group. However, Digit Span Reverse and Spatial Span Reverse were not significantly correlated with either the No-Go or the Go/No-Go tasks. A reduced correlation between these two psychometric tests was expected for the No-Go task, as it does not load highly on working memory. However, the lack of correlation between both the Digit Span Reverse and Spatial Span Reverse tasks and the Go/No-Go task

was not expected. This result may be due to the difficulty of the Go/No-Go task and depleted working memory resources in the AD patient group causing some patients to perform poorly on the task and others to perform well, producing irregular scores and no strong correlations with any of the psychometric tests.

The EC group were found largely to have weak correlations between each combination of neuropsychological assessment and voluntary saccade task, with the exception of one moderate positive correlation between the No-Go task and Trail Making Form B ($r=0.410$, $n=32$, $p<0.05$). Task completion time on the Trail Making Form B test, appears to be associated with the proportion of inhibition errors committed on the No-Go task. The No-Go task requires less working memory resources than the other voluntary saccade tasks, relying more on motor preparation and fixation of a blank space, whilst ignoring a peripheral target. Therefore, this finding may indicate that members of the EC group with relatively poorer psychomotor ability and working memory, as revealed by Trail Making test scores perform less well on the No-Go task.

**Table 3.6** Correlations Between Inhibitory Errors and Psychometric Test Scores for Dementias of Other Types

| | Dementias of other types | | |
|---|---|---|---|
| | **No-Go** | **Anti Gap** | **Go/No-Go** |
| **SMMSE** | -0.520 | 0.012 | -0.436 |
| **EADAS** | 0.619 | -0.061 | 0.128 |
| **Trails A** | 0.619 | 0.377 | 0.235 |
| **Trails B** | 0.270 † | -0.405 † | 0.071 † |
| **DSF** | -0.159 | 0.216 | 0.012 |
| **DSR** | -0.552 | -0.110 | -0.018 |
| **SSF** | -0.466 | 0.111 | -0.199 |
| **SSR** | **-0.710*** | -0.177 | -0.232 |
| **N** | 11 | 10 | 10 |

**Spearman's rank correlation coefficient**
*** Correlation significant at the 0.05 level**
N = 8†; DSF = Digit Span Forward; DSR = Digit Span Reverse; SSF = SpatialSpan Forward; SSR = Spatial Span Reverse

The correlations for the DOT group are reported in Table 3.6. Only one significant correlation was obtained for this group, a moderate association between Spatial Span Reverse - a test highly dependent on working memory - and the No-Go task, r= 0.710, n=11, $p<0.05$), high No-Go inhibition errors being related to low Spatial Span Test scores, which may be simply represent global cognitive impairment, as other correlations were not significant.

Several other correlations were of moderate size for the DOT group, but did not reach significance, for example EADAS cog rating scale and Trail Making Forms A and B with the No-Go; And Trail Making Forms A and B with the antisaccade gap task. Digit Span Reverse produced a moderate correlation with the No-Go task, which grew consistently weaker across the more complex voluntary saccade tasks; which appears to correspond with the reduced error rates in these tasks, compared to those of the AD group (see Figure 3.3). These results appear to indicate impairment of a more diffuse nature and weighing more heavily on processes associated with the No-Go task.

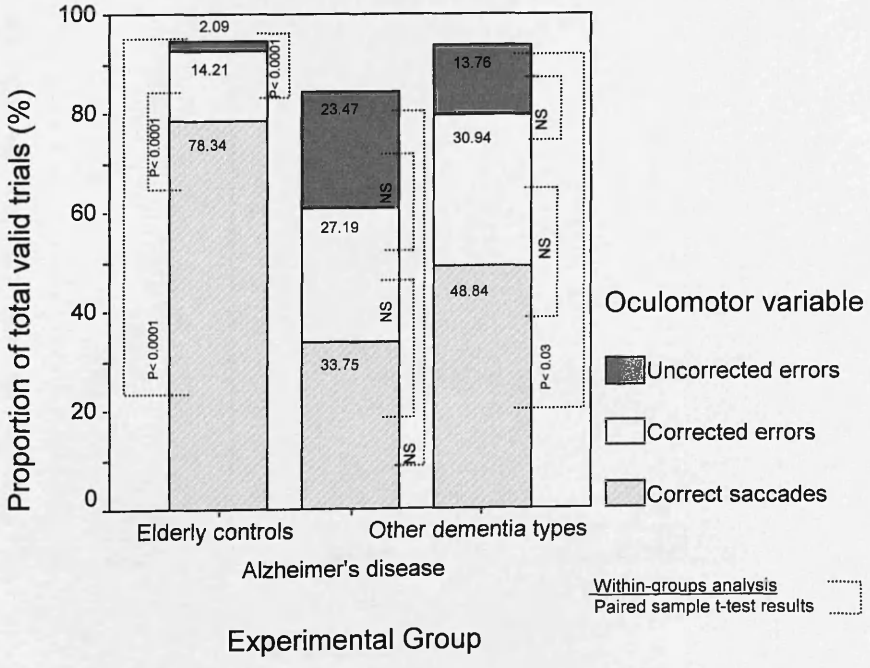
In summary, the most reliable correlations were found for the Alzheimer's disease group, with prominent relationships apparent between the antisaccade gap task and Trail Making Form A, Digit Span Reverse and Spatial Span Reverse. This appears to support the hypothesis that working memory dysfunction in AD will be indicated by relationships between scores on saccadic eye movement tasks and psychometric tests that place a high demand on working memory resources. These measures were not correlated significantly in the EC group, which may indicate that working memory in the EC group was relatively intact, by comparison with that of the AD group. Another observation was that whereas poor AD group scores on psychometric tests generally correspond with high inhibition error rates, the EC group have lower inhibition error rates, but their performance on tests such as Digit Span and Spatial Span is only slightly better than that of the AD group. This suggests that these psychometric tests have poorer resolution in distinguishing between AD and EC participants. Furthermore, the range of tasks may be measuring different aspects of working memory. Correlations of the

DOT group scores on these measures were less strongly correlated, stronger correlations being found between the No-Go task inhibition errors and most of the psychometric scores, indicating a different profile of impairment, to that of the AD group which suggests that perhaps the DOT group had less working memory impairment.

### *3.3.3 Analysis of Corrected and Uncorrected Errors: Self-Monitoring Performance on the Antisaccade Gap Task*

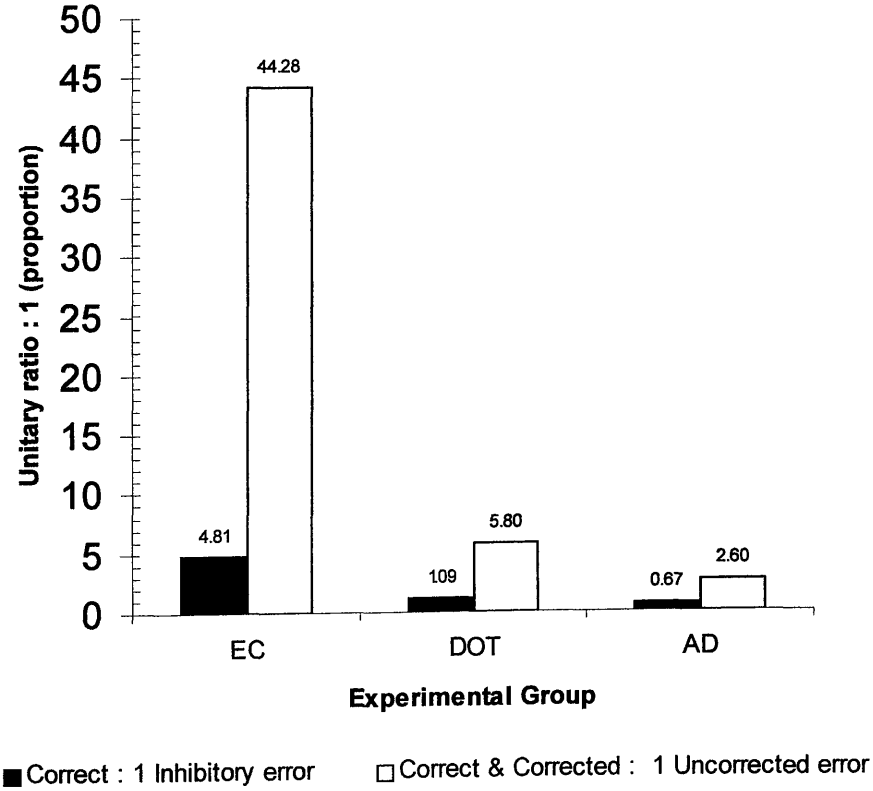
This analysis focuses on the antisaccade gap task at the sub-group level, as inhibitory errors for DPs were investigated in depth in earlier sections. The sub-group proportions of correct saccades are displayed in Figure 3.5, along with the proportions of uncorrected and corrected errors that comprise the proportion of inhibitory errors discussed in Sections 3.3.2.1 & 3.3.3. The proportions of omissions and anticipatory saccades, make up the balance of valid trials are reported in a later section (Section 3.3.3.3).

**Figure 3.5** Stacked Bar Charts Illustrating the Proportions of Correct Saccades, Corrected Errors and Uncorrected Errors by Sub-group for the Antisaccade Gap Task



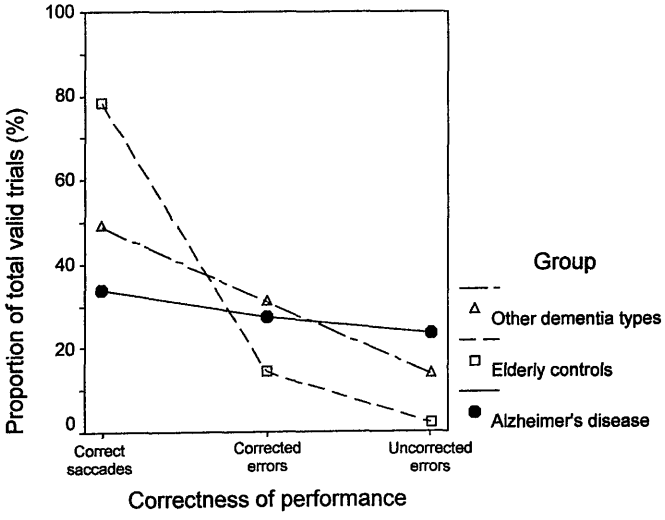
Unitary ratios were calculated for the mean proportions presented in Figure 3.5, to clarify the balance between attention (or awareness), self-monitoring and error correction in the antisaccade gap task. The ratios are displayed as a bar chart in Figure 3.6 below, and are an attempt to visually illustrate clearly the difference between-groups in these abilities. Compared to the AD patient group (2.60:1) and the DOT group (5.88:1), the ratio of correct and corrected error saccades to uncorrected error saccades for the EC group, was found to be extremely large (44.28 : 1). This ratio highlights the difference between the EC group's level of attention or primary conscious awareness and self-monitoring, with the ability to correct mistakes, compared with the significantly lower ratios found for the AD group and DOT group. Unitary ratios of correct saccades to inhibitory errors (uncorrected errors + corrected errors) are also included in the chart for reference and to emphasise the difference between the sub-groups for primary correct action, compared to error.

**Figure 3.6** An Illustration using the Unitary Ratio to Display the Ratio for the Proportion of Correct Saccades to Inhibitory Errors Compared to the Proportion of Correct Saccades+Corrected Error saccades to uncorrected Errors in the Antisaccade Gap Task by Sub-group



To gain an understanding for the spread of data by group for correct saccades, corrected errors and uncorrected errors (in that order), the data were subjected to a two-factor repeated measures mixed ANOVA, forming the factor: *correctness of performance*. Not surprisingly, significant findings were obtained for the main effects of group and correctness of performance, a result expected, as these components correspond with variables already found to be significant in previous between-groups analyses reported in Section 3.3.2.1. The interaction between sub-group and correctness of performance (Figure 3.7) was found to be significant ($F[4,112]=15.81$, $p<0.0001$) suggesting that there were significant differences across the measures by sub-groups. Analysis of the interaction revealed that there was a significant linear trend component with a significant quadratic element ($F[2,56]=9.95$, $p<0.0001$), which indicated that as there were three groups and three measures, the nature of the interaction was fairly complex, but generally indicated a linear decrease in scores across the measures.

**Figure 3.7** Graphs Displaying Correctness of Performance for Sub-groups in the Antisaccade Gap Task




Scheffe post-hoc tests showed that for correctness of performance, no significant differences were present between the EC group and the DOT group ($p>$ 0.1). However, a

significant difference was obtained for the AD group, when compared with both the DOT group and the EC group ($p< 0.01$).

*Within-Groups Effects:* Within-groups analysis on factor correctness of performance, revealed that there was a significant main effect of correctness of performance for the EC group ($F[1.2,33.7]=388.96$, $p<0.0001$; Greenhouse-Geisser correction) and that the DOT group was approaching significance ($F[2,18]=3.33$, $p<0.059$). The main effect of correctness of performance for the AD group, was found to be non-significant ($F[2,32]=0.534$, $p>0.5$ NS).

Trend analysis of correctness of performance, was able to isolate the presence or lack of trends for each sub-group, in the pattern of correct saccades, corrected errors and uncorrected errors, adding to the latter analysis. The EC group was found to have significant linear trend ($F[1,31]=627.46$, $p<0.0001$) and (with a smaller effect size) significant quadratic trend ($F[1,29]=103.01$, $p<0.0001$) components, probably due to the very high proportion of correct saccades compared to errors which flatten out the lower part of the graphs.

No significant trends appeared across the correctness of performance factor for the AD group, as illustrated by the rather flat graph in Figure 3.7, with the low proportion of correct saccades appearing similar to the proportions of corrected and uncorrected errors. However, a significant linear trend was found for the DOT group, across the three levels of the correctness of performance factor ($F[1,9]=6.23$, $p<0.034$).

In summary, the findings indicated (refer to Figures 3.5 & 3.7) that within the AD group patients do not produce significantly different proportions of correct saccades, corrected errors and uncorrected errors, as revealed by the lack of linear trend. In contrast to AD patients, EC participants consistently produced a high proportion of correct saccades with relatively low proportions of corrected errors and a negligible level of uncorrected errors. Therefore, EC participants had a strong linear component due to the high proportion of correct saccades, whereas the low proportions of corrected and uncorrected errors caused an abrupt

tail-off on the graph and also resulted in the presence of a quadratic trend in the data. The DOT group presented with a linear trend across the levels of the factor correctness of performance, due to a moderate correct saccade rate and lessening proportions of corrected errors and uncorrected errors respectively.

Figure 3.5 also has the results from within-groups paired-sample t-tests (comparing paired levels of the factor correctness of performance i.e. correct saccades, corrected errors and uncorrected errors). The paired samples elaborate on the trend analyses and show that the AD group has non-significant differences between any combinations of pairs, hence the lack of any trends found in the trend analysis and the rather flat graph in Figure 3.7. Conversely, the EC group has significantly different (highly reliable) proportions for each combination of pairs in the analysis, due to high correct saccade rate and low inhibitory error rates. For the DOT group however, the proportion of corrected errors increases, resulting in no significant difference from other levels (correct saccades and uncorrected errors); Whereas there is still a significant difference between the proportion of correct saccades (moderate) and uncorrected errors, by virtue of the groups ability to produce relatively fewer uncorrected errors compared to AD group for example. These analyses have demonstrated that trend analysis can differentiate between the sub-groups on the factor for correctness of performance, as set out in the hypotheses.

*Between-Groups Effects:* Between-groups levels of analysis for error type were examined with univariate ANCOVA (controlling for age as a covariate), applied to antisaccade gap task corrected error and uncorrected error data (Table 3.3). Oculomotor variable was the dependent variable and group, independent variable. A significant difference was found between-groups for each analysis, corrected errors ($F[2,55]=3.17$, $p<0.05$) and uncorrected errors ($F[2,55]=8.83$, $p<0.0001$).

Multiple comparisons (Scheffe post-hoc tests) were utilised to examine differences between sub-groups for antisaccade gap task corrected and uncorrected errors. AD patients

produced approximately twice the proportion of corrected errors to that of the EC group (+12.98%), a difference that was approaching significance ($p>0.05$ NS; $d = .8$); therefore, the hypothesis that a significantly higher proportion of errors would be corrected by the AD group, compared to the EC group was not supported on this occasion, although the effect size was large. However, although this finding clearly indicates that the AD group have some capacity to correct errors of inhibition, this is limited, on this occasion to only 53.6% of the total inhibitory errors. Whereas the difference between the EC group and DOT group was significant ($p<0.05$; $d = 1.1$), the DOT group generating more corrected errors than ECs (+16.73%); indicating that the DOT have a greater capacity for error correction, than the AD group as on this occasion the DOT group corrected 69.21% of the total errors of inhibition that they committed.

The uncorrected errors sub-group analysis showed that the AD group created significantly more uncorrected errors with a large effect size in the antisaccade gap task (+21.38%) than the EC group ($p<0.01$; $d = 1.5$). This supports the hypothesis that significantly more uncorrected errors would be committed by the AD group than the EC group, demonstrating that many of the inhibitory errors committed by the AD group remain uncorrected. The DOT group was also found to produce more uncorrected errors than the EC group (+11.69%), but this difference did not reach significance. This is in accord with the previous paragraph and indicates that the DOT group have a better capacity for inhibition error correction, than the AD group.

In summary, the between-groups analysis of corrected errors uncorrected errors revealed a marked difference between the AD group and EC group in the proportion of errors committed and that the DOT group display a similar (but less severe) pattern to the AD (as evidenced in the lack of any significant difference between the two groups). The profile of whether correction is required or initiated or not can be seen most clearly from the trend

analysis which incorporated the proportion of correct saccades. This is measure is crucial, as the AD group commission less correct saccades than both the EC group and DOT group.

### 3.3.3.1 Correlations

Correlations (Spearman's) between antisaccade gap task correct saccades, corrected errors and uncorrected errors, showed several interesting relationships with dementia severity, as measured by the clinical rating scales (Section 2.5, Chapter 2). For the AD group the proportion of correct saccades commissioned was found to be moderately correlated with the CDR ($r=-0.486$, $n=17$, $p<0.05$) and the EADAS cog ($r=-0.505$, $n=17$, $p<0.05$), which indicates that these variables are related to the level global cognitive function and that the ability to generate correct saccades in the AD group was impaired in relation to dementia severity. However, it is interesting to note that the EADAS cog score has a large memory component. These variables, however, did not correlate with the SMMSE, which suggests that this task measures a different array of cognitive functions. No significant relationship was observed between corrected errors and EADAS cog or CDR (both $r = < .3$) for the AD group, although these small correlations did show some limited evidence that lower EADAS cog scores (or CDR) indicate a higher capacity for error correction.

Uncorrected errors committed in the antisaccade gap task were strongly correlated with dementia severity scores on the CDR ($r=0.607$, $n=17$, $p<0.01$) and EADAS cog ($r=0.704$, $n=17$, $p<0.01$). This clearly indicates that as dementia severity increases, uncorrected error also increases, and supports the hypothesis that dementia severity would be related to uncorrected error generation. However, scatter plot evidence showed that although some AD patients produce high uncorrected error rates they still have the ability to generate corrected errors. At stage one (baseline) of the longitudinal analysis, this indicates that AD patients both understand the task and are able to self-monitor their performance which gives support to the hypothesis that corrected error and the ability to monitor performance would be preserved in

the early stages of AD. The most striking correlations for the AD group were found between antisaccade uncorrected error rates and tests which place a large demand on working memory function (Digit Span Reverse, Spatial Span Reverse and Trail Making Form B). The antisaccade gap task uncorrected error rate showed strong correlations with the Digit Span Reverse (r=-0.612, n=17, $p<0.01$), Spatial Span Reverse (r=-0.844, n=17, $p<0.01$) and Trail Making Form B (r=0.494, n=11, $p>0.05$ NS) which just failed to reach significance. These relationships seem to indicate that uncorrected error generation may be related to working memory capacity, or more directly that inhibitory control is related to working memory performance. Additionally, a patient who generates uncorrected errors is more likely to have poor working memory capacity. Finally, there was also a strong correlation between Trail Making Form A and uncorrected inhibitory errors (r=0.737, n=16, $p<0.01$), which suggests a link between lower working memory capacity or visuospatial attention and the generation uncorrected error rates as Trail Making Form A places lower load on working memory.

Correlations for the EC and DOT groups were found to be non-significant in general although interestingly, the DOT group had a significant correlation between the CDR rating and antisaccade gap task corrected errors (r=-0.665, n=10, $p<0.05$), which showed that as dementia severity increased, the ability to correct errors decreased.

#### 3.3.3.2 *Group Comparisons of Inter-saccadic Interval for Corrected Error Saccades in the Antisaccade Task*

The inter-saccadic interval (Table 3.7), resulting when a corrected error is commissioned during the antisaccade gap task (difference between erroneous VGR primary saccade and secondary corrective antisaccade, Section 2.4.3) was analysed with ANOVA for the DP and EC groups.

**Table 3.7** The Inter-saccadic Interval for Corrected Errors in the Antisaccade Gap Task

| | Antisaccade Gap Task | | |
|---|---|---|---|
| **Group** | Mean | SD | N |
| **Dementia patients** | 257.88 | 85.09 | 25 |
| **Elderly controls** | 205.96 | 72.13 | 28 |
| **Alzheimer's disease** | 269.96 | 82.89 | 16 |
| **Other dementia types** | 236.41 | 89.59 | 9 |

This analysis revealed, that the DP group inter-saccadic interval was significantly prolonged by comparison to the EC group (+ 51.92 msecs. F[1,51]=5.78, $p< 0.02$; $d = .7$).

Sub-group analyses found a significant difference between-groups (F[2,50]=3.42, $p<0.041$), multiple comparisons (Scheffe) revealed that the inter-saccadic interval for the AD group was significantly prolonged (+64.0 msecs.) compared with that of the EC group ($p<0.05$; $d = .8$). However, no significant difference was found between the DOT and EC groups. These results support the hypothesis, that the inter-saccadic interval for corrected errors would be significantly prolonged for the AD group, compared with the EC group. This could indicate that there is a disturbance in the processing of the error signal, which is reliant on executive function, a component of higher cognition believed to be depleted in working memory deficit.

### *3.3.3.3 Omissions and Anticipatory Saccades*

The DP group produced a higher proportion of omissions[11] than the EC group in both the reflexive gap and antisaccade gap tasks. However, univariate ANOVA (controlling for age as a covariate) revealed that there were no significant differences between the DP group and the EC group for omissions in the antisaccade gap task (DP, 8.34%; EC, 3.02%; F[1,56]=1.351; $p>0.2$ NS) or the reflexive gap task (DPs, 4.93%; ECs, 4.43%; F[1,57]=0.353; $p>0.5$ NS).

[11] Trials in which no saccade was produced, fixation remaining at the central location 0°.

A higher proportion of anticipatory saccades[12] was found to be generated by the DP group compared with the EC group, in the antisaccade gap task (DP group, 3.89%; EC group 2.37%), but these marginal differences were found to be non-significant using univariate ANOVA ($F[1,56]=1.98$, $p>0.1$ NS). The EC group produced a higher but negligible proportion of anticipatory saccades in the reflexive saccade gap task (DP, 2.41%; EC, 3.68%), this difference found to be non-significant ($F[1,57]=0.195$, $p>0.6$ NS).

## 3.4 Discussion

### 3.4.1 Key Findings

Present study has revealed a number of key findings, which can be summarised as follows:-

1. Voluntary saccade task inhibitory errors were measured across the range of tasks in accord with a putative increase in working memory demand by task (No-Go < antisaccade gap > Go/No-Go) comparing the data between and within-groups. Between-groups analyses of sub-groups on voluntary saccade task, revealed that the AD group and other dementia patient group were significantly different from the EC group, but not from each other. However, within-groups trend analyses revealed a significant *linear trend across the tasks* (as ordered above) for the AD group and for the EC group, but no significant trend for the DOT group.

2. Analysis of relationships between voluntary saccade tasks and neuropsychological assessments that rely on working memory, revealed that the AD group produced strong correlations between the Digit Span Reverse task and the antisaccade gap task, and also between Spatial Span Reverse and the antisaccade gap. Trail Making Task A which is less dependent on working memory

[12] Saccade initiated <80 msecs. after target presentation.

resources, was also strongly correlated with the antisaccade gap task. The EC group showed only small correlations (non-significant) between tasks requiring working memory, whereas the correlations for DOT group, were only small and not significant for these tasks.

3. Correctness of performance was examined by analysis of the proportions of correct saccades, corrected errors and uncorrected errors in the antisaccade tasks. Sub-group analysis revealed that this factor could distinguish between AD group from both the EC group and the DOT group. Trend analysis showed that AD patients have no trend to the factor correctness of performance, whereas the EC group and DOT group have a significant linear trend to the data from these measures. Uncorrected error rates on the antisaccade task are strongly correlated with tasks that require working memory and are also related to dementia severity.

4. A further line of enquiry for the antisaccade gap task was the inter-saccadic interval, derived from the corrected error saccade latency and its comparison between-groups. This measure was found to significantly prolonged for the AD group compared to controls, but was unable to dissociate between dementia sub-groups at stage one of the longitudinal analysis.

5. Differences between-groups in proportions of omissions and anticipatory saccades in the antisaccade gap task were found not to be significant.

The primary goal of this study was to conduct a thorough analysis of error rates in the voluntary saccade tasks (No-Go, antisaccade gap and Go/No-Go), with the aim of investigating the locus of the deficit that causes error in AD. The main area of enquiry was voluntary saccade inhibitory error rate, which was analysed to examine the notion that the principal

underlying problem involves a working memory deficit and furthermore, to establish whether a suitable measure of this component will dissociate between AD, other forms of dementia and healthy ECs.

### 3.4.2 Inhibitory Error Across Voluntary Saccade Tasks and Relationships with Neuropsychological Assessments Requiring Working Memory

Inhibitory error rates were assessed across the voluntary saccade tasks between-groups and within-groups, in an attempt to establish whether the underlying mechanism of inhibitory error in AD is due to a working memory deficit and furthermore, whether this deficit would be detectable via the range of voluntary tasks. Moreover, as discussed in the introduction (Section 3.1) the basis of inhibitory control has long been a source of debate. Therefore, this clinical study could contribute to the understanding of mechanisms underpinning inhibitory control. Should an increase in AD inhibitory errors be found to correspond with greater voluntary saccade task complexity and those inhibitory errors be related to poor performance on neuropsychological assessments that depend of working memory function, then this may provide an important link between working memory and inhibitory errors.

At the between-groups level of voluntary saccade task, which incorporated all three tasks, the finding that the between-groups level of analysis could distinguish between-groups was informative, but this was not carried through to sub-group differentiation of AD and other dementias. Nonetheless, the results were in support of the hypothesis that AD patients would create significantly more inhibitory errors than the EC group in corresponding tasks ranging across voluntary saccade task difficulty and confirms that the AD group do have a dysfunction of inhibitory control which is found to increase linearly across tasks with increasing working memory load. Within-groups trend analysis further reinforced these results, the factor of voluntary saccade task being highly significant for the AD group, but not for DOT group indicating that the DOT group produced less inhibition errors in oculomotor tasks that were highly demanding of working memory resources. However, the factor voluntary saccade task

was significant for the EC group (Figure 3.3) showing a linear trend but with significantly less errors across the range of tasks than the AD group. Therefore, this result again confirmed significant changes across the tasks for the AD and EC group, the trend analysis confirming that the profile of the data for both groups fitted a highly significant linear trend with the simpler task resulting in the least inhibitory errors through to the more difficult Go/No-Go task producing the most inhibitory errors. Thus, the hypothesis was again supported for the AD and EC groups, that there would be a significant and increasing shift in the number of inhibition errors generated in the oculomotor task that requires relatively little working memory through to an oculomotor task that demands a high degree of working memory. Moreover, further pair-wise tests (Table 3.4) within-groups analysing the trend for each group, confirmed a consistent difference between the pairs of tests in the majority of cases for the AD and EC group. Interestingly, no such differences existed for the DOT group as they performed much the same at each task which seems to indicate that the DOT group comprised patients with a range of cognitive deficit and ability, that results in performance being affected fairly evenly on tasks ranging in cognitive load. Most significantly, the hypothesis that AD group performance on voluntary saccadic eye movement tasks would result in proportionate increases of inhibitory error according to task demand and that this increase would be significantly higher than healthy elderly controls was strongly supported by detailed analyses.

Analysis of correlations between scores from neuropsychological assessments that require working memory and inhibitory error rates from the voluntary saccade tasks, were assessed to explore relationships that may suggest deficient working memory in AD patients. Strong and significant correlations revealed relationships between antisaccade inhibition errors and the Digit Span Reverse task (i.e. high inhibition errors = low Digit Span Reverse score. Trail Making Form B was not strongly correlated with any voluntary saccade task, but Trail Making Form A was on both antisaccade tasks. It is interesting to note that only eleven AD patients were able to complete Trail Making Form B, indicating the difficulty that patients had

with this task (the eleven patients scored poorly also). Performance was poor on Form A of the Trail Making Task, but only one AD patient failed to complete this task. Therefore, it can be argued that the Trail Making Form B resulted in a flooring effect, whereas Form A was also difficult for patients resulting in elevated scores, but they could at least complete this task. The Spatial Span Reverse was also moderately correlated (but failed to reach significance) with antisaccade inhibitory errors (high inhibitory errors = low Spatial Span Reverse score.

Interestingly, the AD group scores on the EADAS cog clinical rating scale, were found to be significantly correlated with No-Go task inhibition errors, examination of the scatter plot revealing that dementia severity and No-Go task inhibition errors increased correspondingly. However, proportionately weaker correlations were found between the EADAS cog and the more demanding oculomotor tasks. One explanation for the reduction in correlation strength with voluntary saccade task cognitive demand, (according to the scatter plots) is that antisaccade task inhibitory error rates appear to become worse as a whole for the AD group, with little association to EADAS cog scores. This pattern was even more severe for the Go/No-Go task. These findings appear to signify that inhibitory control will be impeded in these tasks, regardless of dementia severity. A further explanation, is that the lack of association is due to the EADAS cog test being a global measure of cognitive function, which also relies heavily on measures of orientation, recall memory and recognition memory and not working memory. Thus, there is no association between inhibition errors - which are hypothesised to be due to working memory deficit – because the EADAS cog task does not measure working memory, but a range of other faculties that result in variation in the relationship with inhibitory errors. There was a distinct lack of significant correlations for the same measures in the EC group and the DOT group, probably due to a ceiling effect on the EADAS cog test for the EC group and lower inhibition errors, whereas the DOT group appeared to vary in the abilities, perhaps due to the heterogeneity of this group.

Strangely, none of the correlations of the Go/No-Go task inhibition errors with neuropsychological assessments were even moderate in size. It is evident that the Go/No-Go task resulted in the highest proportion of inhibition errors for each group, but it appears that the Go/No-Go task may have caused difficulty or confusion for some AD patients, as the scores were distributed unevenly on the scatter plots without the usual uniformity and linearity for moderate/strong correlations. Therefore, perhaps the cognitive load of the task was too taxing for meagre working memory resources of the AD group. Evidence in support of a working memory dysfunction in the AD group was demonstrated by the results of the Trail Making Form B test (Section 2.5.6). Only eleven of the AD patients were able to complete the task, showing that poor working memory in eight of the patients may have contributed in their ability to participate. Analysis of task completion times for the eleven AD patients who were able to complete the task, revealed a significant difference between the AD patients and healthy elderly controls, AD patients taking significantly longer to carry out the task ($P< 0.01$ Scheffe). In actual fact, the DOT the EC groups also produced scatter plots with a distinct lack of uniformity for the Go/No-Go task inhibition error rates with neuropsychological assessments. The longitudinal chapter of this thesis will revisit this issue.

In Section 3.3.2.1, inhibitory errors were compared across the tasks: No-Go, antisaccade gap and Go/No-Go. Each of these tasks requires volitional control of action and it was argued, that working memory is the principal cognitive mechanism for the facilitation of efficient performance on voluntary tasks that require manipulation of instructions, inhibition of primary prepotent responses and the generation of motor action. Taken together, the findings from this section for the AD group appear to support the hypothesis that inhibitory errors result from a depletion of working memory resources, as evidenced by the increase in errors of inhibition across the range of tasks and corresponding correlations with poor scores (diminished working memory) on tasks requiring working memory. This finding maps onto studies that have demonstrated that depleted working memory resources, results in increased

errors of inhibition of prepotent response(Mitchell et al., 2002; Roberts et al., 1994; Stuyven et al., 2000) and can be applied to the model of Roberts et al. (1994).

### 3.4.3 Correctness of Performance: Corrected and Uncorrected Errors the Capacity for Self-Monitoring

Inhibition errors were examined more closely in Section 3.3.3.1, with the analysis of corrected error and uncorrected error components in comparison with the proportion of correct saccades to form the factor: correctness of performance. Obviously, these three aspects are important in the search for a sensitive profile of oculomotor behaviour in AD, as variation in the proportion of correct saccades denotes an increase or decrease in erroneous activity. Furthermore, analysis of error correction is important, as it represents the capacity for self-monitoring.

In the first instance, unitary ratios were calculated to indicate primary conscious awareness and self-monitoring in the ability to correct mistakes. The unitary ratios were thus derived from the addition of the proportion of correct saccades[13] to the proportion of corrected errors over the proportion of uncorrected errors (lack of awareness/self-monitoring). The ratio of collapsed correct and corrected actions (ability to correct) to uncorrected action, was very in high in the EC group, compared with that of the AD and DOT groups (the AD group having the lowest ratios) which indicates that the EC group had a much higher capacity for conscious awareness and self-monitoring. Additionally, this may also mean that the EC group simply had a more efficient inhibitory control and working memory system.

The hypothesis that mild ADs would have preserved capacity to generate corrected errors and that this proportion of corrected errors would be significantly higher than in the EC group approached significance, whereas the proportion of corrected errors for the DOT group was found to be significantly higher than that of the healthy elderly control group. The

[13] Proportion of total valid trials.

hypothesis that the AD group would generate significantly higher proportions of uncorrected errors than the EC group was also supported, but no significant difference was found between the DOT group and healthy elderly controls. Within-groups paired samples analysis of corrected and uncorrected errors, revealed that although both AD patients and the DOT group produced higher proportions of corrected errors compared to uncorrected errors, the proportions of these two error types did not differ significantly from one another within dementia sub-groups.

These results show that AD patients in the present study were able to generate corrected errors, the proportion of which did not differ significantly to that of healthy controls. However, many AD patient inhibition errors remain uncorrected, whereas healthy elderly controls generate significantly lower proportions of uncorrected errors than AD patients. Thus, the overall requirement for any correction by the EC group is significantly reduced compared with the AD group, by virtue of the EC group's ability to generate correct antisaccades. Therefore, AD patients were found to be significantly impaired in the capacity for error correction, compared to elderly controls.

These findings correspond with the unitary ratios that measured primary conscious awareness and self-monitoring. Importantly, possibly relative to efficient working memory, the EC group carried out the task with comparative efficiency, generating a significantly higher proportion of correct saccades (compared with ADs) and correcting the vast majority of inhibitory errors, leaving only 2.1% of inhibitory errors uncorrected. Thus, the EC group can 1) maintain the task instructions in mind efficiently enough to, 2) perform capably on the task, and 3) self-monitor activity, so as to take corrective action as and when necessary. However, the AD group produced significantly less correct saccades than the EC group, created more corrected errors (approaching significance), but failed to take corrective action for a significantly high proportion of erroneous saccades that remained uncorrected. Therefore, in comparison to the EC group, it appears that the AD group 1) are able maintain the task

instructions in mind, but 2) perform the task poorly, and 3) self-monitor activity so as to rectify some inhibitory errors, but do not perform corrective action reliably as and when required. Thus, error correction in early AD patients, shows some preservation but in the main is dysfunctional when uncorrected errors are accounted for.

Correctness of performance was used in an attempt to include the vital measures (correct saccades, corrected errors and uncorrected errors) discussed in the previous paragraphs. This factor was found to be a useful method of assessing the inhibitory error and error corrective behaviour of AD patients and other groups, on the antisaccade task. The AD group was found to have a significantly lower magnitude of correctness of performance compared with both the EC group and the DOT group. Within-groups, the factor was found to be significant for the EC group and approaching significance for the DOT group, thus indicating significant differences between the component levels/measures of the factor. However, the AD group was not found to be significant on the correctness of performance, revealing no significant differences between the factor levels. These findings were further confirmed by trend analysis, which revealed the profiles for each sub-group, the EC group having a highly significant linear trend and a less significant quadratic component (both antisaccade tasks), the DOT group having significant linear trends for each task and the AD group having no trends, due to the levels of the factor correctness of performance being fairly balanced. Trend analysis of the combination of correct saccades, corrected errors and uncorrected errors appears to be a quite a reliable indicator of AD and seems not to have been conducted in the only previous study of corrected errors and uncorrected errors in AD (Abel et al., 2002). Follow-up analyses of the profiles for corrected errors and uncorrected errors with proportion of correct saccades, will be carried out in the longitudinal chapter of this thesis.

Further analysis, using correlations found that AD severity was related to the ability to generate correct saccades in the antisaccade gap task, however corrected errors was not related to dementia severity. Uncorrected errors were also found to be significantly correlated with

measures of dementia severity. Most importantly, strong correlations were found between uncorrected errors and neuropsychological assessments that require working memory for efficient task performance.

Analysing the constituent parts of inhibitory error and finding weaker correlations with corrected errors, isolated the most vulnerable attribute of AD, the uncorrected error proportion in the antisaccade task and by implication, working memory as uncorrected errors are generated through inhibitory dysfunction and the notion that inhibitory control sub-serves executive function in working memory. In addition to this, there are implications for self-monitoring capacity as working memory is dysfunctional. Why do such a high proportion of inhibitory errors remain uncorrected in AD patients?

There are a number of possible explanations that could plausibly account for the high rate of uncorrected errors in the patients early AD. Firstly, errors that remain uncorrected may result from a dysfunction in the capacity for self-monitoring and error correction. This could result from a disturbance in the ACC and or the DLPFC and pathways connecting with parietal cortex (Garavan, Ross, Murphy, Roche & Stein, 2002; Kiehl et al., 2000; Menon et al., 2001; Schall, Stuphorn & Brown, 2002) i.e. the uncorrected errors are unrecognized or unchecked.

An alternative explanation could be that uncorrected errors are due to the depletion of working memory resources found in the AD group. In the present study, the AD group were found to perform significantly worse than controls on the Spatial Span Reverse, Digit Span Reverse and Trail Making Form B tasks, which all place high demands on working memory resources. Therefore, as the antisaccade task represents a high cognitive load for AD patients, as indicated by the high overall inhibitory error rate, a high proportion of inhibitory errors remain uncorrected. This explanation could also have some overlap with the first explanation in that task which load heavily on working memory have the potential to impede self-monitoring and error correction.

Previous research in healthy individuals has shown that fixations of a stimulus are usually recognized if they are longer than 140 msecs. (Mockler & Fischer, 1999), so are there any further explanations for what was happening with the dementia patients? It is conceivable, that AD patients could have great difficulty in generating a saccade to an empty location, when a visual stimulus is already fixated. Therefore, a third explanation for uncorrected errors, is that errors could remain uncorrected due to disruption of fixation cells in the SC (Dorris & Munoz, 1995; Munoz & Wurtz, 1992, 1993a, 1993b), causing inhibition of the SC movement cells and thereby impeding error correction. This third argument will be further explored in Study II (Chapter 4), where the fixation offset effect (FOE) will be examined. If it is found that the magnitude of FOE was greater for the AD group, then this would support the argument that when an uncorrected error is generated by AD patients in the antisaccade gap task, they have difficulty in disengaging fixation from the already fixated visual stimulus in order to execute a saccade to an empty location.

### 3.4.4 Inter-saccadic Interval for Corrected Error Saccades in the Antisaccade Task

Section 3.3.3.2 analysed the inter-saccadic interval that accompanies the corrected error in the antisaccade task. The measure at this stage (stage one) of the longitudinal analysis showed that the inter-saccadic interval measure could distinguish between the DP group and EC group, DPs having a prolonged inter-saccadic interval. At the sub-group level of analysis, the AD group had an antisaccade corrected error inter-saccadic interval that was significantly prolonged compared with the EC group, but this measure was unable to distinguish between the AD and DOT groups although the DOT group did not differ significantly on this measure from the EC group. This measure may prove interesting in the latter stages of the longitudinal study, as reprocessing time for primary antisaccades, has been found to deteriorate in healthy controls with normal ageing (Olincy, Ross, Young & Freedman, 1997). Therefore, this deterioration may be more pronounced in AD patients compared to controls, and map onto the

inter-saccadic interval for the corrected error saccade. The initiation of the corrective saccades depends on the integrity of numerous pathways in the prefrontal and parietal cortex of the brain. Executive function also depends on circuitry in these regions and therefore, disturbance of these pathways may be related to working memory deficit and ultimately inhibitory dysfunction in the AD group. A more thorough discussion of the neuroanatomical considerations that relate to these findings are addressed in Chapter 9.

No significant differences were found between the groups for other error components in the antisaccade task for this stage of the longitudinal project. Therefore, this study has found contrasting results for anticipatory saccade rates in early AD, compared with the findings of some other studies that indicated high proportions on this variable (Abel et al., 2002; Hotson & Steinke, 1988). This may indicate that the patients in the present study derived a benefit from the pre-test training with the clinical ('bedside') eye movement test, the temporal and spatial characteristics of the experiment and structure of the procedures. Alternatively, the two studies mentioned above both employed predictable target direction, whereas in the present study target direction was randomised. Therefore it is plausible to argue that patients with early AD may anticipate the target if the experiment presents the target in an expected location i.e. if patients are aware of where the target will be which could be related to 'preparatory set' and pre-stimulus activity in the SC (Everling et al., 1998a). However, when direction is unpredictable, as in the present study, fixation and inhibitory control is enhanced, until the target appears.

Further discussion of these findings to include theoretical and neuroanatomical implications is reviewed and deliberated in Chapter 9, the General Discussion of this thesis.

## 3.5 Conclusions

- The present study examined inhibitory control by measuring error rates in voluntary saccade tasks and replicated previous findings of poor inhibitory control in Alzheimer's disease, which was found to be correlated with dementia severity and other neuropsychological measures.

- Alzheimer's disease patient inhibition errors are significantly reduced for voluntary saccade tasks with a low cognitive load compared with tasks of higher cognitive load. Moreover, relationships are found between inhibitory error rates in the antisaccade gap task and psychometric tasks that require working memory.

- It is feasible to argue that working memory and inhibitory control are closely related and that depleted working memory resources as in Alzheimer's disease, appears to result in a lack of goal activation which results in compromised visual attention i.e. capacity to inhibit prepotent response in accordance with the Roberts et al. (1994) methodology.

- Correctness of performance is most usefully analysed by trend analysis, revealing a lack of trend in the profile of Alzheimer's disease patients on the antisaccade gap task variables of correct saccades, corrected errors and uncorrected errors.

- Whilst some capacity for error correction is preserved in early Alzheimer's disease when performing the antisaccade task, a significant proportion of erroneous trials remain uncorrected. These uncorrected errors are significantly related to tasks that require working memory and furthermore, are related to dementia severity. Therefore, it is plausible to argue, that uncorrected errors result from dysfunctional working memory and/or a corresponding self-monitoring deficit. However, it is possible that the error correction deficit may be related to a disruption of fixation neurons in the FEF or SC. This would cause inhibition of movement cells producing a fixation disengagement deficit, thereby impeding error correction. Study II should examine this possibility by examining the fixation offset effect in AD.

# Chapter Four

## Study II: Magnitude of Fixation Offset Effect in Alzheimer's Disease

## 4.1 Introduction

The human oculomotor system generates eye movements that serve to foveate objects for high resolution visual processing. When an object of interest is foveated, the eyes maintain fixation via the fixation reflex (Table 1.1, p. 9). Fixation can be defined as the controlled focus of gaze on a stationary target. Gaze-holding of a stationary target is relatively undemanding of the cognitive system and deficits observed during fixation are not essentially the result of higher cognitive dysfunction. Fixation impairments can be induced by lesions to various areas of the brain, which include the cerebellum, FEF, DLPFC, SMA, inferior parietal lobule, basal ganglia and the SC (Anderson et al., 1994; Leigh & Zee, 1999; Petit et al., 1999). The brain activity of healthy humans during fixation has been shown by neuroimaging studies to involve largely frontal regions in the facilitation of fixation control. These include the SEF, cingulated cortex, precentral gyrus and prefrontal cortex (ventromedial and anterolateral) (Anderson et al., 1994; Petit et al., 1999).

A crucial aspect of fixation is the ability to suppress eye movements that can direct the fovea away from a given location. Inhibitory control formed the basis of Study I, in Chapter 3, and the fundamental processes that enable and initiate inhibitory control of saccades are generated by a mechanism that incorporates opponent neural processes in the SC (Büttner-Ennever & Horn, 1997) as described in Section 1.4.1.2. This mechanism facilitates high-speed interchange between saccade and fixation, thereby enabling the eyes to move toward objects of

interest and then maintain fixation. Thus, these opponent processes have the capacity to activate and inhibit the VGR. When and where the eyes move is enabled by *fixation cells* and *movement cells*. Research has revealed that neurons (fixation cells) in the rostral pole of the SC are active throughout fixation and that their activation is increased when the eyes are fixated on a target. The fixation cells are able to inhibit movement cells. The movement cells are located caudally to the rostral pole neurons and assist with movement of the eyes, but can be inhibited by the fixation cells (Machado & Rafal, 2000b; Munoz & Istvan, 1998; Munoz & Wurtz, 1993a, 1993b; Wurtz & Munoz, 1995), hence the term opponent neural processes.

The VGR (visual grasp reflex - discussed in Sections 1.2 & 1.3.1) is activated when an exogenous event occurs abruptly in peripheral vision, resulting in an involuntary action (reflexive saccade) followed by the maintenance of gaze with the fixation reflex. Endogenous control of fronto-nigral-collicular circuitry enables inhibition of the VGR and fixation reflexes and thereby the production of voluntary saccades (Burman & Bruce, 1997; Everling et al., 1998a). However, voluntary control of saccadic eye movements may be disturbed if these circuits are damaged. For example, as discussed in Chapter 1, damage to the frontal cortex in adults has been found to impede suppression of the VGR (Guitton et al., 1985; Pierrot-Deseilligny et al., 1991b; Rafal et al., 2000).

The properties of visual stimuli used for presentation during eye movement tasks have a crucial bearing on the saccadic and behavioural measures under investigation. The temporal, spatial, and luminance characteristics as well as the number of visual stimuli, can have a direct effect on the programming of eye movements elicited during a given paradigm. Saccade latency and amplitude will be modulated within certain parameters and inhibitory errors are found to be more prevalent under certain experimental conditions (e.g. Reflexive saccade, No-Go or antisaccade tasks; see Chapter 3). Therefore, intra-saccadic visual processing is influenced by pre-saccadic events (Anagnostou & Skrandies, 2001). For example, when stimulus luminance is of higher intensity (e.g. above 10 cd/$m^2$), saccade latency is found to be

reduced as compared with less intense targets which cause latency to be increased (Crawford, 1996; Reuter-Lorenz, Hughes & Fendrich, 1991). Furthermore, displaying two targets simultaneously or sequentially modulates saccade metrics (amplitude), causing an effect referred to as the global or centre-of-gravity effect. This results in an averaging of the ensuing saccade, where the saccade lands at an intermediate location between the two targets (Becker & Jürgens, 1979; Coren & Hoenig, 1972; Crawford & Higham, 2001; Findlay, 1982; Ottes, Van Gisbergen & Eggermont, 1984). Moreover, a visual stimulus presented simultaneously or overlapping temporally with the target of interest, has been found to mediate a high magnitude of inhibitory effect; Observed as an increase in saccade latency, most prominently when located in the central foveal region of the visual field. Interestingly, these effects - referred to as the remote distractor effect - are also observed to occur by varying degrees, when the remote distractor is located in the wider regions of the visual field (Walker et al., 1997), causing the latency for reflexive saccades to the intended target to be prolonged. Walker et al. (1997) suggest that the remote distractor effect is related to the inhibitory processes facilitated by the rostral pole of the SC.

The focus of the present study was to investigate a phenomenon referred to as the fixation offset effect (FOE), and to examine the magnitude of this effect in dementia patients. The FOE involves inhibitory processes and produces effects similar to those described by Walker et al. (1997). Saslow (1967) was the first to describe a reduction in reaction time to peripheral targets, afforded when the fixation point is extinguished prior to target onset. The FOE, also referred to as the gap effect, is demonstrated by a reduction in saccadic latency resulting from the offset of a fixated central visual stimulus preceding (up to 400msecs.) a peripheral target. This is compared with the saccadic latency resulting from tasks were the central fixation stimulus remains visible (overlaps) with the appearance of a peripheral target, in which saccade latency is prolonged. Interestingly, Walker et al. (1997) found that the

magnitude of the remote distractor effect was optimal when the distractor was situated in the central location.

The FOE has been investigated extensively in both prosaccade and antisaccade paradigms (Fischer & Weber, 1992; Klein, 1977; Machado & Rafal, 2000a; Machado & Rafal, 2000b; Reuter-Lorentz, Oonk, Barnes & Hughes, 1995; Reuter-Lorenz et al., 1991) and research has indicated that the FOE is due not the accrual of sensory information (i.e. warning effects from the central fixation point offset), but to the motor aspects of saccade generation, i.e. the programming or execution of saccades (Forbes & Klein, 1996). A number of possible mechanisms have been postulated to produce the FOE, including oculomotor readiness with the fixation mechanisms of the SC (Kingstone & Klein, 1993; Reuter-Lorenz et al., 1991; Tam & Stelmach, 1993), facilitated sensory processing (Reulen, 1984) and attentional disengagement involving the parietal cortex (Fischer & Breitmeyer, 1987; Kawakubu, Maekawa, Itoh & Iwanami, 2002; Posner, Walker, Friedrich & Rafal, 1984).

Neurophysiological research has provided evidence of a neural correlate for the FOE (Dorris & Munoz, 1995). Studies have shown that the benefit of fixation offset on saccade latency is due to a reduction in fixation cell activity and subsequent disinhibition of the VGR by an increase in movement cell activity in the SC on the appearance of the peripheral target (Machado & Rafal, 2000b). Thus, offset of the fixation point reduces activity of fixation cells, decreasing saccade latency (Dorris & Munoz, 1995), whereas, if the fixation point remains on (temporally overlapping with the target), disengagement of fixation from the target will be delayed somewhat due to fixation cell activity and inhibition of the VGR.

According to the argument outlined in the previous paragraph, in the case of exogenous reflexive saccades, fixation (and thereby attention) is disengaged automatically from the central fixation point on the abrupt appearance of a peripheral target. However, for voluntary saccades volitional control can intervene with this process and initiate inhibitory processes to inhibit the VGR and carry out goal-driven tasks providing that working memory resources are

not depleted and therefore executive control undiminished (in agreement with the hypotheses of Chapter 3).

Recent event related potential (ERP) studies have revealed that a number of neural correlates contribute to the FOE, including prefrontal preparatory processes preceding target appearance, enhancement of cortical visual response in gap trials and prolongation of parietal activity in the overlap condition compared with that of the gap condition, prior to saccade execution (Csibra, Johnson & Tucker, 1997). Kawakubu and co-workers (Kawakubu et al., 2002) discovered that target-locked ERPs in the gap task induced automatic processing of attentional disengagement, activity appearing some 60 msecs. prior to onset of the target stimulus. Saccade-locked ERPs showed that pre-saccadic activity appeared earlier and higher in the overlap condition, compared to the gap condition. Thus, it appears that cerebral processing of attentional disengagement can be dissociated by the existence of a temporal gap in saccadic eye movement paradigms.

It has been found that the magnitude of FOE in the antisaccade paradigm is smaller than that found in reflexive saccade paradigm (Reuter-Lorenz et al. (1991) found no significant antisaccade FOE). There is debate about the source of the smaller magnitude FOE in antisaccade tasks. Forbes and Klein (1996) hypothesised that the reduction is due to inhibitory processes required to suppress the VGR, in order to produce an antisaccade correctly, i.e. the FOE is lost during the prolonged latency incurred during antisaccade tasks, caused by the extra processing time brought about by inhibiting the peripheral stimulus and implementing the task instructions. However, Machado and Rafal (2000a) found that in a Go/No-Go task interleaved with a Go/antisaccade task (using both gap and overlap tasks) the FOE was larger in the Go/No-Go task. Given that the Go/No-Go task and the antisaccade task are similar, in that they both require inhibition of the VGR, Machado and Rafal suggest that the reduction in magnitude of FOE in the antisaccade task may not be sufficiently explained by the requirement to inhibit the VGR alone. Furthermore, Machado and Rafal (2000b) postulate that the FOE is

dependent on strategic set and can thus be modulated by the individual, in both reflexive and antisaccade tasks, which appears to correspond with the ERP evidence mentioned above. Machado and Rafal also hypothesise that involuntary and voluntary saccade FOEs depend on activity in separate fixation cell systems. The FOE for reflexive saccades being dependent on fixation cells in the SC and the antisaccade FOE dependent on fixation cell activity in the FEF (Section 1.4.2.1), emphasising cortical control over the SC. Given the reciprocal connections between the FEF and SC and the PEF (and intraparietal areas) and SC, these suggestions seem to map onto the ERP evidence for attentional disengagement.

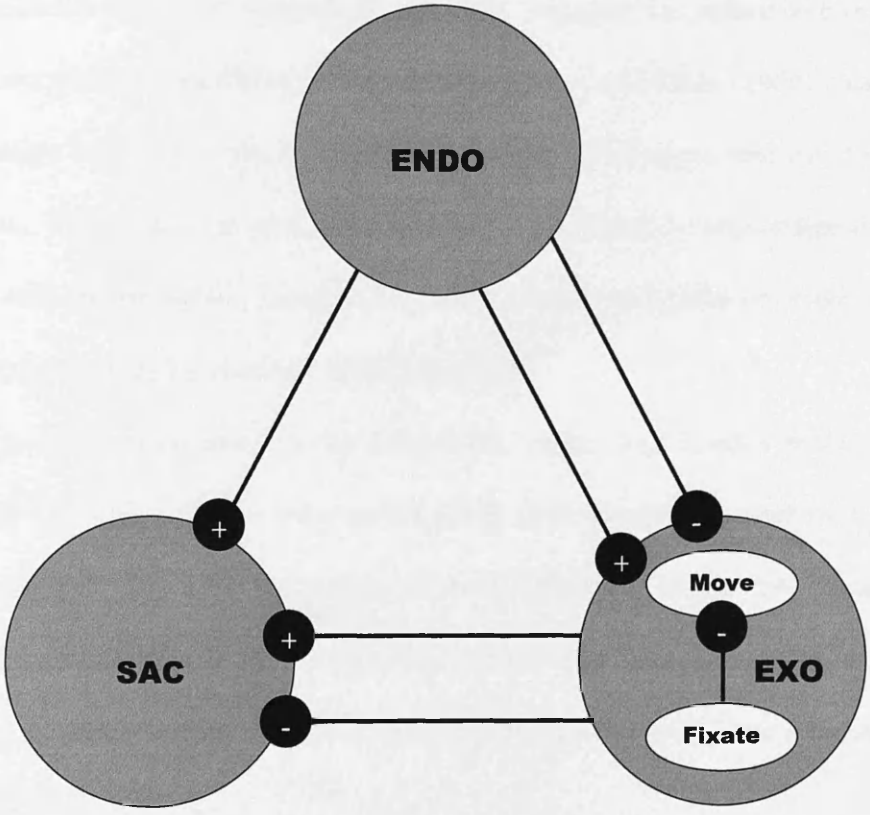
Lesion studies in humans have found that a primary role for the FEF is in the generation of volitional saccades (Section 1.4.2.1) and in the active disengagement of fixation (Pierrot-Deseilligny et al., 1995; Rivaud et al., 1994). Latency of saccades made during the gap paradigm for patients with FEF lesions have been found to be normal (Pierrot-Deseilligny et al., 1991b; Rivaud et al., 1994). However, in the reflexive saccade overlap task, where the fixation point remains on with target onset necessitating active disengagement of fixation from the central fixation point prior to a saccade to the target, latency is increased after a FEF lesion (Rivaud et al., 1994).

Investigations on patients with lesions of the PPC show bilateral increase of the latencies of reflexive saccades in the gap task (Pierrot-Deseilligny, Rivaud, Gaymard & Agid, 1991a; Pierrot-Deseilligny et al., 1987), whereas in the overlap task, latency is even more prolonged (Walker & Findlay, 1996). The distinct increase of latency in the overlap task indicates that the PPC may have a role in the disengagement of fixation, as does the FEF.

The functional basis of saccade generation and control was described in Chapter 1 (Section 1.4). In relation to fundamental neural architecture portrayed in Section 1.4, Forbes and Klein (1996) designed a model (Figure 4.1) based on their research of the FOE in reflexive saccade, antisaccade and verbally induced saccades. The model postulates the functional basis

of exogenous and endogenous saccadic eye movements, by outlining the interaction of neural substrates that control the execution of saccades and the resultant FOE.

**Figure 4.1** The Forbes & Klein Model Illustrating the Functional Activity Between Endogenous (ENDO) and Exogenous (EXO) Systems in the Control of Saccade (SAC) Generation




Source: Forbes & Klein (1996)

In prosaccade paradigms, were saccades are generated toward a stimulus, the natural reflexive mechanisms of the SC are utilized. Thus, the neural systems that orchestrate stimulus driven reflexive saccades (involuntary saccades) can be termed exogenous. However, the antisaccade paradigm requires an eye movement that directs visual gaze in the opposite direction (i.e. mirror location) from the target. The processes involved in the antisaccade task demand that reflexively generated programs of the SC are inhibited and that saccadic parameters for the saccade to the opposite hemifield are correctly planned. As the characteristics of the target are not precisely visible, Forbes and Klein use term endogenous,

for the neural systems involved in the generation of goal-driven antisaccades (Forbes & Klein, 1996; Klein, Kingstone & Pontefract, 1992).

The Forbes and Klein model outlines the sub-systems that are important for the control of exogenous (EXO) and endogenous (ENDO) saccades in the FOE. For the exogenously generated saccades, the model depends on the VGR response, i.e. reflexive programming for the prompt execution of saccades to visual targets. Forbes and Klein (1996) stipulate that the neural substrates involved in the exogenous generation of saccades involve the SC and the parietal cortex. The reader may recall that Section 1.4 discussed the importance of the SC (and connections with the brainstem; Sections 1.4.1.1 & 1.4.1.2) and pathways projecting from the PEF (1.4.2.2) in the generation of involuntary saccades.

Where endogenous saccades are concerned, Forbes and Klein's endogenous system contains the FEF, SEF and prefrontal cortex along with the caudate nucleus and substantia nigra pars reticulata. The SAC component of the model, refers to the final common pathway for the control of saccades in the oculomotor nuclei of the brainstem (described in Sections 1.2.1.1 & 1.4.1), and receives saccade commands through the omnipause neurons, from both the ENDO and EXO systems.

Applied to the fixation offset effect the Forbes and Klein model works as follows:-

> *Reflexive saccades*: For reflexive saccades the ENDO and EXO systems both receive input, but the EXO system generates the majority of saccadic parameters and commands that facilitate foveation, via the VGR. On presentation of the fixation point, the fixation cells of the SC provide a brake by inhibiting movement cells in the SC and providing excitatory stimulation of the inhibitory omnipause neurons in the SAC system. By removing the fixation point, the systems are disinhibited and saccade latency reduced.
>
> *Antisaccades*: For the antisaccade task, Forbes and Klein suggest that inhibitory control is active prior to saccade initiation, as the task is planned or goal-driven. Therefore, the ENDO system tonically inhibits the SC prior to target presentation. This

> inhibition is controlled by the prefrontal cortex. Saccade metrics are generated in accordance with visual input and instructional set of the task, and conducted via the ENDO system in parallel to the EXO and SAC systems. With this approach, inhibition of the SC is sustained and the magnitude of FOE decreased, due to the endogenous saccade program encountering reduced inhibition by the fixation system. (Forbes & Klein, 1996)

Many studies have reported a dysfunction of attention in AD (Baddeley, Baddeley, Bucks & Wilcock, 2001; Della Sala et al., 1992; Parasuraman et al., 1992; Parasuraman & Haxby, 1993; Perry & Hodges, 1999; Scinto et al., 1994; Solfrizzi et al., 2002; Tales, Muir, Bayer & Snowden, 2002), which appears to coincide with the progressive decline in working memory and executive function (Awh & Jonides, 1998; Parasuraman & Greenwood, 1998). There are a number of aspects to attention which include, *sustained attention* (vigilance), *selective attention* and *divided attention.* In the early stages of AD, there appears to be an impairment of selective attention, most prominently, spatial selective attention (Parasuraman & Haxby, 1993). Thus, early in the course of AD the mechanism for the selection of information from a particular region of a scene for focused processing seems to be impaired. The neuropathology of AD was outlined in Chapter 1 (Section 1.5.2.1) and drew attention to the degeneration of frontal, temporal and parietal cortical areas, as revealed by post mortem examination of the AD brain. These regions of the cortex are particularly important for the present study given the role of the parietal cortex in attention (Mesulam, 1981; Posner & Petersen, 1990; Posner, Walker, Friedrich & Rafal, 1987) and the frontal and temporal areas of the cortex for working memory (Nyberg et al., 2003; Owen, Sahakian, Semple, Polkey & Robbins, 1995).

Parasuraman and colleagues (Parasuraman et al., 1992) found that AD patients of mild severity displayed what they refer to as an attention-shifting or disengagement deficit, not unlike that which presents in hemi-neglect patients as a result of damage to the parietal lobe (Posner et al., 1984). Parasuraman et al. (1992) investigated cue-directed shifts of attention in

mildly impaired AD patients, employing a letter-discrimination task. The study revealed that AD patient reaction time benefits for valid cues did not differ from healthy controls, whereas the response time costs for AD patients following invalid cues was significantly higher than that of healthy control participants. Moreover, the findings showed that *focused attention* to spatial locations is preserved in early AD, whereas automatic disengagement of attention generated by the presentation of peripheral cues, is impaired. Furthermore, using PET Parasuraman et al. (1992) also found that the degree of disengagement deficit was correlated with the level of hypo-metabolism in the superior parietal lobe. Interestingly, Parasuraman et al. (1992) concluded that the impaired disengagement of attention in early AD may be due to a disturbance of the cortical pathways connecting the parietal and frontal lobes. Bearing in mind the saccadic eye movement abnormalities reported in AD (e.g. prolonged latency, hypometria, impersistence of gaze, see Section 1.6.3), Study II investigated whether the attention disengagement deficit in AD can be detected using fixation offset paradigms.

According to the literature, only one published study (Abel et al., 2002) has investigated the fixation offset effect in AD. However, Abel et al. only investigated the FOE for reflexive saccades, and did not explore the FOE in an antisaccade paradigm. In the Abel et al study a significant gap effect was found to be present in both AD patients and elderly controls, there was however, no significant difference between-groups in the size of the effect. This is possibly due to the authors using a simultaneous or zero gap task to compare with the gap task. Had the authors employed an overlap task, rather than simultaneous fixation offset/target onset task, a more significant delay may have been recorded for the AD group, due to attentional disengagement deficit.

Abel and co-workers (2002) also found that an inordinate proportion of anticipatory saccades were produced by both AD patients and elderly controls (particularly for AD patients). Unfortunately, the authors did not report the number of anticipations explicitly. From the histograms it looks as though anticipation could have been as high as 35% of all AD

patient trials. A previous study of reflexive saccades reported much lower anticipation rates, with means in the region of 5.5% for AD patients (Shafiq-Antonacci et al., 2003). Other studies appear not to have considered reporting anticipatory saccades or perhaps did not register any significant number during reflexive saccade tasks (Currie et al., 1991; Fletcher & Sharpe, 1986; Nakano et al., 1999; Schewe et al., 1999)[14]. Unfortunately, when taken together with the evidence of anticipatory levels in other studies, the proportion of anticipations during the Abel et al. study is arguably a potential confound for the outcome. It is possible that some methodological reason underpins the high proportions of anticipatory saccades generated in the Abel et al. study. The stimulus was directionally predictable between 0° and 15° and was randomly timed 0.5 – 2 seconds, with no inter-trial interval reported by the authors. It is feasible that the predictability of the direction combined with unpredictable temporal spacing, motivated participants to predict target direction or onset. The instructions were to "*follow the light as soon as it moves*". Did these instructions, along with what appears to have been limited practice, cause participants to anticipate target onset (movement)? Or was it a combination of these factors, leading to a task that was simply too difficult for participants to complete (AD patients and elderly controls) that caused to problem? Moreover, if little or no inter-trial interval was present for the tasks then this could be the reason why participants generated such high proportions of anticipatory saccades.

The present study will attempt to simplify the task and optimise the potential for participation, whilst maintaining the integrity of the task to generate saccadic responses, bearing in mind that the experimental population are elderly people. Therefore, the study used a target eccentricity of only 4° with high saliency.

[14] Fletcher & Sharpe (1986) also reported gaze impersistence and a number of large saccadic intrusions that apparently, on occasion, appeared to be anticipatory. However, no clear distinction was made as to the proportion of anticipatory saccades produced.

### 4.1.1 Aims

The main aim of the present study was to investigate reflexive saccade and antisaccade latency, in AD and elderly controls, using gap and overlap tasks in an attempt to find a sensitive oculomotor marker for AD. A previous study (Abel et al., 2002) reported that the FOE was preserved in AD, but was of the same magnitude as that of controls and did not examine antisaccades. The present study attempted to improve on the methodology employed by Abel et al. (2002). In part, the aim for the present study was to assess whether the attention-shifting or disengagement deficit previously reported in AD was detectable using oculomotor paradigms. Thus, the present study examined the FOE in AD by employing an overlap task in an attempt to maximise fixation disengagement delay, compared with a gap task employed to optimise fixation offset benefits.

The specific hypothesis for Study II was that AD patients would present with an FOE of greater magnitude than that of the EC group. Given the attention disengagement deficit reported by studies of selective attention in AD, it was hypothesised that AD patients would generate saccades to peripheral targets in the reflexive gap task with virtually the same latency as elderly controls, taken that reflexive saccade generation is based in the SC. However, correspondingly in the reflexive overlap condition AD patients would have significantly prolonged latency to peripheral targets compared with the EC group. The prolonged latency results from a delay in fixation disengagement from the central fixation point, hence the hypothesised larger magnitude FOE for the AD group compared with the EC group. If an FOE of greater magnitude was found for the AD group (compared with that of the EC group) as a result of prolonged latency in the reflexive saccade overlap task, this would lend support for the hypothesis that uncorrected errors in the antisaccade gap task (Study I) may be due to a dysfunction of fixation disengagement. Thus, once the target is located inappropriately in the antisaccade task - through impaired inhibitory control of the VGR - it is difficult for the AD patient to generate a corrective saccade into an empty space in the opposite direction whilst

already fixating a target - as fixation cannot be disengaged from the target. It is plausible to suggest that this is possibly brought about by disruption of the opponent neural processes in the SC.

For the antisaccade paradigm, it was hypothesised that the FOE for AD patients would be significantly attenuated, due to the cognitive load that the antisaccade paradigm represents for this group and the reprocessing costs involved in generating an eye movement into the opposite hemifield. Thus, for the AD group, the benefit derived from the gap task when compared with the overlap task will be significantly reduced and saccade latency should be significantly prolonged for both antisaccade tasks. This corresponds with the results from Study I, which indicated that for AD patients the antisaccade task represented a high cognitive load due to diminished working memory function.

Saccade amplitude (accuracy), duration and maximum velocity were also examined. The specific hypotheses here were that, due to parietal disturbances spatial orienting would show a deficit and therefore, that saccadic accuracy would be impaired in AD patients compared with controls in the gap task. Thus AD patients should show no benefit with fixation offset in this task. However, overlap task accuracy should be less impaired, given that the central fixation point is displayed along side the target thereby facilitating accuracy. Given the main sequence (Section 1.3) of saccadic eye movements, the relationship between velocity and amplitude (also for duration and amplitude), it is hypothesised that the difference between-groups for saccadic amplitude should map onto saccade duration and maximum velocity producing similar results.

A further line of enquiry for this chapter was be to examine directional error rates in gap and overlap tasks, to explore whether AD patients derive any benefit from fixation offset. It was hypothesised that no benefit (reduction in error rate) would be derived from fixation offset in either the reflexive saccade paradigm or the antisaccade paradigm. Given the high degree of pre-potency for the reflexive paradigm, the pace facilitated in the gap task may

induce a high level of anticipation and a corresponding number of errors, which exceed the guidance and prolonged latency provided by the overlap task. However, for the antisaccade task, as working memory is somewhat impaired in the AD group, it was hypothesised that inhibitory error rates would again be higher in the gap task as this task causes a high cognitive load due to the instructional set required for the task combined with the fixation point offset. Thus, no benefit will be derived from fixation point offset.

## 4.2 Methods

### 4.2.1 Participants

The participants for this study were from the same pool of dementia patients and elderly control volunteers discussed in Chapters 2 and 3 and at stage one in a longitudinal study. Thus, patients were from the AD Research Project at Lytham Hospital Memory Clinic, United Kingdom and Elderly Control (EC) participants were volunteers from the local community of Lytham. Recruitment methods, criteria for dementia diagnosis and exclusion, and participant health status were discussed in Chapter 2, Section 2.1. Numbers in this study were slightly lower than in Study I, as data for the reflexive overlap condition was missing for some of the experimental population. All participants were right-handed.

**Table 4.1** Clinical Rating Scale Scores

| | Groups | | | | | | Dementia sub-groups | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Elderly control | | | Dementia Patients | | | Alzheimer's disease | | | Other dementia | | |
| | Mean | SD | N | Mean | SD | N | Mean | SD | N | Mean | SD | N |
| **SMMSE** | 29.15 | 1.05 | 26 | 22.22 | 6.20 | 23 | 21.15 | 5.26 | 13 | 23.60 | 7.30 | 10 |
| **EADAS** | 7.54 | 2.28 | 26 | 22.26 | 12.52 | 23 | 23.77 | 9.36 | 13 | 20.30 | 16.10 | 10 |

The Dementia Patient group (N=23; age range = 68–88 years; mean = 77.0; SD = 4.7; male, n=15; female n=8) comprised two sub-groups, AD patients (N=13; age range = 71-88; mean = 77.6; SD = 5.0; male n=8; female n=5) and Dementia of other types [DOT] (N=10; age range = 68-81years; mean = 76.3; SD = 4.4; male n=7; female n=3). The

composition of the EC group (N=26; age range = 62–80 years ; mean = 70.5; SD = 5.0; male n=9; female n=17). Clinical rating scale scores for the groups and sub-groups are shown above in Table 4.1.

### 4.2.2 Assessment of Saccadic Eye Movements

All participants used the same equipment and procedures as in Study II (Chapter 3) which were described in Chapter 2 (Section 2.3). This investigation was a parallel analysis to Study I, in that it involved the oculomotor measures of saccade latency, amplitude, duration and velocity gathered from the reflexive saccade paradigm (gap and overlap paradigm); antisaccade paradigm (gap and overlap tasks). The central fixation point was displayed at $0^{\circ}$ and the target at $\pm 4^{\circ}$ in the horizontal plane, with the direction randomised.

The reflexive saccade and antisaccade paradigms employed two tasks, gap and overlap. A 200 msec. gap was incorporated into the gap tasks as a temporal gap is known to facilitate the disengagement of attention (Fischer & Breitmeyer, 1987). Therefore, given the difficulty that AD patients have in disengaging attention from a visual cue, the gap task was used to facilitate the disengagement of attention. However in the overlap task, the central fixation point was <u>not</u> extinguished at target onset, but remained on, until both were simultaneously extinguished at the end of the trial. Thus, AD patients should have difficulty disengaging the central cue, to shift attention to the peripheral target.

### 4.2.3 Statistical Analysis

SPSS version 11.5 (SPSS Inc., Chicago Ill) was used to conduct statistical analyses. The statistical procedures were the same as those outlined in Section 3.2.3. Firstly, Dementia Patients (DP) were assessed as a group compared with ECs and then the analysis extended to examine the dementia sub-groups (i.e. ADs and Dementia of other types). Oculomotor data from the left and right hemifield were collapsed as no laterality effects were found for any

variables. Oculomotor variables were assessed for normality using the skewness index, and, if necessary, transformed using square root or square for positive (>1) or negative (<-1) skewness respectively (Tabachnick & Fidell, 1996). Analyses were conducted using two-factor repeated measures mixed ANOVA with Bonferroni multiple comparisons, and also one-way ANOVA. For analyses using repeated measures ANOVA, assumptions of sphericity were assessed on each variable using the Mauchly test. The Greenhouse-Geisser epsilon correction of degrees of freedom was used if assumptions of sphericity were violated (Jennings, 1987). Planned contrasts were used to test between-groups hypotheses and pair-wise comparisons (t-test), were applied to within-group analyses. Correlations were investigated using Pearson's product moment correlation coefficient and Spearman's rank order correlation coefficient where appropriate. Between-groups effect sizes for oculomotor variables were calculated with the Cohen's *d* statistic (Cohen, 1988) as in the previous study (see equations in Section 3.2.3.2).

#### 4.2.3.1 *Effects of Age and Education*

The effects of age and education were assessed using Spearman's rank correlation coefficient, to test relationships with oculomotor variables.

#### 4.2.3.2 *Group Comparisons for the Magnitude of Fixation Offset Effect*

The analysis of group differences on saccadic variables was carried out using two-factor repeated measures mixed ANOVA (within-subjects factor levels = oculomotor variables; between-subjects factor = group). Additionally, ANOVA were conducted for each oculomotor variable, with group as the independent variable (patients versus controls) and oculomotor variable as the dependent. Between-groups hypothesis testing was carried out using planned comparisons and within-groups pair-wise comparisons, employing the t-test where used to test within-groups effects. Relationships between clinical rating scales, neuropsychological

assessments and oculomotor variables were assessed using Spearman's rank correlation coefficients (two-tailed).

## 4.3 Results

Skewness (positive) was found to be present for some antisaccade variables (latency, amplitude, duration and maximum velocity), which were transformed to normalise the skewness of distribution. Output for statistical analysis of untransformed scores was found to be generally identical to transformed variables. For clarity of interpretation and descriptive statistics the results given below use untransformed versions (where possible non-parametric analyses of all variables conducted simultaneously for thoroughness, also revealed the same results as ANOVA, but are omitted).

### *4.3.1 Effects of Age and Education*

The oculomotor variables that were included in the present analysis were found to have only small non-significant correlations with age and education in the majority of cases (saccade latency in each task <0.3 NS). However, there were some minor exceptions as age for the EC group, was found to be moderately correlated with maximum velocity for both the reflexive saccade gap task (r=-0.40, n=26, $p<0.05$) and antisaccades tasks (gap, r =-0.42, n=26, $p<0.05$; overlap, r = -0.49, n=25, $p<0.05$). Additionally, a moderate correlation was found for education with amplitude (r=0.43, n=26, $p<0.05$) and also maximum velocity (r=0.43, n=26, $p<0.05$) for the EC group on the antisaccade gap task.

### *4.3.2 Magnitude of Fixation Offset Effect for Reflexive Saccades*

Group descriptive statistics for oculomotor variables used in the present analysis are displayed in Table 4.2.

**Table 4.2** Descriptive Statistics for Oculomotor Measures in the Reflexive Saccade Paradigm

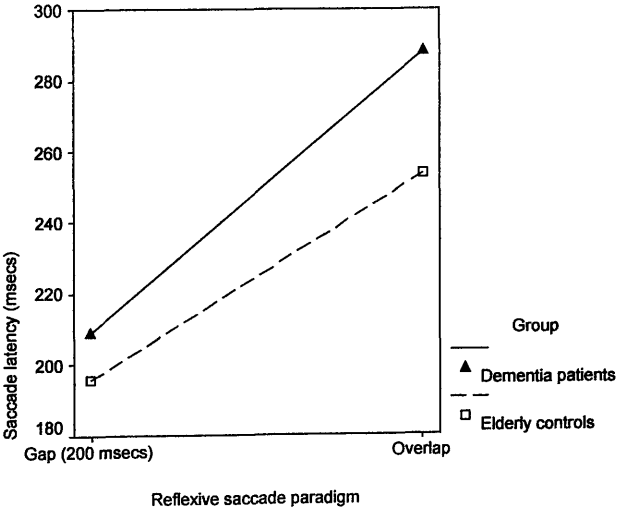
| | Reflexive saccade | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Overlap | | | | | | Gap | | | | | |
| | AD | | EC | | DOT | | AD | | EC | | DOT | |
| Measure | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| Latency (msecs) | 298.63 | 45.40 | 253.58 | 30.83 | 274.72 | 31.94 | 206.05 | 45.40 | 195.67 | 35.08 | 212.22 | 39.97 |
| Amplitude (degs) | 3.10 | 0.60 | 3.38 | 0.81 | 2.98 | 0.84 | 3.09 | 0.63 | 3.04 | 0.63 | 2.69 | 0.82 |
| Duration (msecs) | 46.51 | 7.78 | 50.77 | 8.41 | 47.35 | 8.75 | 47.95 | 8.35 | 48.99 | 8.29 | 46.85 | 9.49 |
| Max. Velocity ($degs^{-1s}$) | 110.25 | 17.32 | 115.04 | 26.52 | 106.77 | 32.03 | 107.03 | 17.59 | 106.82 | 19.78 | 96.50 | 29.20 |

AD = Alzheimer's disease; EC = Elderly control; DOT = Dementia of other types

### *4.3.2.1 Saccade Latency*

*Reflexive fixation offset* was created as the within-subjects factor in a two-factor repeated measures mixed ANOVA, using reflexive gap and overlap saccade latency as factor levels, with DP and EC groups as a between-groups factor. This analysis revealed significant main effects for reflexive fixation offset ($F[1,47]=163.65$, $p<0.0001$) and group ($F[1,47]=6.66$, $p<0.01$). The interaction between group (DPs and ECs) and reflexive fixation offset was found to be significant ($F[1,47]=4.04$, $p<0.05$; see Figure 4.2).

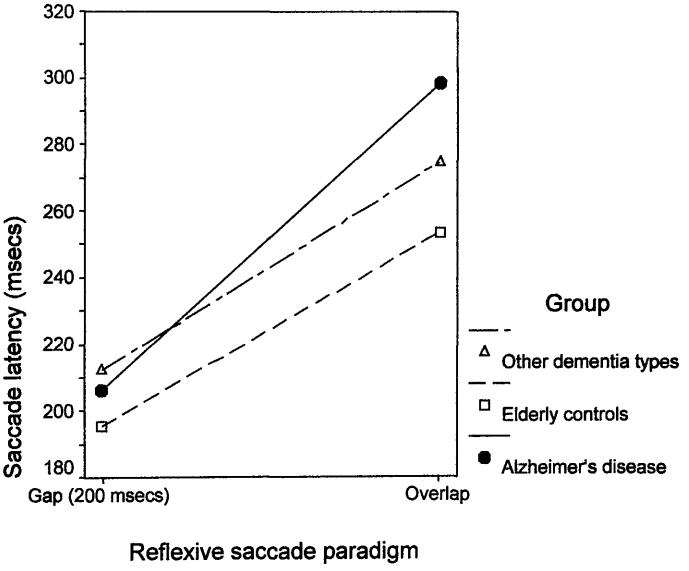
**Figure 4.2** Interaction Between Reflexive Fixation Offset and Group (Dementia Patients and Elderly Controls)




The analysis was repeated with the sub-groups, to investigate whether the interaction existed at the sub-group level. This analysis revealed significant main effects for reflexive fixation offset ($F[1,46]=158.65$, $p<0.0001$) and group ($F[1,46]=3.50$, $p<0.039$). The

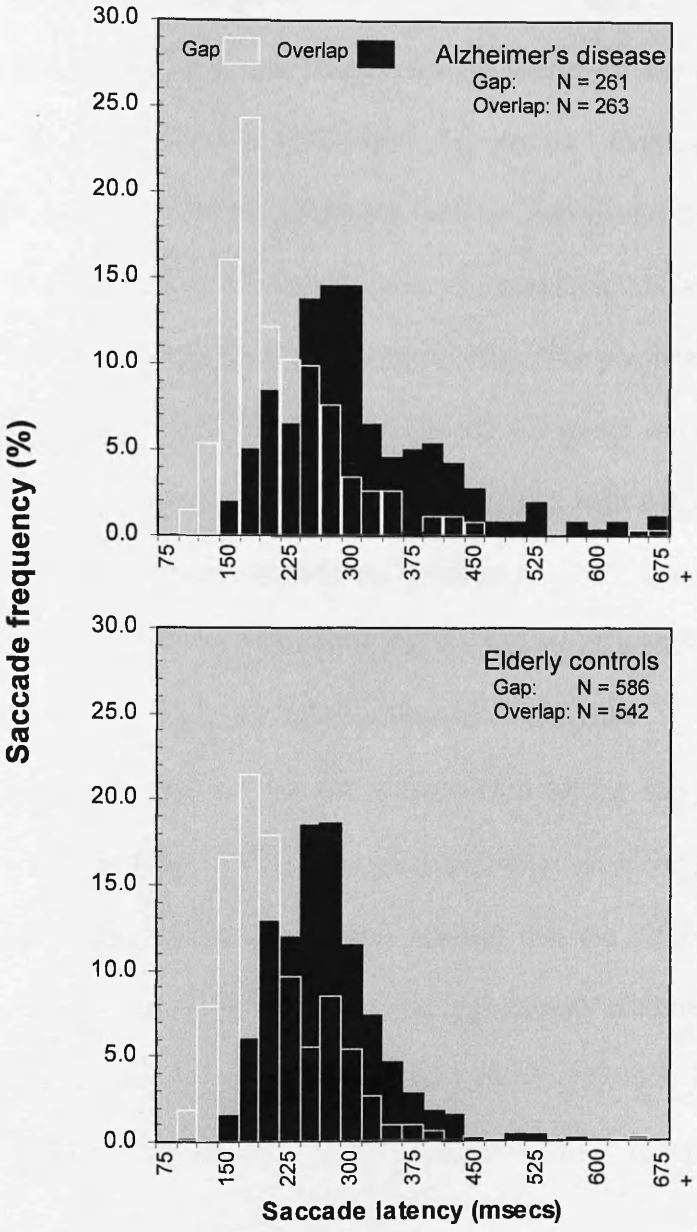
interaction between reflexive fixation offset and group (AP, EC and DOT) was found to be significant ($F[2,47]=4.07$, $p<0.024$; Figure 4.3), indicating that the magnitude of fixation offset effect was significantly different between the groups. Due to the interaction between sub-group and reflexive task, multiple comparisons (Bonferroni) were used to examine the between-group effects for the factor reflexive fixation offset. This analysis showed that the factor was significantly greater for the AD group compared with the EC group ($p<0.05$), however, the DOT group did not differ significantly from ADs or ECs. Therefore, in view of Figure 4.3, the significant interaction was caused by the magnitude of FOE being greater for AD patients compared with EC and DOT groups.

**Figure 4.3** Interaction Between Reflexive Fixation Offset and Group
(Alzheimer's disease, Elderly Controls and Other Dementia Types)




Histograms displaying frequency distributions for reflexive saccade latency in the gap and overlap tasks are displayed for both the AD and EC group below, in Figure 4.4. Figure 4.4 clearly illustrates that the peak for of the reflexive gap task distributions are similar for each group. This confirms the observation in Figure 4.3 displaying the interaction, indicating that the AD group derived a benefit from the gap task that was close to that of the EC group. However, the peak and spread of the distribution for the AD group in the overlap task, is situated subtly to the right, compared with that of the EC group who have a tighter distribution

**Figure 4.4** Histograms Displaying the Frequency of Saccade Latency in the Reflexive Gap and Overlap Tasks




to the left of the display. This shows that in general, reflexive saccade latency in the overlap task was generally prolonged for the AD group, compared with that of the EC group. Hence, the magnitude of the fixation offset effect was larger for the AD group than the EC group. One-way ANOVA with planned contrasts were carried out between-groups at the sub-group level, for each level of the factor: reflexive fixation offset, i.e. reflexive saccade gap task latency and reflexive saccade overlap latency. This analysis was used to test the hypothesis that there would a significant difference between the AD group and the EC group for reflexive

saccade latency in the overlap task, whilst in the reflexive saccade gap task, there should be no significant difference between the groups (hence the use of planned contrasts (Keppel, 1991)).

For reflexive saccade gap task latency, no significant difference was found between-groups with the omnibus ANOVA ($F[2,46]=0.754$, $p>0.4$). Correspondingly, the planned contrasts showed that there was no difference between sub-groups. However, a significant difference was found between sub-groups, with the omnibus ANOVA, for latency in the reflexive saccade overlap task ($F[2,46]=7.133$, $p<0.002$). The planned contrasts between sub-groups on this measure, revealed that the mean for the AD group was significantly prolonged compared with that of the EC group ($t[37]=-3.745$, $p<0.001$), with a large effect size of 1.2 ($d$), whereas no significant differences were found between the DOT group and each of the other groups. This finding supports the hypothesis that the AD group would generate saccades with significantly prolonged latency in the reflexive saccade overlap task.

*Within-Groups Effects:* To aid interpretation of the sub-group interaction with reflexive fixation offset (Figure 4.3), within-group pair-wise t-test comparisons of the gap and overlap tasks were used. These comparisons showed that the difference between gap and overlap reflexive saccade latency (Table 4.2) was significantly different for each group (AD, $t[12]=-8.927$, $p<0.0001$; EC, $t[25]=-8.950$, $p<0.0001$; DOT, $t[9]=-4.537$, $p<0.001$).

Thus, each group derived benefit in the gap task with the fixation point offset:

***Reflexive Saccade Paradigm:***
***Fixation offset effect = overlap task latency – gap task latency***

(AD = 92.6 msecs.; EC = 57.9 msecs.; DOT = 62.5 msecs.) as opposed to the overlap task, where the central fixation point remained on with target onset and throughout the task, which caused primary saccade latency to be significantly prolonged within each group.

In summary, the magnitude of FOE for reflexive saccade latency was found to be significantly larger for the AD group compared with that of the EC, but not significantly larger than that of the DOT group. Additionally, no significant difference was found between the

DOT and EC groups. Whilst the dementia sub-groups produced saccade latencies in the reflexive saccade gap task that were very slightly higher than those of the EC group, no significant differences were present between any of the groups. However, for the reflexive saccade overlap task, the AD group generated saccades with latencies that were significantly prolonged compared to the EC group, whereas the DOT group did not differ significantly from the either the AD or the EC group. Although the magnitude of FOE was found to vary between groups, a significant FOE was found to be present for each sub-group, confirming a benefit from fixation offset.

#### *4.3.2.2 Saccade Amplitude, Duration and Maximum Velocity*

Individual analyses, conducted with two-factor repeated measures mixed ANOVA, were used to examine the reflexive saccade amplitude, duration and maximum velocity data at the sub-group level (group x factor: fixation offset level; i.e gap and overlap tasks; Table 4.1). In each analysis, no significant effects were observed for the main effect of group or for the interaction between group and reflexive fixation offset. However, the main effect of the factor reflexive fixation offset was significant for amplitude and maximum velocity, indicating that overall for these two measures, there were significant differences between gap and overlap tasks (amplitude, $F[1,46]=4.419$, $p>0.04$; maximum velocity, $F[1,46]=4.508$, $p>0.39$). In order to examine specifically where the amplitude and maximum velocity differences between gap task and overlap were located, pair-wise within-groups comparisons were carried out on the data. These tests revealed that there were no significant differences between gap and overlap tasks for the measures of amplitude or maximum velocity in the AD and the DOT groups. However, a significant difference was found between each measure for the EC group (amplitude, $t[25]=-2.547$, $p<0.017$; maximum velocity, $t[25]=-2.133$, $p<0.043$). Interestingly, the saccade amplitude for the EC group was significantly more accurate in the reflexive saccade overlap condition, and maximum velocity was higher (main sequence amplitude and

velocity relationship), supporting the hypothesis of better accuracy; perhaps due to the presence of the central fixation point in the overlap task which facilitate better guidance for the programming of saccade metrics. On examination of the group means (Table 4.1), a similar pattern was present for AD and DOT patients showing that no benefit is obtained in the gap task for these measures. In addition to this, the hypothesis that AD patients would be significantly less accurate than the EC group, when making a reflexive saccade was not supported.

#### *4.3.2.3 Directional Errors*

Descriptive statistics for the directional error rates in the reflexive saccade paradigm are displayed below in Table 4.3.

**Table 4.3** Descriptive Statistics for Directional Error Rates in the Reflexive Saccade Paradigm

| | Reflexive Saccade Task | | | | | |
|---|---|---|---|---|---|---|
| | Overlap errors (%) | | | Gap errors (%) | | |
| **Group** | Mean | SD | N | Mean | SD | N |
| **Elderly controls** | 0.65 | 1.95 | 26 | 1.13 | 2.94 | 26 |
| **Alzheimer's disease** | 1.68 | 2.22 | 13 | 1.94 | 2.24 | 13 |
| **Other dementia types** | 2.08 | 4.50 | 10 | 1.68 | 2.76 | 10 |

The error rates are extremely low for this task, indicating that the reflexive capacity of each group was intact. Analysis of directional error rates in the reflexive saccade paradigm was conducted at the sub-group level to explore whether an FOE was present in the data. This analysis used a two-factor repeated measures mixed ANOVA and revealed no significant differences in the magnitude of fixation offset effect between the sub-groups. Furthermore, no significant difference emerged between sub-groups in the number of errors committed, with the conclusion that negligible error rates were present for the reflexive tasks among the sub-groups and that all groups demonstrated good performance for this task.

### 4.3.3 Magnitude of Fixation Offset Effect for Antisaccades

Descriptive statistics used in the present analysis of the FOE in the antisaccade paradigm, are displayed in Table 4.4 below. Analyses in this section followed much the same pattern as the analyses used in Section 4.3.2.

**Table 4.4** Descriptive Statistics for Oculomotor Measures in the Antisaccade Paradigm

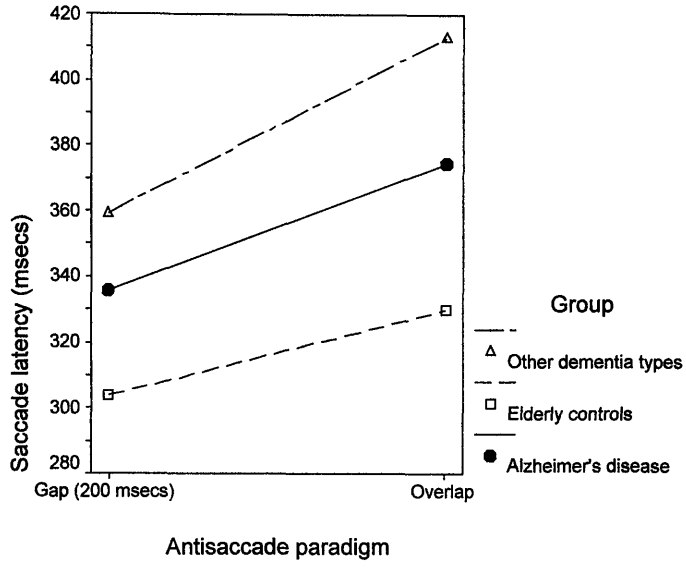
| | Antisaccade | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Overlap | | | | | | Gap | | | | | |
| | AD | | EC | | DOT | | AD | | EC | | DOT | |
| Measure | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| Latency (msecs) | 374.55 | 173.01 | 329.95 | 66.49 | 413.11 | 143.90 | 335.79 | 138.99 | 303.68 | 57.49 | 359.23 | 78.49 |
| Amplitude (degs) | 3.94 | 2.69 | 4.09 | 1.59 | 3.31 | 1.74 | 4.27 | 2.40 | 4.69 | 1.87 | 4.94 | 3.57 |
| Duration (msecs) | 52.38 | 21.01 | 54.90 | 14.25 | 46.87 | 15.43 | 50.46 | 16.00 | 57.44 | 15.52 | 57.92 | 26.85 |
| Max. Velocity ($degs^{-1s}$) | 119.33 | 48.19 | 121.04 | 27.79 | 107.83 | 35.49 | 137.25 | 73.65 | 132.19 | 29.69 | 136.12 | 58.40 |

AD = Alzheimer's disease; EC = Elderly control; DOT = Dementia of other types

#### 4.3.3.1 Antisaccade latency

The antisaccade latency data were subjected to a two-factor repeated measures mixed ANOVA forming the within-group factor *antisaccade fixation offset* with two levels, antisaccade overlap task and antisaccade gap task. Group was the between-group (DP group and EC group) factor. The main effect of antisaccade fixation offset was only approaching significance ($F[1,44]=3.442$, $p>0.07$), but the main effect of group was significant ($F[1,44]=4.621$, $p<0.037$). However, the interaction was not found to be significant which shows that the magnitude of FOE did not differ significantly between-groups. The analysis was carried out again, this time at the sub-group level, but none of the effects were found to be significant (all $p>0.07$). Figure 4.5 shows a line graph to illustrate the spread of data points for sub-group means.

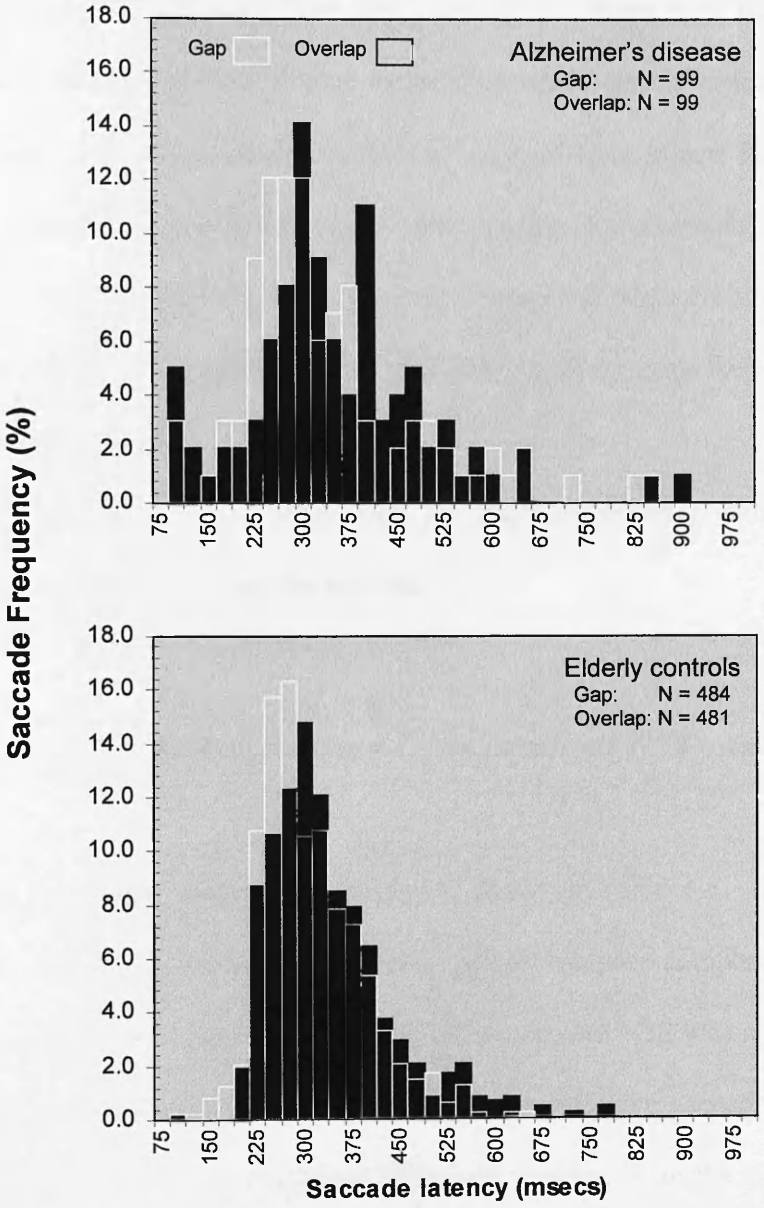
**Figure 4.5** A Line Graph Illustrating the Fixation Offset Effect Within Sub-groups for the Antisaccade Task




In the graph above, latencies are clearly prolonged for the dementia patient sub-groups compared to those of the EC group, in both the overlap task and the gap task. This explains the significant between-groups difference in the DP and EC group analysis, the most prolonged latencies being for the DOT group, compared to the EC group. However, none of these differences reached significance and therefore the null hypothesis could not be rejected on this occasion. Furthermore, there is plainly an FOE present for each group, but the magnitude of this effect is not significantly different between the groups, as revealed by the lack of significant interaction in the factorial ANOVA.

The histograms in Figure 4.6 (above) show the frequency distributions for antisaccade latency in the gap and overlap tasks, for the AD and EC groups. The peaks for the distributions are closer together, for each group than in the reflexive saccade paradigm, indicating that the FOE is smaller in the antisaccade paradigm than in the reflexive saccade paradigm (Figure 4.4). Moreover, the peaks are very similar between-groups, hence no difference in magnitude of FOE. The AD group distribution shows considerably more variability in latency than the EC group distribution, which can be seen in the standard deviations in Table 4.4.

**Figure 4.6** Histograms Displaying the Frequency of Antisaccade Saccade Latency in the Gap and Overlap Tasks




*Within-Groups Effects:* Pair-wise within-group comparisons (t-test), between antisaccade gap and overlap task latency data were used to examine the within-group FOE:

***Antisaccade Paradigm:***
***Fixation offset effect = overlap task latency – gap task latency***

This analysis showed a significant difference for the EC group (t[24]= -2.980, $p$<0.007), which indicates a significant FOE (26.27 msecs.). However, despite the larger difference between

gap and overlap task means for the AD (38.76 msecs.) and DOT (53.88 msecs.) groups, the effects were not significant ($p$>0.3). Thus, the FOE was not found to be significant for the AD and DOT groups, which can be attributed to the high within-group variability of antisaccade latency measures. It is also possible that the lack of significant effects for the patient groups was due to a lack of data points for correct antisaccades. For example, AD group repeated measures antisaccade latency data on the gap and overlap task were derived from only ninety-nine correct saccades. This small number of data points would reduce the reliability and power of this analysis considerably.

To ascertain the level of attenuation for the antisaccade paradigm, the FOE was compared between paradigms using the formula:

***Attenuation of FOE for antisaccades = Reflexive saccade FOE – Antisaccade FOE***

The results of this analysis are displayed above in Table 4.5. The FOEs for each paradigm were compared within-groups using paired samples comparisons (t-test). The within-groups analysis revealed that the for the EC group, the FOE was significantly lower in the antisaccade paradigm compared to the FOE in the reflexive saccade paradigm (t[24]=-4.474, $p$<0.0001). However, no significant difference was found for the dementia sub-groups, due to the high variability of latencies in the antisaccade task.

**Table 4.5** Attenuation of the Fixation Offset Effect in the Antisaccade Paradigm

| | Paradigm | | | | | |
|---|---|---|---|---|---|---|
| | **Reflexive saccade** Fixation offset effect (msecs.) | | **Antisaccade** Fixation offset effect (msecs.) | | **Attenuation of fixation offset effect (msecs.)** | |
| **Group** | Mean | SD | Mean | SD | Mean | N |
| **Elderly controls** | 57.75 | 33.66 | 26.27 | 44.07 | 31.48 | 25 |
| **Alzheimer's disease** | 96.87 | 35.55 | 38.76 | 204.00 | 58.11 | 12 |
| **Other dementia types** | 56.92 | 42.25 | 53.88 | 173.39 | 3.04 | 9 |

In summary these findings support the hypothesis that the FOE for saccade latency would be significantly reduced in the antisaccade paradigm for the AD group, compared to that of the EC group. In fact, due to the extent of variability within AD, and also, the DOT group antisaccade latency, no significant FOE was evident. Moreover, the findings also support the hypothesis that the FOE would be severely reduced for the AD group in the antisaccade paradigm compared to the reflexive saccade paradigm, due to the cognitive load that this paradigm places on the impaired working memory of AD patients. However, the EC group simply presented with a significantly reduced FOE in the antisaccade task compared to the reflexive saccade FOE.

#### *4.3.3.2 Saccade Amplitude, Duration and Maximum Velocity*

Analysis of the saccade amplitude, duration and maximum velocity data presented in Table 4.4 was conducted following the pattern of manipulation used in previous sections. However, no significant findings were shown to be present in any of these measures, with regards to the FOE between-groups or sub-groups.

Interestingly, the amplitude of saccades in the antisaccade overlap task appeared to be more accurate than amplitudes in the antisaccade gap task, although this observation did not reach significance between-groups. However, within-groups pair-wise comparisons (t-test) found that accuracy was not significantly different between the tasks for the AD and DOT groups. Thus, this finding did not support the hypothesis that the AD group would be significantly less accurate in the gap task than the overlap task. For the EC group, the difference between tasks was found to be significant, indicating that saccades were more accurate in the antisaccade overlap task, than the antisaccade gap task ($t[24]= 2.242$, $p<0.034$), due to overshoot in the gap task. A Pearson's correlation revealed only a weak relationship ($r = -0.23$), showing that antisaccade gap task latency was not significantly associated with amplitude. However, the correlation is in the right direction for a potential speed-accuracy

trade-off perhaps for some participants, thus the lower saccade latency is, the less accurate saccade amplitude will be in the antisaccade gap task, perhaps at least for some of the EC group (as indicated by the weak correlation). Within-group analysis of saccade velocity and duration, showed that there was no significant difference between gap and overlap conditions in the antisaccade paradigm for dementia patients. For the EC group however, saccade velocity was found was to be significantly higher in the gap task ($t[24]= 2.679$, $p<0.013$) than in the overlap task, which probably relates to the size of amplitude and the main sequence relationship, as the saccades had significant overshoot in the gap task.

#### *4.3.3.3 Inhibition Errors*

Descriptive statistics for the inhibition errors committed in the antisaccade paradigm are presented below in Table 4.6. Statistical analyses following the same pattern of tests from previous sections of Study II revealed that there was no significant FOE for inhibition errors for any group.

**Table 4.6** Descriptive Statistics for Inhibition Error Rates in the Antisaccade Paradigm

| | Antisaccade Task | | | | | |
|---|---|---|---|---|---|---|
| | Overlap errors (%) | | | Gap errors (%) | | |
| **Group** | Mean | SD | N | Mean | SD | N |
| **Elderly controls** | 14.06 | 11.43 | 24 | 17.56 | 14.03 | 24 |
| **Alzheimer's disease** | 47.83 | 26.57 | 13 | 50.04 | 29.19 | 13 |
| **Other dementia types** | 40.10 | 21.93 | 9 | 45.50 | 27.43 | 9 |

As can be seen in Table 4.6, the error rate was actually higher in the gap task than the overlap task as hypothesised, however this difference was not significant[15]. These findings do not support the hypothesis that for the AD group, the antisaccade gap task error rate would be higher than the antisaccade overlap task error rate, although errors were marginally higher.

[15] Supplementary analysis between antisaccade gap task and overlap task uncorrected errors and also, corrected errors revealed no significant differences within-groups.

In summary, only a negligible, hence, non-significant difference was found for the increase in inhibition errors rates across groups in the antisaccade gap task, compared with inhibition error rates in the antisaccade overlap task. Although it was clear that performance on the antisaccade paradigm was significantly different between the EC group and dementia groups (as emphasised in Study I, Chapter 3), this difference did not extend to between task analysis for the gap and overlap conditions.

## 4.4 Discussion

### 4.4.1 Key findings

The main findings for the present study can be summarised as follows:-

1. The magnitude of fixation offset effect for saccade latency in the reflexive saccade paradigm was found to be significantly greater for the DP group than for the EC group. However, at the sub-group level it was only possible to dissociate AD patients from the EC group, but not the DOT group.
2. There was no significant fixation offset effect for saccade latency in the antisaccade paradigm for the AD or DOT groups, whereas the EC group did have a significant fixation offset effect. The magnitude of fixation offset effect, was significantly attenuated for the EC group in the antisaccade paradigm, as compared with fixation offset effect in the reflexive saccade paradigm.
3. No fixation offset effect was obtained for saccade amplitude, duration and maximum velocity in any group or paradigm. The only significant differences on these measures were within the EC group who produced saccades that were significantly more accurate in the overlap task, in both

the reflexive saccade and the antisaccade paradigms. The EC group also had a significantly higher saccadic maximum velocity in the reflexive overlap task.

4. Directional errors in the reflexive saccade paradigm showed no significant fixation offset effects. In the antisaccade paradigm there was no fixation offset effect for the proportion of inhibition errors, in any of the groups.

The objective of this study was to investigate the FOE in AD, primarily for saccade latency, but also exploring saccade amplitude, duration, maximum velocity and errors. Deficits in the disengagement of attention have been established in a number of studies in AD, and the present study sort to establish the fundamental basis which underpins this attentional dysfunction, in terms of a fixation disengagement deficit. This study attempted to exploit the fixation disengagement deficit, by employing oculomotor paradigms designed with the aim of being sensitive enough to detect the deficit and thus dissociate AD from other groups. The analysis included both involuntary and voluntary saccade paradigms, to compare the magnitude of FOE between paradigms and between groups. A further reason for including the antisaccade paradigm, was to establish how working memory impairment in the AD group may affect attentional processes, given the results of Study I, where working memory impairment was considered as the principal underlying problem that formed the basis of inhibitory error in voluntary saccade tasks for the AD group.

### 4.4.2 Magnitude of Fixation Offset Effect for Reflexive Saccades

The magnitude of FOE for saccade latency in the reflexive saccade paradigm was examined between-groups and revealed a significant interaction between the DP group and EC group. However, although analysis of dementia sub-groups showed that each group was found

to have a significant FOE further analysis revealed that the magnitude of FOE was significantly greater for the AD patient group than for the EC group, though this measure did not significantly dissociate the AD group from the DOT. Furthermore, the magnitude of FOE for the DOT group was not found to be significantly different to that of the EC group. This possibly indicates that the DOT patients may lie somewhere on a continuum, from the FOE of healthy normal elderly controls to a higher magnitude of FOE brought about by AD.

The increased magnitude of FOE for the AD group was isolated to a significantly prolonged saccadic latency in the reflexive saccade overlap task, with a large effect size when compared with the EC group. The present study argues that the significantly prolonged saccadic latency in the reflexive saccade overlap task for AD patients is due to an impairment in the disengagement of fixation, which corresponds with previous studies of attention in AD, that have reported an attention-shifting or disengagement deficit (Parasuraman et al., 1992; Perry et al., 2000). Therefore, it is feasible to argue that the high uncorrected error rates reported for the AD group in Study I, are due to a disruption in the disengagement of fixation.

### 4.4.3 Magnitude of Fixation Offset Effect for Antisaccades

No significant difference was observed between-groups, for the magnitude of FOE in the antisaccade paradigm (saccade latency). Substantial intra-group variability was discovered for saccade latency in the dementia sub-groups, having a deleterious effect on the FOE. It is plausible to suggest that this may have been caused by the relatively small number of data points available for correct antisaccades for the AD and DOT groups, from which the mean latency was derived. However, the EC group were found to benefit from offset of the central fixation point, more consistently in the antisaccade gap task, generating a significant FOE. The EC group antisaccade latency means were derived from nearly 500 correct saccades, a considerably higher number of data points than the dementia patient groups.

There was no significant fixation offset effects for saccadic amplitude, duration or velocity. Conversely, amplitudes were in the main, found to be more accurate in the antisaccade overlap task. For the dementia patient sub-groups, no difference was found between antisaccade gap and overlap metrics, however, EC group saccadic amplitude was found to be significantly more accurate in the antisaccade overlap task.

### 4.4.4 Implications of the Fixation Offset Effect in Alzheimer's Disease

Where AD is concerned, the FOE has only been investigated in one previous study (Abel et al., 2002). Abel et al. (2002) found that the FOE for saccade latency was preserved in AD for reflexive saccade tasks, as the present study has confirmed. However, Abel and co-workers (2002) found that the magnitude of the FOE was no different to that of elderly controls and that both groups generated a large proportion of anticipatory saccades (grossly for the AD group). The present study found a significantly higher magnitude of FOE for the AD group compared with the magnitude of FOE for the EC group, but the AD magnitude was not found to be significantly greater than that of the DOT group. Furthermore, the present study found no evidence of extremely high rates of anticipatory saccades (Section 3.3.5). Additionally, the present study reported saccadic amplitude, duration, velocity and error rates in relation to the FOE, and can confirm that no FOE was present on any of these measures for any group. There were numerous methodological differences between the present study and the study by Abel et al. (2002), which may account for these findings (Section 4.1):

1). Most prominently, Abel et al. used a central fixation point that was extinguished simultaneously with target onset. However, the present study used an overlapping target that was present alongside the fixation point for the duration of each trial. Thus, the capacity for fixation of the central point was optimised. Previous research has demonstrated that a simultaneous fixation point offset and stimulus onset results in a reduced FOE, when compared with the FOE derived from no fixation offset (Forbes & Klein, 1996).

2). The Abel et al. (2002) study employed a target that was predictable in direction, whereas in the present study, the stimulus direction was randomised.

3). The temporal characteristics of the target stimulus in the Abel et al. (2002) study were randomised, whereas in the present study target onset time remained constant.

4). Target eccentricity was ±15° for the Abel et al. study, whereas a 4° target was employed in the present study.

The design of the present study resulted in a higher magnitude of FOE for the AD group, compared with the FOE of the EC group which was found to have been due to the overlap task resulting in saccades of significantly prolonged latency between-groups. Taken together, these results suggest that in the present study, the use of a smaller target eccentricity (±4°) and the randomisation of target direction facilitate participation in the task, making the test easier and more appropriate for elderly participants, most importantly dementia patients. This is in contrast with the Abel et al. study, which used temporal randomisation of stimuli combined with large target eccentricities (e.g. ±15°) and an unreported inter-trial interval, which appear to have induced high rates of anticipatory behaviour.

Given that the Abel et al. (2002) study reported no significant difference between the FOE for AD and controls, it should be noted that the FOE for the control group was found to be marginally larger than that for their AD group. A logical argument in the present study, is that the large magnitude of FOE for the AD group was due to the overlap condition, combined with task parameters that facilitated the ability to participate with a high level of valid trials and minimal anticipatory behaviour. However, the experimental parameters in the Abel et al. (2002) study - which used a central fixation point that was extinguished simultaneously with target onset - did not result in prolonged saccadic latency for their AD group. If Abel et al. (2002) had employed an overlap condition then they may well have found a larger magnitude of FOE for the AD group.

### 4.4.5 Neuroanatomical Considerations

The findings of this study can potentially inform both the understanding of neurodegeneration in AD and the debate over the attenuation of the FOE in the antisaccade paradigm compared to the magnitude of FOE reported in reflexive saccade paradigms. The findings correspond very well with the Forbes and Klein (1996) model illustrated in Figure 4.1, but are also interesting for the control of endogenously generated saccades, given the different accounts of this control between Forbes and Klein (1996) and Machado and Rafal (Machado & Rafal, 2000a; Machado & Rafal, 2000b).

For exogenous saccades there was no significant difference between AD group saccade latency and that of the EC group in the gap task, although typical of most studies in AD, latencies for AD patients were marginally prolonged. Following the Forbes and Klein (1996) model, in the gap task, removal of the fixation point facilitates disinhibition of the SAC system reducing saccade latency, which is intact for all experimental groups. However, in the overlap task, the disinhibition of the SAC system takes longer for all experimental groups, due to the brake effect of the fixation cells on movement cells and stimulation of inhibitory omnipause neurons in the SC, caused by the presence of the central fixation point. For the AD group, a delay in the disinhibition of the SAC system results in a larger magnitude FOE. The larger magnitude FOE may therefore be due to a dysfunction of the fixation neurons in the SC, causing inhibition of the movement cells, i.e. disruption of opponent neural processing (see Section 1.4.1.1). Alternatively there may be a disturbance of input from the PEF to the SC or PEF to the FEF (Sections 1.4.2.1 & 1.4.2.2 respectively), given vital parallel pathways that exist between these areas and the importance of the complex layers in the SC for visual processing, attention (dorsal layers), motor mapping and motor commands (ventral layers) (Section 1.4.1.2). The pathology in AD (Section 1.5.2.1) and the degeneration in parietal areas in early AD could plausibly account for a deficit in the disengagement of fixation and subsequent delay in attending the peripheral target, compared with healthy control participants.

For endogenously generated saccades in the antisaccade task, inhibitory control of the VGR is actively operating prior to saccade initiation, due to the planned nature of the antisaccade task. The ENDO system provides the tonic inhibition of the SC and inhibition is mediated by the prefrontal cortex, so the endogenous saccade program encounters less inhibition from the fixation system. This model is fine for the EC group in the present study with a relatively intact working memory. However, the AD group have been found to have a deficit of working memory, which may impede the preparatory set for the task. Therefore, not only is saccade latency prolonged in both the antisaccade gap and overlap task, due to their cognitive load, but consequently, there is no significant FOE either, as the presence or elimination of the fixation point has little effect when AD patient finds the task demands so high.

Further psychoneural considerations for these findings, in relation to recent literature in the field will be examined in the General Discussion in Chapter 9.

## 4.5 Conclusions

- ✧ The reflexive saccade paradigm incorporating gap and overlap conditions was able to dissociate between early Alzheimer's disease patients and elderly control participants, but could not distinguish between dementias of other types and the other groups.

- ✧ Prolonged saccade latency for the Alzheimer's patients in the reflexive overlap task, appears to be due to prolonged fixation which corresponds with the deficit in the disengagement of attention that has been previously reported by various studies of early Alzheimer's disease.

- ✧ The antisaccade paradigm, comprising gap and overlap tasks resulted in a significantly attenuated FOE for each group and could not dissociate between any of the groups. Only the elderly control group was found to have a reliable FOE in the antisaccade task.

- The antisaccade task appears to exert a high level of cognitive load for the Alzheimer's disease group, resulting in high variability of saccade latency and consequently, a lack of any significant fixation offset effect.

- Uncorrected errors reported in the antisaccacde task in Study I are likely to be due to a difficulty that AD patients have in generating a saccade to an empty location, whilst already fixating a target i.e. fixation disengagement is dysfunctional.

- Saccadic amplitude, duration, maximum velocity and error rates do not result in a fixation offset effect. Therefore, no benefit is derived from the removal of the central fixation point in the gap task for these measures for dementia patients or elderly controls.

- Consideration of experimental design and task parameters are crucial when conducting research with clinical groups.

# Chapter Five

# Study III: Investigating Effects of Age and Disease

## 5.1 Introduction

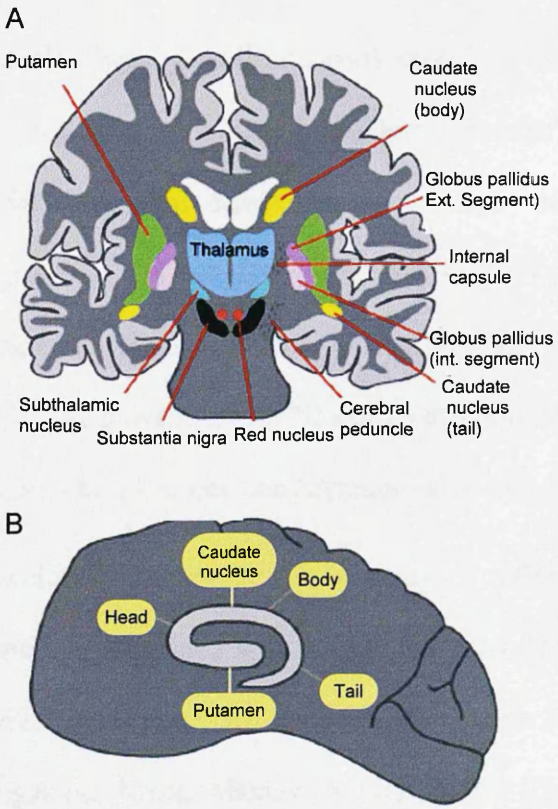
The previous chapters discovered some prominent saccadic abnormalities in dementia and more specifically AD, which included dysfunctional inhibitory control, poor error correction - as indicated by the proportions of inhibition errors that remain uncorrected - and a higher magnitude of FOE in reflexive saccade tasks. Study III aimed to discover whether the findings from Studies I and II could distinguish between control groups other than healthy elderly participants. Therefore, the study seeked to explore more closely, the degree to which normal aging may contribute to the saccadic and behavioural effects reported earlier and also, attempts to ascertain the extent to which the effects are characteristic of the disruption caused by the pathology in dementia. To this end, the present analyses extended the previous studies to include Parkinson's disease (PD) patients so as to examine disease effects and healthy young control (YC) partcipants, to analyse age effects more thoroughly.

### *5.1.1 Parkinson's disease*

The cardinal clinical features of idiopathic PD present as a triad of tremor, rigidity, and akinesia (Gelb, Oliver & Gilman, 1999; Waters, 1999). The principal area of the brain affected in PD is the basal ganglia, which comprises the striatum, globus pallidus (internal and external segments), intralaminar nuclei of the thalamus, subthalamic nucleus and the substantia nigra (comprising the pars reticulata (SNpr) and the pars compacta (SNpc); Figure 5.1). PD is a neurodegenerative disease, the pathology of which affects dopaminergic neurons in the SNpc

causing degeneration of the pathway between the SNpc and the striatum. This results in dopamine depletion in the striatum and leads to the symptoms mentioned above (Waters, 1999). Due to the degeneration of cell bodies in the brainstem, dopaminergic neurons in the caudate nucleus and most prominently in the putamen, also die out (Rosenzwieg, Leiman & Breedlove, 1999a).

**Figure 5.1** Illustration locating the Basal Ganglia in the Human Brain. Coronal section (A) and Sagittal section (B). (from Zigmond etal. 1999)




It is believed that loss of striatal dopamine increases tonic inhibitory outflow from the SNpr, via both the indirect pathway to the external segment of the globus pallidus and subthalamic nucleus, and also via the direct caudate-nigral pathway (DeLong & Georgopoulos, 1981). Some patients develop a marked cognitive decline, generally in the advanced stages of the disease process (Cummings, 1995). This is probably due to diffuse degeneration in the cortex and sub-cortical regions (Lueck, Tanyeri, Crawford, Henderson & Kennard, 1990). The cognitive deficits found in PD are characteristic of fronto-striatal disturbance (Taylor, Saint-

Cyr & Lang, 1986) and it has been found that dysfunction of delayed response and visuospatial working memory can appear at the moderate stage of disease (Brown & Jahanshahi, 1996; Pillon, Dubois, Lhermitte & Agid, 1986). Alexander and colleagues (Alexander, DeLong & Strick, 1986) anatomically defined pathways which link the frontal cortex, thalamus and basal ganglia, via a system of multiple, parallel and partially segregated basal ganglia cortico-thalamic loops. Alexander et al. (1986) suggested that disruption of these neural loops leads to cognitive deficit, due to dopamine deficiency in the DLPFC.

The etiology of Parkinson's disease is still unknown, therefore, distinguishing PD from other forms of disease that include Parkinson-plus syndromes or secondary Parkinson's disease (resulting from infection, toxins or vascular disease) can be clinically difficult. Furthermore, studies assessing diagnostic accuracy via autopsy, found that 15-20% of patients diagnosed with PD were actually misdiagnosed (Hughes, Daniel, Kilford & Lees, 1992; Jellinger, 1996). Therefore, the study of saccadic eye movements in PD can be difficult due to these potentially confounding factors, which should be taken into consideration when assessing findings.

Many studies have found common results in the study of reflexive saccades in PD, showing that performance is normal in patients with mild or moderate PD (Briand et al., 1999; Crawford et al., 1989b; Crevits, Vandierendonck, Stuyven, Verschaete & Wildenbeest, 2004; Fukushima et al., 1994; Kingstone, Klein, Maxner & Fisk, 1992; Kingstone et al., 2002; Kitagawa et al., 1994; Lueck et al., 1992a; Lueck et al., 1990; Mosimann et al., 2005; Shaunak et al., 1999; Vidailhet et al., 1994); Crevits et al. (2004) also reported a significant fixation offset effect. Antisaccade performance is also generally found to be normal for mild to moderate cases of PD (Fukushima et al., 1994; Kingstone et al., 1992; Kingstone et al., 2002; Lueck et al., 1990; Vidailhet et al., 1994), although in severe patients, performance has been found to deteriorate as evidenced by increased error rates and latency (Briand et al., 1999; Kitagawa et al., 1994). Thus, task difficulty does not appear to affect mild Parkinson's patients, but the effects in advanced Parkinson's - when cognitive deficit is likely, probably

reflects disruption of the DLPFC and this possibly relates to working memory function and its relationship with cognitive load of a given task. PD patients tested in saccadic paradigms involving a delay have been found to generate hypometric saccades, which is also the case when the central fixation point overlaps with the signal to generate a saccade (Crawford, Henderson & Kennard, 1989a; Hodgson, Dittrich, Henderson & Kennard, 1999; Lueck, Tanyeri, Crawford, Henderson & Kennard, 1992b; Rivaud-Pechoux et al., 2000; Shaunak et al., 1999). Other studies have also shown that PD patients generate more directional errors on delayed saccade tasks (Armstrong, Chan, Riopelle & Munoz, 2002; Yoshida, Yamada & Matsuzaki, 2002).

### *5.1.2 Normal Aging*

There is good reason to examine healthy ageing more closely by investigating a further healthy control group (YCs) to expand on the role played by healthy elderly control participants in the analyses of Studies I and II. The healthy ageing human brain may lose up to 8% of its mass, due to neuronal deterioration (Dekaban & Sadowsky, 1978) and a reduction of intracellular water content during the lifespan. Neuronal loss causes the degeneration of axons and consequently the loss of inputs to downstream cells. There is some compensation, as the loss of connectivity triggers nerve growth factor, which induces other neurons to sprout out dendritic branches and thus re-innervate at a structural level. However, this plasticity lasts for only a finite period, between fifty and seventy years of age, after which it ceases (Buell & Coleman, 1979). The neuronal loss in normal ageing, occurs mainly in areas of the frontal and temporal cortices (Creasey & Rapoport, 1985), other regions appearing little affected by the ageing process.

The extensive reduction in brain mass during the lifespan can result in a reduction in the capacity of cognitive function, but this varies greatly between individuals. For example, one study found that duration of arithmetic operations were increased and accuracy reduced for

elderly participants compared with younger controls, on working memory tasks that require frontal lobe function when the cognitive load of a task was increased (Oberauer, Wendland & Kliegl, 2003); Whereas processing rates with simpler tasks were equivalent between groups. However, tasks that involved selective access to working memory, showed no deficit for elderly people. Therefore, the ability to carry out tasks appears largely preserved, but information processing speed reduced with age. It is important to acknowledge, that there has been a large amount of research conducted on ageing, which found that working memory performance (executive function) and inhibitory control decline with age (Bowles & Salthouse, 2003; Chiappe, Hasher & Siegel, 2000). Studies have shown that if nonrelevant information is not suppressed – purportedly due to poor inhibitory control – working memory performance is impeded (Andres, Van der Linden & Parmentier, 2004; Hasher, Stoltzfus, Zacks & Rypma, 1991; Hasher, Zacks & May, 1999). Much of this research thus supports the inhibition-reduction model of proposed by Hasher and Zacks, which hypothesises that age-related deterioration of working memory is a consequence of the diminution in ability to inhibit irrelevant information. Accordingly, Hasher and Zacks postulate, that inhibition is a central mechanism in determining what information enters working memory and the consequential effects that this has on various types of cognitive function (Hasher & Zacks, 1988). When inhibitory control is poor the timing of relevant and nonrelevant information is compromised, which causes working memory to become cluttered and consequently results in the production of inappropriate responses.

The study of saccadic eye movements in healthy ageing has revealed that there are subtle changes in saccade latency for both reflexive and antisaccades. For example, various studies have revealed that saccadic latency for reflexive saccades is prolonged in elderly participants compared with younger controls (Abel, Troost & Dell'Osso, 1983; Carter, Obler, Woodward & Albert, 1983; Kaneko, Kuba, Sakata & Kuchinomachi, 2004; Munoz, Broughton, Goldring & Armstrong, 1998; Olincy et al., 1997; Shafiq-Antonacci et al., 1999;

Sharpe & Zackon, 1987; Spooner, Sakala & Baloh, 1980; Sweeney, Rosano, Berman & Luna, 2001; Warabi, Kase & Takamasa, 1984). However, the study of saccadic accuracy in reflexive tasks, as indicated by saccade amplitude, appears to be little affected by age (Shafiq-Antonacci et al., 1999; Sweeney et al., 2001; Warabi et al., 1984), although not all studies are in agreement with this (Olincy et al., 1997; Sharpe & Zackon, 1987). Interestingly, attentional shifting prior to target onset has also been found unaffected by age (Kaneko et al., 2004).

Performance by elderly participants on antisaccade tasks, has shown that antisaccade latency is significantly prolonged, compared with that of young controls (Munoz et al., 1998; Nieuwenhuis et al., 2000; Olincy et al., 1997; Shafiq-Antonacci et al., 1999; Sweeney et al., 2001). Furthermore, a number of studies have found that antisaccade error rate is increased significantly in healthy elderly participants compared with young controls (Fukushima et al., 1994; Nieuwenhuis et al., 2000; Olincy et al., 1997; Shafiq-Antonacci et al., 1999; Sweeney et al., 2001). However, the capacity for error correction following inhibitory error, appears to be intact in healthy elderly participants (Olincy et al., 1997; Sweeney et al., 2001).

### 5.1.3 Aims

The aim of the study was to examine salient findings from the earlier studies (I and II), in comparison to data gathered from additional control groups that included PD patients and YC participants. This was done in order to explore whether it was possible to distinguish between age effects and disease effects in the salient outcomes from the EC, DOT and AD groups. As saccadic control in mild to moderate PD has been found largely to be normal for reflexive and antisaccade tasks, this group should provide a convenient method for examining disease effects more closely and thereby distinguish more clearly the significant results revealed for the AD group. The inclusion of a young control group should also provide a method to further establish, which effects are due to dementia and which effects occur as a consequence of normal ageing.

The first hypothesis for this study was that PD patients would perform significantly better i.e. generating less inhibition errors than the AD group across the range of voluntary saccade tasks which demand varying degrees of working memory resources, as working memory function should be relatively intact in the PD group. Furthermore, performance of PD patients should not differ significantly from that of healthy elderly control participants. However, performance of the YC group should be significantly better than each of the other groups, as inhibition errors have been found to increase as a function of normal ageing.

It is also hypothesised, that the ability to self-monitor performance in the PD group should be significantly increased by comparison with the AD group, as indicated by inhibition errors generated in the antisaccade gap task. A further hypothesis, is that the PD group's capacity to correct erroneous saccades should be similar to that of the EC group, however, uncorrected error rates should be significantly lower than the AD group, indicating that self-monitoring capacity and correctness of performance in the PD group is relatively intact. Furthermore, the ability to self-monitor performance and generate correction for inhibition errors should not vary significantly between the YC, PD and EC groups as the capacity to carry out tasks in the elderly has been found to affect processing time and not the ability to carry out the task (Oberauer et al., 2003). Therefore, there should be no significant difference between the uncorrected error rates for these groups. However, the YC, PD and EC groups should produce significantly less uncorrected errors than the AD group, as the AD group are believed to have a deficit in the disengagement of attention (Parasuraman et al., 1992; 1993) and thus a disturbance in ability to generate a saccade to an empty location, once already fixating a target (all be it erroneously).

An additional hypothesis concerns the magnitude of the FOE in the reflexive saccade paradigm. The hypothesis here, is that the magnitude of FOE should be significantly larger for the AD group, by comparison to the PD and YC groups, whereas the magnitude of FOE for the EC group should not differ significantly from that of the PD and YC. Attentional deficits in

AD have been reported in numerous previous studies. As a neural correlate for the FOE has been located in the SC (Dorris & Munoz, 1995), this hypothesis is in accord with the notion of a disturbance in the disengagement of fixation (inhibition of movement cells by fixation cells) when already viewing a visual stimulus, particularly when the stimulus is fixated at a central location.

## 5.2 Methods

### 5.2.1 Participants

Participants for this study included patients diagnosed with mild to moderate idiopathic PD (N=25; age range = 48–74 years; mean = 62.8; SD = 7.4; male, n=16; female n=9) recruited from the Departments of Neurology and Neurophysiology, Royal Preston Hospital, Lancashire Teaching Hospitals NHS Trust, Lancashire, U.K. All were diagnosed on the basis of clinical evaluation by consultant neurologist, including motor function assessment with the Webster Rating Scale[16] (Webster, 1968) and the Hoehn and Yahr classification (Hoehn & Yahr, 1967) mean score = 2.2; SD = 0.83. PD patients were also free of dementia and assessed with the SMMSE and the EADAS cog. Due to clinical restraints of the study, it was not possible to test the PD patients 12 hours post medication, as suggested by previous clinical investigations of PD (Langston et al., 1992). Twenty-three of the PD patients were taking medication of levodopa and three patients were not taking any PD related medications. Patients were excluded under the criteria discussed in Chapter 2 (Sections 2.1), thus none of the patients were taking anticholinergic drugs or any medication known to affect cognition or oculomotor function and therefore, any additional medications conformed to those outlined in Sections 2.2.1 and 2.2.1.1. All patients gave written informed consent prior to participation in the study[17].

[16] Unfortunately the Webster Rating Scale scores were unavailable at the time of writing this thesis.

[17] Ethical approval for this study was granted by Lancaster University Research Ethics Committee and the Local Research Ethics Committee for the NHS Trust (2001).

YC participants were recruited from the postgraduate student population at Lancaster University[18] (N=17; age range = 22–27 years; mean = 23.82.5; SD = 1.8; male, n=8; female n=9). All YC participants reported good health, via health questionnaire and gave written informed consent.

Dementia patients and EC participants were from the same groups reported in Chapters 3 and 4. The AD patients (N=17; age range = 70-88; mean = 76.9; SD = 4.9; male n=12; female n=5) and DOT (N=11; age range = 68-81years; mean = 75.8; SD = 4.4; male n=7; female n=4). The composition of the EC group was (N=33; age range = 58–85 years ; mean = 70.5; SD = 6.0; male n=13; female n=20).

### 5.2.2 Assessment of Saccadic Eye Movements

All participants used the equipment, task protocol and experimental procedures described in Chapter 2 (Section 2.3), which involved the reflexive saccade gap and overlap paradigm; No-Go and Go/No-Go paradigms; and antisaccade gap and overlap paradigm with a central fixation point displayed at $0^{\circ}$ and target at $\pm 4^{\circ}$ in the horizontal plane, presented randomly by direction. Therefore, it was possible to examine inhibitory control and also, the fixation offset effect. Unfortunately, it was not possible to gather Go/No-Go task data from the Parkinson's disease group.

As in Chapter 3, the reflexive gap task was presented first, which is particularly important for testing inhibitory control, in order to enhance or maximize the prepotent response and also to avoid potential carry-over effects from voluntary saccade paradigms (Roberts et al., 1994). Furthermore, Perry and Hodges (Perry & Hodges, 1999) highlight that dementia patients are more amenable when less cognitively demanding tasks are administered first. As is Chapter 3, directional errors in the reflexive saccade gap task were omitted from the analyses as so few were made (see Table 5.3).

[18]I am very grateful to Sue Tetley for collecting the healthy young control group data as part of her postgraduate MSc. degree research.

### 5.2.3 Statistical Analysis

Statistical analyses were carried out using SPSS version 11.5 (SPSS Inc., Chicago Ill). As in the previous studies laterality effects were absent from all variables, therefore data from left and right hemifields were collapsed. The skewness index was used to assess the normality of oculomotor variables, and variables transformed using square root or square, for positive (>1) or negative (<-1) skewness respectively (Tabachnick & Fidell, 1996). Analyses were conducted on the salient findings from previous studies, to include the PD and YC groups. These procedures incorporated one-way analysis of variance (ANOVA) or two-factor repeated measures mixed ANOVA with trend analysis. For analyses using repeated measures ANOVA, Mauchly's test was conducted on each variable to assess assumptions of sphericity. If assumptions of sphericity were violated, the Greenhouse-Geisser epsilon correction of degrees of freedom were used (Jennings, 1987). Group comparisons involved post hoc analyses using the Sheffe test and also, where specific hypotheses where tested, the Least Significant Difference t-test was used to evaluate the fixation offset effect. Within-groups pair-wise comparisons (t-test), were applied where applicable. Correlational investigations were conducted using Spearman's rank order correlation coefficient.

## 5.3 Results

Skewness was found to be present as in the previous studies for some variables, which was transformed to normalise the distribution. As in previous the studies, statistical analysis of transformed variables generated output that was practically the same as that produced by untransformed scores, therefore for clarity of interpretation and descriptive statistics, the results given below use untransformed versions.

### 5.3.1 Clinical Rating Scales and Neuropsychological Assessment

Clinical rating scale and neuropsychological assessment scores are displayed in Table 5.1. There was only slight difference in performance between the EC and PD groups across the range of tests (only Verbal Fluency scores were available for the YC group).

**Table 5.1** Clinical Rating Scale and Neuropsychological Assessment Scores to include Parkinson's Disease Patients and Young Control Participants

| | Groups | | | | | | | | | Dementia sub-groups | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Elderly control | | | Young control | | | Parkinson's disease | | | Alzheimer's disease | | | Other dementia | | |
| | Mean | SD | N | Mean | SD | N | Mean | SD | N | Mean | SD | N | Mean | SD | N |
| **SMMSE** | 29.09 | 1.13 | 33 | - | - | | 28.92 | 1.29 | 25 | 21.35 | 4.72 | 17 | 24.00 | 7.06 | 11 |
| **EADAS** | 7.79 | 2.46 | 33 | - | - | | 6.68 | 2.46 | 25 | 22.76 | 9.35 | 17 | 19.27 | 15.65 | 11 |
| **VFlu** | 38.42 | 10.63 | 33 | 34.12 | 10.17 | 17 | 36.60 | 10.50 | 25 | 22.59 | 10.32 | 17 | 22.55 | 11.07 | 11 |
| **DSF** | 10.30 | 2.28 | 33 | - | - | | 9.80 | 1.78 | 25 | 8.65 | 2.23 | 17 | 8.91 | 2.26 | 11 |
| **DSR** | 7.39 | 2.36 | 33 | - | - | | 6.72 | 2.28 | 25 | 5.06 | 2.46 | 17 | 5.91 | 3.30 | 11 |
| **SSF** | 7.45 | 1.80 | 33 | - | - | | 8.04 | 1.46 | 25 | 5.53 | 2.07 | 17 | 5.09 | 2.17 | 11 |
| **SSR** | 6.73 | 1.18 | 33 | - | - | | 7.08 | 1.38 | 25 | 4.24 | 2.11 | 17 | 4.45 | 2.07 | 11 |

Vflu=Verbal Fluency; DSF=Digit Span Forward; DSR = Digit Span Reverse; SSF=Spatial Span Forwards; SSR=Spatial Span Reverse

For the SMMSE, EC and PD scores were virtually the same, whereas on the EADAS cog, the PD group performed marginally better than the EC group. However, the EC group performed slightly better than the PD group at each of the other tests. The dementia sub-groups are shown to have performed more poorly on all tests than the EC and PD groups. Univariate ANOVA was conducted to assess between-group differences statistically for each measure. The omnibus ANOVA results showed that there were significant differences between-groups on each test (Table 5.2).

Multiple comparisons using the Scheffe post-hoc test revealed that the PD group generated test scores which were significantly better than both the AD group and the DOT group, on the SMMSE, EADAS cog, Verbal Fluency, Spatial Span Forward and Spatial Span Reverse ($ps<0.01$). Importantly, no significant difference was found between the PD group and EC group on the same measures ($ps>0.6$ NS).

**Table 5.2** Between-Groups Statistical Analyses for Clinical Rating Scale and Neuropsychological Assessment Scores

| Test | Omnibus between-groups ANOVA |
|---|---|
| SMMSE | F[3,82]= 25.58, $p$<0.0001 |
| EADAS cog | F[3,82]= 25.10, $p$<0.0001 |
| Verbal fluency | F[4,98]= 9.85, $p$<0.0001 |
| Digit Span Forward | F[3,82]= 2.76, $p$<0.047 |
| Digit Span Reverse | F[3,82]= 3.58, $p$<0.017 |
| Spatial Span Forward | F[3,82]= 11.17, $p$<0.0001 |
| Spatial Span Reverse | F[3,82]= 16.82, $p$<0.0001 |

Young Control data only available for Verbal Fluency test

However, the conservative error correction afforded by the Scheffe test resulted in the difference between the PD group and AD group for the Digit Span Reverse test failing to reach significance (where a simple between-groups t-test result was significant t[40]=-2.24, $p$<0.03). The EC group score for Digit Span Reverse was shown to be significantly better than that of the AD group ($p$<0.05), but not significantly different from the DOT group or PD group. None of the groups differed significantly from each other on Digit Span Forwards, when compared using the Scheffe test. The YC group were found to perform significantly better than the AD group on the Verbal Fluency test ($p$<0.05), but were not significantly different from the EC ($p$>0.7), PD ($p$>0.9) or DOT ($p$>0.09) groups.

These results appear to confirm the assertion that the PD group was dementia free, as measured by the clinical rating scales and the fact that PD scores did not differ significantly to those of the EC group. Moreover, the PD group actually scored marginally lower than the EC group on the EADAS cog test (high EADAS cog scores indicate poor performance). Furthermore, the PD group did not differ significantly from the EC group on any of the

neuropsychological assessments. In addition to this, the EC and PD groups performed marginally higher than the YC group on the Verbal Fluency test, reputed to be a test of frontal lobe function. Therefore, the implication is that of better frontal lobe function (at least for Verbal Fluency) for the PD and EC groups than for the YC group.

### 5.3.2 Group Comparisons of Saccadic Error Rates

#### 5.3.2.1 Comparing Inhibitory Errors Across Voluntary Saccade Tasks

Inhibitory error rates were compared across the No-Go, antisaccade gap and Go/No-Go oculomotor tasks levels, to assess the effects of age and disease on the findings revealed in Section 3.3.2.1. Descriptive statistics are displayed in Table 5.3 below. The Go/No-Go task was not administered to the PD patients, therefore a separate analysis was carried out on the No-Go and antisaccade gap task data alone, so as to include this group.

**Table 5.3** Descriptive Statistics for Error Analysis with Parkinson's Disease Patients and Young Controls

| | | Groups | | | | | | | | | Dementia sub-groups | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | EC | | | YC | | | PD | | | AD | | | DOT | | |
| | | Mean | SD | N | Mean | SD | N | Mean | SD | N | Mean | SD | N | Mean | SD | N |
| Antisaccade Gap | Correct saccades (%) | 78.34 | 14.77 | 32 | 88.03 | 9.68 | 17 | 68.62 | 19.55 | 25 | 33.75 | 27.40 | 17 | 48.84 | 29.03 | 10 |
| | Inhibition errors (%) | 16.30 | 12.82 | 32 | 10.77 | 9.26 | 17 | 27.50 | 17.05 | 25 | 50.66 | 27.49 | 17 | 44.70 | 25.99 | 10 |
| | Uncorrected errors (%) | 2.09 | 5.50 | 32 | 0.99 | 1.84 | 17 | 2.02 | 4.73 | 25 | 23.47 | 23.25 | 17 | 13.76 | 20.42 | 10 |
| | Corrected errors (%) | 14.21 | 11.88 | 32 | 9.78 | 9.48 | 17 | 25.48 | 16.51 | 25 | 27.19 | 21.74 | 17 | 30.94 | 24.76 | 10 |
| Go/No-Go | Inhibition errors (%) | 35.78 | 27.70 | 32 | 7.26 | 7.84 | 17 | - | - | | 63.39 | 32.32 | 17 | 45.79 | 23.78 | 10 |
| No-Go | Inhibition errors (%) | 10.31 | 13.32 | 32 | 4.12 | 6.18 | 17 | 17.24 | 23.53 | 25 | 28.49 | 27.35 | 17 | 41.82 | 31.57 | 11 |
| Reflexive saccade Gap | Correct saccades (%) | 90.98 | 9.87 | 32 | 98.74 | 3.33 | 17 | 88.07 | 9.31 | 25 | 89.88 | 12.10 | 17 | 91.67 | 12.22 | 11 |
| | Directional errors (%) | 0.92 | 2.06 | 32 | 0.25 | 1.04 | 17 | 2.26 | 2.46 | 25 | 2.22 | 2.99 | 17 | 1.91 | 2.89 | 11 |
| | Uncorrected errors (%) | 0.13 | 0.74 | 32 | 0.25 | 1.04 | 17 | 0.27 | 1.34 | 25 | 0.49 | 1.39 | 17 | 0.76 | 1.70 | 11 |
| | Corrected errors (%) | 0.79 | 1.67 | 32 | 0.00 | 0.00 | 17 | 2.00 | 2.32 | 25 | 1.72 | 2.97 | 17 | 1.15 | 1.96 | 11 |

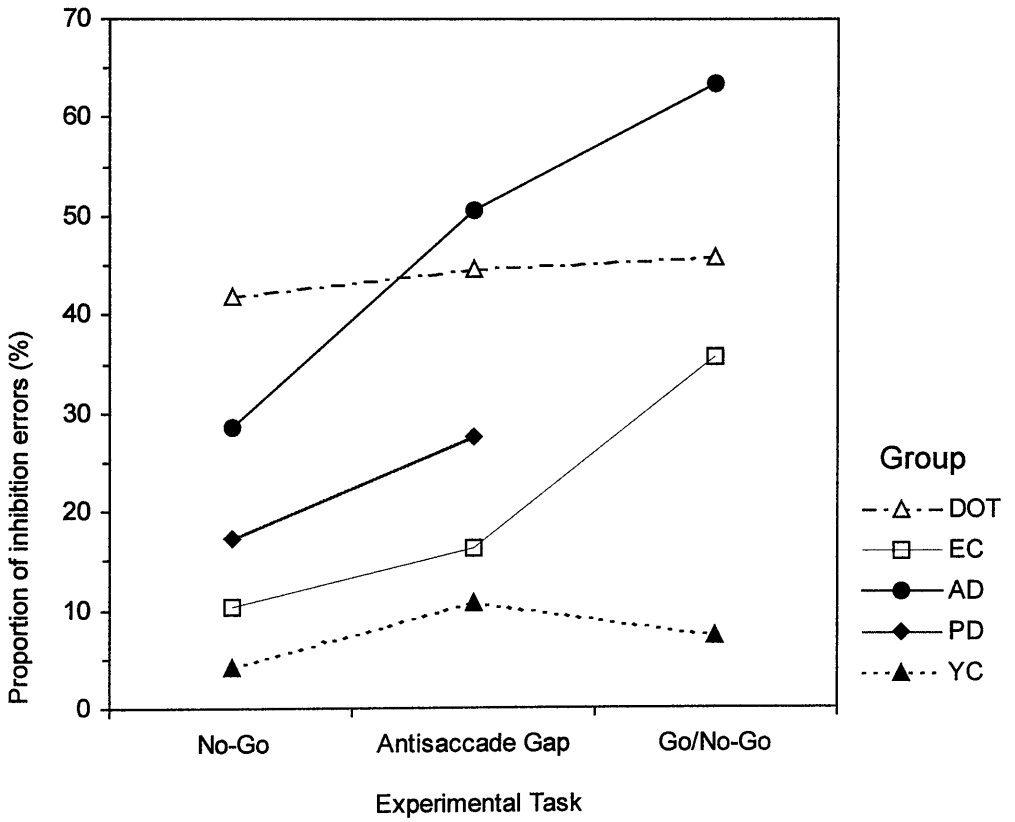
EC = Elderly control; YC = Young control; PD = Parkinson's disease; AD = Alzheimer's disease; DOT = Dementia of other types



5 Investigating Effects of Age and Disease

Whereas Study I revealed a linear increase in inhibitory error rates for each group across the oculomotor tasks according to working memory load, the present study found that the YC and PD groups both produced higher error rates in the antisaccade gap task compared to the No-Go task only. The inhibitory error rate was marginally lower for the YC group in the Go/No-Go task than the antisaccade gap task, which appears to be an exception to the rule. However, it was not possible to examine whether there was a linear increase in error from the antisaccade task to the Go/No-Go task for the PD group, due to the lack of data for this task (Figure 5.2).

**Figure 5.2** Inhibitory Errors Across Voluntary Saccade Tasks




For the statistical analysis, firstly a two-factor repeated measures mixed ANOVA, with the three task levels forming the within-subjects factor: *voluntary saccade task* (as in Study I) and the between-groups factor: *group* (YC, EC, AD and DOT) was calculated. The interaction

between voluntary saccade task and group was found to be significant F[5.4, 130.6]= 4.64, $p<0.001$, indicating that there were significant differences between the groups in the number of errors generated across the range of tasks. The corresponding sub-groups interaction found in Section 3.3.2.1 was also found to be significant, therefore, the present interaction appeared somewhat more complex and probably the result of the high antisaccade error rate for the AD group, relative to EC and YC scores and also a lower Go/No-Go task error rate for the YC group (Figure 5.2).

The main effects of the factors: voluntary saccade task and group, were also significant (Voluntary saccade task, F[1.8, 130.6]= 20.32, $p<0.0001$; Greenhouse-Geisser correction; Group, F[3, 72]= 21.09, $p<0.0001$), which shows that there were significant differences between the overall error rates on each oculomotor task and supports the hypothesis that inhibitory error rate would vary as a function of task cognitive load; specifically, that there would be significant overall differences between-groups respectively. Post-hoc comparisons using the Scheffe test on voluntary saccade task revealed that performance of the YC and EC groups did not differ significantly. However, both the AD and DOT groups were found to perform significantly poorer on this factor than the YC group ($ps< 0.01$), the AD group also significantly poorer than the EC group. Therefore, poor performance on this factor is dissociable from the effects of normal ageing.

To examine the PD group a further two-factor repeated measures mixed ANOVA was carried out on the within-groups factor: voluntary saccade task. For this analysis, the factor voluntary saccade task comprised just two levels, No-Go and antisaccade gap task (due to the lack of Go/No-Go data for the PD group, Figure 5.2) and the between-groups factor five levels, comprising the participant sub-groups (PD, YC, EC, AD and DOT). The interaction was not found to be significant (F[4, 96]= 1.9, $p>1.0$ NS). The main effects of voluntary saccade task and group were both significant (Voluntary saccade task, F[1, 96]= 22.64, $p<0.0001$; Group, F[4, 96]= 14.2, $p<0.0001$), again showing that there were overall differences in the error rates

generated across the tasks and between the groups, respectively. Scheffe post-hoc comparisons of the factor: voluntary saccade task, showed that there was no significant difference between the YC and PD groups, YC and EC groups or the PD or EC groups for this factor. However, significant differences were noted between the YC group and the AD and DOT groups ($ps<0.01$); the PD and the AD group ($p< 0.05$); and the EC group and the AD and DOT groups ($ps<0.01$). The difference between the PD group and the DOT group was only approaching significance ($p<0.06$) due to the conservative precaution to avoid *familywise* type I error afforded by the Scheffe test. These results emphasise that the magnitude of change in error rate from the No-Go task to the antisaccade gap task was significantly greater for the AD group compared to the PD, YC and the EC groups, whilst for the DOT group, the difference was most pronounced for the YC and EC groups. A within-groups trend analysis also showed that the profile of the YC group data across the three voluntary saccade tasks had no significant trends (i.e. linear, quadradic etc.), as indicated by the rather flat YC line graph illustrated in Figure 5.2. These findings support the hypotheses that error rates would be greater for the AD group than control groups on oculomotor tasks that require higher working memory resources and that the AD error rates would increase linearly across the saccadic tasks. These effects are distinguishable from normal ageing and PD another neurological disease.

Univariate ANOVA was conducted to examine the differences between-groups on each oculomotor task (Go/No-Go task without the PD group). The results showed that there were significant differences overall between-groups for each task (No-Go, $F[4,96]= 15.78$, $p<0.0001$; antisaccade gap, $F[4,97]= 7.78$, $p<0.0001$; and Go/No-Go, $F[3,72]= 14.27$, $p<0.0001$).

Post-hoc Scheffe multiple comparison tests showed that in the No-Go task, the YC group generated significantly less inhibitory errors than both the AD ($p< 0.05$) group and the DOT group ($p<0.01$), whereas, no significant difference was found between the YC, PD and EC groups. As the working memory demand of the No-Go task is low, it was expected that

there would be no significant difference between the proportion of inhibitory errors generated by the YC, PD and EC groups on this task. The PD group generated significantly less errors than the DOT group ($p<0.05$), but generated non-significantly less inhibitory errors than the AD group. Whereas Study I revealed that the EC group generated significantly less errors than the AD and DOT groups. The No-Go task inhibitory error rate therefore appears to be able to distinguish between healthy young and old participants, but not between the PD and AD disease groups.

For the antisaccade gap task, Scheffe tests revealed that the YC group generated significantly less inhibitory errors than both the AD group ($p<0.01$) and the DOT group ($p<0.01$). However, no significant difference was found between inhibitory error rates for any combination of the YC, PD and EC groups. The PD group, like the YC group and the EC group in Study I, also created significantly less inhibitory errors than the AD group ($p<0.01$), but although the PD group produced less inhibitory errors than the DOT group, this difference did not reach significance ($p>1.0$ NS). Furthermore, PD group correlations between oculomotor tasks and neuropsychological assessments that place high demands on working memory resources were found to be non-significant. Therefore, the antisaccade inhibitory error rate appears to be able to distinguish between the effects of both normal healthy ageing and PD which also corresponds with the hypothesis that error rates will be lower in these groups, than in the dementia groups and also, that error rates would increase linearly as a function of task cognitive load most significantly for the AD group due to working memory deficit.

For the Go/No-Go task, multiple group comparisons revealed that the YC group created significantly less errors than each of the groups included in the analysis (PDs not included) i.e. AD, DOT and EC ($ps<0.01$). Whereas Study I revealed a significant difference between the healthy EC group and AD group, the present results seem to indicate that the Go/No-Go task

inhibitory error rate appears to deteriorate as a function of both normal healthy ageing through the life, which in turn is dissociable from AD effects.

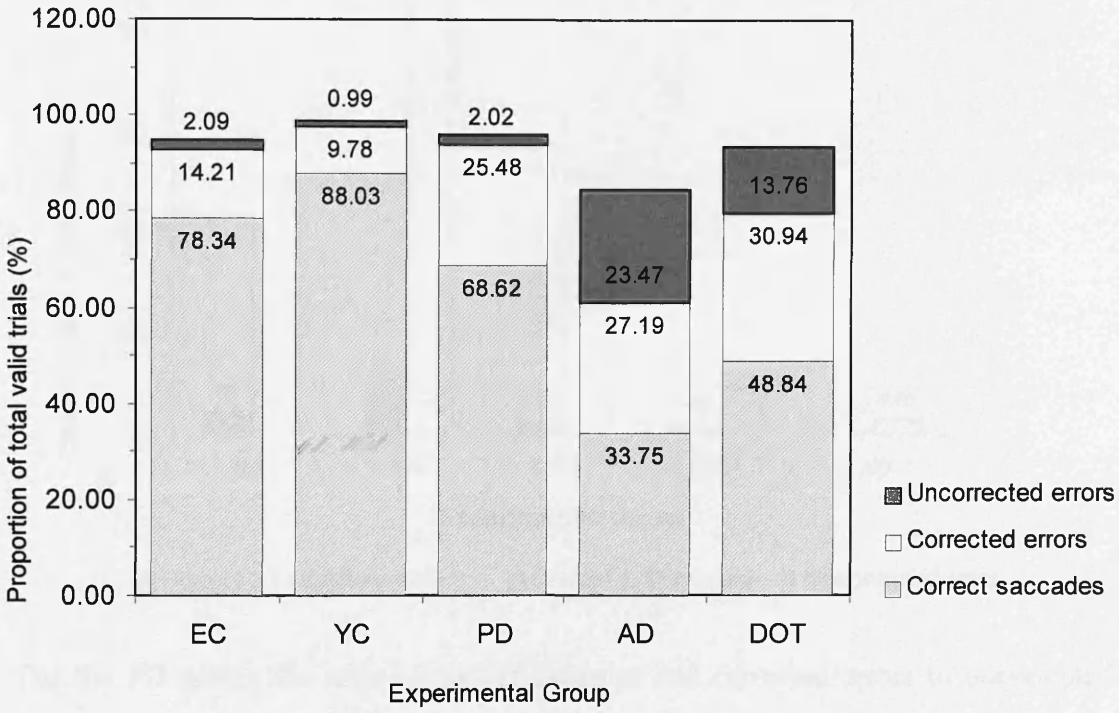
In summary, taken together the above findings specifically show that when the cognitive load for oculomotor tasks places low to moderate demands on working memory resources (No-Go and antisaccade), inhibitory error rates increase linearly with no significant difference between the rates of healthy young and elderly controls, and PD patients. However, the significantly lower inhibitory error rates for these three control groups, compared with the higher rate for AD patients, demonstrates that AD can be dissociated from the three control groups, which control for age and disease. When the cognitive load of the oculomotor task was high (as in the Go/No-Go task), healthy young controls were found produce significantly less inhibitory errors than all other experimental groups (although no data was available to confirm this for the PD group). Therefore, it appears that oculomotor tasks with high cognitive load have the capacity to dissociate between the effects of AD and healthy ageing. Furthermore, younger people do not necessarily find the Go/No-Go task more demanding than the No-Go or the antisaccade task, whereas this is not the case with healthy elderly or diseased groups. In fact, pair-wise within-groups comparisons confirmed this, revealing that YC group inhibitory error rates in the antisaccade gap task and Go/No-Go tasks were not significantly different ($t[16]= 1.05$, $p>0.312$ NS), neither was there a significant difference between YC error rates in the No-Go and Go/No-Go tasks ($t[16]= 1.29$, $p>0.216$ NS). However, there was a significant linear increase in YC group inhibitory errors in the antisaccade gap task, compared with the No-Go task ($t[16]= 2.46$, $p<0.026$). The same linear increase from No-Go to antisaccade gap task inhibitory error rates was also significant for the PD group ($t[24]= 2.07$, $p<0.049$).

### 5.3.3 *Analysis of Corrected and Uncorrected Errors: Self-Monitoring Performance on the Antisaccade Gap Task*

The components of the inhibitory error rate in the antisaccade gap task - corrected and uncorrected errors - were analysed to investigate further, the effects of age and disease

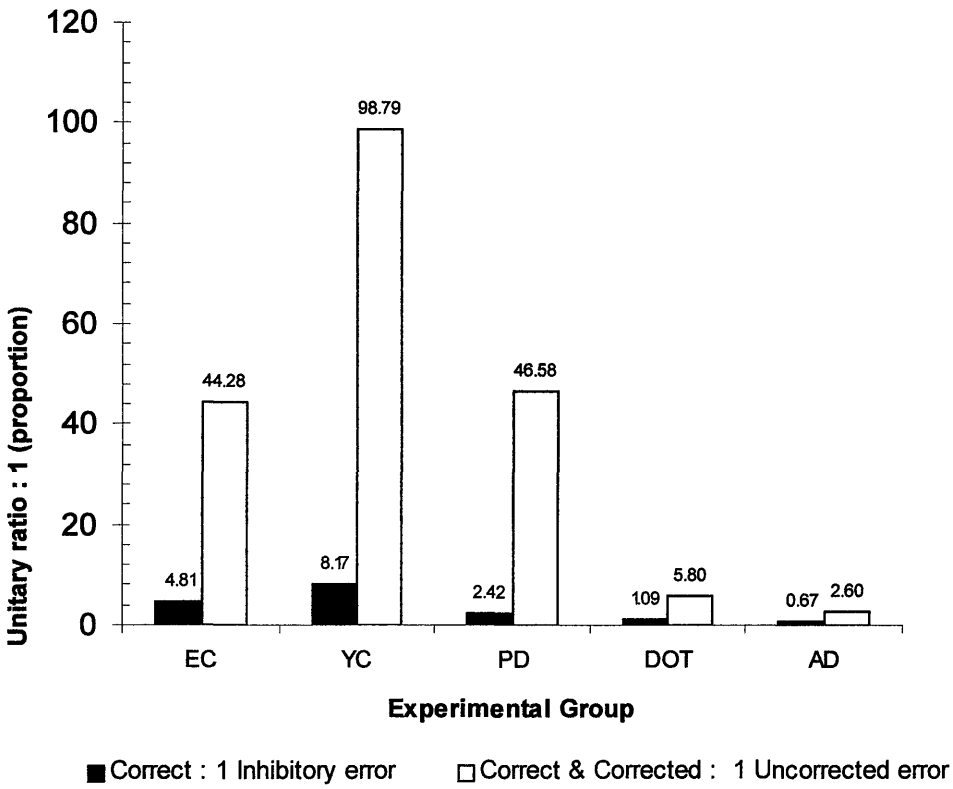
by including the YC and PD groups. The proportions of correct saccades, corrected errors and uncorrected errors are displayed below in Figure 5.3.

**Figure 5.3** Stacked Bar Charts Illustrating the Proportions of Correct Saccades, Corrected Errors and Uncorrected Errors Including Parkinson's Disease Patients and Young Controls




The mean proportions of correct saccades, corrected errors and uncorrected errors were also evaluated as unitary ratios to compare the balance between attention, self-monitoring and error correction for the YC and PD groups, with the output from Study I. The ratios are displayed in Figure 5.4 below. The ratio of correct and corrected error saccades to uncorrected errors for the YC group was very high (98.79:1). This appears to have been due to the high correct saccade rate, extremely low uncorrected error rate and the majority of inhibitory errors having been corrected (Figure 5.4), which demonstrates good task awareness and self-monitoring capacity, and thus the ability to efficiently take corrective action when necessary. The YC group ratio was actually found to be over twice that of the EC group ratio (44.28:1) for correct and corrective saccades to uncorrected saccades.

**Figure 5.4** An Illustration using the Unitary Ratio to Display the Ratio for the Proportion of Correct Saccades to Inhibitory Errors Compared to the Proportion of Correct Saccades + Corrected Error saccades to uncorrected Errors in the Antisaccade Tasks by Sub-group



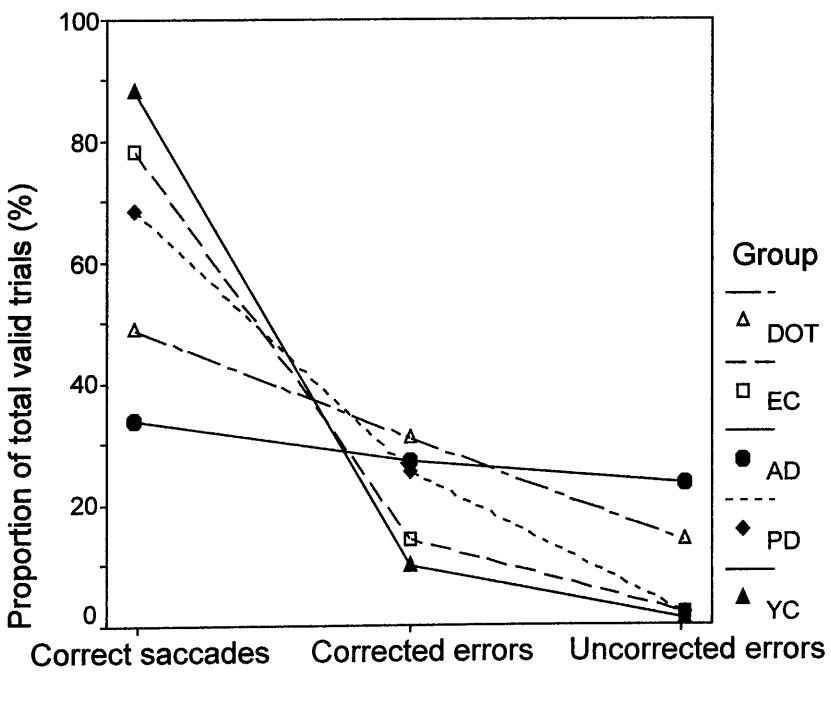

For the PD group, the ratio of correct saccades and corrected errors to uncorrected errors (46.58:1) was in fact higher than that of the EC group. Although in this instance, this was the result of a high corrected error rate, i.e. although the PD group have higher combined inhibitory error rate (and lower correct saccade rate) than the EC group (not significantly different, see Section 5.3.2.1), a high proportion of PD errors were corrected. Consequently, the PD group were found to have a low uncorrected error rate, which was virtually indistinguishable from that of the EC group (Figure 5.3). Thus, it would appear that whilst the PD group produced a higher proportion of combined inhibitory error, than the EC group, the capacity of the PD group for error correction demonstrates task understanding, awareness and therefore, intact ability for self-monitoring. Unitary ratios expressing the ratio of correct saccades to inhibitory errors (uncorrected errors + corrected errors) are also incorporated into

Figure 5.4, to highlight the difference across the groups for correct primary saccadic action compared with erroneous saccades.

The findings from the present study reinforce the data from Study I and make plain, that the antisaccade error rates for the dementia subgroups can be dissociated from age and a disease effect. To examine this more closely and statistically, the data for correct saccades, corrected errors and uncorrected errors were subjected to a two-factor repeated measures mixed ANOVA, to form the factor: *correctness of performance* and the experimental groups were included as the between-groups factor so as to compare the YC and PD groups along with groups with earlier analyses.

A significant interaction was found between correctness of performance and group ($F[6.8,162.97]= 14.70$, $p<0.0001$; Greenhouse-Geisser correction), which demonstrates clearly that there were differences in the magnitude of correctness of performance across the groups (Figure 5.5). The line graphs in Figure 5.5 illustrate that the YC and EC groups have a similar shape to their data but that the YC group's correctness of performance is more efficient than all other groups, closely followed by the EC group and then PD group.

**Figure 5.5** Graphs Displaying Correctness of Performance in the Antisaccade Gap Task for Parkinson's Disease Patients and Young Controls



The main effects of correctness of performance ($F[1.70,162.97]= 183.73$, $p<0.0001$) and group ($F[4,96]= 10.59$, $p<0.0001$) were both significant, showing that there were omnibus differences in the levels of the factor: correctness of performance and between the groups. Visual examination of the graphs in Figure 5.5, shows that the efficiency of correctness of performance gradually reduces by group down to the AD group, who produce a rather flat line across the levels of the factor. As previously reported in Section 3.3.3.1, trend analysis of the AD data revealed that there were no significant trends in the data, whereas significant linear trends were present within the EC group and DOT group data. Trend analysis carried out across the levels of the factor correctness of performance within the YC group and PD group data, revealed a significant linear trend for both groups (YC, $F[1,16]= 1371.56$, $p<0.0001$; PD, $F[1,24]= 227.7$, $p<0.0001$), although, as with the EC group, there was also a significant quadratic trend component in the YC group data ($F[1,16]= 98.99$, $p<0.0001$); due to the high proportion of correct saccades which is in contrast to the flattening out in the tail of the graph, to illustrate error proportions. To expand on the trend analysis, within-groups paired-samples t-tests were conducted on the YC and PD groups data, between the various combinations of the levels of the factor, correctness of performance and are displayed in Table 5.4.

**Table 5.4** Within-group t-tests Comparing Proportions of Correct Primary Saccades, Corrected Errors and Uncorrected Errors

| Within-group pair-wise | YC group | PD group |
|---|---|---|
| Correct saccade vs Uncorrected error | ($t[16]= 37.03$, $p<0.0001$ | ($t[24]= 15.09$, $p<0.0001$ |
| Correct saccade vs Corrected error | ($t[16]= 16.99$, $p<0.0001$ | ($t[24]= 6.24$, $p<0.0001$ |
| Corrected error vs Uncorrected error | ($t[16]= 3.62$, $p<0.002$ | ($t[24]= 6.78$, $p<0.0001$ |

The results of the within-groups paired samples t-tests show a familiar pattern to that found for the EC group in Section 3.3.3.1, where a significant difference is present between

each level of the factor: correctness of performance. This is in direct contrast to the AD group, where there is no significant difference between levels of the factor.

To examine the specific differences between the error proportions for each group, between-groups analysis of oculomotor error type was conducted to include the YC and PD group data. Univariate ANOVA revealed significant differences between groups for both corrected errors ($F[4,96]= 5.35$, $p<0.001$) and uncorrected errors ($F[4,96]= 12.16$, $p<0.0001$). Multiple comparisons using the Scheffe post-hoc test revealed that for corrected errors, the YC produced a significantly lower proportion than the DOT group ($p<0.05$), whereas although the YC group generated less corrected errors than the AD and PD groups, this difference was only approaching significance ($p>0.05$ NS). There was no significant difference between the YC group and the EC group for the proportion of corrected errors ($p>0.9$). The proportion of corrected errors for the PD group was not found to be significantly different from any other group ($p>0.05$).

The multiple comparisons output for uncorrected error rates showed that the YC group generated significantly less uncorrected errors than the AD group (as did the EC group; $ps<0.01$). The PD group also created significantly less uncorrected errors than the AD group ($p< 0.01$). However, there were no significant differences between the proportions of uncorrected errors committed by the PD, YC and EC groups ($ps>0.9$). This is in support of the hypothesis that these groups would perform in a similar fashion with regard to the number of errors that remain uncorrected; as they either make higher proportions of correct saccades or are able to correct the majority of errors. Additionally, no significant difference was found between the DOT group uncorrected error rate and any other group, although they did generate more uncorrected errors than the YC, EC and PD groups but less uncorrected errors than the AD group. It should be noted, that the Scheffe test applies a very conservative adjustment to avoid family-wise error. When a t-test was used to assess the groups (with no precaution against Type I error) the YC, PD and EC groups were still found not to differ significantly

from each other and of course, to have generated significantly less uncorrected errors than the AD group, moreover, they were found to generate significantly less uncorrected errors than the DOT group. Furthermore, using the simple t-test also revealed that the DOT group created significantly less uncorrected errors than the AD group ($p<0.05$).

Taken together, these findings support the hypotheses that the capacity for error correction and the proportions of errors that remain uncorrected will not be significantly different between the YC, PD and EC groups. Moreover, that the uncorrected error rate will discriminate between these groups and the AD group's overall error correction capacity, taking into account the proportion of errors that remain uncorrected.

### 5.3.4 Magnitude of Fixation Offset Effect for Reflexive Saccade Latency

The present analysis investigated the FOE for saccade latency in the reflexive saccade paradigm, comparing the subset of data for AD, DOT and EC groups from Study II, with the data gathered from the YC and PD groups. The descriptive statistics for this data set are displayed below in Table 5.6. The magnitude of FOE for the YC and PD groups was calculated and compared to the groups using the formula:-

***Fixation offset effect = Reflexive overlap task latency – Reflexive gap task latency***

The FOEs for each group are displayed below in Figure 5.6. The YC group were found to have the smallest magnitude of FOE and the largest difference from other groups. The magnitude of FOE for the EC, PD and DOT groups was very close in size, with the AD group

**Table 5.5** Descriptive Statistics for Reflexive Saccade Latency with Parkinson's Disease Patients and Young Controls Added to the groups

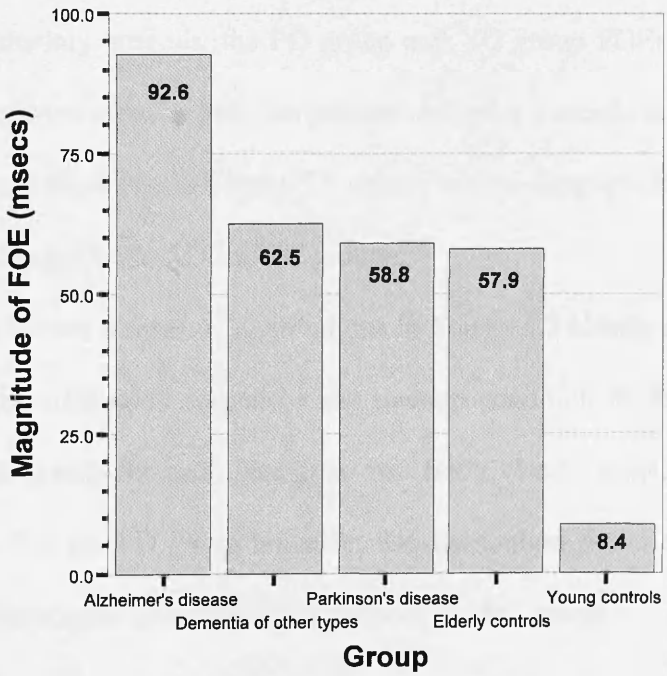
| | Reflexive saccade paradigm | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | EC | | YC | | PD | | AD | | DOT | |
| **Task** | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| **Overlap** | 253.58 | 30.83 | 211.24 | 44.42 | 242.29 | 74.79 | 298.63 | 45.40 | 274.72 | 31.94 |
| **Gap** | 195.67 | 35.08 | 202.79 | 28.93 | 183.46 | 50.21 | 206.05 | 45.40 | 212.22 | 39.97 |

EC = Elderly control; YC = Young control; PD = Parkinson's disease; AD = Alzheimer's disease; DOT = Dementia of other types

generating the highest magnitude of FOE. A one-way ANOVA was conducted on the FOE magnitude data, to include the YC and PD groups along with the other groups. The omnibus ANOVA was found to be significant ($F[4,86]= 8.01$, $p<0.0001$), showing that there were significant differences in the magnitude of FOE between-groups.

Group comparisons of FOE magnitude, revealed that the YC group FOE magnitude was significantly smaller than that of each of the other groups ($p<0.01$). However, no significant difference was found between the PD and EC groups ($p>0.9$ NS) and also between the DOT group and these groups ($ps>0.7$).

**Figure 5.6** The Magnitude of Fixation Offset Effect in the Reflexive Saccade Paradigm for Young Controls and Parkinson's Disease Patients Compared with Elderly Controls and Dementia Patients




The magnitude of FOE for the PD, EC and YC groups was also observed to be significantly lower than that of the AD group ($p<0.05$, $p<0.05$ and $p<0.01$ respectively), but as reported in Study II, the difference observed between the AD and DOT groups did not reach significance. One-way ANOVA was used to explore the between-groups differences for gap

and overlap task reflexive saccade latency. A significant difference was found between the group means for the overlap task ($F[4,86]= 6.12$, $p<0.0001$), but not for the gap task ($p>0.2$).

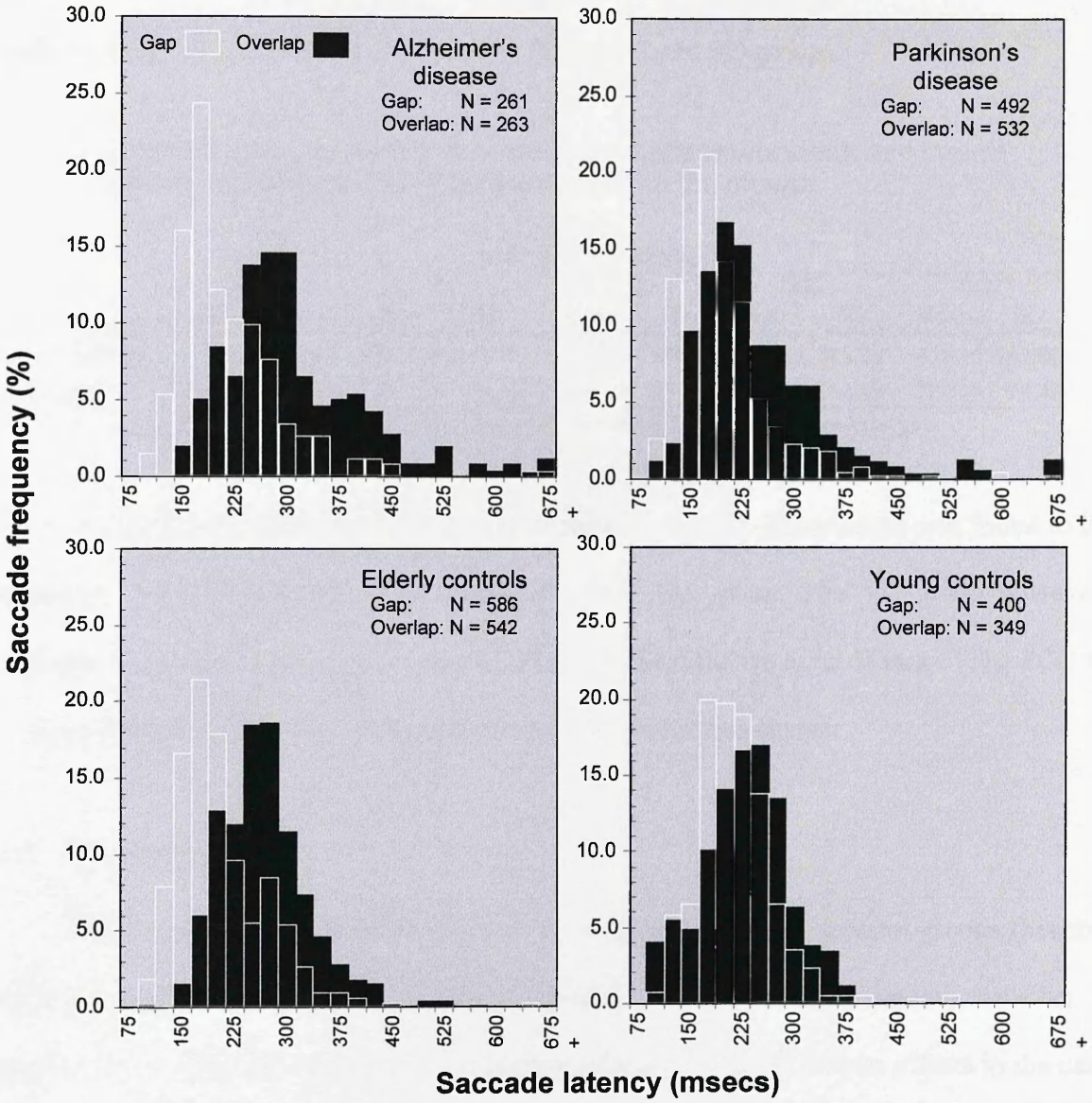
Taken together, these results indicate that both age and dementia affects the magnitude of FOE, as evidenced by the significant difference between the magnitude of FOE for the YC group and that of the EC, PD and DOT groups. However, whilst the AD group FOE was significantly greater than that of the PD, EC and YC groups, it was not found to be significantly different from the FOE of the DOT group[19]. Therefore, these findings suggest that the magnitude of FOE can distinguish between dementia and the effects of normal healthy ageing and also another neurological disease, PD. However, the magnitude of FOE could only discriminate marginally between the dementia sub-groups included in this study i.e. the AD and DOT groups.

As a supplementary analysis, the PD group and YC group FOEs were also examined within-groups. Frequency distributions for primary reflexive saccade latency in the gap and overlap conditions, are displayed in Figure 5.7 below, which compares the histograms for the YC and PD groups alongside the AD and EC groups.

The saccade latency frequency distributions in Figure 5.7 clearly show that for the YC group, there was little disruption caused by the overlap condition during which there is no fixation offset, as the peaks for each histogram run fairly closely together indicating only a negligible all FOE. For the PD group however, the distribution peaks are slightly separated indicating an FOE that is more pronounced than that of the YC group.

[19] This may have been due to variability in the DOT group resulting from the small number of participants in this group (n= 11). The standard error of mean (SE) for the DOT group was found to be 13.8, which was higher than the SE for the other groups that had more participants (AD = 10.4; PD = 10.5; EC = 6.5; YC = 9.3). Therefore, increasing the DOT sample size in a future study could potentially result in a significant difference between the AD and DOT groups.

**Figure 5.7** Histograms Displaying the Frequency of Saccade Latency in the Reflexive Gap and Overlap Tasks




Within-groups paired samples t-tests confirmed that there was no significant difference between reflexive gap and overlap task latency for the YC group, i.e. the YC group do not produce a significant FOE ($t[16]= -0.9$, $p>0.3$ NS). However, for the PD group, a significant FOE was found to be present, the reflexive overlap task resulting in significantly prolonged latency by comparison to the reflexive gap task latency ($t[24]= -5.58$, $p<0.0001$.

The antisaccade paradigm did not result in any salient findings for the dementia sub-groups in Study II. Therefore, the descriptive statistics presented in Table 5.6 below, purely serve to inform the reader of the observations for the YC and PD groups.

**Table 5.6** Descriptive Statistics for Antisaccade Latency with Parkinson's Disease Patients and Young Controls Added to the groups

| | Antisaccade paradigm | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | EC | | YC | | PD | | AD | | DOT | |
| | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| **Overlap** | 329.95 | 66.49 | 251.56 | 60.54 | 340.45 | 104.5 | 374.55 | 173.01 | 413.11 | 143.90 |
| **Gap** | 303.68 | 57.49 | 242.99 | 39.28 | 298.66 | 60.76 | 335.79 | 138.99 | 359.23 | 78.49 |

EC = Elderly control; YC = Young control; PD = Parkinson's disease; AD = Alzheimer's disease; DOT = Dementia of other types

A significant within-groups FOE was present for the PD group which was found to be marginally larger (non-significantly) than that of the EC group. The YC group however, generated a non-significant within-groups FOE (as in the reflexive saccade task). The FOE in the antisaccade paradigm will not be examined any further in this chapter.

## 5.4 Discussion

The purpose of the present study was to introduce additional control groups (healthy young participants and Parkinson's disease patients) into this thesis, to examine whether it would be possible to distinguish between healthy normal ageing and disease effects in the data from the previous studies.

### 5.4.1 Key findings

There are several key findings that the present study has produced, which are pertinent to the earlier studies in this thesis:-

1. Performance scores for patients with mild PD and EC participants on clinical rating scales and neuropsychological assessments were found *not* to vary significantly.

2. PD neuropsychological assessment and clinical rating scale scores were found to correlate only weakly and non-significantly with voluntary oculomotor tasks, indicating that the PD group performance was virtually indistinguishable from the EC group.

3. Verbal fluency scores for PD patients, EC and YC participants - that are believed to be a measure of frontal lobe function - were found not to differ significantly between the groups. Therefore, this finding suggests that frontal lobe function for this activity is equivalent for these groups.

4. AD inhibitory error rates generated across the voluntary saccade task range were greater than those generated by the PD, EC and YC groups.

5. The factor for correctness of performance in the antisaccade task, was found to be non-significantly different between the YC, PD, EC and DOT groups. However, these groups were found to differ significantly on this factor, from the AD group.

6. The proportion of inhibition errors that remain uncorrected in the antisaccade task was found not differ significantly between the YC, EC and PD groups, whereas a significant difference was found between these groups and the AD group.

7. The magnitude of FOE in the reflexive saccade paradigm was found to be significantly greater for the dementia sub-groups, than for the YC, PD and EC groups. However, as revealed earlier, this measure did not distinguish between the AD and DOT dementia sub-groups, perhaps due to the small DOT sample size.

### 5.4.2 Inhibitory Error Across Voluntary Saccade Tasks and Relationships with Neuropsychological Assessments Requiring Working Memory

The previous analysis (in Study I) of inhibition errors across the voluntary saccade tasks, revealed that there was a significantly higher proportion inhibition errors for the AD and DOT groups, than there was for the EC group. Furthermore, for the AD group there was a significant linear increase in inhibition error rate according to cognitive load of oculomotor task (i.e. No-Go > antisaccade gap > Go/No-Go) and additionally, antisaccade inhibition errors were found to correlate strongly with neuropsychological assessments known to place high demands on working memory resources. Whereas the EC group also showed a linear increase in inhibitory error rate across the tasks, the error rates for oculomotor tasks with higher cognitive load correlated only very weakly with neuropsychological assessments that place a high demand on working memory resources. In the present study, the YC group was examined in comparison to the findings from the earlier analysis and it was found that the YC group produced an inhibitory error rate on the factor: voluntary saccade task that was non-significantly different to that of the EC group and furthermore, no significant trend was present across the tasks for the YC group. Further analysis showed that whilst YC group inhibition errors were significantly lower than AD and DOT group inhibition errors on the No-Go, antisaccade and Go/No-Go tasks, the YC and EC group only differed significantly on the Go/No-Go task, the YC group generating significantly less errors.

Unfortunately, the present analysis for the PD group was limited, as data were only available for the No-Go and antisaccade tasks. Nevertheless, compared with the YC and EC groups, the PD group was found to generate a non-significantly higher proportion of inhibition errors on these two voluntary saccade tasks. Whereas compared with the AD and DOT groups, the PD group generated less inhibitory errors on both tasks. Thus, PD group performance was indistinguishable from the YC and EC groups, but distinguishable from the AD and DOT groups.

In light of the YC group creating significantly lower proportions of inhibitory errors on the Go/No-Go task than all other groups and these errors being non-significantly different to the YC antisaccade task inhibitory error rate, these findings suggest that the YC group found each voluntary task somewhat less taxing of executive control. It is plausible to argue that this ability is due to greater working memory resources in young adults.

Taken together these findings suggest that working memory capacity decreases with healthy normal ageing, however, the effects of PD and healthy normal ageing are indistinguishable. In contrast, the deterioration in working memory capacity for dementia patients, in particular those with AD, is in turn dissociable from the effects of healthy normal ageing and PD. Moreover, the working memory capacity for each of these groups is indicated by oculomotor tasks that require voluntary control of saccades.

### 5.4.3 Correctness of Performance: Corrected and Uncorrected Errors the Capacity for Self-Monitoring

Differences in the magnitude of correctness of performance across groups - highlighted by the interactions in Figure 5.6 - illustrated that this factor could distinguish the AD group from each of the other groups, a finding that was confirmed statistically. In addition to this, within-groups analysis of correctness of performance also revealed that the PD and YC groups had a significant linear trend to their factor profiles. In sum, these findings verify that the effects reported in the inhibitory error analyses are characteristic of AD and dissociable from the effects of normal ageing and also from the pathology associated with PD. The finding that the uncorrected error rate could distinguish between the AD group and all other groups using a simple t-test was compelling even though this discrimination did not survive the conservative correction applied by the Scheffe multiple comparison test to protect against *family* type I error.

The findings from the present study serve to substantiate the robustness of the data from Study I and emphasise the effectiveness of the factor: correctness of performance in

distinguishing AD from other groups. Moreover, the findings also show that antisaccade uncorrected error rates for the dementia sub-groups, can be dissociated from age and disease effects and that this measure appears to be a sensitive indicator for AD.

### 5.4.4 Magnitude of Fixation Offset Effect for Reflexive Saccades

The FOE for the AD group was found to be significantly larger than that for the PD and YC groups. However, the FOE for the PD group was found to be virtually the same as that for the EC group, whereas the YC group produced a non-significant FOE (within-groups), with a magnitude that was significantly smaller than that of all other groups.

Perhaps this finding reinforces the notion put forward in Chapter 4, that FOE magnitude falls on a continuum that increases as a function of age and/or disease, i.e. the FOE becomes more pronounced with age and even more evident with dementia of the Alzheimer's type. For the YC group, the parameters employed in the reflexive saccade overlap task did not have the effect of prolonging saccade latency (in comparison to reflexive gap task latency), whereas for the other groups the experimental set-up was such, that a significant FOE was induced.

In summary, these findings indicate that under the experimental parameters employed for the present series of tasks (Appendix 11), healthy elderly participants, PD patients and dementia patients (in particular AD) were sensitive to the effects of a central fixation point that remains illuminated when a peripheral target appears (overlap condition), in that a saccade was generated with prolonged latency. This is compared with the gap paradigm - during which the central fixation point was extinguished prior to peripheral target onset (with a 200 ms stimulus onset asyncrony) - where there was no significant difference in saccade latency between all of the groups.

## 5.5 Conclusions

- ✧ AD inhibitory error rates generated across the voluntary saccade tasks ranging from low to high in terms of the demands placed on working memory resources, are distinguishable from the effects of normal ageing and PD.

- ✧ Oculomotor tasks that require voluntary control appear to rely on efficient working memory function for successful completion.

- ✧ Antisaccade uncorrected error rates can be dissociated from age and disease effects and that this measure appears to be a sensitive indicator for AD.

- ✧ Reflexive saccade FOE magnitude increases as a function of normal ageing, however, the FOE is further enlarged as a result of dementia; the largest FOE caused by AD.

# Chapter Six

## Study IV: Medicated and Non-Medicated Alzheimer's Disease Patients

*Pharmacological Effects of Acetylcholinesterase Inhibitors*

### 6.1 Introduction

The purpose of the present study was to examine the possible implications of pharmacological compounds on the findings revealed by Studies I and II. As discussed in Chapter 2 (Section 2.2.2.1), some dementia patients were prescribed with anti-dementia drugs at an early point in their dementing illness. A comparison was drawn between dementia patients who were taking medication with acetylcholinesterase inhibitors (AChEIs) and those who were not, in performance on saccadic eye movement paradigms, neuropsychological assessments and clinical rating scales. The aim was to establish the extent to which medication with these compounds could represent a potential confound within the results from the earlier studies of the present thesis.

Acetylcholine (ACh) is a neurotransmitter that is important for the autonomic nervous system's function (involuntary control) at neuromuscular junctions throughout the body. Disruption of ACh in this system affects motor control and coordination. However, ACh is also crucial to the CNS and diffuse cholinergic systems also modify the actions of other neurotransmitters throughout many areas of the brain (Bullock et al., 1992; Snyder, 1996). There are three main cholinergic regions in the brain, comprising pathways that project neurons from i). the pontine reticular formation, to the amygdala, thalamus, basal forebrain and spinal cord; ii). the nucleus basalis of Meynert and nuclei of the diagonal band, i.e. the

basal forebrain, which send vast projections to the cerebral cortex; and iii). the septum which forms the septohippocampal pathway (Deutch & Roth, 1999). Histopathologic analyses of the brains of AD patients have revealed a decline in ACh (Beach et al., 2000; Coyle et al., 1983; Davies & Maloney, 1976; Giacobini, 1990) - and other neurotransmitters, as outlined in Section 1.5.2.1- resulting in cholinergic deficits (Greig et al., 2001; Perry, Perry, Blessed & Tomlinson, 1977) which cause dysfunction attention and memory (Davis et al., 1992; Perry et al., 1978; Perry et al., 2000; Rogers, Farlow, Doody, Mohs & Friedhoff, 1998).

Numerous studies have shown a reduction in choline acetyl transferase (CAT) activity - the enzyme that converts choline to ACh - in the brains of AD patients compared to healthy controls. Moreover, CAT activity was found to correlate with severity of cognitive symptoms and the extent of pathological changes (Perry et al., 1977; Perry et al., 1978; Roth & Hopkins, 1953). The study of AD brains at post mortem has also revealed depletion of cholinergic neurons (Whitehouse et al., 1981; Whitehouse et al., 1982), due to degeneration caused by neuritic plaques and neurofibrillary tangles (Tomlinson & Corsellis, 1984). These pathological changes in AD involve cholinergic neuronal pathways that project from the basal forebrain to the cerebral cortex and hippocampus (Arendt, Bigl, Tennstedt & Arendt, 1985). These structures are believed to be involved in the function of memory, attention, learning, and other cognitive processes (Kopelman, 1986; Perry et al., 1977). Numerous animal and human studies have confirmed the link between CNS cholinergic systems and cognition (Everitt & Robbins, 1997; Francis et al., 1999; McGaughy, Everitt, Robbins & Sarter, 2000). Furthermore, recent pharmacological studies have demonstrated that administration of the anticholinergic drug procylidine, impairs cognitive test performance (Zachariah et al., 2002), alertness (Sharma et al., 2002) and the disruption of prepulse inhibition – an operational measure of sensorimotor gating (Kumari et al., 2001).

In Studies I, II & III of the present thesis, the antisaccade task was used as a volitional saccadic eye movement task in experimental groups of healthy control participants, PD patients

and dementia patients. The cognitive processes that are involved in the antisaccade task include attention (covert and overt), inhibitory control and working memory (Section 1.3.2.1) (Mitchell et al., 2002; Roberts et al., 1994; Stuyven et al., 2000; Walker et al., 1998) and it is likely that central cholinergic pathways play an important role in mediating these functions (McGaughy et al., 2000). Furthermore, a study recently discovered that administration of nicotine to schizophrenic patients and healthy controls, enhanced antisaccade task performance – reduced error rates – (Dépate et al., 2002), most likely due to the effects of nicotine on nicotinic cholinergic receptor sites. Taken together, these studies highlight the importance of the cholinergic system in neurocognitive function.

### *6.1.1 The Action of Acetylcholinesterase at the Synapse*

Acetylcholinesterase (AChE) is an enzyme that is produced in cholinergic neurons of the brain and stored in the postsynaptic membrane at locations adjacent to ACh receptor sites. On stimulation, ACh - stored in synaptic vesicles in the terminal part of neurons, inside the presynaptic membrane - is diffused across the synaptic cleft to the postsynaptic membrane, where it binds at cholinergic receptor sites. When ACh binds at receptor sites AChE is released and inactivates ACh, by breaking it down the into its constituent parts, choline and acetic acid (Snyder, 1996). The choline and acetic acid then migrate across the synaptic cleft to re-uptake sites on the pre-synaptic membrane, where ACh is synthesised and stored in synaptic vesicles ready for use (Snyder, 1996). Therefore, AChE has the effect of stabilising and restraining the action of ACh (BMA, 2001).

### *6.1.2 Pharmacological Action of Acetylcholinesterase Inhibitors*

As already discussed, due to neurodegenerative processes, cholinergic activity is diminished in areas of the AD brain that are linked to efficient cognitive function. Therefore, the additive effect of AChE in breaking down deficient levels of ACh is conducive to a

progressive further decline in memory function and other aspects of cognition. In view of this, researchers realised that there was a potential therapeutic benefit - cognitive enhancement - that may be gained, by modifying the action of AChE at the synapse, i.e. prolong the action of ACh by inhibiting the action of the enzyme AchE (Davis & Mohs, 1982; Davis, Mohs, Rosen, Greenwald & Horvath, 1983). AChEIs are a class of drugs that block the action of AChE (Greig et al., 2001; NICE, 2001). At the synaptic and molecular level, it is unknown precisely how AChEIs actually work, however, it is believed that cholinergic function is enhanced, resulting in a modest improvement of cognition for patients with Alzheimer's type dementia (Christensen, Maltby, Jorm, Creasey & Broe, 1992; Raffaele et al., 1996; Rogers et al., 1998). Moreover, is postulated that the mechanism by which this enhancement works, is through reversible inhibition in the hydrolysis of ACh by cholinesterase, thereby increasing the concentration of ACh at the synapse (Greig et al., 2001). In the early stages of dementia, this can lead to enhanced cognitive function, increased alertness and a slowing in the rate of deterioration from disease (Almkvist, Jelic, Amberla, Hellstrom-Lindahl & Meurling, 2001; Nordberg et al., 1998; Wolfson et al., 2002). However, AChEIs do not allay the progression of disease and therapeutic effects may decrease with the progression of neurodegeneration, as functional integration within the cholinergic system diminishes (NICE, 2001). There were three AChEIs involved in the medication of patients in the present project. These were donepezil and rivastigmine, which are reversible inhibitors of AchE and galantamine, which is also a reversible inhibitor of AChE and also has nicotinic receptor agonist properties.

Study IV will explore the data within the treatment sub-groups of the dementia patients in the present thesis, in an attempt to ascertain the potential pharmacological influence of AChEIs on oculomotor task performance. This analysis was only feasible for stage one of the longitudinal project, as the vast majority of dementia patients commenced drug therapy by stage two.

### 6.1.3 Aims

The main aim of the present study was to examine whether medication with AChEIs enhanced performance on oculomotor measures and neuropsychological assessments in the dementia patient groups. Medicated and non-medicated groups of dementia patients with mild to moderate symptoms were compared, which included an analysis of AD sub-groups. The main hypothesis for Study IV, was that due to potential cognitive enhancement by the administration of AChEIs, patients receiving medication would demonstrate superior cognitive function indicated by significantly better performance scores on neuropsychological assessments and saccadic eye movement measures.

## 6.2 Methods

### 6.2.1 Participants

The dementia patients for this study comprised the pool of patients from the earlier studies of this thesis and demographic details are discussed in Chapter 2. Patients were from the AD Research Project at Lytham Hospital Memory Clinic, United Kingdom. Recruitment methods, criteria for dementia diagnosis and exclusion, and participant health status were discussed in Chapter 2, Section 2.1. All patients were right-handed.

The present analyses consisted of the dementia patient (DP) group as a whole comprising the sub-groups DP medicated (N=13; age range = 68–84 years; mean = 74.9; SD = 4.5; male, n=11; female n=2) and DP non-medicated (N=15; age range = 71–88 years; mean = 77.8; SD = 4.6; male, n=8; female n=7). A further analysis examined the AD patients, to include AD medicated (N=9; age range = 70-84; mean = 76.0; SD = 4.2; male n=7; female n=2) and AD non-medicated (N=8; age range = 71-88; mean = 77.9; SD = 5.7; male n=5; female n=3). There was no analysis conducted on the dementia of other types (DOT) medicated/non-medicated sub-groups, due to a very low number of patients taking medication.

### 6.2.2 Assessment of Saccadic Eye Movements

The equipment, task protocol and experimental procedures were described in Chapter 2 (Section 2.3), and involved the reflexive saccade gap task; No-Go and Go/No-Go paradigms; and antisaccade gap task. The central fixation point was displayed at $0^{\circ}$ and target presented randomly at $\pm 4^{\circ}$ in the horizontal plane, as discussed in the previous studies.

### 6.2.3 Statistical Analysis

The statistical analyses for this study involved a series of one-way ANOVA, to examine between-group differences for medicated and non-medicated sub-groups (for the DP group as a whole and the AD group).

## 6.3 Results

### *6.3.1 Effects of Age and Education*

ANOVA showed that there was no significant difference in age or the number of years spent in education (Table 6.1), between DP medicated and non-medicated groups (Age, $F[1,26]=2.81$, $p>0.1$ NS; Education, $F[1,26]=0.42$, $p>0.8$ NS). An age and education analysis was also carried for the AD medicated and non-medicated sub-groups and revealed that there were no significant differences between these sub-groups (Age, $F[1,15]=0.60$, $p>0.4$ NS; Education, $F[1,15]=0.003$, $p>0.9$ NS).

### *6.3.2 Clinical Rating Scales and Neuropsychological Assessment*

Table 6.1 displays clinical rating scale and neuropsychological assessment scores (means) for the medicated and non-medicated sub-groups (for dementia patient group as a whole and also for the AD group).

For the DP group as a whole, no significant difference was found to be present between medicated and non-medicated sub-groups on the clinical rating scales (SMMSE, $F[1,26] = 3.45$, $p>0.08$ NS ; EADAS cog, $F[1,26] = 2.72$, $p>0.1$ NS), as was the case for the AD

**Table 6.1** Education, Clinical Rating Scale and Neuropsychological Assessment Scores for Medicated and Non-Medicated Dementia Patients

| | Dementia group | | | | | | Alzheimer's disease | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Medicated | | | Non-medicated | | | Medicated | | | Non-medicated | | |
| | Mean | SD | N | Mean | SD | N | Mean | SD | N | Mean | SD | N |
| **Education** (yrs) | 12.08 | 1.75 | 13 | 12.27 | 2.92 | 15 | 12.56 | 1.74 | 9 | 12.50 | 2.27 | 8 |
| **SMMSE** | 20.31 | 6.10 | 13 | 24.20 | 4.99 | 15 | 20.56 | 3.64 | 9 | 22.25 | 5.83 | 8 |
| **EADAS** | 25.31 | 13.89 | 13 | 18.00 | 9.41 | 15 | 23.11 | 9.25 | 9 | 22.38 | 10.08 | 8 |
| **VFlu** | 19.77 | 11.01 | 13 | 25.00 | 9.58 | 15 | 22.11 | 11.34 | 9 | 23.13 | 9.79 | 8 |
| **DSF** | 8.54 | 2.57 | 13 | 8.93 | 1.91 | 15 | 8.89 | 2.62 | 9 | 8.38 | 1.85 | 8 |
| **DSR** | 4.23 | 2.89 | 33 | 6.40 | 2.35 | 15 | 4.78 | 3.11 | 9 | 5.38 | 1.60 | 8 |
| **SSF** | 4.85 | 2.34 | 13 | 5.80 | 1.78 | 15 | 5.33 | 2.18 | 9 | 5.75 | 2.05 | 8 |
| **SSR** | 3.31 | 1.84 | 13 | 5.20 | 1.86 | 15 | 3.78 | 1.86 | 9 | 4.75 | 2.38 | 8 |

Vflu=Verbal Fluency; DSF=Digit Span Forward; DSR = Digit Span Reverse; SSF=Spatial Span Forward; SSR=Spatial Span Reverse

medicated and non-medicated sub-groups (SMMSE, $F[1,15] = 0.53$, $p>0.48$ NS; EADAS cog, $F[1,15] = 0.25$, $p>0.88$ NS). For neuropsychological assessments, the DP group analysis showed that there was no significant difference between medicated and non-medicated sub-groups for Verbal Fluency, Digit Span Forward and Spatial Span Forward scores. Interestingly, however, the non-medicated DP sub-group produced significantly higher scores than the medicated sub-group for Digit Span Reverse ($F[1,26] = 4.79$, $p< 0.038$) and Spatial Span Reverse ($F[1,26] = 7.27$, $p<0.012$). However, this result was likely to be due to variability within the groups, brought about by the various types of dementia. Analysis of AD medicated and non-medicated sub-group neuropsychological assessment scores, revealed that there were no significant differences on any of the tests.

### *6.3.3 Saccadic Error Rates*

Descriptive statistics for the analysis of saccadic errors are displayed in Table 6.2. Inhibition error rates were found to be marginally higher for medicated groups than for non-medicated groups on each paradigm, with only one exception, this being for AD medicated patients who generated less inhibition errors than non-medicated patients, on the No-Go task.

**Table 6.2** Descriptive Statistics for Error Analysis

| | | Dementia group | | | | | | Alzheimer's disease | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Medicated | | | Non-medicated | | | Medicated | | | Non-medicated | | |
| | | Mean | SD | N | Mean | SD | N | Mean | SD | N | Mean | SD | N |
| Antisaccade Gap | Correct saccades (%) | 29.13 | 18.35 | 12 | 47.51 | 32.81 | 15 | 29.49 | 18.40 | 9 | 38.60 | 38.97 | 8 |
| | Inhibition errors (%) | 56.43 | 16.19 | 12 | 42.07 | 31.77 | 15 | 55.67 | 17.32 | 9 | 45.03 | 36.28 | 8 |
| | Uncorrected errors (%) | 29.02 | 23.66 | 12 | 12.55 | 18.96 | 15 | 26.19 | 23.93 | 9 | 20.40 | 23.69 | 8 |
| | Corrected errors (%) | 27.41 | 19.59 | 12 | 29.52 | 25.24 | 15 | 29.48 | 21.91 | 9 | 24.63 | 22.75 | 8 |
| Go/No-Go | Inhibition errors (%) | 68.92 | 23.16 | 12 | 47.22 | 32.42 | 15 | 63.39 | 32.32 | 9 | 45.79 | 23.78 | 8 |
| No-Go | Inhibition errors (%) | 38.03 | 31.98 | 13 | 30.00 | 27.26 | 15 | 28.49 | 27.35 | 9 | 41.82 | 31.57 | 8 |
| Reflexive saccade Gap | Correct saccades (%) | 89.04 | 13.40 | 13 | 91.92 | 10.84 | 15 | 91.11 | 11.03 | 9 | 88.49 | 13.84 | 8 |
| | Directional errors (%) | 2.26 | 3.30 | 13 | 1.95 | 2.67 | 15 | 1.87 | 3.04 | 9 | 2.61 | 3.10 | 8 |
| | Uncorrected errors (%) | 0.65 | 1.58 | 13 | 0.56 | 1.48 | 15 | 0.00 | 0.00 | 9 | 1.05 | 1.94 | 8 |
| | Corrected errors (%) | 1.62 | 2.72 | 13 | 1.40 | 2.57 | 15 | 1.87 | 3.03 | 9 | 1.56 | 3.09 | 8 |



6 Pharmacological Effects of Acetylcholinesterase Inhibitors

However, none of the between-group one-way ANOVA, i.e. for DP medicated and non-medicated sub-groups and between AD medicated and non-medicated sub-groups, were found to be significant for any saccadic variables. Therefore, the analyses confirmed that inhibition error rates and corrected and uncorrected error components for medicated and non-medicated sub-groups were indistinguishable.

### 6.3.4 Saccade Latency

Analyses of saccadic latency were carried out on the sub-group means (Table 6.3 below) for reflexive saccade (gap and overlap) and antisaccade (gap and overlap) paradigms. The output showed that there were no significant differences between medicated and non-medicated DP sub-groups, and further analysis found that this was also the case for the AD medicated and non-medicated sub-groups.

**Table 6.3** Saccade Latency for Reflexive and Antisaccade Paradigms

**Reflexive saccade paradigm**

| | Dementia group | | | | Alzheimer's disease | | | |
|---|---|---|---|---|---|---|---|---|
| | Medicated | | Non-medicated | | Medicated | | Non-medicated | |
| Task | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| **Overlap** | 292.23 | 53.72 | 285.66 | 332.61 | 308.34 | 63.18 | 292.56 | 33.82 |
| **Gap** | 194.65 | 38.19 | 215.12 | 42.66 | 196.67 | 44.95 | 204.99 | 44.43 |

**Antisaccade paradigm**

| | Dementia group | | | | Alzheimer's disease | | | |
|---|---|---|---|---|---|---|---|---|
| | Medicated | | Non-medicated | | Medicated | | Non-medicated | |
| | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| **Overlap** | 385.74 | 179.08 | 359.46 | 129.83 | 344.38 | 149.37 | 355.74 | 179.21 |
| **Gap** | 376.18 | 97.72 | 309.95 | 107.89 | 375.74 | 108.74 | 265.07 | 118.93 |

## 6.4 Discussion

The present study was carried out with the aim of establishing whether dementia patients – in particular those with AD – taking medication of AChEIs would exhibit enhanced saccade dynamics and behavioural characteristics compared with non-medicated patients on

involuntary and voluntary saccade tasks. Additionally, cognition and global function was also compared in the two sub-groups, using neuropsychological assessments and clinical rating scale scores.

### 6.4.1 Key findings

Key findings from the present study are summarised as follows:-

1. Medication with AChEIs was not found to enhance performance on clinical rating scales and neuropsychological assessments.

2. Primary saccade latency for reflexive and voluntary tasks, were found to be non-significantly different between medicated and non-medicated AD patient groups.

3. Behavioural characteristics, namely inhibition error rates committed on reflexive and voluntary saccade tasks, were found not to vary significantly between medicated and non-medicated AD patient groups.

4. Corrected errors and uncorrected error rates did not differ significantly between medicated and non-medicated AD patients.

### 6.4.2 Clinical Rating Scales and Neuropsychological Assessment

The findings from statistical analysis of clinical rating scale and neuropsychological assessment scores showed that there was no significant difference between medicated and non-medicated patients on the vast majority of tests. Furthermore, the only significant differences that were demonstrated concerned the DP non-medicated sub-group, were scores on the Digit Span Reverse and Spatial Span Reverse tests were significantly higher than those of the DP medicated group. A plausible suggestion as to the cause of this outcome is that the result was

due to the mixture of dementia types present in the study. Importantly, the AD medicated/non-medicated sub-group analysis, found no statistically significant differences between the sub-groups for any of the tests. For the context of the present study, this a salient methodological finding, as it confirms that AD patients taking treatment of AChEIs, were at no advantage compared with non-medicated patients. Moreover, these results show that medicated patients were unlikely to represent a confound for the project as a whole as there was no drug induced cognitive enhancement. As such, the findings do not support the hypothesis underpinning Study IV, that medicated sub-groups would have superior cognitive performance. For the majority of AD patients in the present study, medication was only initiated for a relatively short period of time prior to test (approximately 4 weeks at test[20]). Therefore, a longer period treatment with AChEIs prior to testing may have resulted in an improvement in test performance as found in previous studies (Edwards, O'Connor, Button, Goodman & Norton, 2002; Jones et al., 2004; Wolfson et al., 2002) . These studies highlighted the efficacy of AChEIs in the treatment of AD, by their capacity to improve cognition by reducing ADAS-cog scores (by 4 - 5 points) and increasing MMSE scores (by 1- 2 points) at around twelve weeks of medication. However, some studies have found that not all AD patients derive benefit from treatment (Edwards et al., 2002; NICE, 2001)

### 6.4.3 Involuntary Saccades

The finding that there was no significant difference between medicated and non-medicated AD patients in primary saccade latency and behavioural characteristics for reflexive saccade tasks was not too surprising. The reflexive gap task analysis in Study II showed that there were no significant differences between AD patients and elderly control participants, so medicated AD patients would not be expected to exceed the performance of normal healthy controls. Furthermore, the initiation of reflexive saccades relies heavily on the SC and

[20] Although the average was 11 weeks, as some patients had been taking medication for a longer period.

brainstem, in association with the PEF and FEF and not on prefrontal areas of cortex such as the DLPFC, which is involved with the inhibition of reflexive saccades and higher order processing (hence the negligible error rates). Sections 1.4.1.2 and 4.4.5 discussed how fixation cells inhibit movement cells in the SC and Section 1.4.2.1 described the important role played by the FEF, with it's reciprocal connections with the SC, via the mediodorsal thalamus. Due to the characteristics of the reflexive gap paradigm, movement cells in the SC would be disinhibited and free to generate a saccade on time, due to the removal of the central fixation point 200 ms prior to the onset of the peripheral target. If any difference was to have been anticipated between medicated and non-medicated patients in the reflexive saccade paradigms, it would have been more likely to have occurred in the reflexive overlap task, as a significant difference was observed in Study II between AD patients and elderly controls. It is important to remember, that AD patients generated saccades with prolonged latency in the overlap task, thus resulting in an FOE that was significantly larger in magnitude to that of controls. Therefore, it is conceivable that AD patients, medicated with AChEIs, could potentially have had improved fixation disengagement in the reflexive overlap task, afforded by enhanced attentional processing via the pathways between the PEF and FEF (fixation and movement cells are also found in the FEF) thereby reducing saccade latency to a level comparable with that of elderly controls. However, as the results in the present study revealed, medicated AD patients drew no benefit over those that had not commenced treatment.

### 6.4.4 Voluntary Saccades

The proportion of inhibitory errors on voluntary saccade tasks (No-Go; antisaccade gap and Go/No-Go), was found not to differ significantly between medicated and non-medicated AD patient groups. These findings were somewhat surprising, as voluntary saccades require working memory and importantly, inhibitory control. Thus, voluntary saccades rely on executive control mediated by the frontal lobe, specifically reciprocal connections between the

DLPFC, ACC, FEF, SEF and PEF. Therefore, it is plausible to suggest, that AD patients medicated with acetylcholinesterase inhibitors should perform more efficiently than non-medicated AD patients, due to cognitive enhancement via the neural pathways involved in higher order processing of voluntary saccade tasks. These findings both affirm and correspond with the findings discussed in the previous sections, that medication with acetylcholinesterase inhibitors does not induce any significant improvement in performance on voluntary saccade tasks, compared with non-medicated patients. Therefore, these findings do not support the cognitive enhancement hypothesis for medicated patients in this study. However, as mentioned earlier, it is feasible that benefits from medication with acetylcholinesterase inhibitors may have emerged after longer periods of taking the drugs. Thus, the results do not rule out the possibility that acetylcholinesterase inhibitors could in the longer term, reduce inhibition error rates.

## 6.5 Conclusions

- ✧ Cognitive enhancement - as indicated by improved clinical rating scale and neuropsychological assessment scores - did not result from medication with AChEIs for the small cohort of dementia patients included in the present study. This may have been due to insufficient time for the full pharmacological benefit of the drugs to exert an effect as the majority of patients had only been taking the medication for a short time.

- ✧ Saccade dynamics and behavioural characteristics of AD patients on medication with AChEIs are negligibly different to those of non-medicated patients on involuntary or voluntary oculomotor tasks.

- ✧ Cognitive enhancement may potentially transpire, further to longer treatment periods of medication with acetylcholinesterase inhibitors, which could manifest in longitudinal analyses.

# Chapter Seven

## Study V: Longitudinal Analysis of Saccadic Eye Movement and Cognitive Performance in Alzheimer's Disease

## 7.1 Introduction

This study examined the data from a sample of AD patients and EC participants who were systematically re-assessed over time on saccadic eye movement tasks, clinical rating scales and neuropsychological assessments. The study was longitudinal from baseline testing, with subsequent test sessions taking place at six monthly intervals to provide a total of four data sets. The main goal of the present study, therefore, was to examine only salient findings from the previous studies over time, so as to determine which oculomotor variables or cognitive tests are sensitive to the progression of AD.

The investigation of eye movements in AD over time has been limited, previously only two studies having explored the progression of AD via repeated measures (Bylsma et al., 1995; Hutton, 1985). Both of these studies reported that AD patients have a deficit in fixation stability or smooth pursuit tracking, characterised by saccadic intrusions. Bylsma (1995) found that the inability of AD patients to inhibit intrusive saccades on a fixation task correlated with the baseline measure of MMSE and with the decrease in MMSE over time, i.e. increased cognitive impairment. This measure was shown to be more sensitive to the progression of AD than reflexive saccade latency through repeated test sessions.

Studies I, II and III of the present thesis provided an extensive account of baseline cognitive and saccadic performance in dementia patients (including sub-group analyses for AD

and other types of dementia) compared with that of healthy elderly controls (ECs), healthy young controls and mild Parkinson's disease patients (Study III: age and disease effects). The most salient finding from Studies I and III, was the generation of inappropriate reflexive saccades by AD patients during voluntary saccade tasks due, apparently, to a deficit in the ability to inhibit the VGR. These reflexive saccades were termed inhibitory errors and committed by dementia patients in violation of task instructions. It was postulated that the proportion of inhibition errors corresponded, largely, with the cognitive load of a given saccade task and as a function of task pre-potency. Furthermore, the cognitive load of a given saccade task was reflected in the level of demand placed on working memory resources. Participants were found to generate least inhibition errors during the No-Go task (task outlined in Section 2.3.3.3.1) and the proportion of errors committed increased linearly through the antisaccade gap task (outlined in Section 2.3.3.3.1), to the Go/No-Go task (see Section 2.3.3.3.1).

A further salient finding from Studies I and III was that AD patients were found to produce a high proportion of inhibition errors that remain uncorrected, whilst performing the antisaccade gap task. Analysis of the factor: *correctness of performance* showed that the EC, YC, PD and DOT groups were significantly different to the AD patient group and that the AD group presented with no trend (flat profile) in their profile plot on this factor. Compared with AD patients, other groups tend to generate significantly higher proportions of correctly commissioned saccades, lower error components, i.e. lower proportions of corrected errors (apart from DOTs who tend to correct inhibition errors at a higher ratio than ADs) and lower proportions of uncorrected errors.

An additional salient finding revealed by Studies II and III was that AD patients generate an FOE for reflexive saccade latency which is of significantly higher magnitude to that of the EC, YC and PD groups, although, the magnitude of FOE was not significantly different from that of the sub-group of dementia patients with other types of dementia. To reiterate, it is of significance to note that the significant findings summarised above, were

reliable baseline measures. Moreover, importantly these measures were able to discriminate between AD and other groups, of significance distinguishing the AD group from the effects of normal ageing, Parkinson's disease (another neurological disease) and education. An obvious extension of the previous studies, therefore, is to explore longitudinal data, for any changes in these factors over time.

For the factor *voluntary saccade task*, which incorporates three voluntary saccade tasks (No-Go; antisaccade gap; Go/No-Go), what would be expected to happen to the inhibitory error rates over time? Working memory is required for each of the tasks which comprise the factor, but each task places different demands on working memory resources: No-Go = low; antisaccade = moderate; Go/No-Go = High (see Table 3.1). Previous research has shown working memory to deteriorate over time in AD (Baddeley, Bressi, Della Sala, Logie & Spinnler, 1991), so it may be the case that inhibitory error rates will simply increase linearly over time for each task. Alternatively, the progression of AD over time may not be reflected on every task to the same degree, as the working memory component of each task is different. Furthermore, working memory does not operate purely in isolation, it is thus important to consider other fundamental components of behaviour and cognition which are required to perform the tasks successfully, such as inhibitory control, attention, representation and fixation mechanisms.

Correctness of performance, the factor comprising variables derived from the antisaccade gap task (correct saccades; corrected errors; uncorrected errors) may provide a sensitive measure of self-monitoring capacity over time in AD patients. The high antisaccade uncorrected error rate for AD patients was notably one of the most salient findings of baseline performance in the AD group. Moreover, the factor correctness of performance was able to discriminate the AD group from both the EC and DOT groups. Given the nature of cognitive deterioration in AD overtime, it is feasible that correctness of performance may be sensitive to

the progression of AD, because of deteriorating self-monitoring capacity and consequently, an increased uncorrected error rate.

The magnitude of reflexive saccade FOE may be found to increase over time for AD patients, but may also reach a ceiling level for reflexive response. Obviously, this factor is dependent on the comparison of saccade latency in reflexive gap and overlap tasks. As was found in Studies II and III, saccade latency was prolonged in the reflexive saccade overlap task at baseline. However, it is conceivable that reflexive overlap task saccade latency could become more prolonged over time, plotting the progression of AD as a function of neurodegeneration and consequentially an increasing fixation disengagement deficit.

The MMSE has been shown previously to detect a 1 – 2 point change in AD patients over a 12 month inter-test interval, for patients taking medication of AChEI's (Edwards et al., 2002) and 9 month inter-test interval for a study involving non-medicated patients (Bylsma et al., 1995). Therefore, it is of interest to determine as to whether any of the factors, i.e. voluntary saccade task, correctness of performance or magnitude of reflexive FOE (or any of the variables comprising the factors) possesses sufficient resolution, to detect changes in AD cognition over the eighteen month time span of a longitudinal study.

An obvious predicament for the researcher in any longitudinal study of dementia is that of subject mortality. Unfortunately, the present study was no exception to the problem of intermittent availability or attrition of participant numbers, due to illness or death. In fact, a large proportion of the original sample examined in the earlier studies from this thesis, were not included in the present analyses. For the current study, participants were required to be present at each stage of the project, i.e. without any missed visits, to gain a truly representative pattern of activity over time. Therefore, the account given was derived fully from repeated measures data, with other participants excluded from the study as a result of missing eye movement data occurring at a particular stage further to baseline measurement.

### 7.1.1 Aims

The aims of the present study were to investigate further the salient findings from stage one, i.e. baseline, of the longitudinal study so as to examine whether any of the factors are sensitive to the progression of AD over time (from baseline through further test sessions at 6, 12 and 18 months). The study examined both within- and between-groups differences, to include analyses of saccade dynamics and behavioural characteristics and also an extensive and detailed analyses of clinical rating scales and neuropsychological assessments.

### 7.1.2 Hypotheses

The specific hypotheses for this study were: 1) Further to deterioration of working memory capacity over time, a significant increase in voluntary saccade task magnitude will be found for the AD patient group, indicating that inhibition error rate is sensitive to the progression of AD. 2) The increase in inhibitory errors across time will increase in proportion to the cognitive load of a given task. 3) There will be significant difference between the AD group and EC group on the factor for correctness of performance, as AD group correct saccade proportions decrease and uncorrected errors increase over time, suggesting that the capacity of AD patients to self-monitor performance deteriorates over time. 4) Due to a decline in fixation disengagement capacity, the magnitude of reflexive saccade FOE for the AD group will become greater over time. 5) An alternative hypothesis here, is that the magnitude of reflexive saccade FOE will not increase, but that there will be a linear increase in saccade latency for *both* reflexive saccade tasks (i.e. gap and overlap tasks) as a result of sensorimotor dysfunction developing over time. 6) Clinical rating scale scores should be significantly poorer to those of control participants and will demonstrate a decline in global function over time, whereas no change should be evident for the EC group. 7) AD patients will score more poorly than the EC group on neuropsychological assessment tasks which require working memory (e.g. Digit Span, Spatial Span [in particular the reverse forms] and Trail Making Form

B) and frontal lobe function (e.g. Verbal Fluency, Trail Making Forms A and B) and furthermore, there will be a significant decline in performance over time for AD patients, whereas performance of the EC group should decline less markedly. 8) Performance on tests that require minimal working memory and mainly load on psychomotor ability (such as the Gibson Spiral Maze and Trail Making Form A), should be virtually the same for the AD and EC groups at baseline, but show a decline in performance for the AD group over time. 9) National Adult Reading Test (NART) scores should be non-significantly different between-groups at baseline. However, although this task has been regarded as a reliable predictor of pre-morbid IQ, scores over time will be expected to decline in the AD group due to language deficits caused by problems with lexical access through memory dysfunction.

## 7.2 Methods

### 7.2.1 Participants

Dementia patients (DP) and EC participants for the present study comprised those people who consistently attended all test sessions. As in the earlier studies, dementia patients were volunteers from the AD Research Project at Lytham Hospital Memory Clinic, United Kingdom. The EC participants were volunteers from the local community of Lytham. The methods for recruitment, AD diagnosis criteria and health status for the experimental population, were discussed in Chapter 2, Section 2.1. All participants were right-handed. Analyses for the DP group was derived from a reduced baseline group (N=15; age range = 70-88; mean = 76.5; SD = 4.5; male n=9; female n=6) and this was also the case for the AD sub-group (N=11; age range = 70-88; mean = 76.6; SD = 5.0; male n=8; female n=3). Unfortunately, it was not possible to carry out a longitudinal analysis for the DOT dementia sub-group, due to subject mortality. The EC group was obtained from the baseline group of EC participants (N=27; age range = 58–85 years ; mean = 71.2; SD = 6.1; male n=11; female n=16).

### 7.2.2 Assessment of Saccadic Eye Movements

All eye movement tasks were conducted using the 'Express Eye' eye movement recording system, task protocol and experimental procedures described in Chapter 2 (Section 2.3). So as to extend baseline measures, tasks for this study included the reflexive saccade gap and overlap paradigm, No-Go and Go/No-Go paradigms and the antisaccade gap and overlap paradigm, as discussed in the previous studies. The central fixation point was displayed at $0^{\circ}$ and the target stimulus presented randomly in the right or left visual field at $\pm 4^{\circ}$ of visual angle in the horizontal plane.

### 7.2.3 Statistical Analysis

Statistical analyses were carried out using SPSS version 11.5 (SPSS Inc., Chicago Ill). Firstly, dementia patients (DP) were assessed as a group compared with ECs and then the analyses were conducted on the AD sub-group with the EC group. No laterality effects were found for any variables either at baseline or for any subsequent test sessions, therefore, data from left and right hemifields were collapsed as in the previous studies. Normality of oculomotor variables was assessed using the skewness index, and variables transformed using square root or square, for positive (>1) or negative (<-1) skewness respectively (Tabachnick & Fidell, 1996).

Analyses were conducted using variously, two or three-factor repeated measures mixed ANOVA, One-way ANOVA, trend analysis and Bonferroni pair-wise comparisons as applicable and t-tests. For analyses using repeated measures ANOVA, assumptions of sphericity were assessed on each variable using the Mauchly test. The Greenhouse-Geisser epsilon correction of degrees of freedom was used if assumptions of sphericity were violated (Jennings, 1987). Spearman's rank order correlation coefficient was used to examine relationships within the data. Effect sizes for between-groups analyses of oculomotor variables

were calculated using Cohen's d statistic (Cohen, 1988) as in the earlier studies (see equations in Section 3.2.3.2).

## 7.3 Results

Corresponding with earlier studies, some saccadic variables were found to have some positive skewness, which when transformed to normalise the skewness of distribution, generated virtually identical output to untransformed scores. Therefore, for clarity of interpretation and descriptive statistics, the results given below use untransformed versions (were possible non-parametric analyses of all variables conducted simultaneously for thoroughness, also revealed the same results as ANOVA but are omitted from these sections).

### *7.3.1 Longitudinal Group Comparisons of Clinical Rating Scale and Neuropsychological Assessment scores*

A summary of clinical rating scale and neuropsychological assessment scores (group means) from longitudinal test sessions is displayed in Table 7.1 below. Both clinical rating scales showed a change of two points through the four tests sessions for the dementia group (SMMSE = decrease and EADAS cog = increase). However, with the AD group, the change was somewhat less pronounced on the SMMSE (-1.55). Interestingly, the EADAS cog detected an increase of 3.82 in the AD group over the four test sessions. The reader may recall from Chapter 2 (Sections 2.5.1 and 2.5.2 respectively), that a decease in SMMSE score equals a poorer score, whereas the opposite is true for the EADAS cog i.e. higher scores equal poorer scores. The clinical rating scales were assessed statistically using separate two-factor repeated measures mixed ANOVA.

**Table 7.1** Descriptive Statistics for Longitudinal Clinical Rating Scale and Neuropsychological Assessment Scores

| | Dementia Patients | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Baseline | | 6 months | | 12 months | | 18 months | | |
| Test | Mean | SD | Mean | SD | Mean | SD | Mean | SD | N |
| SMMSE | 23.80 | 2.98 | 24.20 | 3.08 | 24.00 | 3.82 | 21.87 | 3.89 | 15 |
| EADAScog | 18.00 | 7.07 | 18.13 | 6.03 | 18.67 | 7.35 | 20.27 | 12.51 | 15 |
| DSF | 9.07 | 2.19 | 9.07 | 2.02 | 9.00 | 2.20 | 9.07 | 2.55 | 15 |
| DSR | 5.93 | 2.43 | 5.73 | 2.25 | 5.47 | 2.03 | 5.13 | 2.56 | 15 |
| SSF | 6.00 | 2.04 | 5.80 | 1.57 | 5.33 | 1.95 | 6.07 | 2.02 | 15 |
| SSR | 5.13 | 1.51 | 5.40 | 2.23 | 5.73 | 1.83 | 5.00 | 2.10 | 15 |
| Gibson SM | 70.55 | 29.62 | 67.88 | 26.28 | 69.57 | 26.00 | 69.32 | 29.08 | 15 |
| Verbal fluency | 27.20 | 7.88 | 26.67 | 8.83 | 27.13 | 9.66 | 25.67 | 9.21 | 15 |
| Trails A | 54.68 | 13.04 | 54.38 | 13.00 | 49.27 | 15.27 | 54.38 | 24.95 | 15 |
| Trails B | 131.85 | 50.57 | 147.82 | 68.04 | 121.81 | 39.53 | 133.68 | 48.73 | 15 |
| NART | 107.67 | 10.20 | 107.20 | 10.19 | 107.07 | 10.19 | 106.73 | 11.73 | 15 |

| | Elderly Controls | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Baseline | | 6 months | | 12 months | | 18 months | | |
| Test | Mean | SD | Mean | SD | Mean | SD | Mean | SD | N |
| SMMSE | 29.22 | 1.09 | 28.85 | 1.46 | 29.22 | 0.93 | 29.48 | 0.80 | 27 |
| EADAScog | 7.96 | 2.53 | 6.26 | 2.54 | 5.56 | 2.36 | 5.59 | 2.19 | 27 |
| DSF | 10.33 | 2.48 | 10.22 | 2.26 | 9.85 | 2.27 | 10.22 | 2.19 | 27 |
| DSR | 7.52 | 2.42 | 7.07 | 1.75 | 7.44 | 2.24 | 7.67 | 2.20 | 27 |
| SSF | 7.52 | 1.74 | 7.26 | 1.43 | 7.52 | 1.83 | 7.48 | 1.58 | 27 |
| SSR | 6.85 | 1.26 | 6.93 | 1.64 | 6.74 | 1.32 | 7.04 | 1.53 | 27 |
| Gibson SM | 63.87 | 20.53 | 60.44 | 14.40 | 59.05 | 14.04 | 56.36 | 10.89 | 27 |
| Verbal fluency | 37.85 | 11.10 | 40.26 | 11.07 | 42.37 | 9.71 | 44.04 | 10.51 | 27 |
| Trails A | 42.11 | 13.31 | 34.13 | 7.29 | 30.71 | 6.66 | 32.31 | 7.51 | 27 |
| Trails B | 80.30 | 26.54 | 71.50 | 28.60 | 63.51 | 15.55 | 59.74 | 14.60 | 27 |
| NART | 114.15 | 12.92 | 115.37 | 11.76 | 116.56 | 10.46 | 117.15 | 10.99 | 27 |

| | Alzheimer's disease (Dementia Patients sub-group) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Baseline | | 6 months | | 12 months | | 18 months | | |
| Test | Mean | SD | Mean | SD | Mean | SD | Mean | SD | N |
| SMMSE | 23.00 | 2.68 | 23.82 | 3.12 | 23.27 | 4.15 | 21.45 | 4.27 | 11 |
| EADAScog | 19.45 | 6.68 | 19.18 | 6.00 | 20.18 | 7.60 | 23.27 | 13.46 | 11 |
| DSF | 9.09 | 2.39 | 8.91 | 2.26 | 9.45 | 2.34 | 9.45 | 2.88 | 11 |
| DSR | 5.64 | 2.69 | 5.91 | 2.59 | 5.45 | 2.34 | 4.73 | 2.87 | 11 |
| SSF | 6.18 | 2.27 | 5.73 | 1.62 | 5.45 | 2.16 | 6.27 | 2.24 | 11 |
| SSR | 5.00 | 1.67 | 5.45 | 2.54 | 5.73 | 2.10 | 4.82 | 2.44 | 11 |
| Gibson SM | 70.14 | 28.06 | 68.61 | 28.32 | 69.78 | 27.07 | 72.01 | 32.98 | 11 |
| Verbal fluency | 27.09 | 7.05 | 26.36 | 9.23 | 27.73 | 10.90 | 25.36 | 10.40 | 11 |
| Trails A | 59.25 | 11.26 | 55.55 | 14.02 | 49.21 | 17.83 | 57.01 | 30.30 | 11 |
| Trails B | 130.38 | 60.70 | 159.86 | 81.82 | 124.75 | 48.60 | 148.03 | 52.39 | 11 |
| NART | 108.00 | 11.27 | 107.09 | 11.55 | 106.73 | 11.46 | 105.73 | 13.24 | 11 |

DSF=Digit Span Forward; DSR = Digit Span Reverse; SSF=Spatial Span Forwards; SSR=Spatial Span Reverse; Gibson SM = Gibson Spiral Maze (secs); Trails A = Trail Making Form A (secs); Trails B = Trail Making Form B(secs); NART = National Adult Reading Test.

#### 7.3.1.1 The Standardised Mini-Mental State Examination

A two-factor repeated measures mixed ANOVA was conducted on the four data sets of SMMSE scores, i.e. from baseline through to 18 months, forming the repeated measures factor of *SMMSE test session*, with group (DP group as a whole and EC group) as the between-groups factor, to investigate changes over time in SMMSE scores. The main effect of SMMSE test session was found to be significant ($F[2.41, 120] = 2.97$, $p<0.047$), as was the main effect of group ($F[1, 40] = 102.03$, $p<0.0001$), indicating that overall, there was a significant difference over time on the SMMSE and between DP and EC group scores. The interaction between SMMSE test session and group was also significant ($F[3, 120] = 6.47$, $p<0.0001$), which shows that there were differences in the performance of the two groups over time on the SMMSE. A single-factor within-groups repeated measures ANOVA for the DP group on the SMMSE test session factor, revealed that main effect of SMMSE test session was significant ($F[3, 42] = 2.02$, $p<0.04$), polynomial trend analysis revealing a significant quadratic trend ($F[1, 14] = 4.96$, $p<0.043$) to be present in the data over test sessions (*time*). Bonferroni pair-wise comparisons of the levels of the factor SMMSE test session revealed that there was a significant decrease in the DP scores at 18 months from 12 months ($p<0.01$), but no significant difference was found between any other test session comparisons. Conversely, the within-groups repeated measures ANOVA for the EC group resulted in non-significant findings, which shows that the EC group did not change over time.

These results highlight that the SMMSE was able to detect the deterioration in dementia severity for the DP group and that this was present after 18 months, whereas the healthy EC group showed no change in their mental status. Additional analyses using between-groups one-way ANOVA (with Bonferroni adjustment) at each test session were highly significant at each stage (Table 7.2 [A] below), showing that the DP group performed significantly more poorly than the EC group, at each SMMSE test session.

**Table 7.2** Longitudinal Statistical Analyses (ANOVA) Between-Groups for Clinical Rating Scales and Neuropsychological Assessments

**A**

| Test | Dementia Patients vs. Elderly Controls: Baseline | 6 months | 12 months | 18 months |
|---|---|---|---|---|
| SMMSE | F[1,40]= 73.13, $p < 0.0001$* | F[1,40]= 44.44, $p < 0.0001$* | F[1,40]= 46.41, $p < 0.0001$* | F[1,40]= 97.89, $p < 0.0001$* |
| EADAScog | F[1,40]= 44.82, $p < 0.0001$* | F[1,40]= 80.34, $p < 0.0001$* | F[1,40]= 73.67, $p < 0.0001$* | F[1,40]= 35.87, $p < 0.0001$* |
| DSF | F[1,40]= 2.73, $p > 0.1$ | F[1,40]= 2.72, $p > 0.1$ | F[1,40]= 1.39, $p > 0.2$ | F[1,40]= 2.39, $p > 0.1$ |
| DSR | F[1,40]= 4.11, $p < 0.049$ | F[1,40]= 4.60, $p < 0.038$ | F[1,40]= 8.01, $p < 0.007$* | F[1,40]= 11.47, $p < 0.002$* |
| SSF | F[1,40]= 6.50, $p < 0.015$ | F[1,40]= 9.38, $p < 0.004$* | F[1,40]= 13.15, $p < 0.001$* | F[1,40]= 6.35, $p < 0.016$ |
| SSR | F[1,40]= 15.58, $p < 0.0001$* | F[1,40]= 6.44, $p < 0.015$ | F[1,40]= 4.25, $p < 0.046$ | F[1,40]= 13.016, $p < 0.001$* |
| GSM | F[1,40]= 0.74, $p > 0.3$ | F[1,40]= 1.42, $p > 0.2$ | F[1,40]= 2.93, $p > 0.09$ | F[1,40]= 4.39, $p < 0.044$ |
| Verbal flu | F[1,40]= 10.75, $p < 0.002$* | F[1,40]= 16.66, $p < 0.0001$* | F[1,40]= 23.83, $p < 0.0001$* | F[1,40]= 32.07, $p < 0.0001$* |
| Trails A | F[1,40]= 12.46, $p < 0.001$* | F[1,40]= 39.10, $p < 0.0001$* | F[1,40]= 28.22, $p < 0.0001$* | F[1,40]= 23.69, $p < 0.0001$* |
| Trails B | F[1,40]= 20.84, $p < 0.0001$* | F[1,40]= 24.80, $p < 0.0001$* | F[1,40]= 47.93, $p < 0.0001$* | F[1,40]= 65.23, $p < 0.0001$* |
| NART | F[1,40]= 2.79, $p > 0.1$ | F[1,40]= 5.10, $p < 0.029$ | F[1,40]= 8.08, $p < 0.007$* | F[1,40]= 8.26, $p < 0.006$* |

**B**

| Test | Alzheimer's Disease Patients vs. Elderly Controls: Baseline | 6 months | 12 months | 18 months |
|---|---|---|---|---|
| SMMSE | F[1,36]= 106.1, $p < 0.0001$* | F[1,36]= 46.58, $p < 0.0001$* | F[1,36]= 51.11, $p < 0.0001$* | F[1,36]= 90.89, $p < 0.0001$* |
| EADAScog | F[1,36]= 60.55, $p < 0.0001$* | F[1,36]= 89.19, $p < 0.0001$* | F[1,36]= 83.33, $p < 0.0001$* | F[1,36]= 45.14, $p < 0.0001$* |
| DSF | F[1,36]= 2.00, $p > 0.1$ | F[1,36]= 2.64, $p > 0.1$ | F[1,36]= 2.36, $p > 0.6$ | F[1,36]= 0.800, $p > 0.3$ |
| DSR | F[1,36]= 4.42, $p < 0.042$ | F[1,36]= 2.60, $p > 0.1$ | F[1,36]= 6.01, $p < 0.019$ | F[1,36]= 11.68, $p < 0.002$* |
| SSF | F[1,36]= 3.87, $p > 0.057$ | F[1,36]= 8.32, $p < 0.007$* | F[1,36]= 8.98, $p < 0.005$* | F[1,36]= 3.58, $p > 0.067$ |
| SSR | F[1,36]= 13.9, $p < 0.001$* | F[1,36]=4.53, $p < 0.040$ | F[1,36]= 3.23, $p > 0.08$ | F[1,36]= 11.49, $p < 0.002$* |
| GSM | F[1,36]= 0.587, $p > 0.4$ | F[1,36]= 1.40, $p > 0.2$ | F[1,36]= 2.60, $p > 0.1$ | F[1,36]= 4.93, $p < 0.033$ |
| Verbal flu | F[1,36]= 8.81, $p < 0.005$* | F[1,36]= 13.46, $p < 0.001$* | F[1,36]= 16.58, $p < 0.0001$* | F[1,36]= 24.82, $p < 0.0001$* |
| Trails A | F[1,36]= 18.30, $p < 0.0001$* | F[1,36]= 40.74, $p < 0.0001$* | F[1,36]= 27.18, $p < 0.0001$* | F[1,36]= 24.86, $p < 0.0001$* |
| Trails B | F[1,36]= 16.24, $p < 0.0001$* | F[1,36]= 23.34, $p < 0.0001$* | F[1,36]= 42.75, $p < 0.0001$* | F[1,36]= 84.18, $p < 0.0001$* |
| NART | F[1,36]= 1.896, $p > 0.1$ | F[1,36]= 3.91, $p > 0.056$ | F[1,36]= 6.53, $p < 0.015$ | F[1,36]= 7.50, $p < 0.010$* |

***Significant after Bonferroni adjustment alpha level .013; per longitudinal psychometric test.**

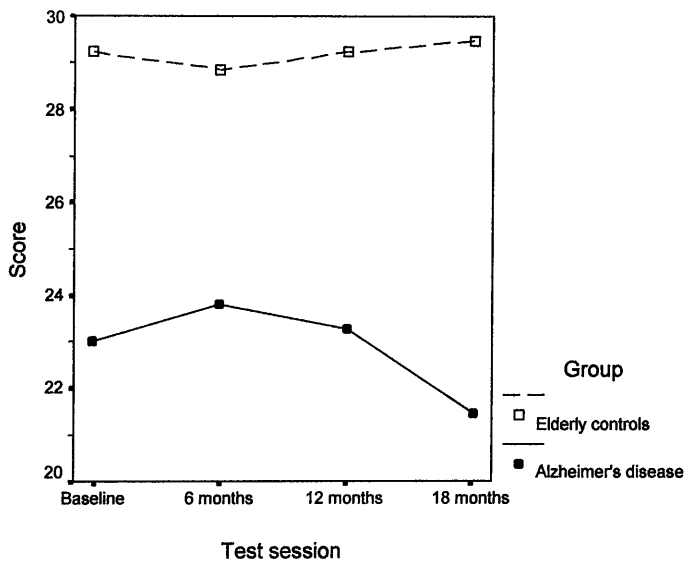
DSF=Digit Span Forward; DSR = Digit Span Reverse; SSF=Spatial Span Forwards; SSR=Spatial Span Reverse; GSM = Gibson Spiral Maze; Verbal flu = Verbal fluency; Trails A = Trail Making Form A; Trails B = Trail Making Form B; NART = National Adult Reading Test.

The same analytical procedure was carried out with the AD sub-group data to investigate how their cognitive performance changed over time, as measured by the SMMSE. The main effect of group was significant ($F[1, 36] = 114.0$, $p<0.0001$), showing that there were significant differences between AD and EC group scores in the omnibus ANOVA. Although the main effect of SMMSE test session was non-significant the interaction between SMMSE test session and group (Figure 7.1) was found to be significant ($F[3, 108] = 5.158$, $p<0.002$), showing that there were differences between the AD group and EC group for the change in SMMSE scores over time. Between-groups one-way ANOVA (with Bonferroni adjustment) at each test session were highly significant at each stage (Table 7.2 [B] above), showing that

the AD group performed significantly more poorly than the EC group, at each SMMSE test session. Bonferroni pair-wise comparisons between the levels of the SMMSE test session AD within-groups data showed there was a significant difference between 12 months and 18 months ($p<0.01$), but not other test sessions.

These findings show that although there is significant quantitative change during the later test sessions for the AD group, the changes between *baseline* and the later stages are only qualitative. In fact, as can be observed in the data profile (Figure 7.1), AD test session scores appear to be nearly quadratic. Polynomial contrasts showed that a quadratic trend was approaching significance ($F[1, 10] = 4.43, p>0.06$ NS).

**Figure 7.1** Graph Displaying the Interaction Between SMMSE Test Session and Group (Alzheimer's Disease and Elderly Controls)




In summary, these results show that the SMMSE was able to detect significant changes in dementia group global function over time and that it was possible to distinguish these differences clearly from control group performance. This supports the hypothesis that the clinical rating scale scores for dementia patients i.e. ADs, should be significantly poorer to those of control participants and that the test should detect a decline in global function over time, whereas no change should be evident for the EC group.

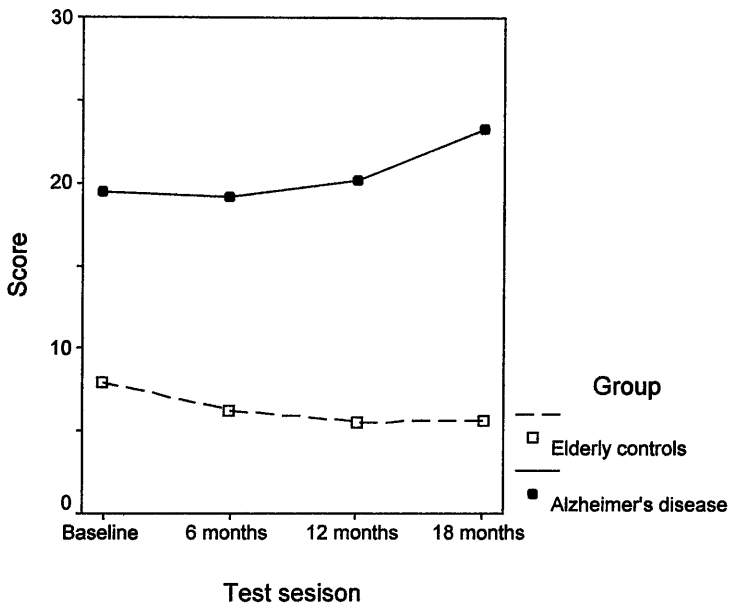
### 7.3.1.2 The European Alzheimer's Disease Assessment Scale Cognitive Sub-Test

A two-factor repeated measures mixed ANOVA was calculated to analyse the test session data for the EADAS cog, from baseline through to 18 months. For this analysis, *EADAS cog test session* was the repeated measures factor (four levels) and group (DP and EC groups) the between-groups factor. The main effect of the factor EADAS cog test session was not significant. However, the main effect of group was significant ($F[1,40] = 71.79$, $p<0.0001$), showing that overall, there was a significant difference between the two groups. The interaction between EADAS cog test session and group was found to be significant ($F[3, 120] = 3.085$, $p<0.047$), which indicates that the groups performed differently on the EADAS cog over time. Single-factor within-groups repeated measures ANOVA of the factor EADAS cog test session, revealed that there were no significant effects for the DP group. However, for the EC group, the within-groups analysis showed that the main effect of the factor EADAS cog test session was significant ($F[3, 78] = 9.89$, $p<0.0001$) and that a significant linear trend was present in the profile of the test session data ($F[1, 26] = 119.24$, $p<0.0001$), confirming that EC group scores significantly decreased/improved linearly over the 18 month period. Bonferroni pair-wise comparisons on the EC group test session data verified this, showing that baseline scores were significantly different to subsequent retest scores at 6 ($p<0.05$), 12 and 18 months (both $p<0.01$). However, comparisons between other test sessions, i.e. 6 months with 12 and 18 months or 12 months with 18 months were found to be non-significant, which indicates that further to a decrease after baseline measurement, there was only marginal changes in EC group scores at later stages. Between-groups analyses using one-way ANOVA (with Bonferroni adjustment), showed that there was a significant difference between-groups at each test session (Table 7.1 [A]). This was due to DP group scores being were significantly higher that EC group scores at each test session from baseline to 18 months.

The analyses were repeated with the AD sub-group and EC group as the between-groups factor in the two-factor repeated measures mixed ANOVA. The main effect of group was

found to be significant (F[1, 36] = 86.86, $p<0.0001$), indicating that there were differences overall, between the AD and EC groups. The main effect of EADAS cog test session was not significant, however, the interaction between EADAS cog test session and group was significant (F[3, 108] = 5.009, $p<0.003$), which shows that there were differences in group performance over the test sessions (Figure 7.2).

**Figure 7.2** Graphical Representation of the Interaction Between EADAS cog Test Session with Group (Alzheimer's Disease and Elderly Controls)




Within-groups analysis of the AD group repeated measures factor EADAS cog test session found no significant effects. Between-groups analysis comparing the AD and EC groups showed that there were significant differences between the groups at each stage of the longitudinal project (Table 7.2 [B]). This was due to the AD group producing a significantly higher score than the EC group at each test session from baseline through to 18 months. In summary, the EADAS cog was able to detect subtle within-group changes from baseline through to 18 months for the DP group and the AD sub-group, however, these differences were only qualitative and not statistically significant. A clear dissociation was observed between the EC group and dementia groups in EADAS cog performance over time. Elderly healthy controls demonstrated a significant linear improvement in their test scores over time, from a

baseline mean that lay well within the bounds of scores that would raise any concern. These results support the hypothesis that the clinical rating scale test score should be significantly poorer to those of control participants and that cognition should decline as a function of time.

#### *7.3.1.3 Digit Span*

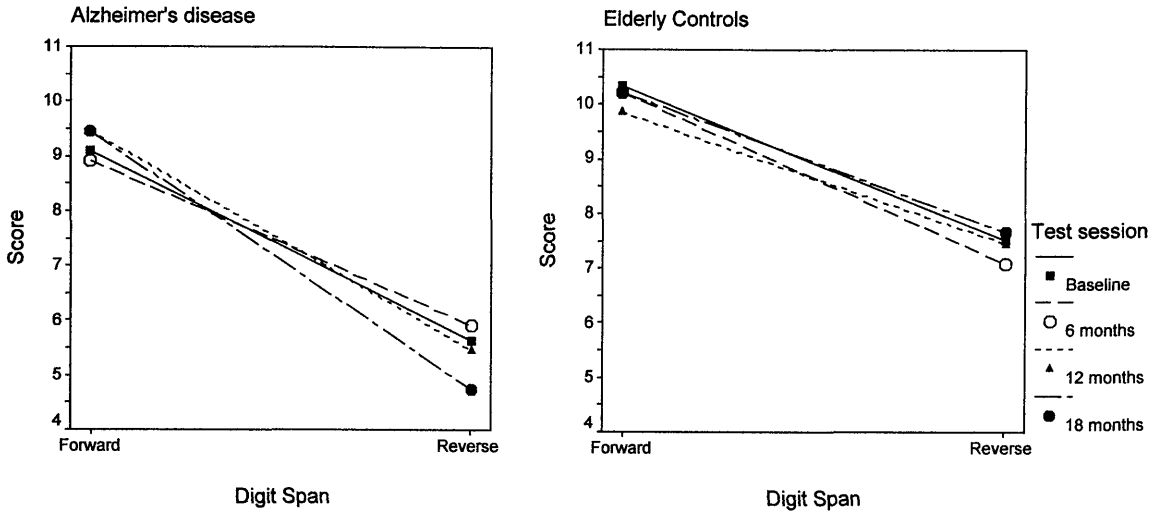
The scores from both the Digit Span Forward and Digit Span Reverse tests are examined together in this section to assess the difference in performance between the two tasks over time. As can be seen in Table 7.1 performance on the Digit Span Forward test appeared not to change over time for any of the groups, although overall, it seems that the EC group produced scores that were generally about 1 point (10.2 = grand mean over time) above both the whole DP group (9.1) and AD sub-group (9.2). Digit Span Reverse test scores were observed to be about 3.5 points lower than Digit Span Forward scores for the dementia patient groupings (DP = 5.6; AD = 5.4, grand mean over time) and also 2.8 points lower for controls. It is fairly normal to find a difference of approximately 2 points between the Forward and Reverse forms of the test (Black & Strub, 1978; Lezak, 1995).

A three-factor repeated measures mixed ANOVA was carried out on the Digit Span Forward and Reverse data from the four tests sessions. *Test session* formed the first repeated measures factor with four levels (baseline, 6 months, 12 months adn18 months) and *Digit Span test* formed another repeated measure factor with two levels (Forward and Reverse). The between-groups factor was group (comprising DP and EC groups). The only significant effects were the main effect of Digit Span test ($F[1, 40] = 4.13$, $p<0.049$) and the main effect of group ($F[1, 40] = 6.30$, $p<0.016$). Therefore, these results show that overall, there was a significant difference between scores on the Digit Span Forward (9.6) and Digit Span Reverse (6.5) tests, and that there was a significant difference between the overall group scores (DPs 7.31 and ECs 8.79).

*Between-Groups Effects:* To examine the main effect of group and task more closely, between-groups analyses using one-way ANOVA (with Bonferroni correction) at each test session can be seen in Table 7.2 (A). For the Digit Span Forward task, there was no significant difference at baseline through to the test session at 18 months. The DP group scored lower than the EC group at each test session, however, due to the bonferroni adjustment only the scores from the 12 months and 18 months test sessions were found to be significantly lower than the EC group i.e. without Bonferroni adjustment, the DP group score significantly lower than the EC group at each stage of testing. This supports the hypothesis that tests which place a high demand on working memory - in this case the Digit Span Reverse task – will be performed less efficiently for dementia patients than for control participants. However, the hypothesis that there would be a significant decrease in performance for dementia patients over time was not supported.

The procedure for the analyses of Digit Span Forward and Digit Span Reverse was replicated for the AD sub-group, with the AD and EC groups forming the levels of the between-groups factor in a three-factor repeated measures mixed ANOVA. *Test session* formed the first repeated measures factor with four levels (baseline, 6 months, 12 months adn18 months) and *Digit Span test* again formed the other repeated measure factor with two levels (Forward and Reverse). The main effects of Digit Span Test and Group were significant (Digit Span test, $F[1, 26] = 254.53$, $p<0.0001$; Group, $F[1, 36] = 4.54$, $p<0.040$), as was the interaction between Digit Span Test and Group ($F[1, 36] = 6.76$, $p<0.013$). Thus, these result show that overall, there was a significant difference between scores on the Digit Span Forward task (9.7) and Digit Span Reverse task (6.4) and also, that the groups performed significantly differently to each other (EC = 8.8 and AD = 7.3). Futhermore, the interaction shows that the groups performed differently on some level of the factor Digit Span test. The three-way interaction (Figure 7.3) between test session x Digit Span Test x Group, was also significant ($F[3, 108] = 2.97$, $p<0.035$).

**Figure 7.3** A Graph Displaying the Three-Way Interaction Between Digit Span Test Session (baseline, 6 months, 12 months, 18 months), Digit Span Test (Forward and Reverse) and Group (ADs and ECs)




This higher-order interaction is due to the interaction of the factors Digit Span task and test session, not being the same at the levels of the between-groups factor: group. As can be seen in Figure 7.3, AD group scores for the Digit Span Reverse task are less clearly defined from the EC group at the 6 months test session, a sharper decrease only being evident at the 12 and 18 month stage. Whereas Digit Span Forward scores increased at later test sessions which may play a large part in the significant three-way interaction. No other effects were found to be significant.

*Between-Groups Effects*: Between groups analyses using one-way ANOVA (with Bonferroni adjustment, Table 7.2 [B]) showed that the AD group scored significantly lower than the EC group on the Digit Span Reverse task at the 18 month test session. However, the difference between the groups was not significant at baseline, 6 months and 12 months[21]. No significant difference was found between the AD and EC groups for the Digit Span Forwards task at any test session.

*Within-Groups Effects*: Two-factor within-groups repeated measures ANOVA were conducted on the AD and EC group data. The main effect of Digit Span task was found to be

[21] The difference at baseline and 12 months was not significant due to the stringency of the Bonferroni adjustment.

significant for both groups (AD, F[1, 10] = 120.94, $p<0.0001$; EC, F[1, 26] = 154.09, $p<0.0001$), showing that overall, both the AD and EC sub-groups performed with higher scores on the Digit Span Forward task, compared with the Digit Span Reverse task. Paired samples t-tests of the Digit Span Forward with Digit Span Reverse scores, found that there was a significant difference within the AD group at each test session: Baseline, t[10]= 5.68, $p<$ 0.0001; 6 months, t[10]= 5.40, $p<0.0001$; 12 months, t[10]= 11.21, $p<0.0001$ and 18 months, t[10]= 6.62, $p<0.0001$. The same was also found for the EG group: Baseline, t[26]= 6.98, $p<$ 0.0001; 6 months, t[26]= 8.20, $p<0.0001$; 12 months, t[26]= 7.71, $p<0.0001$ and 18 months, t[26]= 8.99, $p<0.0001$. These findings show that although there was no change in scores over time, Digit Span Reverse scores were significantly lower than Digit Span Forward score at each test stage.

The two-factor within-groups repeated measures analysis for both the AD and EC groups, enables a clearer understanding of the three-way interaction, found in the three-factor repeated measures mixed ANOVA, where group was added as a third factor. The within-groups analyses both show that there are significant differences on the factor of Digit Span Test, demonstrating that Digit Span Forward scores are higher than Digit Span Reverse scores. However, test session and the interaction between this factor and Digit Span test, were not significant in either of the analyses. Thus, the introduction of the third factor - the between-groups factor of group (AD and EC) - caused the significant higher-order three-way interaction between Digit Span test session, Digit Span Test and Group. This shows that the groups perform significantly differently from each other over time, across the tasks. These findings support the hypothesis that tasks loading highly on working memory, in this case the Digit Span Reverse will result in a lower performance for AD patients than the EC group, and that AD scores will decline over time due to a decline in working memory function.

### 7.3.1.4 Spatial Span

Both forms of the Spatial Span task - Forward and Reverse - are analysed together in the following analyses so as to investigate changes in performance on the two tasks over time. On examination, the data for these two tests (Table 7.1) appear to show only marginal changes over the sequence of tests sessions for each of the groups. There also seems to be little difference between Spatial Span Forward and Spatial Span Reverse scores both within and between each group. To examine these observations statistically, a three-factor repeated measures mixed ANOVA was carried out on the data, firstly with the whole DP and EC groups as the between-groups factor and then the analysis is repeated with the AD sub-group and EC group as the between-groups factor. The design incorporated two within-groups factors (repeated measures) which were *Test session* with four levels (baseline, 6 months, 12 months adn18 months) and *Spatial Span test* with two levels (Forward and Reverse). In the first analysis with DP and EC groups, the main effect of test session was found to be non-significant as was the interaction between this factor and group. This shows that there were no differences over time between the two groups, when Spatial Span test scores (Forward and Reverse) are collapsed. The main effects of Spatial Span task and group were both significant (Spatial Span Task, $F[1, 40] = 9.98$, $p<0.003$; group, $F[1, 40] = 15.71$, $p<0.0001$), which demonstrates that there were significant differences overall, between the scores for Spatial Span Forwards (6.6) and Spatial Span Reverse (6.1). Therefore, Spatial Span Reverse scores were lower collapsed across groups. Collapsed across tasks, the DP group (5.6) produced significantly lower scores than the EC group (7.2), hence the significant between-groups difference. No other effects were found to be significant.

*Between-Groups Effects*: To examine the between-groups effects more closely, a series of one-way ANOVA (with Bonferroni adjustment) were conducted between the DP and EC groups on each task at each test session. The results (Table 7.2 [A]) showed that on the Spatial Span Forward task, DP group scores were significantly lower than EC group scores at

the 6 and 12 months tests sessions, but the baseline and 18 month sessions failed to reach significance, resulting from the Bonferroni correction. For the Spatial Span Reverse task, again, DP group scores were found to be significantly lower than EC group scores but this time the scores were significantly lower at baseline and at 18 months. Scores at the 6 and 12 month tests sessions failed to pass the stringent Bonferroni correction.

The three-factor repeated measures mixed ANOVA was repeated, with the AD sub-group and EC group as the between-groups factor. The main effects of Spatial Span test ($F[1, 36] = 10.59$, $p<0.002$) and group ($F[1, 36] = 11.73$, $p<0.002$) were found to be significant. However, no other effects or interactions were significant.

*Between-Groups Effects*: Between-groups analyses (AD and EC) of the Spatial Span test scores at each test session were conducted using one-way ANOVA (with Bonferroni adjustment; Table 7.2 [B]). For the Spatial Span Forwards test, AD patients were found to generate significantly lower scores than the EC group at the 6 month and 12 month test sessions, whereas the difference between the two groups at baseline and 18 months was only approaching significance. For the Spatial Span Reverse task, AD group scores were found to be significantly lower than EC group scores measured at basline and 18 months. The test session at 6 months failed to reach significance due to the Bonferroni adjustment.

In summary, scores on the Spatial Span Forward and Spatial Span Reverse tests were found not to change significantly over time within the DP, AD and EC groups. However, the DP and AD groups were found to perform significantly more poorly than the EC group overall, when test scores were collapsed. For the Spatial Span Forward task, both the DP group as a whole and the AD sub-group generated scores that were significantly lower than those of the EC group at the 6 month and 12 month test sessions, indicating that performance was better for DP and AD groups when measured at baseline and interestingly, at 18 months. However, for the Spatial Span Reverse test, the DP group and AD sub-group scores were found to be

significantly lower than the EC group at baseline and 18 months, demonstrating an improvement in DP and AD scores when tested at 6 months and 12 months.

The Spatial Span Reverse task was found to be more difficult than the Spatial Span Forward task, and this was found to be the case over the four test sessions. These results are in support of the hypothesis that the Spatial Span Reverse task – which places a high demand on working memory resources – would result in lower scores for the dementia patients than healthy controls, but do not support the hypothesis that dementia patient scores will deteriorate over time.

#### *7.3.1.5 Gibson Spiral Maze*

The scores for the Gibson Spiral Maze (representing time in seconds) are displayed in Table 7.1. This analysis purely examines whether the groups differred in speed of task completion, the motor component of the test. There appears to be little change on this test, from baseline measurement and through the later test sessions, for both the DP group as a whole and the AD sub-group. For the EC group there is a decrease in the time taken to complete the task at baseline from that measured at successive test sessions. However, a further supplementary assessment of the data using the CAPE credit scoring system (Section 2.5.10, Table 4), was adopted in an analysis to incoporate error rates (see Section 2.5.10) into the final score (Table 7.3 below).

**Table 7.3** Longitudinal Gibson Spiral Maze Credit Scores (CAPE Scoring System)

| | Gibson Spiral Maze Credit Score | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Baseline | | 6 months | | 12 months | | 18 months | | |
| Group | Mean | SD | Mean | SD | Mean | SD | Mean | SD | N |
| **EC** | 11.52 | 0.58 | 11.26 | 0.81 | 11.44 | 0.51 | 11.63 | 0.49 | 27 |
| **DP** | 10.47 | 1.36 | 10.73 | 1.39 | 10.73 | 0.88 | 10.47 | 1.41 | 15 |
| **AD** | 10.36 | 1.50 | 11.00 | 1.55 | 10.73 | 1.00 | 10.36 | 1.50 | 11 |

To examine task completion times, isolate the motor component and compare the DP and EC groups on the task, a two-factor repeated measures mixed ANOVA was used. *Test session* was the repeated measures factor comprising four levels (baseline, 6 months, 12 months and 18 months) and the factor group (DP and EC groups) as the between-groups factor. The main effects of test session and group and the interaction between these two factors were found to be non-significant. Therefore, these results suggest that for the Gibson Spiral Maze task there were no differences over test sesssions with groups collapsed. Furthermore, there was no significant difference between the two groups in the magnitude of change over time, as indicated by the lack of interaction between Gibson Spiral Maze test session and group. Additionally, there was no difference evident between the DP and EC groups, when test session was collapsed to analyse the overall group difference.

Analysis of the AD sub-group group data was included in the same procedures as above. The two-factor repeated measures mixed ANOVA was found to result in no significant effects. This means that there were no differences over test sesssions with the AD sub-group and EC group data collapsed. Additionally, there was no significant difference between the two groups in the magnitude of change over time, as evidenced by no interaction between test session and group. Also, there was no difference found between the AD and EC groups when test session was collapsed to analyse the overall group difference[22].

*Scores Incorporating Error Rates*: A supplementary analysis of AD and EC group Gibson Spiral Maze scores was carried out next, using the CAPE credit scoring sytsem so as to introduce error rate in the investigation. This analysis used a two-factor repeated measures ANOVA as in previous analyses, but the repeated measures factor of Gibson Spiral Maze test session - which previously comprised test *completion times* - was substituted by the *credit score* for each teat session (Table 7.3). The main effect of group was found to be significant ($F[1,36] = 15.91$, $p<0.0001$), which shows that overall the groups performed differently from

[22] For information purposes only, suplementary between-group one-way ANOVA are displayed in Table 7.2 [A&B].

one another. Comparison of main effects confirmed that the AD group scored lower than the EC group ($p<0.01$, Bonferroni). The main effect of test session was found to be non-significant, showing that when group data were collapsed, there was no difference between sessions in the omnibus ANOVA. The interaction between test session (credit score) and group was close to significance ($F[3,108] = 2.65$, $p>0.052$ NS), which emphasizes that there was a slight difference in the magnitude of change over time between AD and EC group scores.

To examine the AD and EC between-group differences more closely, one way ANOVA was conducted on the credit scores from each test session. This analysis showed that the AD group scored significantly more poorly than the EC group at baseline ($F[1,36] = 11.99$, $p<0.001$), 12 months ($F[1,36] = 8.59$, $p<0.006$) and 18 months ($F[1,36] = 15.64$, $p<0.0001$). However, there was no significant difference between the groups at the 6 months test stage ($p>0.5$). Within-groups analyses revealed that there were no significant changes for either group from baseline to testing at 18 months.

In summary, the present analysis found that the DP group, AD patient sub-group and EC group did not show any significant change over time in Gibson Spiral Maze test completion times. The EC group performed the task in a shorter time (i.e. faster rates) than the DP group and AD sub-group. However, when error rates were incorporated into the investigation by analysis of credit scores, it was found that the AD group produced lower scores than the EC group at each stage, with the exception of the test session at 6 months where there was no difference. There was no change in credit scores over time.

When the above findings are considered in light of task completion times or motor speed, they are in support of the hypothesis that performance of AD patients and the EC group on the Gibson Spiral Maze task - which is mainly a test of psychomotor ability - should be virtually indistinguishable at baseline. In contrast, when the results are examined to include error rate/accuracy, it is clear that AD patients generate more errors than controls, which does

not support the hypothesis that the AD group would perform no differently to the EC group at baseline. Therefore, although AD patients have little problem with speed of action, they produce higher error rates than controls. Additional analyses found that the hypothesis that AD patients would show a decline in performance over time was not supported.

#### *7.3.1.6 Verbal Fluency*

The Verbal Fluency data shown in Table 7.1 indicate that the performance of the DP group and AD sub-group did not appear to change over the tests sessions. However, this was in contrast to the EC group who seem to have improved at consecutive test sessions. Furthermore, EC group performance appears to achieve considerably higher scores, than the other groups from baseline and through each test session.

In the first instance, a two-factor repeated measures mixed ANOVA was conducted, to investigate the Verbal Fluency data from the four tests sessions by DP and EC groups. *Test session* formed the repeated measures factor with four levels (baseline, 6 months, 12 months adn18 months) and group was the between-groups factor (DP and EC groups). The main effect of Verbal Fluency test session was not significant, showing that overall (omnibus ANOVA), when the group data are collapsed to compare test sessions there is no difference between test sessions. The main effect of group was found to be significant ($F[1, 40] = 24.05$, $p<0.0001$), which shows that when the test sessions are collapsed, there was a significant overall difference between-groups. The interaction between Verbal Fluency test session and group was also significant ($F[3, 120] = 4.38$, $p<0.006$) highlighting that the groups performed differently over time.

A single-factor within-groups repeated measures ANOVA on the DP group data for Verbal Fluency test session data, showed that the there was no significant effect on this factor. This indicates that DP group Verbal Fluency scores did not change significantly over time from baseline. The single-factor within-groups repeated measures ANOVA was repeated for

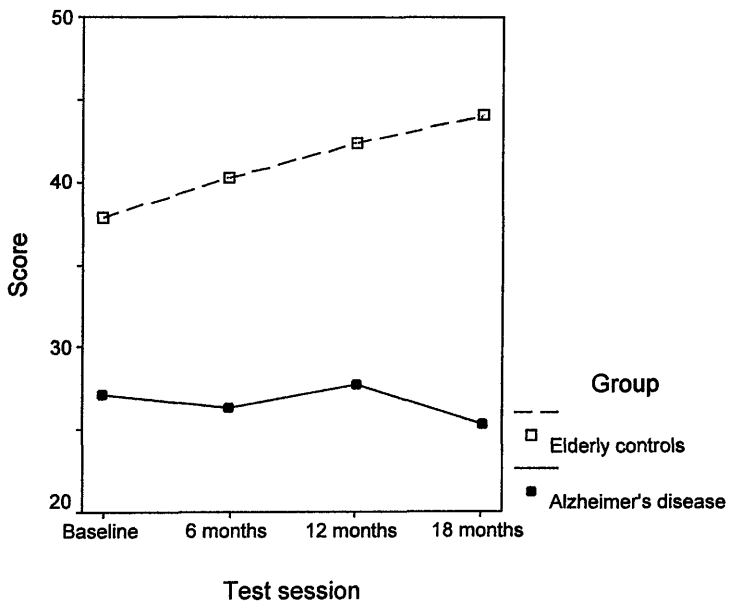
the EC group data. The output from this analysis revealed that there was a significant main effect for this factor ($F[3, 78] = 8.408$, $p<0.0001$), which shows that there were significant differences within the Verbal Fluency tests sessions over time. Trend analysis with polynomial contrasts showed that there was a significant linear trend in the data, as scores increased (improved) over time from baseline through to 18 months ($F[1, 26] = 32.14$, $p<0.0001$). Bonferroni pair-wise comparisons of the EC group Verbal Fluency test session data revealed that there was a significant difference between the scores at baseline and 12 months ($p<0.01$) and 18 months ($p<0.01$). There was also a significant difference between the scores at 6 months and 18 months ($p<0.05$). No significant difference was found between baseline scores and scores at 6 months ($p>0.6$) and between scores at 12 months and 18 months ($p>1.0$). These results suggest that the linear trend is caused by a steep increase in scores, which is most evident between baseline through to the latter two tests sessions (12 and 18 months). However, the increase is less prominent between scores at 12 months and 18 months. Between-groups analyses of DP group and EC group scores at each test session, using one-way ANOVA (with Bonferroni adjustment) showed that there were significant differences between the groups at each of the four test sessions (Table 7.2 [A]). This result was due to the EC group score more highly than the DP group at each stage.

The analysis using a two-factor repeated measures mixed ANOVA, was replicated to include the AD sub-group with the EC group, as the between-groups factor. Verbal Fluency test session again formed the repeated measures factor with four levels (baseline, 6 months, 12 months adn18 months). The main effect of verbal fluency test session was found to be non-significant. However, the main effect of group was significant ($F[1, 26] = 32.14$, $p<0.0001$), showing that the were significant differences between the groups overall when the test sessions were collapsed on the repeated measures. This was due to the EC group having a significantly higher overall mean score. The interaction (Figure 7.4) between Verbal Fluency test session

and group was found to be significant ($F[3, 108] = 3.55$, $p<0.0001$) revealing that the groups scored differently over the test sessions.

A single-factor within-groups repeated measures ANOVA was applied to the AD sub-group data on the factor Verbal Fluency tests session. This analysis showed that there were no significant effects and that the interaction in Figure 7.4, between Verbal fluency test session and group, was due to the incraese over time in the EC group scores (as described above where a linear trend was found in the EC group scores which due to an increase over time). Between-groups analysis with one-way ANOVA (with Bonferroni correction) examining the AD sub-group and EC group, resulted in a significant difference for each test session (Table 7.2 [B]). Again, this was due to the EC group scores being significantly higher than the AD sub-group at each test session.

**Figure 7.4** Graphical Representation of the Interaction Between Verbal Fluency Test Session and Group (Alzheimer's Disease and Elderly Controls)




In summary, the EC group scored significantly higher on the Verbal Fluency test, than the whole DP group and AD sub-group at each test session. The DP group and AD sub-group scores did not change over time, whereas the EC group showed a significant improvement, scores increasing with a linear trend over time from baseline to 18 months. These findings

support the hypothesis that AD group Verbal Fluency scores will be significantly lower than control group scores. However, the findings do not support the hypothesis that AD group scores will significantly decrease over time, as no significant changes were found to be present in the scores from baseline through successive test sessions.

#### *7.3.1.7 Trail Making*

On cursory examination of the Trail Making test data in Table 7.1, a noticeable difference was observed between Form A and Form B task completion times, Form A taking less time to complete than Form B for each group. For the DP group as a whole and the AD sub-group, times on both forms appeared to be more prolonged than those of the EC group, most strikingly so for Form B. For the DP and AD sub-group, times on Form A did not appear to change over time, whereas for the EC group Form A completion times seemed to decrease somewhat linearly over time. On Form B, DP group and AD sub-group times appear to fluctuate over time, however, the EC group times for Form B appeared to decrease linearly over the test sessions from baseline measurement through to 18 months.

To examine test form, test session and group effects, the data were subjected three-factor repeated measures mixed ANOVA, firstly to include the DP and EC groups and then this analysis was repeated with the AD sub-group and EC group. In the first three-factor repeated measures mixed ANOVA, the repeated measures factor of *Test session* was created with four levels (baseline, 6 months, 12 months and 18 months). *Trail Making test form* was created as a second repeated measures factor, with two levels (Form A and Form B). The between-groups factor was group (comprising DP and EC groups). The main effects of test session ($F[3, 111] = 5.82$, $p<0.001$), Trail Making test form ($F[1, 37] = 180.53$, $p<0.0001$) and group ($F[1, 37] = 48.28$, $p<0.0001$) were found to be significant. Therefore, this indicated that overall, i) there were significant differences over time when Trail Making test form data was collapsed; ii) that there was a significant overall difference between Trail Making Form A and

Form B, when test session and group data was collapsed, and; iii) The EC and DP groups performed significantly differently from each other when test form and test session data were collapsed. Significant interactions were observed between Trail Making test session and group ($F[3, 111] = 3.14$, $p<0.028$), and also between Trail Maiking test form and group ($F[1, 37] = 180.53$, $p<0.0001$). These results show that the groups performed significantly differently from each other both over time and on test form (A and B).

In order to investigate the within-groups effects, two-factor within-groups repeated measures ANOVA were carried out for the DP and EC groups. The only significant result for the DP group was on the factor of Trail Making test form ($F[1, 11] = 49.01$, $p<0.0001$). Trend analysis, using polynomial contrasts, revealed a significant cubic trend within the Trail Making test session factor ($F[1, 11] = 5.81$, $p<0.035$), confirming that scores fluctuate across the test sessions from baseline through to 18 months.

The within-groups analysis was repeated for the EC group, again using a two-factor repeated measures ANOVA. The main effect of Trail Making test session was significant ($F[2.22, 57.59] = 15.52$, $p<0.0001$), which shows that there were differences within the test sessions across time with the test forms collapsed. The factor of Trail Making test form was also significant ($F[1, 26] = 167.06$, $p<0.0001$), i.e. overall there was a significant difference between the Trail Making test forms. The EC group interaction, between Trail Making test session and Trail Making Test was found to be bordering on significance ($F[3,78] = 2.71$, $p<0.051$), which demonstrates that the EC group performed differently over time on the two test forms i.e. the magnitude of change in task completion time from baseline to the 18 months was different in Form B compared with Form A. Trend analysis, using polynomial contrasts, revealed a significant linear component to the interaction ($F[1, 26] = 6.81$, $p<0.015$), as test completion times decreased over time. To examine this more closely, within-group Bonferroni pair-wise comparisons of the EC group Trail Making test sessions were conducted by test form. For Trail Making Form A, there a significant difference was found when comparing

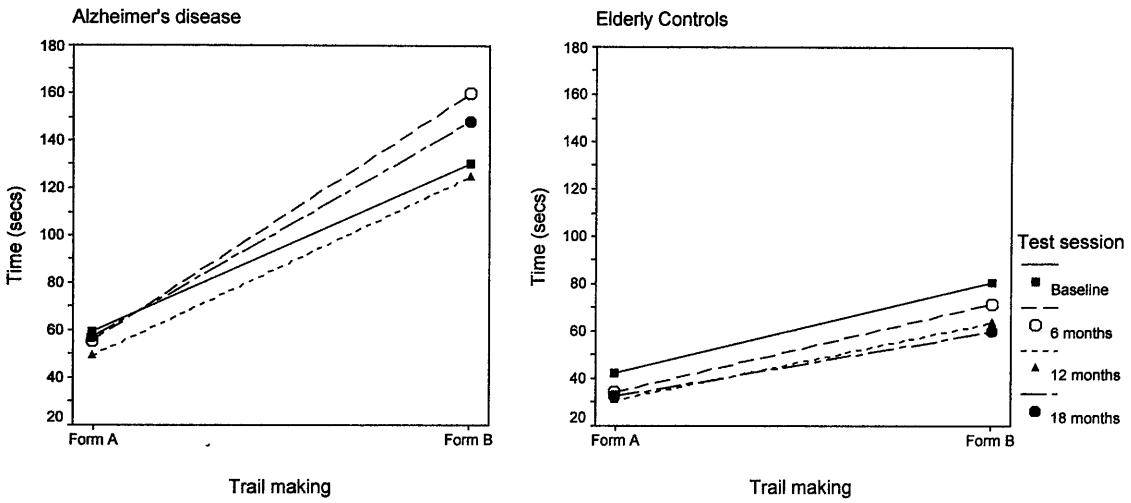
baseline with each subsequent test session ($p<0.01$). A significant difference was also found between the 6 month and 12 month test sessions ($p<0.05$), but not between 6 months and 18 months or 12 months and 18 months (test time actually increased slightly at 18 months!). Therefore, this suggests that the rate of change for the decreasing Form A completion times, was most prominent over the first three test sessions leading and only marginal in the latter stages. For Trail Making Form B, there was a slightly different pattern of significance between test sessions for the decrease in test completion time across test sessions. Baseline was not found to be significantly different from the test at 6 months ($p>0.2$), but was significantly slower than testing at 12 months ($p<0.05$) and 18 months ($p<0.01$). There was no significant difference between other test session combinations. Thus, it is plausible to suggest that although test completion times clearly decrease, gradually becoming faster from baseline through subsequent test sessions, this decrease is significant in the early test sessions but only marginal between 12 months and 18 months.

Differences between the DP and EC groups on each Trail Making test from were next assessed at each tests session using one-way ANOVA (with Bonferroni adjustment, see Table 7.2 [A]). For Trail Making Form A and for Form B, the EC group was significantly faster than the DP group at each test session (i.e. from baseline through to 18 months).

To examine the AD sub-group, the three-factor repeated measures mixed ANOVA was repeated, the repeated measures factor of *Trail Making test session* was created with four levels (baseline, 6 months, 12 months and18 months). *Trail Making test form* was created as a second repeated measures factor with two levels (Form A and Form B). The between-groups factor was group, this time comprising the AD sub-group with the EC group. For this analysis all main effects and interactions were significant. The output of the main effects and interactions for three-factor ANOVA to include the AD and EC groups, can be summarised as follows: Trail Making test session ($F[2.3,76.6] = 4.93$, $p<0.007$); Interaction between Trail Making test sesion x group ($F[3,99] = 4.66$, $p<0.004$); Trail Making test form ($F[1,33] =$

137.20, $p<0.001$); Interaction between Trail Making test form x group (F[1,33] = 25.55, $p<0.0001$); Interaction between Trail Making test session and Trail Making test form (F[3,99] = 3.38, $p<0.021$); Three-way interaction (Figure 7.5) between Trail Making test session, Trail Making test form and group (F[3,99] = 3.77, $p<0.013$).

**Figure 7.5** A Graphical Representation of the Three-Way Interaction Between Trail Making Test Session (baseline, 6 months, 12 months, 18 months), Trail Making Test (Form A and Form B) and Group (ADs and ECs)




The synopsis for this output is as follows: i) there were significant overall differences between Trail Making test sessions, when group scores were collapsed; ii) the groups differed in their performance when the test sessions were collapsed, irrespective of test form; iii) there was an overall difference between Trail Making Form A and Form B when group times were collapsed; iv) the groups performed significantly differently on the form of test, with test session data collapsed; v) overall, i.e. with groups collapsed, the magnitude of change is different on the Trail Making test forms over the test sessions; vi) there is a higher-order interaction which is due to the interaction of Trail Making test form and Trail Making test session being significantly different for each group.

A two-factor within-groups repeated measures ANOVA was used to assess the AD sub-group data. The only significant effect, was the main effect of Trail Making test form (F[1,7.0]

= 25.06, $p<0.002$), which shows that there were significant differences overall, between test Form A and test Form B, Form B being significantly slower to complete than Form A (Bonferroni: $p<0.01$).

Table 7.2 (B), shows the summarised statistical output for a series of one-way ANOVA (with Bonferroni adjustment) that were used to examine the differences between AD sub-group and EC group data for each test form at each of the testing sessions. The EC group was found to be significantly faster than the AD sub-group on both the Trail Making Form A task and Trail Making Form B task at each test session, i.e. baseline through to 18 months.

In summary, all groups performed significanlty faster on completing Form A than From B, of the Trail Making test. Both the DP group as a whole and the AD sub-group, performed significantly differently from the EC group on each of the task forms and over time. The DP group and AD sub-group showed some fluctuation in task completion times over time, but no significant increase (deterioration) or decrease (improvement) between baseline and 18 months was observed for either Form A or Form B of the Trail Making test. EC group performance was found to improve significantly on each test form over time, i.e. test completion times decreased significantly btween baseline and 18 months.

#### *7.3.1.8 National Adult Reading Test: Predicted Measure of Pre-morbid IQ*

The opportunity was taken to evaluate the NART for it's stability over time, as a *predictor* of pre-morbid IQ. To evaluate the test, two-factor repeated measure mixed ANOVA were used to analyse the predicted IQs from the DP and EC groups and in a separate analysis, the AD sub-group and EC group. For the first analysis, the repeated measures factor was *NART session* and the between-groups factor was group (DP and EC groups). The main effect of NART session was not found to be significant, which shows that there were no overall differences across time when group sessions were collapsed. However, the interaction between NART session and group was significant ($F[3,120] = 5.60$, $p<0.001$), indicating that the groups

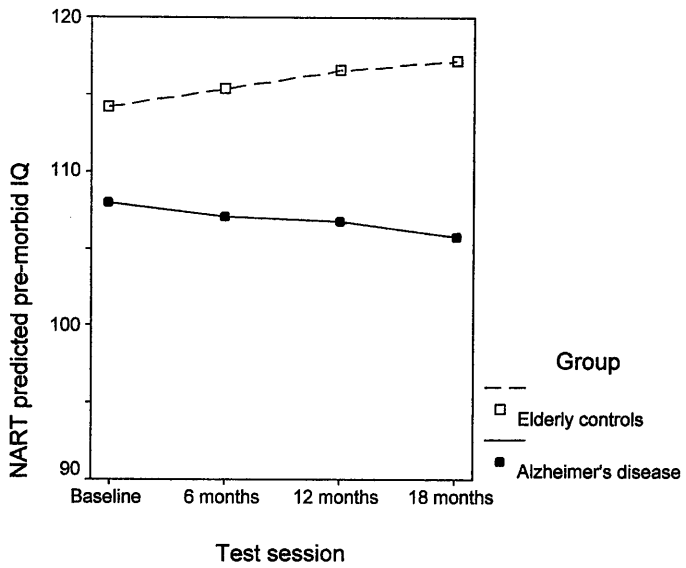
performed differently from each other over time. The main effect of group was also significant ($F[1,7.0] = 25.06$, $p<0.002$), which shows that there was an overall difference between the groups, when the scores from the NART session were collapsed over sessions.

Between-groups analyses at each test session were carried out using one-way ANOVA (with Bonferroni correction, Table 7.2[A]). The analysis revealed that there was no significant difference between the groups at baseline and also, at 6 months (the 6 month session did not reach significance due to Bonferroni adjustment). At the 12 months and 18 months stages, there was a significant difference detected between the two groups.

Within-groups analyses, using single-factor repeated measures ANOVA for each group on the factor NART session, showed that the difference in groups in the later stages of testing was caused by EC group scores increasing over time (Factor: NART test session ($F[3, 78] = 9.22$, $p<0.0001$). Trend analysis, with polynomial contrasts also showed that the profile of EC group scores over time from baseline to 18 months, was due to a significant linear increase in the scores ($F[1, 26] = 22.53$, $p<0.0001$). However, the within-groups analysis for the DP group, did not find any significant effects. In summary, this means that DP group scores do not change significantly over time, whereas the EC group scores did change (improved). The two-factor repeated measure mixed ANOVA was repeated for the AD sub-group. Again, the repeated measures factor was NART session and the between-groups factor was group (with AD sub-group and EC groups). The main effect of NART session was found to be non-significant, but the interaction between NART session and group was significant ($F[3, 108] = 7.70$, $p<0.0001$) which highlights that there was a significant difference between the groups in their performance over time (Figure 7.6).

Between-groups analyses at each test session were carried out using one-way ANOVA (with Bonferroni correction, Table 7.2[B]). The results of this analysis showed that there was no significant difference between the groups when tested at baseline, 6 months and 12 months (12 months failed due to Bonferroni correction).

**Figure 7.6** A Graph Representing the Interaction Between National Adult Reading Test Session and Group (Alzheimer's Disease and Elderly Controls)




However, there was a significant difference between the groups at 18 months, with the EC groups scoring more highly that the AD group. This corresponds with an analysis of years spent in education, which revealed no significant difference between the groups (mean number of years: EC = 11.9; AD = 12.0; $p > 0.9$, NS).

A within-groups analysis of the AD sub-group, using a single-factor repeated measures ANOVA on the factor NART session, showed that the factor of NART test session was not significant and the polynomial contrasts for trend analysis showed that there was a linear trend that was only approaching significance ($F[1, 10] = 4.05$, $p > 0.07$ NS). A paired samples t-test between AD group baseline and 18 months NART test session scores, showed that the difference between these two test sessions was approaching significance ($t[10] = 2.11$, $p > 0.06$ NS), as scores declined over time.

To summarise, at baseline the EC group predicted IQ scores did not differ significantly from those of the DP group as a whole, or the AD sub-group, which supports the baseline measurement hypothesis of no difference between-groups. Over time, the EC group scores improved significantly by comparison to the DP group, which did not change over time.

However, in contrast AD sub-group scores did show a subtle decline over time but this fall off from baseline to the 18 months test session just failed to reach significance. This finding does not support the hypothesis that AD scores would decline significantly over time, on this occasion. However, it is plausible to suggest that the reliability of the NART to predict pre-morbid IQ with dementia patients at different levels of severity - as is reflected in the longitudinal scores resulting from the present study - should be treated with caution.

### 7.3.2 Longitudinal Group Comparisons of Saccadic Error Rates

#### 7.3.2.1 Comparing Inhibitory Error Rates Across Voluntary Saccade Tasks Over Time

Cursory analysis of inhibition errors committed during voluntary saccade tasks (see Table 7.4 below), appeared to show that error rates increased as a function of cognitive load for a given task, i.e. as in Studies I and III, least errors were committed in the No-Go task, next the antisaccade task and finally, the Go/No-Go task resulting in the highest proportion of inhibition errors. In the earlier studies of this thesis *voluntary saccade task* was used as a repeated measures factor in ANOVA to examine the three voluntary tasks. In the present analyses, this factor was examined to investigate whether there were any changes over time, both between and within groups. The data were subjected to three-factor repeated measures mixed ANOVA, firstly to look at the DP group along with ECs and then the AD sub-group compared with ECs. Therefore, *test session* formed the first repeated measures factor with four levels (baseline, 6 months, 12 months and 18 months) and the second repeated measures factor was voluntary saccade task (inhibition error rate for each voluntary task), with group as the between-groups factor.

**Table 7.4** Descriptive Statistics for Longitudinal Saccadic Eye Movement Data

**Dementia Patients**

| | | Baseline | | | 6 months | | | 12 months | | | 18 months | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Test | Mean | SD | *d* | Mean | SD | *d* | Mean | SD | *d* | Mean | SD | *d* | N |
| Inhibition errors (%) | No-Go | 22.00 | 16.87 | 0.9 | 21.00 | 26.44 | 0.4 | 17.11 | 19.42 | 0.6 | 27.00 | 29.08 | 1.3 | 10 |
| | Anti-saccade | 32.75 | 20.69 | 1.1 | 28.87 | 13.39 | 1.0 | 33.04 | 17.90 | 1.1 | 33.87 | 30.70 | 1.0 | 10 |
| | Go/No-Go | 49.60 | 32.40 | 0.5 | 49.27 | 27.04 | 1.1 | 48.26 | 31.68 | 1.2 | 47.13 | 26.16 | 1.1 | 10 |
| Anti (%) | Correct saccades | 52.45 | 26.18 | -1.4 | 59.31 | 18.23 | -1.1 | 53.81 | 23.36 | -1.5 | 55.15 | 35.59 | -1.2 | 13 |
| | Corrected error | 22.96 | 15.71 | 0.7 | 24.22 | 12.01 | 0.7 | 30.18 | 17.50 | 1.0 | 23.50 | 21.49 | 0.6 | 13 |
| | Uncorrected errors | 11.85 | 17.25 | 0.9 | 7.61 | 12.03 | 1.1 | 9.02 | 27.46 | 0.5 | 18.02 | 32.79 | 0.9 | 13 |
| Reflexive (msecs) | Gap task | 206.04 | 46.92 | 0.3 | 204.70 | 40.58 | 0.3 | 208.31 | 54.83 | 0.2 | 205.57 | 47.34 | 0.0 | 10 |
| | Overlap task | 281.08 | 37.65 | 1.0 | 277.67 | 30.22 | 1.2 | 266.13 | 25.34 | 0.5 | 268.22 | 45.53 | 0.4 | 10 |

*d* = Cohen's d; effect size when patient group compared with Elderly Control group

**Elderly Controls**

| | | Baseline | | 6 months | | 12 months | | 18 months | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Test | Mean | SD | Mean | SD | Mean | SD | Mean | SD | N |
| Inhibition errors (%) | No-Go | 10.00 | 11.77 | 12.22 | 18.05 | 8.88 | 11.39 | 4.94 | 10.10 | 27 |
| | Anti-saccade | 15.61 | 13.32 | 15.66 | 12.53 | 15.96 | 14.39 | 15.84 | 10.30 | 27 |
| | Go/No-Go | 34.81 | 28.62 | 29.97 | 20.45 | 28.82 | 22.98 | 34.96 | 25.44 | 27 |
| Anti (%) | Correct saccades | 79.42 | 15.82 | 78.50 | 17.25 | 80.89 | 14.82 | 82.11 | 11.37 | 27 |
| | Corrected error | 13.91 | 12.13 | 15.35 | 12.50 | 15.32 | 13.61 | 15.23 | 10.42 | 27 |
| | Uncorrected errors | 1.70 | 5.81 | 0.31 | 1.12 | 0.63 | 1.96 | 0.62 | 1.90 | 27 |
| Reflexive (msecs) | Gap task | 194.75 | 36.69 | 194.55 | 31.10 | 199.82 | 32.19 | 206.70 | 47.32 | 22 |
| | Overlap task | 251.08 | 27.50 | 242.45 | 29.25 | 250.88 | 32.89 | 253.15 | 41.29 | 22 |

**Alzheimer's disease (Dementia Patients sub-group)**

| | | Baseline | | | 6 months | | | 12 months | | | 18 months | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Test | Mean | SD | *d* | Mean | SD | *d* | Mean | SD | *d* | Mean | SD | *d* | N |
| Inhibition errors (%) | No-Go | 26.67 | 15.06 | 1.3 | 21.67 | 27.87 | 0.5 | 20.00 | 24.49 | 0.8 | 31.67 | 34.30 | 1.6 | 6 |
| | Anti-saccade | 42.07 | 19.19 | 1.8 | 29.87 | 14.76 | 1.1 | 37.72 | 14.53 | 1.5 | 41.30 | 31.39 | 1.6 | 6 |
| | Go/No-Go | 61.78 | 30.45 | 0.9 | 53.93 | 27.54 | 1.1 | 59.39 | 33.77 | 1.2 | 61.91 | 20.77 | 1.1 | 6 |
| Anti (%) | Correct saccades | 41.49 | 21.58 | -2.2 | 54.34 | 18.25 | -1.4 | 46.26 | 20.36 | -2.1 | 46.29 | 35.89 | -1.8 | 9 |
| | Corrected error | 26.22 | 15.31 | 1.0 | 22.81 | 12.05 | 0.6 | 32.94 | 17.20 | 1.2 | 25.36 | 21.47 | 0.7 | 9 |
| | Uncorrected errors | 15.71 | 19.75 | 1.3 | 10.99 | 13.24 | 1.6 | 12.11 | 33.02 | 0.7 | 24.51 | 37.97 | 1.3 | 9 |
| Reflexive (msecs) | Gap task | 189.36 | 34.18 | -0.1 | 189.33 | 34.21 | -0.2 | 194.39 | 50.27 | -0.1 | 187.16 | 33.85 | -0.4 | 7 |
| | Overlap task | 281.39 | 38.82 | 1.0 | 272.91 | 33.15 | 1.0 | 259.59 | 23.22 | 0.3 | 253.11 | 44.79 | 0.0 | 7 |

*d* = Cohen's d; effect size when patient group compared with Elderly Control group;

Anti (%) = antisaccade gap task; Reflexive (msecs) = Reflexive saccade paradigm latency in milliseconds

*Dementia Patients and Elderly Controls:* For the DP vs. EC group analysis, the main effect of test session and the interaction of this factor with group did not reach significance. This indicates that there was no significant change over time in the proportion of inhibition errors when group data was collapsed, and also, that the magnitude of change in performance over time was no different for the DP and EC groups. However, the main effects of voluntary saccade task ($F[2,70]=35.17$, $p<0.0001$) and group ($F[1, 35] = 12.53$, $p<0.001$)

were found to be significant, which indicates that there was a significant difference overall between the saccadic tasks and also, that there was a significant overall difference in the performance of each group. The higher-order three-way interaction (test session x voluntary saccade task x group) was found to be non-significant.

*Between-Group Effects*: As the between-group factor was significant, one-way ANOVA (with Bonferroni correction) was used to examine DP and EC group inhibitory errors on each task (Table 7.5 [A]). For the No-Go task, no significant differences were found between the two groups at baseline, 6 months and 12 months, whereas by 18 months a significant difference was present. This was due to an increase in the proportion DP group inhibition errors (large effect, Table 7.4). For the antisaccade task, significantly more inhibition errors were produced by the DP group than the EC group, at each test session (with large effect sizes, Table 7.4).

**Table 7.5** Longitudinal Statistical Analyses (ANOVA) Between-Groups for Saccadic Eye Movement Data

**A**

| | | Dementia Patients vs. Elderly Controls | | | |
|---|---|---|---|---|---|
| | Test | Baseline | 6 months | 12 months | 18 months |
| Inhibition errors (%) | No-Go | F[1,36]= 5.97, $p < 0.02$ | F[1,36]= 1.33, $p > 0.2$ | F[1,36]= 2.56, $p > 0.1$ | F[1,36]= 12.12, $p < 0.001$* |
| | Anti-saccade | F[1,36]= 8.86, $p < 0.005$* | F[1,36]= 7.83, $p < 0.008$* | F[1,36]= 9.02, $p < 0.005$* | F[1,36]= 7.38, $p < 0.01$* |
| | Go/No-Go | F[1,36]= 1.82, $p > 0.1$ | F[1,36]= 5.45, $p < 0.025$ | F[1,36]= 4.24, $p < 0.047$ | F[1,36]= 1.64, $p > 0.2$ |
| Anti (%) | Correct saccades | F[1,39]= 16.47, $p < 0.0001$* | F[1,39]= 10.47, $p < 0.003$* | F[1,39]= 19.95, $p < 0.0001$* | F[1,39]= 13.06, $p < 0.001$* |
| | Corrected error | F[1,39]= 4.026, $p > 0.052$ | F[1,39]= 4.53, $p < 0.04$ | F[1,39]= 8.67, $p < 0.006$* | F[1,39]= 2.73, $p > 0.1$ |
| | Uncorrected errors | F[1,39]= 7.72, $p < 0.008$* | F[1,39]= 10.03, $p < 0.003$* | F[1,39]= 2.56, $p > 0.1$ | F[1,39]= 7.76, $p < 0.008$* |
| Reflexive (msecs) | Gap task | F[1,31]= 0.55, $p > 0.4$ | F[1,31]= 0.60, $p > 0.4$ | F[1,31]= .305, $p > 0.5$ | F[1,31]= .004, $p > 0.9$ |
| | Overlap task | F[1,31]= 6.48, $p < 0.016$ | F[1,31]= 9.77, $p < 0.004$* | F[1,31]= 1.68, $p > 0.2$ | F[1,31]= .861, $p > 0.3$ |

**B**

| | | Alzheimer's Disease Patients vs. Elderly Controls | | | |
|---|---|---|---|---|---|
| | Test | Baseline | 6 months | 12 months | 18 months |
| Inhibition errors (%) | No-Go | F[1,32]= 8.93, $p < 0.005$* | F[1,32]= 1.1, $p > 0.3$ | F[1,36]= 2.95, $p > 0.09$ | F[1,32]= 12.74, $p < 0.001$* |
| | Anti-saccade | F[1,32]= 16.5, $p < 0.0001$* | F[1,32]= 5.94, $p < 0.021$ | F[1,32]= 11.2, $p < 0.002$* | F[1,32]= 12.83, $p < 0.001$* |
| | Go/No-Go | F[1,32]= 4.27, $p < 0.047$ | F[1,32]= 5.95, $p < 0.021$ | F[1,32]= 7.32, $p < 0.011$* | F[1,32]= 5.82, $p < 0.022$ |
| Anti (%) | Correct saccades | F[1,35]= 32.28, $p < 0.0001$* | F[1,35]= 12.87, $p < 0.001$* | F[1,35]= 30.48, $p < 0.0001$* | F[1,35]= 21.55, $p < 0.0001$* |
| | Corrected error | F[1,35]= 6.10, $p < 0.019$ | F[1,35]= 2.45, $p > 0.1$ | F[1,35]= 9.93, $p < 0.003$* | F[1,35]= 3.62, $p > 0.06$ |
| | Uncorrected errors | F[1,35]= 11.27, $p < 0.002$* | F[1,35]= 18.23, $p < 0.0001$* | F[1,35]= 3.43, $p > 0.07$ | F[1,35]= 11.27, $p < 0.002$* |
| Reflexive (msecs) | Gap task | F[1,28]= 0.118, $p > 0.7$ | F[1,28]= 0.14, $p > 0.7$ | F[1,28]= 0.115, $p > 0.7$ | F[1,28]= 1.02, $p > 0.3$ |
| | Overlap task | F[1,28]= 5.28, $p < 0.03$ | F[1,28]= 5.42, $p < 0.028$ | F[1,28]= 0.42, $p > 0.5$ | F[1,28]= 0.00, $p > 0.9$ |

*Significant after Bonferroni adjustment alpha level .013; per longitudinal block

Anti = antisaccade gap task; Reflexive = Reflexive saccade paradigm

The Go/No-Go task analysis resulted in no significant difference between the two groups at baseline and 18 months. Interestingly, at the 6 month and 12 months test stages, the EC group had a reduction in the proportion of inhibition errors committed, but this did not survive the Bonferroni correction (although the effect size was large, $d$ = 1.1 and 1.2 respectively).

*Within-Groups Analyses for Dementia Patients*: To investigate voluntary saccade task simple effects, within-groups analyses were conducted using within-groups repeated measures ANOVA for the DP group and the EC group. For the DP group analysis, the main effect of voluntary saccade task was significant ($F[2,18]=13.67$, $p<0.0001$), showing that the DP group performed differently on the range of voluntary saccade tasks, with test session collapsed (the main effect of test session was not examined). Trend analysis revealed that there was a significant linear trend across the tasks ($F[1,9]=49.18$, $p<0.0001$), with the No-Go task resulting in least inhibition errors, followed by the antisaccade task and the Go/No-Go with the highest rate. Overall (i.e. sessions collapsed), Bonferroni pair-wise comparisons revealed that the antisaccade task inhibition error rate did not differ significantly from either the No-Go or the Go/No-Go tasks ($p>0.2$ and 0.06 respectively), although the difference between the No-Go and antisaccade tasks was approaching significance. However, the No-Go task inhibition error rate was found to be significantly lower than that of the Go/No-Go task ($p<0.01$). These findings show, that there is a distinct change in the proportion of errors that result in a task with low cognitive demand, through to tasks with high demand on working memory resources. The interaction between voluntary saccade test session and voluntary saccade task, was not found to be significant. This result indicates that although there appears to be some change over time for inhibition errors - with a fall in error rates at 6 months from baseline and then increasing up to 18 months (for the No-Go and antisaccade tasks) - this change is only qualitative and subtle for the DP group.

*Within-Groups Analyses for Elderly Controls:* The within-groups analysis for EC group inhibition errors on the voluntary saccade tasks showed a similar pattern to that of the DP group, with the main effect of voluntary saccade task significant ($F[2,52]=29.205$, $p<0.0001$). This demonstrates that overall there was a significantly different performance across tasks by the EC group. Trend analyses showed that there was a significant linear trend in the proportion of inhibition errors committed by the EC group across tasks ($F[1,26]=59.436$, $p<0.0001$), the trend following that of the DP group with least errors in the No-Go task through antisaccade and Go/No-Go tasks. Bonferroni pair-wise comparisons of the collapsed session data showed that overall the EC group produced significantly less inhibitory errors on the No-Go task when compared with both the antisaccade and Go/No-Go tasks ($p<0.05$ and $p<0.01$). Inhibition errors in the antisaccade task were also found to be significantly lower than in the Go/No-Go task ($p<0.01$).

*Alzheimer's Disease Patients and Elderly Controls:* A three-factor repeated measures mixed ANOVA was repeated, this time to include the AD sub-group and EC group as the between-groups factor. As in the previous analysis, the first repeated measures factor was test session (four levels: baseline, 6 months, 12 months and 18 months) and the second, voluntary saccade task (No-go, antisaccade and Go/No-Go). The results for the main effects were very similar to those found in the previous analysis with the DP group. The main effect of test session and the interaction of this factor with group were not significant, which indicates that there was no significant change over time in the proportion of inhibition errors when AD sub-group and EC group data were collapsed. Furthermore, the magnitude of change in performance over time was no different for the AD and EC groups. However, the main effects of voluntary saccade task ($F[2,62]= 31.85$, $p<0.0001$) and group ($F[1, 31] = 21.615$, $p<0.0001$), were found to be significant, although the interaction between these two factors was not significant. Nonetheless, these findings show that there were overall significant differences

between the saccadic tasks and in the performance of each group. The higher-order three-way interaction (test session x voluntary saccade task x group) did not reach significance.

*Between-Group Effects:* As the main effect of group was significant, differences between the AD sub-group and EC group inhibitory error rates were investigated using one-way ANOVA (with Bonferroni correction) to examine on each task (Table 7.5 [B]). The No-Go task analyses revealed a significant difference between-groups at baseline, as AD patients produced more inhibition errors than controls (large effect for Cohen's *d*, Table 7.4). However, by 6 months the difference between the group error rates was non-significantly different, as AD inhibition errors had *reduced* by 5.0% (and there was a slight *increase* of 2.2% for the EC group). By 12 months, the AD sub-group error rate had reduced further, but by a negligible 1.0% and the EC group error rate continued to fall by a further 3.3%, but the test session group means were non-significantly different. However, by the 18 month stage, the difference between groups was significant, which was due to a large increase in the proportion AD sub-group inhibition errors (11.7%), whereas the EC group mean was reduced by a further 3.9% (large effect size, $d$=1.6). In the antisaccade task, significantly more inhibition errors were produced by the AD sub-group than the EC group, at the baseline, 12 months and 18 months test sessions (with large effect sizes). However, due to Bonferroni correction (and a large reduction of 12.2% in the AD sub-group error rate), the 6 month test session data was non-significantly different between the groups, with the EC group error rate remaining static across the test sessions. In the Go/No-Go task AD patients were found to have a higher error rate that the EC group at each test session. However, as can be seen in Table 7.5 [B], this difference was only significant at the 12 month stage, with the Bonferroni correction resulting in the failure of the tests to reach significance at baseline, 6 months and 18 months, although effect sizes using Cohen's *d* were all large (Table 7.4).

*Within-Groups Analyses for Alzheimer's Disease Patients:* A within-groups analysis was conducted on the AD sub-group data, using a repeated measures ANOVA to examine the voluntary saccade task. The main effect of voluntary saccade task was significant ($F[2,18]=13.67$, $p<0.0001$), which demonstrates that the AD sub-group generated different inhibition error proportions on the range of voluntary saccade tasks, with test session collapsed. Trend analysis revealed that there was a significant linear trend across the tasks ($F[1,5]=420.59$, $p<0.0001$). As was found for the other groups, the AD group trend emerged because least inhibitory errors were produced in the No-Go task, followed by the antisaccade task and the highest error rate being in the Go/No-Go. Overall (i.e. sessions collapsed), Bonferroni pair-wise comparisons revealed that the antisaccade task inhibition error rate did not differ significantly from either the No-Go or the Go/No tasks ($p>0.5$ and 0.1 respectively). However, the No-Go task inhibition error rate was found to be significantly lower than that of the Go/No-Go task ($p<0.01$). As in the DP group analysis, these findings show that there is a clear change in the proportion of inhibition errors as a function of the cognitive demand for a given voluntary task.

To summarise the findings from the results of the present analyses, there was a non-significant difference in the magnitude of the factor of voluntary saccade task and this finding did not change as a function of time for either group. This finding does not support the hypothesis that there would be a significant linear increase in magnitude for voluntary saccade task for the AD group over time. However, it was found that there was a significant overall difference in error rate (irrespective of tests session or group) between each of the voluntary saccade tasks. Inhibitory error rate was found to increase with a significant linear trend, as a function of voluntary saccade task type. The No-Go task was found to elicit the lowest proportion of inhibitory errors, with the antisaccade task resulting in moderate error rates and the Go/No-Go task the highest number of errors. This finding supports the notion that inhibitory error rate increases with the cognitive load of a voluntary saccade task. It is

important to note, that both the dementia patient group as a whole and the AD sub-group, were found to produce significantly more errors overall (task and session errors collapsed) when compared with elderly controls.

At task level, significant between-group differences were found, which varied by session. AD patients were found to have higher error rates than controls on the No-Go task at baseline, which was then reduced at the 6 month and 12 month test sessions, until rising to significance again at 18 months (a very similar pattern was present for the DP group). In the antisaccade task, inhibition errors were significantly higher for the AD patients than controls (and in the dementia group analysis at all test sessions) at baseline, 12 months and 18 months, although the 6 months test just failed to reach significance due to the Bonferroni adjustment. For the Go/No-Go task, only the test session at 12 months was found to result in a significantly higher inhibition error rate for the AD patients than elderly controls, further to the stringency of the Bonferroni correction; the baseline, 6 months and 18 months error rates failing to reach the conservative alpha level. Thus, had the precaution for family-wise type error not been taken by using Bonferroni, the AD group would have been found to generate significantly higher error rates than elderly control at all test sessions (the DP analysis resulted in no significant difference at each session for the Go/No-Go task.

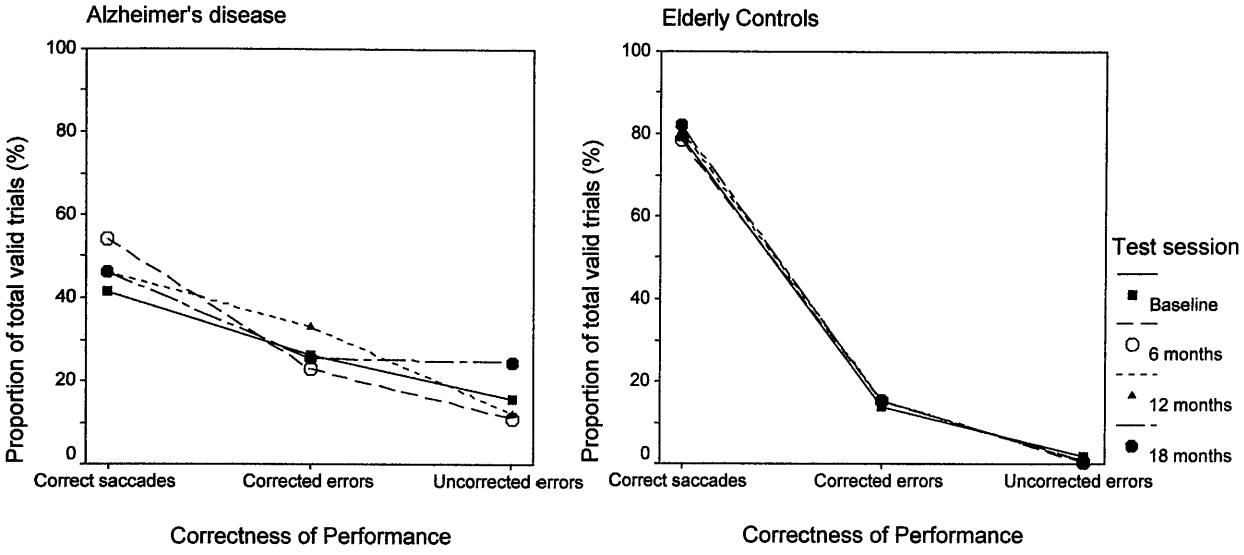
#### *7.3.2.2 Longitudinal Analysis of Corrected and Uncorrected Errors: Self-Monitoring Performance on the Antisaccade Gap Task Over Time*

Study I found that the profile of the factor *correctness of performance* was able to discrimnate between the AD patient group and both EC and DOT groups. Therefore, for reasons of brevity, this section will conduct analyses on the AD sub-group and EC groups only. To analyse the difference between groups over time on the factor for correctness of performance, a three-factor repeated measures mixed ANOVA was carried out. The first repeated measures factor was *test session*, with four levels (baseline, 6 months, 12 months and 18 months) and the second repeated measures factor was *correcteness of performance*

with three levels (correct saccade, corrected errors and uncorrected errors). The between-groups factor was group with two levels (ADs and ECs).

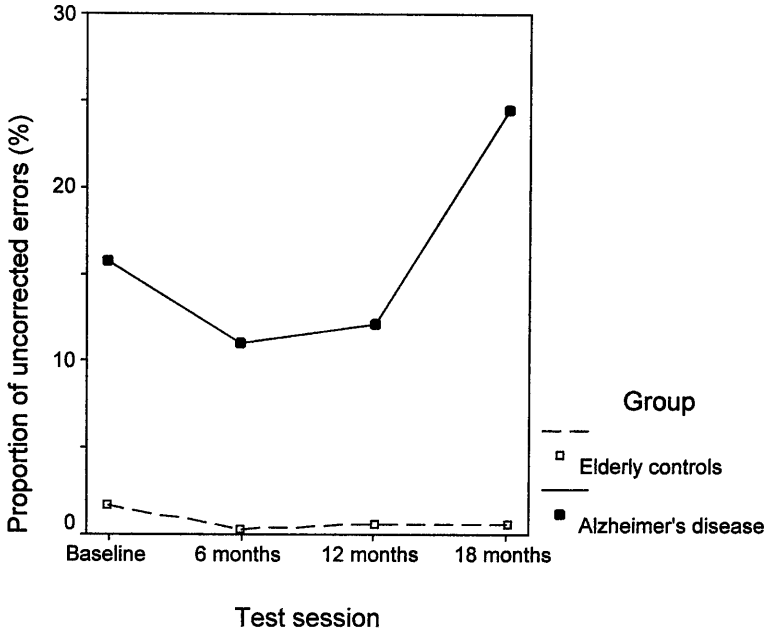
The main effect of correctness of performance was found to be significant ($F[2,68]=103.77$, $p<0.0001$), as was the interaction of this factor with group ($F[2,68]=22.372$, $p<0.0001$). These findings signify that with data for test sessions and groups collapsed, there was a significance difference within the factor levels and also, that there was a reliable difference between the groups in the magnitude for correctness of performance with test sessions collapsed. The main effect of test session was also found to be significant ($F[3,102]=9.067$, $p<0.0001$), which shows that there were differences over the test sessions with group and correctness of performance collapsed. The interaction between test session and group was also found to be significant ($F[3,102]=3.159$, $p<0.028$), demonstrating that the groups performed differently over time in their correctness of performance. The main effect of group was also significant ($F[1,34]=15.53$, $p<0.0001$), which revealed that there was an overall difference in the performance of the two groups, when all data were collapsed across variables and test sessions. However, the three-way interaction (test session x correctness of performance x group) did not reach significance ($F[6,204]=1.873$, $p>0.08$ NS; Figure 7.7). Nonetheless, it is clear by looking at the three-way interaction in Figure 7.7, that whilst the EC group did not change in correctness of performance over time, there was a marginal change for the AD group and also, a subtle improvement in the magnitude of correctness of performance on testing at 6 months; indicated by the reduction in errors which was balanced by an increase in correct saccades.

**Figure 7.7** A Graph Displaying the Longitudinal Perspective for Alzheimer's Disease Patients and Elderly Controls for the Factor of Correctness of Performance on the Antisaccade Task




*Between-Group Effects*: A series of one-way ANOVA (with Bonferroni correction) were conducted to examine the differences between-groups on the variables comprising the factor for correctness of performance over time (Table 7.5[B]). The proportion of correct saccades was found to be significantly lower for the AD patients at each test session, which was further endorsed by the large effect sizes shown in Table 7.4. The corrected error rate almost reached significance at baseline, with the AD group producing a higher proportion of corrected errors than the EC group; But the Bonferroni correction resulted in it lying just outside significance. The only significant difference for the corrected error rates was at 12 months, again due to AD patients producing a higher corrected error rate than the EC group. For the uncorrected error rates, a significant difference was found at baseline, 6 months and 18 months as a result of higher proportions of uncorrected errors being committed by the AD group at each test session (Figure 7.8). The test session at 12 months was only approaching significance.

**Figure 7.8** A Graph to Display Longitudinal Antisaccade Uncorrected Error Rates for Alzheimer's Disease Patients and Elderly Controls




*Within-Groups Analyses for Alzheimer's Disease Patients*: To analyse the changes across time within groups on the factor correctness of performance, a two-factor within-groups repeated measures ANOVA (i.e. the factors: test session and correctness of performance) was conducted on the AD data. The main effects of test session and correctness of performance were both found to be significant ($F[3,24]=4.19$, $p<0.016$ and $F[2,16]=3.74$, $p<0.046$, respectively). These results show that there were significant differences over time with the levels of correctness of performance collapsed. Bonferroni pair-wise comparisons revealed that the only significant difference was between baseline and 18 months ($p<0.05$). Additionally, when test sessions were collapsed, there was a reliable difference within the levels of correctness of performance, although Bonferroni comparisons did not reveal any significant differences between the levels of correctness of performance collapsed over test sessions. The interaction between test session and correctness of performance did not reach significance, which showed that there was no significant change in the magnitude (or profile) of correctness of performance for the AD

patients over time. This was further confirmed by the lack of any significant trends in the data using polynomial contrasts.

*Within-Groups Analyses for Elderly Controls:* The two-factor within-groups repeated measures ANOVA was repeated with the EC group data. The main effects of test session ($F[3,78]=2.99$, $p<0.036$) and correctness of performance ($F[1.07,27.75]=483.904$, $p<0.016$; Greenhouse-Geisser correction) were both found to be significant, whereas the interaction between the two factors was non-significant. This indicates that EC group correctness of performance did not change in magnitude over time. Trend analysis revealed that there was a significant linear trend in profile for correctness of performance ($F[1,26]=1295.3$, $p<0.0001$), as was found in Study I. Furthermore, Bonferroni pair-wise comparisons showed that overall there was a significant difference between every combination of the variables comprising correctness of performance (all $p<0.01$).

In summary, it was found that the factor correctness of performance was able to distinguish between AD patients and the EC group as in Study I, with controls possessing a linear profile to their data and AD patients presenting with no significant trends. Surprisingly, there was only a subtle change over time in the factor for correctness of performance for the AD group and no change for the EC group (Figure 7.9), which suggests that this factor is insufficiently sensitive for the detection of quantitative short-term change, due to the progression of AD or the effects of normal healthy ageing over time. On this occasion, these findings do not support the hypothesis that the magnitude of correctness of performance would change over time for the AD group, compared with that of elderly controls. However, the trend in the EC group and lack of trend in the AD group was repeated over the test sessions. AD patients were found consistently, to commission significantly less correct saccades than the EC group at each test session. Furthermore, uncorrected error rates were also significantly higher in proportion than EC uncorrected error rates over test sessions and there was a tendency for corrected errors to be generally higher for AD patient group, although at 18

months this was less pronounced, as a function of increasing correct saccades and uncorrected errors.

### 7.3.3 Longitudinal Analysis of the Reflexive Saccade Fixation Offset Effect

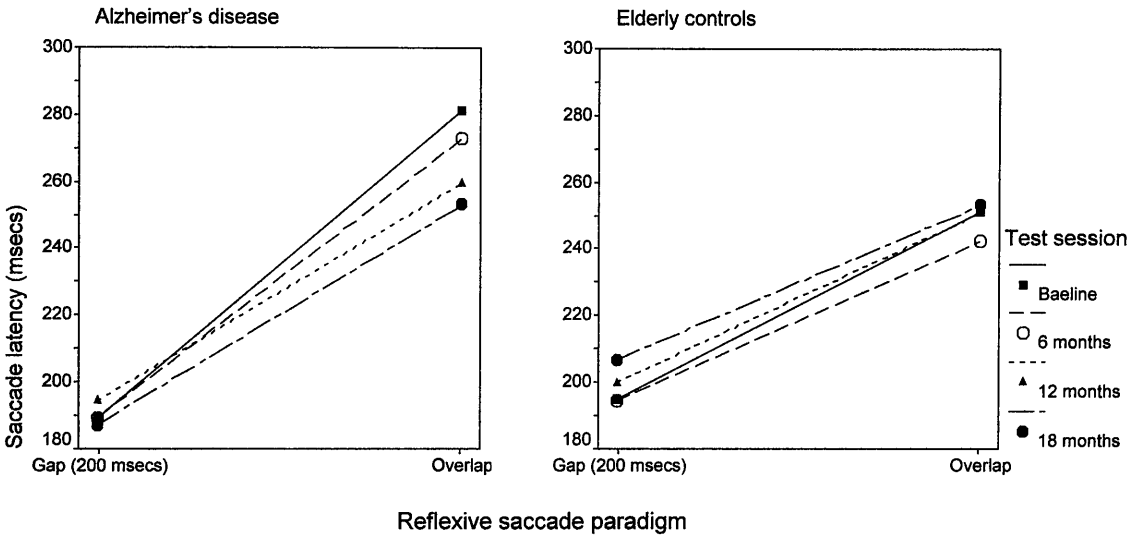
The magnitude of reflexive saccade FOE for latency was investigated in Studies II and III of this thesis, and revealed that AD patients produced a greater magnitude FOE, than that of elderly and young healthy control participants and also, Parkinson's disease patients. The present study will extend baseline analyses, by investigating whether or not the magnitude of reflexive FOE changes over time in AD patients, compared with EC performance, the focus being on the AD and EC group (i.e. excluding the overall DP group analysis).

On cursory examination, the longitudinal data presented in Table 7.4 for the AD and EC groups (reduced from baseline) appear to be very similar to those observed in Studies II and III of the present thesis. There seems to be a negligible difference between-groups for saccade latency in the reflexive saccade gap task and a more prominent difference between-groups in the reflexive saccade overlap task (AD patients with prolonged latency). Therefore, both groups present with a noticeable FOE. The longitudinal data were manipulated using a three-factor repeated measures mixed ANOVA. The first repeated measures factor was *test session*, comprising four levels (baseline, 6 months, 12 months and 18 months) and the second repeated measures factor was *reflexive fixation offset,* with two levels (gap and overlap). As with earlier analyses, the between-groups factor was group (two levels: AD and EC).

The main effect of reflexive fixation offset was found to be significant ($F[1,27]=99.337$, $p<0.0001$), demonstrating an overall significant difference between the gap and overlap task group (collapsed) data. The main effects of reflexive fixation offset test session and group, failed to reach significance, as did the interaction between these two factors showing respectively, that with group data collapsed there was only marginal change over time and that with task and test session data collapsed, there was only a negligible difference between the groups. Importantly, the interaction between the factor of reflexive fixation offset

and group was significant (F[1,27]= 4.238, $p$<0.049). This finding suggests that the groups had a significantly different magnitude of FOE somewhere within the longitudinal data (Figure 7.9). The three-way interaction between reflexive saccade test session, reflexive fixation offset and group did not reach significance, showing that there was no significant change in the magnitude of FOE over time between-groups.

**Figure 7.9** A Graphical Representation of Reflexive Saccade Fixation Offset Effect Over Time for the Alzheimer's Disease and Elderly Control Groups

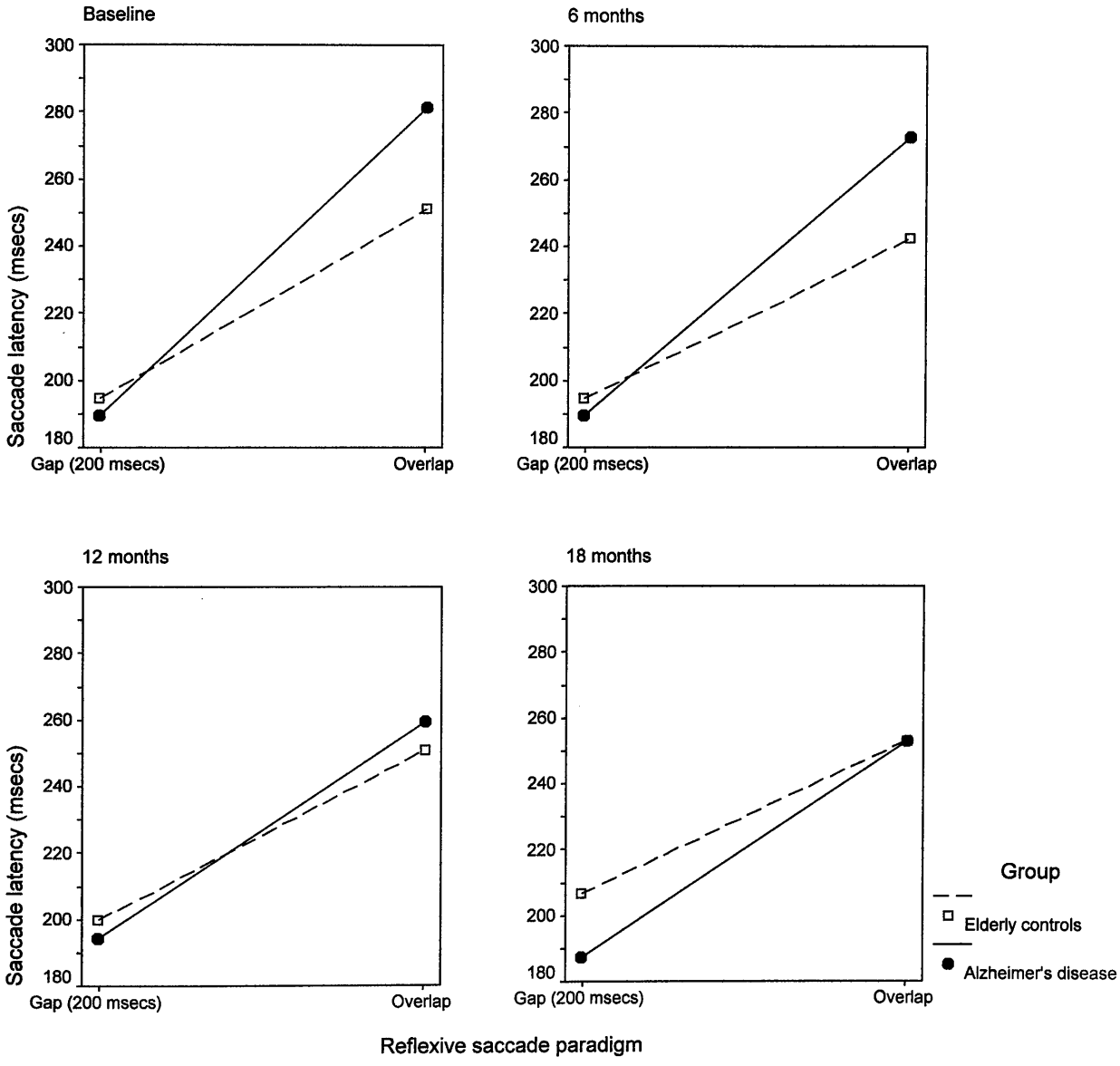



In order to investigate the significant interaction between reflexive fixation offset and group more closely, a series of two-factor repeated measures mixed ANOVA were carried out to explore interactions over the time course of the FOE in relation to the progression of AD (Figure 7.10). The interaction between reflexive fixation offset and group was found to be significant at baseline (F[1,27]= 6.0, $p$<0.021) and 6 months (F[1,27]= 4.364, $p$<0.046), but non-significant at 12 months and 18 months. Interestingly, this finding demonstrates that there was a reduction in the difference between groups over time for the magnitude of FOE, which was apparently due to a reduction in the magnitude of FOE for the AD group.

*Between-Group Effects*: One-way ANOVA (displayed in Table 7.5 [B]) were used to assess between-group differences in saccade latency reflexive saccade tasks at each longitudinal test session and elucidate more clearly, the components of the above interactions.

For the reflexive saccade gap condition, no significant difference was found between-groups at baseline or any subsequent test session. However, for the reflexive saccade overlap task, large effect sizes (Table 7.3) were observed between the means at baseline ($d = 1.0$) and 6 months ($d = 1.0$). A small effect size was present at 12 months ($d = 0.3$), but no effect was found at 18 months.

**Figure 7.10** Reflexive Saccade Fixation Offset Effect: Two-Way Interactions at each Test Session for the Alzheimer's Disease and Elderly Control Groups



As only a small number of theoretically based comparisons were made to test the hypothesis of prolonged saccade latency for the AD group, in comparison with the EC group on the overlap condition, it is reasonable to exclude Bonferroni adjustment (Keppel, 1991) and therefore, to accept the significant outcome from the ANOVA in Table 7.5 [B]. Thus, reflexive saccade overlap task latency for the AD group was found to be significantly prolonged compared with that of the EC group, at baseline and 6 months, but not for the test sessions at 12 months and 18 months.

*Within-Groups Analyses for Alzheimer's Disease Patients:* A two-factor within-groups repeated measures ANOVA was applied to the AD group data, to assess the factors of reflexive fixation offset test session and reflexive fixation offset. This analysis revealed a significant main effect for reflexive fixation offset ($F[1,6]= 29.96$, $p<0.002$), which shows that overall, there was a significant difference between gap and overlap tasks. A pair-wise comparison conformed that reflexive saccade gap task latency was significantly lower than that of reflexive saccade overlap latency ($p<0.01$). However, no other effects were significant, which suggests that the magnitude of FOE *within* the AD group did not change significantly over time. Paired-samples t-tests carried out between gap and overlap conditions at each test session, confirmed that a significant FOE was present at each stage of testing: baseline, $t[6]= -5.29$, $p< 0.001$; 6 months, $t[6]= -3.853$, $p< 0.008$; 12 months, $t[6]= -3.028$, $p< 0.023$; 18 months, $t[6]= -4.399$, $p< 0.005$.

*Within-Groups Analyses for Elderly Controls:* The above within-groups analyses were carried out on the EC group, which resulted in a very similar set of results. In the two-factor within-groups repeated measures ANOVA, the main effect for reflexive fixation offset was found to be significant ($F[1,21]= 77.925$, $p<0.0001$), demonstrating an overall significant difference between gap and overlap tasks. A pair-wise comparison showed that reflexive saccade gap task latency was significantly lower that of reflexive saccade overlap latency ($p<0.01$). No other effects were significant which highlights that the EC group FOE

magnitude did not change significantly over time. Paired-samples t-tests carried out between gap and overlap conditions at each test session, verified a significant FOE at each test session: baseline, t[21]= -8.830, $p<0.0001$; 6 months, t[21]= -6.925, $p<0.0001$; 12 months, t[21]= -7.059, $p<0.0001$; 18 months, t[21]= -4.803, $p<0.005$.

In summary, the results from the present section show that AD patients and EC participants both generate a significant FOE at each test session (within-groups). Longitudinal analyses revealed that whilst the AD group had a FOE that was of significantly greater magnitude than the EC group at baseline and 6 months, this was reduced at 12 months and 18 months, to a magnitude that was non-significantly different from that of the EC group. This finding does not support the hypothesis that the magnitude of FOE for the AD group would increase over time, by comparison with that of the EC group. The alternative hypothesis, that the AD group magnitude of reflexive saccade FOE would not increase, but that there would be a linear increase in saccade latency for *both* reflexive saccade tasks, i.e. gap and overlap tasks, also was not supported. This was evidenced by no change in reflexive gap task latency and interestingly, a reduction in reflexive overlap task latency over test sessions resulting in the reduced FOE magnitude for the AD group over time. However, the change over test sessions in overlap task latency within the AD group was not found to be significant.

## 7.4 Discussion

The present study was used to systematically evaluate the performance of AD patients on oculomotor and neuropsychological tasks longitudinally, to elucidate which variables are most sensitive to the progression of AD over time. This was achieved by recording data over repeated measures at six monthly inter-test session intervals, for patients who were able to attend test sessions consistently from baseline, through to 18 months (i.e. four data sets).

### 7.4.1 Key findings

The present study revealed a number of key findings, which extend the earlier studies in this thesis, to project a longitudinal perspective:-

1. The clinical rating scales - SMMSE and EADAScog - were able to distinguish between performance of AD patients and EC participants over time, demonstrating that they are sensitive to the progression of AD.

2. Neuropsychological assessments that place relatively high demands on working memory resources, i.e. Digit Span Reverse, Trail Making Form B and Spatial Span, were found to discriminate between AD and EC groups.

3. Verbal fluency scores for AD patients were significantly lower than those of EC participants. However, the verbal fluency test did not detect any change in AD over time, indicating that some aspects of frontal lobe function remain preserved in AD.

4. AD group predicted IQ scores did not differ significantly from the EC group at baseline. However, a significant change was observed between the groups in performance on the NART over time. The NART should be treated with caution as a measure of pre-morbid IQ.

5. Psychomotor ability for AD patients, as indicated in performance on the Gibson Spiral Maze was well preserved.

6. Inhibitory error rate was found to increase linearly, as a function of the cognitive load of voluntary saccade task. The factor of voluntary saccade task was found not to change significantly as a function of

time, for either the AD or EC group. However, inhibition error rate overall (magnitude), was found to be significantly higher for the AD group compared with that of the EC group.

7. The factor correctness of performance was found to distinguish between-groups overall and the characteristic trend profile of EC performance as noted in Study I, was clearly evident at each test session. However, only marginal change was observed longitudinally for the AD group, as a function of an increased uncorrected error rate.

8. A significant reflexive saccade FOE was found for both the AD and EC group at each stage of longitudinal assessment. The magnitude of FOE for the AD group was found to be significantly greater that that of the EC group at baseline and 6 months, but no difference was found between the two groups at 12 months and 18 months. Thus, there was a reduction in FOE for the AD group over time.

9. Qualitative observation at 6 months of AD group voluntary saccade task inhibitory error rates, indicated a reduction, which may have been due to the subtle effects of medication with acetylcholinesterase inhibitors.

### 7.4.2 Longitudinal Assessment of Clinical Rating Scales

The MMSE and ADAScog clinical rating scales have, in recent years become the mainstay in the United Kingdom (and much of the Western world) for assessment of global function in dementia, alongside clinical appraisal. The present study monitored dementia patient performance longitudinally and compared this with control participants to evaluate the sensitivity of the tests to detect the progression of AD over time. The SMMSE and

EADAScog were both able to distinguish between performance of AD patients and EC participants longitudinally, but only the SMMSE demonstrated reliable quantitative sensitivity to the progression of AD.

For the SMMSE, the profile of AD test session data over the period of 18 months, tended to fluctuate somewhat. It is plausible to suggest that this fluctuation may have been due to the subtle benefit derived by some patients from medication with AChEIs, which were fully prescribed (apart from one patient) by the 6 months stage of the longitudinal project. As can be seen in Figure 7.1, there was an elevation in AD scores at 6 months from baseline, but by the 12 months test session this had decreased back towards baseline level. However, by 18 months the scores diminished rather rapidly from measurement at 12 months, perhaps as drug therapy became ineffective.

EADAScog scores were more static for the AD group from baseline to 6 months, but subtle increase was apparent by the 18-month stage of testing. However, the EC group scores demonstrated a significant to improvement or practice effect. Both tests examine orientation, attention and short-term memory, as part of their repertoire. It may be the case, that as time went on through the tests sessions, the EC group began to anticipate the nature of the tasks and prior to attending subsequent test sessions prepare for example, perhaps by making a mental note of the date. It is plausible to suggest that the EC participants were able to adapt to test conditions more easily that AD patients, perhaps understanding how tasks would be administered. Many EC participants reported that they looked forward to their visit and how much they enjoyed taking part in the study. Conversely, by and large AD patients had no recollection of ever having attended previous test sessions, did not remember the researcher and had no idea why they should even be at the hospital.

The present findings correspond with results from previous research, which also found that the MMSE was sensitive to cognitive decline in dementia over time (Folstein et al., 1975; Teng et al., 1987). Previous studies have also noted that the MMSE is most sensitive in

distinguishing moderate to severe patients from healthy controls (Folstein et al., 1975; Knight, 1992), however, the present thesis has shown that the test can clearly discriminate between mild to moderate AD patients and healthy elderly controls. The EADAScog findings for the present study are in contrast to a previous study, in which the authors of the ADAScog recorded a significant 6 point increase over a 12 month period for AD patients and no significant change in the performance of control participants (Rosen et al., 1984). The results from the present study may be a reflection of the relatively small AD group sample size, caused by attrition of AD patient numbers over time.

### 7.4.3 Longitudinal Neuropsychological Assessments

*Digit Span:* The present study showed that patients with AD performed significantly more poorly than EC participants on the Digit Span Reverse task at baseline and at the 18 months test session, whereas on the Digit Span Forward test, no significant difference was found between the groups at any of the test sessions. In addition to this, AD group Digit Span Reverse task performance was shown to deteriorate over time in relation to the EC group, as highlighted by the three-way interaction between Digit Span test, Digit Span test session and group.

The Digit Span test is fundamentally an assessment of executive function and measures short-term auditory memory. The Forward and Reverse forms of the test both require working memory and are largely believed to involve the frontal and temporal lobes (Gerton et al., 2004) see Section 2.5.7. The PET study by Gerton and colleagues outlined in Section 2.5.7, found that the Forward and Reverse forms of the Digit Span test, activate overlapping neuroanatomy that is responsible for working memory. Prominently, the right DLPFC, bilateral IPL and ACC were metabolised during both tasks, with the level of activation increasing linearly as task difficulty escalated in the Digit Span Forwards task. However, in the Digit Span Reverse task supplementary areas were recruited in particular bilateral activation of the DLPFC, the left IPL

and Broca's area. The Digit Span Reverse test necessitates coherent mental-tracking with increased cognitive load, due to simultaneously holding the forward string of digits in memory and generating the reversal procedure. This is in contrast to the comparatively straightforward repetition of digits, for the Digit Span Forward task. Vitally important to the present study, performance on the test also involves attention and concentration (Kaufman et al., 1991), which are, it is plausible to suggest related to inhibitory control. The finding that AD group performance on the Digit Span Forward test did not differ significantly from that of the EC group, confirms that low loading on working memory resources (i.e. short-term auditory memory) for the AD group was relatively well preserved and remained so over time. Conversely, the Digit Span Reverse test results indicate that higher loading on working memory resources induces poor performance in AD patients and it is plausible to suggest, that working memory performance is perhaps compromised in AD by a disturbance of the DLPFC.

*Spatial Span:* The results from the Spatial Span tests showed that AD patients found both sub-tests difficult, with no significant difference in performance between the sub-tests at any test session and compared with healthy elderly control participants (i.e. ADs produced lower scores). However, neither group deteriorated significantly over time.

The findings for the between-groups comparisons (with Bonferroni adjustment, Table 7.2 [B]) were somewhat puzzling. At baseline, AD group performance on the Spatial Span Reverse test was found to be significantly poorer than that of the EC group, but at 6 months and 12 months, there was no significant difference between the groups. The test at 6 months failed to reach significance as a result of the Bonferroni correction. However, by the test session at 18 months, AD patients generated scores that were again significantly lower than those of the EC group. This result is inline with other findings in the present study (reported above), which noted an improvement in test performance at around the 6 months test session, with deterioration on subsequent stages. Comparison of AD and EC longitudinal Spatial Span Forward scores revealed results that were in contrast to Spatial Span Reverse findings. AD

Spatial Span Forward scores were lower than those of the EC group, which approached significance at baseline, however, it is perplexing that scores at 6 months and 12 months were significantly poorer than those of the EC group, but then improved somewhat at 18 months. AD performance on the Spatial Span Reverse test should be expected to be poorer than performance on the Forward sub-test and poorer than EC group performance. This is a plausible suggestion, due to the higher demand that the Spatial Span Reverse test places on working memory resources and the fact that AD working memory is somewhat compromised, particularly when patients are approaching a moderate degree of dementia severity.

The prominent observation from these findings is that AD patients under perform compared with ECs, on both sub-tests of the Spatial Span test. These findings reflect the dependency on working memory for successful completion of the Spatial Span test and the dysfunction that AD patients present with, both in terms of working memory and spatial attention. In fact, when a supplementary analysis was conducted on Spatial Span Total scores (i.e. combining Forwards and Backwards test scores), one-way ANOVA revealed that AD patients performed significantly more poorly than ECs at each test stage (Table 7.6).

**Table 7.6** Longitudinal Statistical Analyses (ANOVA) Between-Groups for Spatial Span Total Scores

| Spatial Span Total | | | |
|---|---|---|---|
| **Baseline** | **6 months** | **12 months** | **18 months** |
| $F[1,36]= 9.41$ $p< 0.004$ | $F[1,36]= 8.47$, $p< 0.006$ | $F[1,36]= 7.87$, $p< 0.008$ | $F[1,36]= 11.33$, $p< 0.002$ |

As outlined in Chapter 2 (Section 2.5.11), previous research has shown that the Spatial Span test is most sensitive in discerning patients with frontal lobe lesions, from those with temporal lobectomy (right or left) or controls (Canavan et al., 1989). Moreover, the test has also been found to distinguish between AD patients and controls (Corkin, 1982; Sullivan et al., 1986), results which are consistent with those of the present study. Further to the basic capacity for encoding of visual stimuli, the Spatial Span task places demand on a number of

other cognitive components during completion. The task requires mental tracking, entailing short-term visual memory, which incorporates sequential, spatial and kinaesthetic coding. Additionally of significance, the task necessitates the maintenance of information over time and response selection preceding overt execution of response. It is feasible to argue, that these cognitive components generally comprise working memory.

The neuroanatomical substrate of working memory is believed to be located in the prefrontal cortex, namely the DLPFC (Goldman-Rakic, 1999; Sawaguchi & Goldman-Rakic, 1994), hence patients with frontal lobe lesions perform poorly on the Spatial Span test due to the high demand placed on working memory resources, which are functionally compromised due to lesioning in these patients. Correspondingly, therefore, it is highly likely that AD patients perform poorly on the task due to a working memory deficit. The spatial working memory element of the Spatial Span test appears to play a major role in AD patient performance, as simple tasks that requiring motor preparation and/or low cognitive load e.g. Gibson Spiral Maze or Digit Span Forwards, pose little problem for the AD patient with mild to moderate dementia severity.

*Gibson Spiral Maze*: The Gibson Spiral Maze test is chiefly a test of psychomotor ability and the present study found that the test was not sensitive to the progression of AD over time and the magnitude of change did not differ from that of the EC group. Importantly, these findings highlight that dementia patients with AD are able to carry out simple visual tracking tasks with motor components (but of low cognitive load), at a speed that matches control participants in performance. This was also found to be the case longitudinally, as it was found that AD test performance at the final test session (18 months)- where AD patient cognition had deteriorated by a number of points (see Section 7.4.2) - was only approaching significance when compared with the EC group.

The analysis of task completion times in the Gibson Spiral Maze was found only to represent part of what was actually happening during AD testing. When credit scores that

include task error rates were analysed, AD patients were shown to perform more poorly than controls at each stage of testing, appart from that at 6 months (which may again be explained by the subtle effects of medication with AChEIs). These results are concomitant with frontal lobe dysfunction and it appears that AD patients seem unable to inhibit erroneous action whilst concurrently maintaining a rapid pace in order to achieve a swift task completion time, in accordance with the rules of the task. Arguably, this behaviour is perhaps analogous to errors of inhibition committed by AD patients during voluntary saccade tasks, reported in earlier studies of the present thesis. In view of the outcomes from the credit score analysis the reults taken together, show that AD psychomotor ability is in fact rather poor by comparison with that of controls.

An additional finding of the present study was that the Gibson Spiral Maze was insufficiently sensitive to detect the progression of disease over time, neither in the analysis for speed of task completion or surprisingly, credit scores.

*Verbal Fluency*: The Verbal Fluency test was found to result in significantly poorer scores for AD patients than EC participants at each stage of testing. Whereas no significant change was found in the AD group over time, the EC group actually improved with a significant linear trend, from baseline to 18 months. The results for the AD patients show that they are less capable of performing tasks that require frontal lobe - executive function for effortful retrieval, than healthy elderly control participants. However, the Verbal Fluency test does not detect any deterioration in AD scores over time, performance remaining rather static longitudinally for the 18-month period. Thus, the results from the present project suggest that this particular version of verbal (phonemic) fluency is not sensitive to the progression of AD over time, bearing in mind that this was only a short-term, i.e. 18 months project.

*Trail Making*: Results from the Trail Making test showed that each group took significantly longer to complete Form B than Form A. The reader may recall from the outline of the test in Chapter 2 (Section 2.5.6) that Form A is principally a gauge of psychomotor

speed and psychomotor coordination, whereas Form B is sensitive to visual sequencing, search-shift strategy and working memory. Thus, Form B places a greater cognitive load on mental resources, due to the simultaneous management of multiple information streams in working memory. The DP group as a whole and the AD sub-group performed significantly more poorly than the EC group on each task form and over time. The DP group and AD sub-group showed some subtle fluctuation in task completion times over time, - actually worsening at 6 months - but no significant increase (deterioration) or decrease (improvement) between baseline and 18 months was evident for either Form A or Form B. These findings were in contrast to those of healthy elderly controls, who showed significant improvement in performance over the 18-month period, on both Form A and Form B of the test.

The findings for Trail Making Form A appear reflect the nature of the task, in that although the task places a low load on working memory, it is primarily a test of psychomotor ability. However, frontal lobe function plays an important role for efficient completion of this task, and thus the finding that the DP group and AD sub-group performed more poorly than the EC group supports the hypothesis that tasks requiring frontal lobe function will be performed more poorly by AD patients. However, the hypothesis that there would be a deterioration in AD performance over time on tests of this sort was not supported, perhaps due to psychomotor ability deteriorating slowly in AD patients (as seen over time for the Gibson Spiral Maze AD longitudinal data).

Trail Making Form B places a high demand on working memory with the concurrent manipulation of information along with a psychomotor component. Therefore, it was not surprising to see that all groups performed significantly more slowly in completing this task. The finding that the DP group and the AD sub-group performed with significantly prolonged Form B completion times - by comparison to the EC group – supports the hypothesis that the AD group would perform more poorly on tasks that have a high working memory component. However, Form B did not detect deterioration in AD performance over time, which does not

support the hypothesis that the test would identify changes over time, from baseline to 18 months, postulated on the basis of detecting a decline in working memory performance.

Research using electrophysiological recordings proposes that both forms of the trail making test require the activation of frontothalamic regions of the brain (Segalowitz et al., 1992). Thus, the results from the present study imply that AD patients have a disturbance of these areas, but that this disorder does not decline in the short-term. An alternative explanation is that the test is insufficiently sensitive enough to detect a change over time. Furthermore, the results indicate that these regions are well preserved during the process of normal ageing, as denoted by the improvement in performance reflected in the performance of health elderly control participants.

*National Adult Reading Test*: The results from the present longitudinal study of the NART data confirmed the hypothesis that there would be no significant difference between the groups in predicted IQ at baseline. However, overtime a significant difference emerged by the 18 months test session, between the EC group scores and those in the DP and AD group analyses. The difference in magnitude of change over time was in part due to a significant linear improvement in the EC group scores, which were likely due to practice effects. In contrast, the DP and AD analyses showed only subtle (non-significant) within-groups decline in scores over time, although for the AD group, the difference between scores at baseline and 18 months was close to significance. Therefore, as the change in AD predicted IQ over time was only subtle, the hypothesis that there would be significant change between baseline and 18 months was not supported on this occasion.

Given the change found in AD group scores over the 18-month test session period, it is important to note that caution should be exercised with regards to the reliability of the NART as a tool for the estimation of pre-morbid IQ for AD patients at different levels of dementia severity. It is a plausible to suggest that the NART may be prone to underestimate pre-morbid IQ. The findings from the present study correspond with conclusions drawn from previous

studies of NART scores for AD patients. Earlier research has reported a drop in performance over time (Cockburn, Keene, Hope & Smith, 2000; Paque & Warrington, 1995; Patterson, Graham & Hodges, 1994), a relationship between NART and dementia severity (Paolo, Troster, Ryan & Koller, 1997; Taylor, 1999) and has questioned the reliability of the NART as a tool for predicting pre-morbid IQ (Cockburn et al., 2000; Conway & O'Carroll, 1997; Law & O'Carroll, 1998; Taylor, 1999). It is likely that the deterioration over time of AD patient NART scores reflects a decline in reading ability, which commences in early dementia.

### 7.4.4 Longitudinal Investigation of Voluntary Saccade Tasks

Longitudinal analysis of the factor volunatry saccade task, revealed that there was no significant difference between or within the groups, in the rate of change for the magnitude for this factor over time. Importantly, this finding shows that the voluntary saccadic eye movement tasks, as manipulated in the present analysis, do not actually detect a any change in inhibition errors and correspondingly, working memory performance over time for AD patients. Therefore, this finding does not support the first hypothesis, that due to deterioration of working memory capacity over time a significant increase in voluntary saccade task magnitude would be found for the AD patient group in comparison to controls. Additionally, the findings also fail to support the second hypothesis that an increase in inhibitory errors across time will increase in proportion to the cognitive load of a given task. However, it is important to note that the present study was recorded over an 18-month period only. Therefore, a longer study may have revealed an elevation of the inhibition error rate on the antisaccade and Go/No-Go tasks corresponding with working memory dysfunction and in accord with the working memory deficit previously reported in AD (Baddeley et al., 1991).

The most notable changes recorded over time were for the AD group, whose inhibition error rate on the antisaccade gap task was found to fall on testing at 6 months and then increase again on subsequent test sessions at 12 and 18 months. In fact, it

emerged that the increase in error rate from 6 months to 12 months was significant. Figure 7.7 clearly illustrates the longitudinal change in error rate for each task. Therefore, an important message from these data, is that there appears to be a reduction in error rate by the 6 months test session, albeit marginal and qualitative for the No-Go and Go/No-Go task, but nontheless present for each task. It is plausible to suggest that these subtle reductions in error rate, could be due to cognitive enhancement brought about by medication with AChEIs. Study IV found no significant difference between medicated and non-medicated AD patients at baseline testing. However, by the 6 month test session all but one of AD patients were recieving medication AChEIs.

Due to attrition of AD patients over the longitudinal test sessions, a change was apparent in the present study, for the proportion of inhibition errors recorded at baseline as compared with that reported in both Study I and III. The inhibition error rate was lower in the analysis for the present study for each voluntary saccade task (see Table 7.7).

**Table 7.7** Inhibition Error Rate in Studies I and III compared with Baseline measurement in Study V

| | | Inhibition error rate | | |
|---|---|---|---|---|
| | Task | Studies I & III Mean | Present study (V) Mean | fall |
| Elderly Controls | No-Go | 10.31 | 10.00 | 0.31 |
| | Anti-saccade | 16.30 | 15.61 | 0.69 |
| | Go/No-Go | 35.78 | 34.81 | 0.97 |
| Alzheimer's disease | No-Go | 28.49 | 26.67 | 1.82 |
| | Anti-saccade | 50.66 | 42.07 | 8.59 |
| | Go/No-Go | 63.39 | 61.78 | 1.61 |

Most markedly, the AD group mean for the antisaccade task was reduced by 8.59% in the present study, with a smaller decrease for the No-Go and Go/No-Go tasks. Intuitively, it can be argued then, that some patients with higher error rates were unable to continue with subsequent sessions or were intermittent in attendance for the repeated

measures study (and so excluded from the present analysis) which is a reflection of their illness, i.e. moderate AD corresponds with higher error rates. Therefore, the reduction of AD group numbers - as a consequence of the study only including complete repeated measures across the four test sessions - is likely to have reduced the power of the preset study considerably. However, the reduction in baseline score in the present study had little effect on the difference between the AD and EC group scores at baseline on the No-Go and antisaccade tasks, as both were found to be significantly different, the AD group generating more errors on each task (as in the earlier studies). However, the difference between the AD and EC group inhibition error rates on the Go/No-Go task failed to reach significance - due to Bonferroni adjustment - which was likely due to the reduction in the number of AD patients.

### 7.4.5 Longitudinal Assessment for Correctness of Performance

The present study analysed the factor for correctness of performance longitudinally and it emerged, that correctness of performance was able to distinguish between the profile of AD patients and the EC group as previously discovered in Study I. The key finding is that AD patients present with no significant trends to the profile of their data across the variables, which constitute the levels of the factor correctness of performance, whereas controls always generate a linear profile to their data. Interestingly, the factor for correctness of performance was found not to change significantly over time for either the AD or EC group. This observation shows that this factor is not sensitive to the short-term effects of ageing or to the progression of AD, but remains consistent over time. However, it is important to remember that the present longitudinal study was of 18 months duration only and a longer study may have revealed a long-term sensitivity to the progression of AD.

The results of the present study do not support the hypothesis that the magnitude of correctness of performance would change over time for the AD group, compared with that of

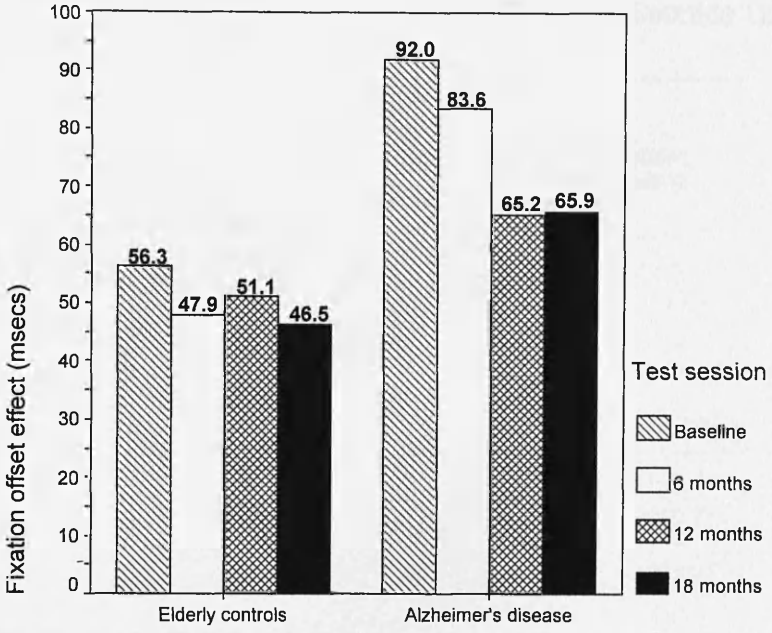
elderly controls. It is a reasonable argument to suggest that given time, as AD becomes more severe - perhaps in an extended version of this study - the uncorrected error rate of AD patients should *increase*, along with a corresponding decrease in corrected error and correct saccade rates as the capacity of patients to self-monitor performance continues to decline. This would of course potentially result in a linear profile appearing in the AD data, however, the profile would be the reverse of that found in healthy ageing. Of course, by this hypothetical stage, it could also be argued that AD patients would be so severely afflicted by the ravages of neurodegeneration, that the reliability of antisaccade task compliance would be extremely diminished. Therefore, it is most practicable and helpful that the profile for correctness of performance is able to detect AD in the early stages of dementia, particularly as this could potentially facilitate early diagnosis of the disease.

### 7.4.6 Longitudinal Reflexive Saccade Fixation Offset Effect

The longitudinal analysis of reflexive saccade FOE showed that AD patients and EC participants generated a significant FOE at each test session. As in Studies II and III, the magnitude of FOE for the AD group was found to be significantly greater than that of the EC group at baseline and on testing at 6 months, despite the reduction in group membership due to attrition of the sample over time. Interestingly, on comparing the magnitude of FOE between-groups at each test session, it emerged that the AD group magnitude of FOE actually declined over the period of 18 months, to a level that was non-significantly different to that of the EC group at both the 12 months and 18 months stages (see Figure 7.11 below). The hypothesis for this analysis was that the magnitude of FOE would increase over time for the AD group, compared with that of the EC group. This was based on the findings from previous research, which described dysfunctional attention in AD (Baddeley et al., 2001; Della Sala et al., 1992; Perry & Hodges, 1999) and specifically, an attention-shifting or disengagement deficit

(Parasuraman et al., 1992). Thus, the findings from the present study do not support this hypothesis; conversely, the outcome was precisely the opposite.

**Figure 7.11** A Bar Chart Displaying the Reflexive Saccade Fixation Offset Effect for Elderly Control Participants and Alzheimer's Disease Patients Over Time

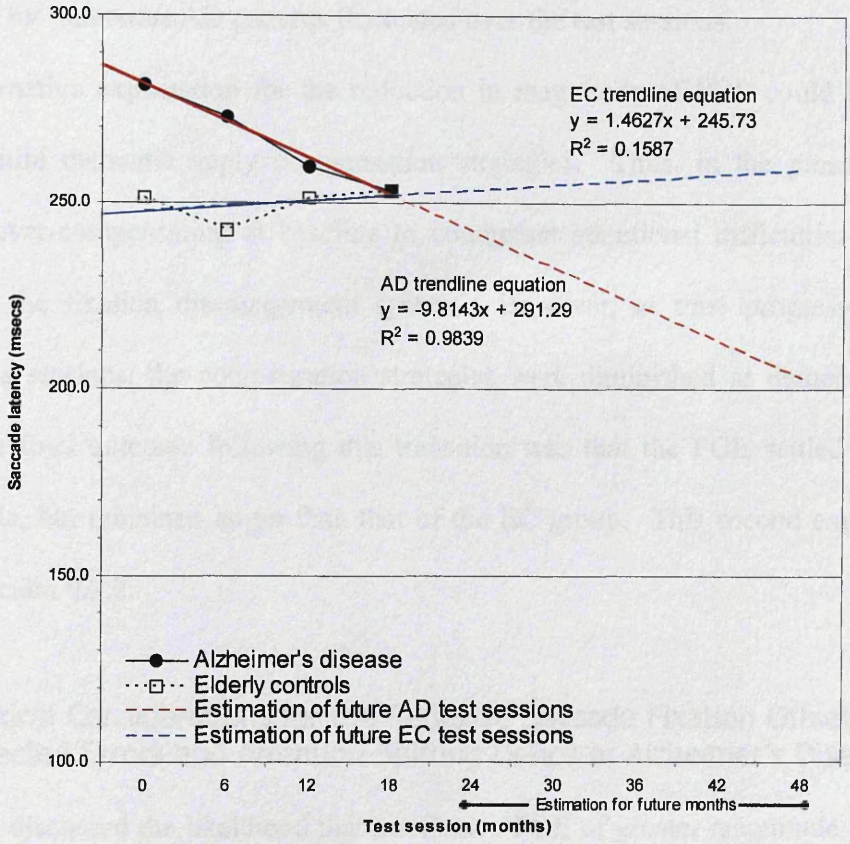



Two explanations are offered here to account for the change in FOE in the AD group over time. The first explanation could be that overlap task saccade latency becomes less prolonged as a result of deterioration in the fixation system. This notion would map onto the findings of Bylsma et al. (1995), where a fixation task was found to be sensitive to the progression of AD as a consequence of intrusive saccades, but this proposal works in counter fashion to a fixation *disengagement* deficit. Thus, it is plausible to suggest that in the long-term, overlap saccade latency may continue to fall past that of the EC group as suggested in Figure 7.12 to a point where the FOE is extinguished completely for AD patients. This idea is implemented in Figure 7.12, by comparing AD and EC group means on the longitudinal reflexive saccade overlap task. The graph clearly shows a steady linear decrease across test sessions in AD group latency. It is tempting to fit a linear trend line to the data, as in Figure

7.12, calculated using the least squares fit represented by the following equation, where $m$ is the slope and $b$ is the intercept:-

$$y = mx + b$$

**Figure 7.12** A Graphical Representation of Longitudinal Reflexive Saccade Overlap Task Latency with Projected Trend line to Estimate Future Saccade Latency




The linear trend line in Figure 7.13, demonstrates that reflexive overlap saccade latency fell over the 18 months of testing from baseline. The R-squared value – the coefficient of determination – is extremely high (0.9839), which shows that the estimated values for the trend line very closely correspond to the observed latency data from the actual tests sessions and consequently, that the trend line is highly reliable. Furthermore, the trend line estimates AD reflexive overlap saccade latency for future hypothetical test sessions at 24 – 48 months and plainly predicts that by 48 months, reflexive overlap saccade latency will fall to just above 200 msecs., very close to that of the reflexive saccade gap task. However, as the trend line uses

the group means in the diagram to generate the estimation, the analysis is limited and should be treated with caution. The actual individual patient data points for the AD group were found not to contain a linear profile when trend analysis was applied to the data set using polynomial contrasts. Whereas several AD patients (approximately 57%) obviously presented with a decline in reflexive saccade overlap task latency over time (profile as in Figure 7.12), reflexive overlap latency for numerous AD patients fluctuated over the test sessions.

An alternative explanation for the reduction in magnitude of FOE could be that AD patients with mild dementia apply compensation strategies. Thus, in the present analysis patients were over-compensating at baseline to counteract attentional difficulties caused by dysfunction of the fixation disengagement system. However, as time progressed through subsequent tests sessions, the compensation strategies were diminished as dementia severity increased. The final outcome following this transition was that the FOE settled down to a lower magnitude, but remained larger than that of the EC group. This second explanation is expanded in Section 9.3.2.

### 7.4.7 Theoretical Considerations for the Reflexive Saccade Fixation Offset Effect, Uncorrected Errors and Attention-Shifting Deficit in Alzheimer's Disease

Study II discussed the likelihood that a reflexive FOE of greater magnitude for the AD group (compared with ECs) and a correspondingly high uncorrected error rate, could be due to a dysfunction of fixation disengagement. The theory was that once a target was captured inappropriately in the antisaccade task via poor inhibitory control of the VGR, AD patients have difficulty in generating corrective saccades into empty space in the opposite direction whilst already fixating the target, i.e. fixation cannot be disengaged from the target. Furthermore, this situation is possibly brought about by disruption of the opponent neural processes in the SC. The present study has shown that the AD group data are consistent with this theory at baseline and six months. However, at 12 months and 18 months there is a clear dissociation between magnitude of FOE and the uncorrected error rate. There is no

disengagement deficit at 18 month when uncorrected errors are at a maximum. Therefore, these findings suggest that uncorrected errors are not due to a deficit in the disengagement of attention from fixation, but due to a diminished self-monitoring capacity through a deficit in working memory brought about by a dysfunctional inhibitory control system.

Further consideration of the theoretical and neuroanatomical implications for the findings of of this discussion will be addressed in Chapter 9.

## 7.5 Conclusions

- ✧ The Standardised Mini Mental State Examination and The European Alzheimer's Disease Assessment Scale, were found to be sufficiently sensitive to detect the progression of AD over time.

- ✧ Medication with acetylcholinesterase inhibitors appears to induce subtle and qualitative cognitive enhancement for a period of between approximately 6 and 12 months. Peak performance appears to manifest at approximately 6 months following commencement of medication. The enhancement effect is observed for voluntary saccade inhibition errors, neuropsychological assessments and clinical rating scales.

- ✧ The Digit Span Reverse test was sensitive to the progression of AD over time. The test places a high cognitive load on working memory resources. Therefore, AD patients present with a decline working memory performance over time.

- ✧ Caution should be exercised when employing the NART as a measure of pre-morbid IQ, as the test has a tendency to underestimate IQ. AD patient scores are liable to decline over time.

- ✧ The inhibition error rate for voluntary saccade tasks is not sensitive to the progression of Alzheimer's disease over time.

- ✧ The factor correctness of performance does not change significantly over time in AD. The uncorrected error rate appears to change most prominently, in accord with the progression of AD.

- ✧ The pronounced FOE in early AD is possibly caused by over compensation, to counter disturbance of the fixation system. The magnitude of reflexive saccade FOE reduces over time for AD patients, as compensation strategies can no longer cope with disturbance in the fixation system.

- ✧ Dissociation between magnitude of FOE and uncorrected error rate emerges over time for AD, suggesting that uncorrected errors are not caused by a dysfunctional attention-shifting system, but by a diminished self-monitoring capacity caused through working memory deficit, induced by dysfunctional inhibitory control.

# Chapter Eight

## Study VI: Evaluating Saccadic Eye Movements in The Prediction of Dementia

*Comparison of Saccadic Eye Movements & Neuropsychological Assessments*

## 8.1 Introduction

Previous studies of the present thesis attempted to isolate sensitive cognitive and oculomotor markers for AD and other forms of dementia, which could distinguish between the effects of disease and normal ageing. The salient findings revealed by the earlier studies are now examined in Study VI, to ascertain the predictive capacity of oculomotor paradigms and neuropsychological assessments in the diagnosis of mild to moderate dementia.

The NINCDS-ADRDA criteria for diagnosis of AD (McKhann et al., 1984) applies a stringent cut-off for case classification, which ensures good specificity. However, to guard against low sensitivity, which would otherwise result in the exclusion mild cases in the early stages of AD, patients attending memory clinics for evaluation are usually assessed with a wide range of neuropsychological assessments, as the NINCDS-ADRDA guidelines offer only limited direction as to how many neuropsychological assessments should be conducted (Bucks & Loewenstein, 1999). Clinical psychologists require an extensive psychometric background for patients experiencing memory problems, as a patient may potentially have one of a number of illnesses such as dementia, brain tumor, or depression manifesting as a pseudodementia. Thus, selective psychometric assessment is a useful aid to diagnosis, with the purpose of: i). Establishing whether a memory and/or other cognitive deficits are present; ii). Assessing the type and extent of dysfunction; iii). Providing support for the approach taken with treatment;

iv). Giving a baseline measure as a comparison for plotting change over time. Neuropsychological assessments complement the clinical tests carried out by medical doctors (Section 2.1.1) and are a vital part of the overall multi-disciplinary approach to patient care. However, conducting extensive neuropsychological assessment is time consuming and potentially fatiguing for patients. Many memory clinics have developed batteries comprising well known neuropsychological assessment tests, some examples follow: - *The Bristol Memory Disorders Clinic - University of Bristol Department of Care of the Elderly and Frenchay Healthcare National Health Service Trust* - this battery comprises 14 different tests which are labour intensive to administer; *The Wien Center for Alzheimer's Disease and Memory Disorders - University of Miami Department of Psychiatry and Behavioural Sciences and the Mount Sinai Medical Center* - a battery comprising 17 different tests, with some sub-tests also, which in total takes several hours to administer and as a consequence fatiguing for the patient; *The Consortium to Establish a Registry for Alzheimer's Disease* - This battery comprises 7 main tests, but there are some sub-tests; again test time duration long (Morris et al., 1989) (Bucks & Loewenstein, 1999). Some of the tests from these batteries are included in the present study. The present analysis incorporated a small range of commonly used tests, which were included in the research project at Lytham Hospital (Section 2.5) and attempted to show which tests are most informative for the diagnosis of dementia, i.e. a minimum number of neuropsychological assessments and/or saccadic eye movement variables that can predict dementia. Obviously, the clinical rating scales (EADAScog & SMMSE) are not included in the present regression analyses, as scores from these tests were fundamental to the initial diagnosis of dementia (i.e. were used for the classification of patients with a probable dementia caused by a neurodegenerative disease). Thus, it is of immense interest to establish whether supplementary neuropsychological assessments are more powerful than oculomotor variables in classifying dementia patients and EC participants.

### 8.1.1 Aims

The main aim of the present study was to examine more closely the diagnostic utility of saccadic eye movement paradigms in mild to moderate dementia. This was done by comparing baseline measurement on variables from oculomotor paradigms (antisaccade task error rates and reflexive saccade latency) with neuropsychological assessment scores. This analysis attempted to address the following important questions: 1. Are any of the saccadic eye movement variables sufficiently sensitive enough to reliably predict mild to moderate dementia? 2. Is it possible to use a small number of neuropsychological assessments - a reduced set - to reliably predict mild to moderate dementia? 3. Should insufficient sensitivity be present with either approach in isolation, is there an ultimate regression model that can utilise the practical benefits of combining variables from eye movement tasks along with a reduced set of neuropsychological assessment tests? If such a model could be derived from these variables is it conceivable that the model could be applied in association with clinical rating scales and the standard medical examination for diagnosing dementia?

In an attempt to answer these questions, logistic regression analyses were conducted in an attempt to find the most efficient regression model, sensitive to the detection of early dementia. In the first instance, error components from the antisaccade gap task were evaluated as predictors of dementia, because the earlier studies showed that dementia patients generated higher proportions than controls on components from this task. No-Go and Go/No-Go task inhibition error rates were also evaluated later in the model. A further model, examined reflexive saccade overlap task latency as a potential predictor of dementia, since the magnitude of FOE was found to be significantly greater for the dementia groups than that of controls (Studies II & III).

Other regression models were also examined that included neuropsychological assessment scores. Of particular interest here, were tests that place a high demand on working

memory function and/or dissociated between dementia and EC groups. Therefore, the primary focus of this analysis was on Digit Span, Spatial Span and Trail Making test scores.

## 8.2 Methods

### 8.2.1 Participants

The participants for this analysis comprised AD and EC participants from Study I (AD patient group N=17; age range = 70-88; mean = 76.9; SD = 4.9; male n=12; female n=5. EC group N=32; age range = 58–85 years; mean = 70.5; SD = 6.1; male n=12; female n=20). The group with dementias of other types were evaluated later in the study by the final models. Descriptive statistics for neuropsychological assessment and eye movement tasks from baseline assessment are shown below in Table 8.1.

**Table 8.1** Descriptive Statistics for Saccadic and Neuropsychological Variables

| | | | Elderly Controls | | | Alzheimer's Disease | | |
|---|---|---|---|---|---|---|---|---|
| **Eye Movement Variables** | | | Mean | SD | N | Mean | SD | N |
| Antisaccade | Gap | Uncorrected errors (%) | 2.09 | 5.50 | 32 | 23.47 | 23.25 | 17 |
| | | Corrected errors (%) | 14.21 | 11.88 | 32 | 27.19 | 21.74 | 17 |
| | | Omissions (%) | 3.02 | 5.04 | 32 | 10.19 | 10.70 | 17 |
| | | Anticipatory (%) | 2.37 | 4.00 | 32 | 5.42 | 5.81 | 17 |
| Go/No-Go | Gap | Inhibition errors (%) | 35.78 | 27.70 | 32 | 63.39 | 32.32 | 17 |
| No-Go | Gap | Inhibition errors (%) | 10.31 | 13.32 | 32 | 28.49 | 27.35 | 17 |
| Reflexive saccade | Overlap | Latency (msecs) | 253.58 | 30.83 | 26 | 298.63 | 45.40 | 13 |
| **Neuropsychological Assessments** | | | | | | | | |
| Verbal Fluency Total | | | 38.38 | 10.80 | 32 | 22.59 | 10.32 | 17 |
| Trail Making Form A Time (secs) | | | 41.64 | 12.76 | 32 | 77.67 | 33.16 | 16 |
| Trail Making Form B Time (secs) | | | 81.24 | 26.70 | 32 | 150.34 | 63.44 | 11 |
| Digit Span Forward | | | 10.25 | 2.30 | 32 | 8.65 | 2.23 | 17 |
| Digit Span Reverse | | | 7.31 | 2.35 | 32 | 5.06 | 2.46 | 17 |
| Spatial Span Forward | | | 7.41 | 1.81 | 32 | 5.53 | 2.07 | 17 |
| Spatial Span Reverse | | | 6.75 | 1.19 | 32 | 4.24 | 2.11 | 17 |
| *Day - Night inhibition task (score /20) | | | 19.88 | 0.55 | 32 | 19.12 | 1.65 | 17 |
| *Motor Perseveration (score /5) | | | 5.00 | 0.00 | 32 | 4.59 | 1.06 | 17 |
| Gibson Spiral Maze: Time (secs) | | | 65.12 | 20.36 | 32 | 86.38 | 50.18 | 17 |

*Groups responding at or near to ceiling

### 8.2.2 Assessment of Saccadic Eye Movements

As this is a supplementary analysis, participants thus used the equipment, task protocol and experimental procedures described in Chapter 2 (Section 2.3) and subsequent chapters, to include the antisaccade gap, reflexive saccade overlap, No-Go and Go/No-Go paradigms.

### 8.2.3 Statistical Analysis

Statistical analyses were carried out by means of SPSS version 11.5 (SPSS Inc., Chicago Ill). The present study used sequential logistic regression to predict group membership of AD and EC participants (i.e. disease/no disease) from a range of eye movement and cognitive predictors (regressors). Correspondingly, in predicting group membership the category classification output from logistic regression analysis provides information regarding a number of positive and negative outcomes, as listed below in Table 8.2.

**Table 8.2** Possible Positive and Negative Outcomes from the Logistic Regression Analyses

| Outcome type | Description |
|---|---|
| True positive | Dementia patient, correctly predicted |
| True negative | Elderly control participant, correctly predicted |
| False positive | Elderly control participant, incorrectly predicted |
| False negative | Dementia patient, incorrectly predicted |

Thus, the analysis can provide estimated probabilities regarding the sensitivity and specificity of a given model or test. Traditionally, the medical profession has applied the following definitions for the sensitivity and specificity of a test in predicting the health status of patients: -

- *Sensitivity*: Measure of reliability of a screening test, based on the proportion of people with a specific disease who react positively to the test (the higher the sensitivity the fewer false negatives).

- *Specificity*: The proportion of people free from disease (controls) who react negatively to the test, i.e. the higher the specificity, the fewer false positives (*Oxford Medical Dictionary*, 2002).

The present analysis used response operating characteristic (ROC) curves to plot model sensitivity (true positives) as a function of false negative rates (1 - specificity), to demonstrate the trade-off between the two outcomes.

Whilst it is appreciated that using two or more predictors will yield better predictions, with the present experimental population comprising fairly low numbers, the temptation to enter a large number of variables into the equation was avoided. The ratio of cases to variable is an important consideration in logistic regression, as too few cases relative to the number of predictors, can lead to failure of model convergence; The maximum likelihood solution is impossible when the outcome groups are perfectly separated (Hosmer & Lemeshow, 1989; Tabachnick & Fidell, 1996).

Logistic regression does not hold the same assumptions regarding data as other predictive statistical approaches (such as multiple regression or discriminant function). Consequently, it is not necessary for predictors to be normally distributed, linearly related or have equal variance in each group (Tabachnick & Fidell, 1996). Moreover, logistic regression can accommodate any mix of continuous, discrete or dichotomous variables. However, care should be taken to avert multicollinearity and singularity in the predictor set. The model to estimate the true probabilities ($\pi_j$) for group membership, used the following logistic function:

$$\textit{Probability (Dementia)} = \pi_j = \frac{Exp(L_j)}{1+Exp(L_j)}$$

The equation estimates probabilities of one outcome or another, directly as a non-linear function of the best linear arrangement of predictors, producing two outcomes. Where $\pi_j$ is the estimated probability that the $j^{th}$ case is in

one category or another, *Exp* is the exponential and $L_j$ is some linear combination of predictors. $L_j$ is a standard linear regression equation, where $L_j = b_0 + b_1(X_j)$; with constant $b_0$, slope $b_1$ and predictor (s) $X_j$. The above is used along with a loss function for maximum likelihood estimation as a measure of the discrepancies between observed and estimated values, enabling the evaluation of a given model. The loss function used for the present procedure was the –2 log(likelihood) statistic.

## 8.3 Results

### *8.3.1 Correlation of Neuropsychological Assessments and Saccadic Eye Movement Variables with Clinical Rating Scales*

Correlations for oculomotor variables and neuropsychological assessment scores with clinical rating scale scores are displayed below in Table 8.3.

**Table 8.3** Correlations Between Clinical Rating Scales Scores, Saccadic Variables and Neuropsychological Assessment Scores

| | | | Elderly Controls | | | Alzheimer's Disease | | |
|---|---|---|---|---|---|---|---|---|
| **Eye Movement Variables** | | | SMMSE | ADAScog | N | SMMSE | ADAScog | N |
| Antisaccade | Gap | Uncorrected errors (%) | -0.065 | 0.000 | 32 | -0.691 | 0.687 | 17 |
| | | Corrected errors (%) | -0.197 | -0.019 | 32 | 0.285 | -0.283 | 17 |
| | | Omissions (%) | 0.277 | -0.019 | 32 | -0.336 | 0.252 | 17 |
| | | Anticipatory (%) | 0.148 | -0.115 | 32 | 0.136 | 0.087 | 17 |
| Go/No-Go | Gap | Inhibition errors (%) | 0.171 | -0.140 | 32 | -0.009 | 0.122 | 17 |
| No-Go | Gap | Inhibition errors (%) | -0.386 | 0.061 | 32 | -0.325 | 0.454 | 17 |
| Reflexive saccade | Overlap | Latency (msecs) | -0.229 | 0.315 | 26 | -0.525 | 0.373 | 13 |
| **Neuropsychological Assessments** | | | | | | | | |
| Verbal Fluency Total | | | 0.427 | -0.103 | 32 | 0.685 | -0.648 | 17 |
| Trail Making Form A Time (secs) | | | 0.061 | 0.013 | 32 | -0.657 | 0.584 | 16 |
| Trail Making Form B Time (secs) | | | -0.399 | -0.096 | 32 | -0.253 | -0.023 | 11 |
| Digit Span Forward | | | 0.427 | -0.281 | 32 | 0.422 | -0.061 | 17 |
| Digit Span Reverse | | | 0.392 | -0.229 | 32 | 0.294 | -0.027 | 17 |
| Spatial Span Forward | | | -0.233 | 0.296 | 32 | 0.499 | -0.239 | 17 |
| Spatial Span Reverse | | | 0.036 | 0.166 | 32 | 0.777 | -0.714 | 17 |
| *Day - Night inhibition task | | | -0.039 | -0.107 | 32 | 0.619 | -0.600 | 17 |
| *Motor Perseveration | | | ** -- | ** -- | 32 | 0.641 | -0.576 | 17 |
| Gibson Spiral Maze: Time (secs) | | | -0.182 | 0.008 | 32 | -0.669 | 0.780 | 17 |

* Groups responding at or near ceiling. ** EC group no correlation, Motor Pers. = constant/ceiling.

The correlations provide an indication of the association between a given oculomotor measure or neuropsychological assessment score and dementia severity. These relationships thus, offer one method of assistance in selecting a reasonable set of predictors for regression analyses - as the overall goal of the analysis is to account for the data set in terms of a minimum number of predictors. More importantly, the correlations are a useful aid in the decision as to which predictors should be given the highest priority, i.e. a priori order of entry, for sequential logistic regression. Thus, predictors where entered into logistic regression models sequentially, based on assigning the highest priority to predictors that were expected to most strongly predict dementia (and differentiate between dementia patients and ECs). However, analyses were broken down into a number of stages in an attempt to obtain as much information as possible from all candidate predictors, given that small correlations can be important for this type of analysis.

Given the outcome from earlier studies in the present thesis, it was clear that for the first saccadic eye movement model, antisaccade gap task error rates would probably provide the most useful saccadic indicator of dementia and that these predictors should be given the highest priority for sequential entry. Furthermore, it was considered that inclusion of inhibition error rates from other saccadic tasks, such as those in the No-Go and Go/No-Go tasks would also be informative and provide useful insight into the predictive capacity for a range of error rates. Therefore, inhibition errors from the No-Go and Go/No-Go tasks were entered into the model, following antisaccade task error variables. Reflexive saccade overlap task latency was considered separately, due to a reduced data set for this variable.

The neuropsychological assessment logistic regression model firstly included predictors that were associated with working memory function, followed by variables from tasks that place demands on frontal lobe function. The rationale for this approach is based on previous evidence that AD patients have a working memory deficit, which at least in the early stages of

dementia, is more prominent than frontal lobe dysfunction (Baddeley et al., 1991; Becker, 1988; Morris, 1994). A final set of analyses attempted to build-up a model that combines both oculomotor variables and neuropsychological assessment variables to form an ultimate model.

### 8.3.2 Predicting Dementia from Neuropsychological Assessments

In view of the correlations presented in Table 8.3 and the desire to employ a minimum number of predictors or tests, the following predictors were selected for sequential logistic regression. Spatial Span Reverse was allocated the highest priority, as it places a high demand on working memory resources and also resulted in the strongest correlation for the dementia group, with SMMSE and EADAScog scores. Trail Making Form A was also considered to warrant high priority status in the model, as the correlations with clinical rating scales were found to be moderate to strong for the dementia group. Furthermore, Trail Making Form A also places demand on working memory resources, albeit low demand for sequencing and requires frontal lobe function for the psychomotor component. Although the dementia group correlations between the Digit Span Reverse test and clinical rating scales were only small, the test was included on the basis that it places a high demand on working memory resources. Verbal Fluency and the Gibson Spiral Maze are both frontal lobe tasks and in the present analysis, were found to correlate with dementia group clinical rating scales scores. Therefore, both tests were evaluated in the regression model.

Trail Making Form B was excluded from this analysis, firstly, because the correlations for the dementia group between this measure and clinical rating scale scores were small and secondly, because the number of patients able to complete the test was reduced. This would have the effect of reducing the possible number of cases in the data set and thereby reduce the robustness of the analysis. Furthermore, if a high proportion of patients with *early dementia* find test completion too difficult, consequential floor effects render the test of little diagnostic utility. The Day/Night Response Inhibition test and Motor Perseveration test were also

excluded from the analyses. This was based on the finding that both the dementia and EC groups were found to respond virtually at ceiling level on each test. Thus, neither group can be considered to have found either test demanding and therefore, the diagnostic capacity of each test is negligible (at least in the early stages of AD) due to ceiling effects. Digit Span Forward and Spatial Span Forward were also excluded, as these two tests both place a lower load on working memory resources.

A sequential logistic regression analysis was performed on neuropsychological assessments that require i) working memory resources and ii) frontal lobe function, to assess prediction of group membership for the category of dementia or EC. The first block to be entered into the model, Spatial Span Reverse, Trail Making Form A and Digit Span Reverse was found to be significant against the constant only model, $\chi^2$ (3, N=48) = 34.312, $p<0.0001$, showing that this *block* of predictors reliably distinguished between dementia patients and EC participants. However, examination of the parameter estimates revealed the Wald statistic for Digit Span Reverse to be non-significant for the prediction of dementia (z = 0.266, $p>0.6$), whereas Trail Making Form A was significant (z = 6.894, $p<0.009$) and Spatial Span Reverse (z = 3.791, $p<0.052$) virtually significant. Therefore, Digit Span Reverse was excluded from the model and the analysis re-run, to include only Spatial Span Reverse and Trail Making Form A in the model. This model was also found to be significant against the constant only model $\chi^2$ (2, N=48) = 34.032, $p<0.0001$. Importantly, this model resulted in a Chi-square value that was virtually the same as that of the previous model, but now for only 2 degrees of freedom. Moreover, removal of Digit Span Reverse from the model had the effect of decreasing the loss by only 0.28. It is worth noting that the 5% level of reliability for Chi-square is 3.84, for one degree of freedom. Therefore, any change in loss has to deliver at least this value to be of significant use in a model. Elimination of the Digit Span Reverse from the model, resulted in parameter estimates with significant Wald statistics for both the Spatial Span Reverse (z =

4.758, $p<0.029$) and Trail Making Form A ($z = 6.949$, $p<0.008$). The predictive success of this model was promising, at this stage of the sequential procedure, with 75.0% of dementia patients and 96.9% of EC participants correctly predicted, with an overall success rate of 89.6%.

Verbal Fluency was the next variable to be entered into the model and although inclusion of this variable indicated a reliable change from the previous model $\chi^2$ (3, N=48) = 43.956, $p<0.0001$, the specificity of the model was reduced, with only 90.6% of EC participants correctly predicted and the overall success rate thereby reduced to 85.4%. Sensitivity remained unchanged for dementia patients with 75.0% of patients correctly predicted. Examination of the Wald statistic in the parameter estimates also showed that Verbal Fluency did not contribute significantly to disease status ($z = 3.499$, $p>0.07$), therefore, Verbal Fluency was omitted from the analysis.

The Gibson Spiral Maze task was entered into the model along with Spatial Span Reverse and Trail Making Form A. This model showed a reliable accumulative loss that was significant compared with the previous model, $\chi^2$ (3, N=48) = 47.830, $p<0.0001$ (see Table 8.4).

**Table 8.4** Accumulative Loss for the Logistic Regression Model with Neuropsychological Assessments

| Variable | Model Loss | Change in Loss $\chi^2$ | df | Accumulative Change in Loss $\chi^2$ | df | p-level |
|---|---|---|---|---|---|---|
| **Constant only** (initial -2 Log Likelihood) | 61.105 | | | | | |
| **Spatial Span Reverse** | 39.652 | 21.453 | 1 | 21.453 | 1 | 0.0001 |
| **Trail Making Form A** | 27.073 | 12.579 | 1 | 34.032 | 2 | 0.0001 |
| **Gibson Spiral Maze** | 13.276 | 13.798 | 1 | 47.830 | 3 | 0.0001 |

Inspection of the parameter estimates (Table 8.5) revealed that each of the variables in the model reliably contributed to the prediction of disease status. Prediction success was

impressive, with 93.8% of dementia patients and also 93.8% of EC participants correctly predicted. The overall success rate was therefore 93.8%. The $R^2$ (Negelkerke) for this final model was high ($R^2 = .876$), showing that the variables in this model were able to account for a large amount of variance in disease status.

**Table 8.5** Parameter Estimates for the Logistic Regression Model with Neuropsychological Assessments

| Variable | B | S.E. | Wald | df | Sig. | Exp(B) |
|---|---|---|---|---|---|---|
| **Spatial Span Reverse** | -3.251 | 1.603 | 4.114 | 1 | 0.043 | 0.039 |
| **Trail Making Form A** | 0.379 | 0.168 | 5.088 | 1 | 0.024 | 1.461 |
| **Gibson Spiral Maze** | -0.203 | 0.094 | 4.660 | 1 | 0.031 | 0.816 |
| Constant | 12.237 | 7.927 | 2.383 | 1 | 0.123 | 206195.772 |

The parameter estimates for the present model showed that the odds ratio for Trail Making Form A (*Exp(B) in Table 8.5, i.e. the exponential of the log odds ratio (B)*) demonstrates a change in the likelihood of dementia by a factor of 1.461, based a one unit change, i.e. for each 1 second increase in time taken to complete the test. The Gibson Spiral Maze odds ratio indicated that the likelihood of dementia increases by a factor of 0.816, for each unit increase in time (seconds). However, Spatial Span Reverse showed little change in the likelihood of dementia for a 1 unit decrease in score, with a low odds ratio (0.039).

The above model comprising three neuropsychological assessments can therefore be applied to individual cases for the prediction dementia using the following equation:

$$\text{Probability of Dementia} = \frac{e^{b_0+b_1X_1+b_2X_2+b_3X_3}}{1+e^{b_0+b_1X_1+b_2X_2+b_3X_3}}$$

$$= \frac{e^{12.237+(-3.251)(X_1)+(0.379)(X_2)+(-0.203)(X_3)}}{1+e^{12.237+(-3.251)(X_1)+(0.379)(X_2)+(-0.203)(X_3)}}$$

Taking the constant and B coefficients and individual scores on each variable ($X_j$) a probability of greater than 0.5 = dementia, using a classification cut-off point of 0.5 and the equation solved for the outcome of dementia coded as 1 and no disease 0.

### 8.3.3 Predicting Dementia from Saccadic Eye Movement Variables

Examination of dementia patient correlations for antisaccade error rates showed antisaccade gap task uncorrected errors to be strongly correlated with both the SMMSE and EADAScog clinical rating scale scores (i.e. uncorrected errors are related to the severity of dementia). Small correlations were also found for dementia patients' antisaccade gap task corrected errors and omissions with the clinical rating scales scores, whereas anticipatory saccades were only weakly correlated. The No-Go task inhibition error rate for dementia patients correlated with the SMMSE (small) and the EADAScog (moderate), however, for the Go/No-Go task, there was no correlation with the SMMSE and only an extremely weak correlation with the EADAScog. Only very weak to small correlations were found to exist for the EC group on all variables.

Reflexive saccade overlap task saccade latency was excluded from this analysis, as the number of cases for which data were available produces a reduced set, i.e. including this variable would have reduced the number of cases in the overall sample. Therefore, a separate analysis was conducted to investigate the value of this variable as a predictor of dementia.

A sequential logistic regression analysis was performed on the saccadic error components of the antisaccade gap, No-Go and Go/No-Go tasks. The antisaccade gap task was given the highest priority, due to the ability of variables derived from this task, to distinguish between groups in the earlier studies of this thesis. In the first block, antisaccade uncorrected errors, corrected errors, omissions and anticipatory saccades were entered into the model which was significant compared with the constant only model $\chi^2$ (4, N=49) = 34.345, $p<0.0001$, showing that this set of predictors was able to discriminate between dementia

patients and EC participants. However, examination of the parameter estimates showed that the Wald statistic for antisaccade anticipatory saccades did not significantly predict dementia ($z = 0.876$, $p>0.3$), whereas the other three variables in the model did make a significant prediction for dementia (corrected errors, $z = 4.278$, $p<0.039$; uncorrected errors, $z = 4.717$ $p<0.030$; and omissions, $z = 5.763$, $p<0.016$). In view of this observation, a re-run of the analysis was carried out with the exclusion of the variable, anticipatory saccades. This analysis showed that a combination of antisaccade corrected errors, uncorrected errors and omissions resulted in a model that again, was significant against the constant only model $\chi^2$ (3, N=49) = 33.461, $p<0.0001$ (Table 8.6).

**Table 8.6** Accumulative Loss for the Logistic Regression Model with Saccadic Eye Movement Variables

| Variable | Model Loss | Change in Loss $\chi^2$ | df | Accumulative Change in Loss $\chi^2$ | df | p-level |
|---|---|---|---|---|---|---|
| **Constant only** (initial -2 Log Likelihood) | 63.262 | | | | | |
| **Antisaccade corrected errors** | 56.568 | 6.694 | 1 | 6.694 | 1 | 0.0100 |
| **Antisaccade uncorrected errors** | 37.175 | 19.393 | 1 | 26.087 | 2 | 0.0001 |
| **Antisaccade omissions** | 29.801 | 7.374 | 1 | 33.461 | 3 | 0.0001 |

However, with the exclusion of the anticipatory saccade variable, this model was more efficient as it only used 3 degrees of freedom at the expense of a small non-significant reduction in the Chi-square value (.884). Observation of the parameter estimates for the three remaining variables in the model, showed that when not controlling for anticipatory saccades, antisaccade corrected errors and uncorrected errors had a higher value for the Wald statistic and that there was a negligible reduction in the value of the Wald statistic for antisaccade omissions (see Table 8.7).

These results affirm that each of these variables is able to reliably predict disease status in the present model. The predictive capacity of this model was reasonable, with 82.4.0% of dementia patients and 96.9% of EC participants correctly predicted and an overall success rate of 91.8%. The $R^2$ (Negelkerke) for this model ($R^2 = .683$) demonstrated that a strong level of variance was accounted for in disease status.

**Table 8.7** Parameter Estimates for the Logistic Regression Model with Saccadic Eye Movement Variables

| Variable | B | S.E. | Wald | df | Sig. | Exp(B) |
|---|---|---|---|---|---|---|
| **Antisaccade corrected errors** | 0.084 | 0.037 | 5.044 | 1 | 0.025 | 1.088 |
| **Antisaccade uncorrected errors** | 0.113 | 0.046 | 5.918 | 1 | 0.015 | 1.119 |
| **Antisaccade omissions** | 0.160 | 0.068 | 5.506 | 1 | 0.019 | 1.174 |
| Constant | -4.339 | 1.273 | 11.622 | 1 | 0.001 | 0.013 |

For the next block of sequential input, No-Go and Go/No-Go inhibition error rates were entered into the model. However, entry of these two variables as a *block* did not result in a significant improvement from the previous model $\chi^2$ (2, N=49) = .614, $p>0.7$, and although the overall model remained significantly different from the constant only model $\chi^2$ (5, N=49) = 33.074, $p<0.0001$, the loss was reduced. Furthermore, examination of the parameter estimates revealed that neither No-Go ($z = 0.578$, $p>0.4$) or Go/No-Go ($z = 0.140$, $p>0.7$) inhibition error rates, was a significant predictor of disease status. In view of this analysis, the previous model comprising antisaccade corrected errors, uncorrected errors and omissions was found to be the best set of saccadic eye movement variables that could reliably classify dementia patients and EC participants.

The odds ratios (Table 8.7, Exp (B)) for antisaccade error components showed that there was a change in the likelihood of dementia, by a factor of 1.119 for uncorrected errors, 1.174 for omissions and 1.088 for corrected errors, for each unit / % change / increase in error rate.

A separate analysis with a reduced data set was conducted on the reflexive overlap task saccade latency. However, it was found that this variable was unable to significantly contribute as a predictor of dementia.

As with the earlier analysis of neuropsychological assessments, the parameter estimates and individual scores on each variable ($X_j$) for the regression model using the three antisaccade variables can thus be used for the prediction of dementia in individual cases, using the following equation (again, a probability of greater than 0.5 = dementia; using a classification cut-off point of 0.5 and the equation solved for the outcome of dementia coded as 1/no disease 0):

$$\text{Probability of Dementia} = \frac{e^{b_0+b_1X_1+b_2X_2+b_3X_3}}{1+e^{b_0+b_1X_1+b_2X_2+b_3X_3}}$$

$$= \frac{e^{-4.339+(0.084)(X_1)+(0.113)(X_2)+(0.160)(X_3)}}{1+e^{-4.339+(0.084)(X_1)+(0.113)(X_2)+(0.160)(X_3)}}$$

### 8.3.4 Combining Saccadic Variables and Neuropsycgological Assessments in a Logistic Regression Model to Predict Dementia

The next analysis investigated the possibility of formulating a logistic regression model that would generate a superior equation by combining predictive components revealed in the previous analysis of neuropsychological assessments and saccadic eye movement variables (Sections 8.3.2 & 8.3.3). Examination of correlations between the key saccadic eye movement and neuropsychological assessment predictors, showed that AD antisaccade gap task uncorrected error rates were highly correlated with Trail Making Form A (.845) and Spatial Span Reverse (-.812) scores. In view of this finding, antisaccade uncorrected errors were omitted from the analysis, on the grounds that they would be a source of multicollinearity. Therefore, models concentrated on two saccadic variables, antisaccade gap task corrected

errors and omissions, and three neuropsychological assessments, Trail Making Form A, Spatial Span Reverse and Gibson Spiral Maze.

A sequential logistic regression was carried out on the key saccadic and neuropsychological assessment variables, found in the previous sections, to be favourable in the prediction of dementia. The most impressive logistic regression model, delivering greatest predictive success was found to be a combination of antisaccade gap task omissions, Trail Making Form A, Spatial Span Reverse and Gibson Spiral Maze scores. These predictors resulted a model that was significant against the constant only model $\chi^2$ (4, N=48) = 47.952, $p$<0.0001 (Table 8.8), suggesting that the predictors as a set, reliably distinguished between dementia patients and EC participants. Antisaccade corrected errors were excluded from this final model, as they were not found to contribute to overall predictive success. Negelkerke's $R^2$ for the final model was very strong at .877, showing that a high level of variance was accounted for in disease status. The predictive success of the model was impressive with 93.8% of dementia patients and 96.9% of EC participants correctly predicted and an overall success rate of 95.8%.

**Table 8.8** Accumulative Loss for the Logistic Regression Model with Saccadic Eye Movement and Neuropsychological Assessment Variables

| | Model | Change in Loss | | Accumulative Change in Loss | | |
|---|---|---|---|---|---|---|
| **Variable** | **Loss** | **$\chi^2$** | **df** | **$\chi^2$** | **df** | **p-level** |
| **Constant only** (initial -2 Log Likelihood) | 61.105 | | | | | |
| **Antisaccade omissions** | 53.287 | 7.818 | 1 | 7.818 | 1 | 0.0050 |
| **Trail Making Form A** | 31.378 | 21.909 | 1 | 29.727 | 2 | 0.0001 |
| **Spatial Span Reverse** | 26.456 | 4.922 | 1 | 34.649 | 3 | 0.0001 |
| **Gibson Spiral Maze** | 13.152 | 13.304 | 1 | 47.952 | 4 | 0.0001 |

The regression coefficients, Wald statistics and odds ratios are displayed below in Table 8.9. The equation derived from the regression model combining antisaccade and

neuropsychological assessment variables to calculate the probability of dementia for individual cases from the parameter estimates (Table 8.9) and individual scores on each variable ($X_j$), is as follows (as with the previous analyses, a probability of greater than 0.5 = dementia; using a classification cut-off of 0.5 and the equation solved for the outcome of dementia coded as 1/no disease 0):

$$\text{Probability of Alzheimer's} = \frac{e^{b_0+b_1X_1+b_2X_2+b_3X_3+b_4X_4}}{1+e^{b_0+b_1X_1+b_2X_2+b_3X_3+b_4X_4}}$$

$$= \frac{e^{11.526+(0.027)(X_1)+(0.367)(X_2)+(-3.120)(X_3)+(-0.199)(X_4)}}{1+e^{11.526+(0.027)(X_1)+(0.367)(X_2)+(-3.120)(X_3)+(-0.199)(X_4)}}$$

**Table 8.9** Parameter Estimates for the Logistic Regression Model with Saccadic Eye Movement and Neuropsychological Assessment Variables

| Variable | B | S.E. | Wald | df | Sig. | Exp(B) |
|---|---|---|---|---|---|---|
| **Antisaccade omissions** | 0.027 | 0.078 | 0.120 | 1 | 0.730 | 1.027 |
| **Trail Making Form A** | 0.367 | 0.167 | 4.858 | 1 | 0.028 | 1.444 |
| **Spatial Span Reverse** | -3.120 | 1.613 | 3.741 | 1 | 0.053 | 0.044 |
| **Gibson Spiral Maze** | -0.199 | 0.093 | 4.579 | 1 | 0.032 | 0.820 |
| Constant | 11.526 | 8.101 | 2.024 | 1 | 0.155 | 101274.200 |

However, the Wald statistics indicate that in the present model only Trail Making Form A ($z = 4.858$, $p<0.028$) and the Gibson Spiral Maze ($z = 4.579$, $p<0.032$) reliably predict AD, whereas Spatial Span Reverse just failed to reach significance ($z = 3.741$, $p<0.053$). Antisaccade omissions do not appear to be a reliable predictor of dementia in the present model, when controlling for the three neuropsychological assessments.

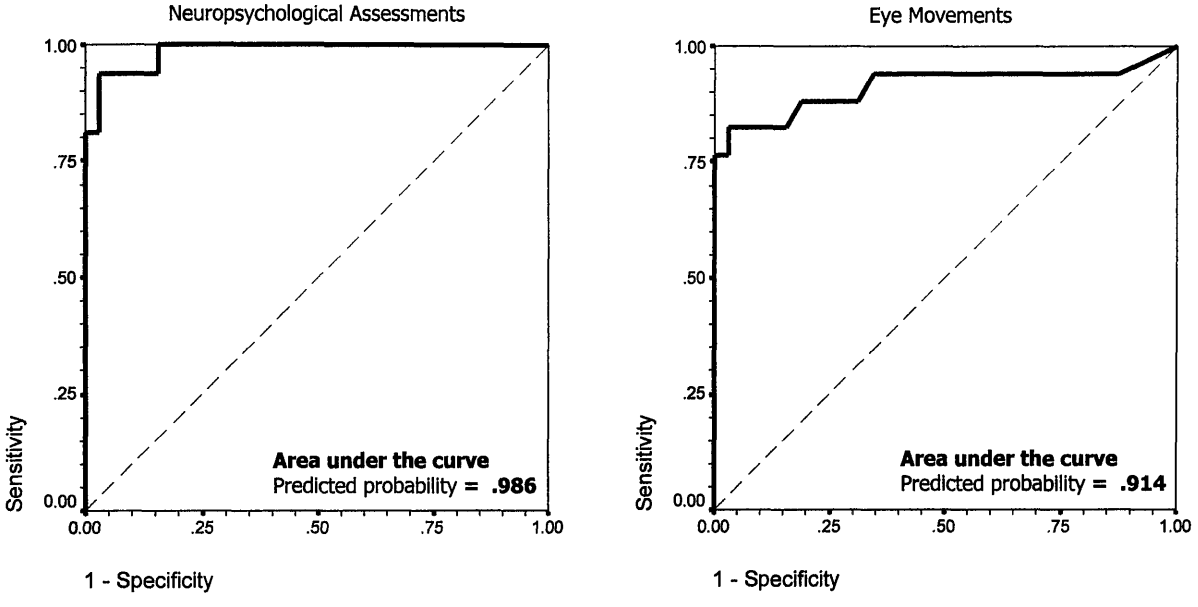
Therefore, although the overall predictive success of the model combining neuropsychological assessments and antisaccade omissions was improved by 3.1%, compared with the neuropsychological assessment only model (Section 8.3.1), the combined model in the present analysis showed that there was little to be gained by combing the two types of variable. In the original neuropsychological assessment *only* model, the total loss had a Chi-square value of 47.830, for *three* degrees of freedom (Table 8.4) and the $R^2$ was .876. On introducing antisaccade omissions into the equation, the Chi-square value only increased by 0.122, to give a total loss of 47.952 with *four* degrees of freedom – clearly, a *non-significant* improvement. Additionally, the $R^2$ value only increased to .877 demonstrating that virtually no extra variance was accounted for by the model.

In summary, sensitivity of the original neuropsychological assessment *only* model was impressive at 93.8% as was specificity, also at 93.8%. For the saccadic eye movement *only* model, sensitivity was less pronounced at 82.4% (i.e. lower true positive probability), however, at 96.9%, specificity (higher true negative and lower false positive probability) was slightly higher. In the model *combining* neuropsychological assessments and saccadic eye movements variables, sensitivity remained unchanged from that achieved in the neuropsychological assessment *only* model, at 93.8% (no change in true positive probability), however, the specificity of this model showed improvement by increasing to 96.9% (higher true negative and lower false positive probability).

Figure 8.1 above displays ROC curves which plot sensitivity (true positives) as a function of false negatives (1 – specificity), i.e. the trade-off between the two, to demonstrate the detectibility of dementia for a given model. The curves actually show the true positive performance of the models at every observed value of their true negative. Since the values are trade-offs, it is always possible for a model to perform very well in one direction at the expense of the other. What the ROC curve does is to make this trade-off explicit for each value of one

parameter versus the other. The present results show that the area under the curve is >0.9 for both models, i.e. the neuropsychological assessment *only* model and the eye movements *only* model, suggesting near perfect detectibility performance for each model.

**Figure 8.1** Receiver Operating Characteristic Curves for Neuropsychological Assessment and Eye Movement Models with Dementia Patients




## 8.4 Discussion

### 8.4.1 Key findings

The key findings from the present study are summarised as follows:-

1. Behavioural characteristics of the antisaccade task are sensitive in the detection of early dementia.
2. Error components of the antisaccade gap task, specifically corrected errors, uncorrected errors and omissions form a useful logistic regression model with high specificity and, which is able to predict dementia with a good level of sensitivity.

3. A reduced set of neuropsychological assessments, namely the Spatial Span Reverse, Trail Making Form A and Gibson Spiral Maze tests are able to predict dementia with a high degree of both specificity and sensitivity.

4. No advantage was found by combining saccadic eye movement variables and neuropsychological assessments in an attempt to form a superior model.

5. Variables derived from just *one* antisaccade task can be used to predict Dementia, whereas the neuropsychological assessment model requires that *three* separate tests be conducted.

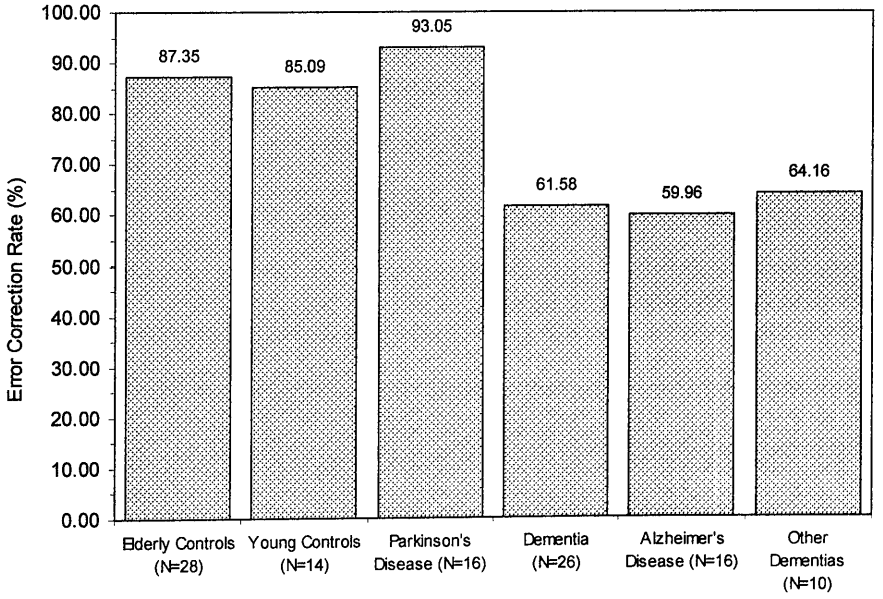
6. Sensitivity was higher in the neuropsychological assessment model, than for the saccadic eye movement model, however, both models had high specificity. ROC curves indicated that both models perform at > 0.9 detectibility.

### 8.4.2 Towards Interpretation

Although the present analyses were conducted on the AD patient group data (and ECs), it is vital to note that the models are useful in predicting dementia generally, rather than specifically AD. Uncorrected and corrected error rates were prominent in the data for the dementia group as a whole (comprising AD and DOT sub-groups). Therefore, it is feasible that the proportions recorded for these variables in the present thesis could be generalized to dementia. However, it is important to recognize that antisaccade task inhibition errors are not exclusive to the clinical groups of AD and the other forms of dementia that are reported in the present thesis, In fact, as demonstrated in Studies I and III, healthy control and PD participants

also make errors of inhibition. Additionally, many studies of schizophrenia have also examined antisaccade error rate (Crawford, Haeger, Kennard, Reveley & Henderson, 1995a, 1995b; Hutton & Kennard, 1998; Hutton et al., 1998; Hutton et al., 2001; Klein et al., 2000a; Klein, Brugner, Foerster, Muller & Schweickhardt, 2000b; McDowell, Myles-Worsley, Coon, Byerley & Clementz, 1999; Nieman et al., 2000; Straube, Riedel, Eggert & Muller, 1999; Thaker, Cassady, Adami, Moran & Ross, 1996; Thaker, Nguyen & Tamminga, 1989; Thaker et al., 2000) and some studies also investigated error correction (Clementz, McDowell & Zisook, 1994; Crawford et al., 1998; McDowell & Clementz, 1997). However, interestingly the analysis of error correction in schizophrenia has shown that correction rates (calculated as: corrected error/total inhibition error x 100) are significantly higher at 81-92% (Clementz et al., 1994; Crawford et al., 1998; McDowell & Clementz, 1997), than those found for dementia patients in the present thesis: Dementia patients as a whole (61.58%) or the sub-groups (AD, 59.96%; DOT, 64.14%). Moreover, the correction rates in schizophrenia do not tend to differ from the rates found for PDs, ECs or YCs (Figure 8.2). Therefore, is plausible to conclude that low error correction rate or a high proportion of errors that remain uncorrected is a specific characteristic of early dementia. Furthermore, it can be argued that the error correction rate is a sensitive marker of dementing illness.

**Figure 8.2** Antisaccade Gap Task Error Correction Rate



### 8.4.3 Performance of the Logistic Regression Models

For the present study, it was considered both useful and necessary to verify the performance of the each logistic regression model, although this was only possible to a limited extent due to the small number of participants available. Therefore, in an attempt to evaluate the models, both the saccadic eye movement model and the neuropsychological assessment model were applied to the baseline data of patients from the other clinical groups in the present thesis, i.e. the DOT sub-groups and Parkinson's disease patients. This simple test is advantageous for the study in a number of ways. Firstly, two of the dementia sub-groups (i. Mixed Dementia; and ii. Vascular Dementia) actually had a diagnosis of mild dementia, thus, it is feasible to use these patients as a way of testing the models, a procedure which should indicate dementia for the majority of cases for a reliable model. Secondly, as discussed in Chapter 1, it is widely accepted that many MCI patients may actually be at an early stage of dementia (See, Chapter 1, Section 1.6.4) therefore, it is important to consider the MCI patients from the present study in light of this notion, to assess whether either model can predict any early dementia and then reflect on this outcome in view of the present mental status of each patient. Thirdly, a small proportion of PD patients develop Parkinson's dementia as the disease becomes more advanced. Therefore, it is informative to examine the data from the twenty-five PD patients that were included earlier in this thesis (Study III, Chapter 5), to investigate whether either model predicts dementia for any of these cases and then evaluate this prediction in view of the present mental status of each patient. As the PD patients were found to have a high (good) error correction rate, the number of cases with a positive prediction of dementia, were expected to be minimal. A summary of the outcome from each of these assessments is shown below in Table 8.10. For identification purposes, the participants are allocated a simple number in the table.

**Table 8.10** Testing the Models by Application to Clinical Groups

| | Participant | Diagnosis | Age (at test) | Year (initial test) | Clinical Rating Scales | | Logistic regression model disease status | | Post test follow-up (2005) |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | SMMSE | ADAScog | EM | NP | |
| Dementia group | 1 | MCI | 77 | 2001 | 28 | 9 | dementia | healthy | Memory defict, easily confused. Vaguely remembered participation. |
| | 2 | MCI | 80 | 2002 | 27 | 12 | dementia | healthy | Severe memory deficit, Does not remember S. Higham or participation. |
| | 3 | MCI | 77 | 2002 | 29 | 10 | healthy | healthy | Progressive memory dysfunction. Does not remember S. Higham or participation. |
| | 4 | Mixed dementia | 81 | 2001 | 30 | 8 | dementia | healthy | Severe dementia, residential care. |
| | 5 | Mixed dementia | 68 | 2002 | 28 | 13 | dementia | dementia | Does not remember participating. |
| | 6 | Mixed dementia | 78 | 2002 | 23 | 12 | healthy | healthy | Severe memory defict, easily confused. Could not remember S.Higham or participation. |
| | 7 | Vascular dementia | 78 | 2001 | 24 | 15 | dementia | healthy | Mild dementia, cannot remember participation or S. Higham. |
| | 8 | Vascular dementia | 79 | 2001 | 24 | 25 | healthy | dementia | *Severe memory deficit, Does not remember S. Higham or participation. |
| | 9 | Vascular dementia | 76 | 2002 | 27 | 22 | dementia | dementia | *Deceased* |
| | 10 | Vascular dementia | 77 | 2002 | 19 | 23 | dementia | dementia | Severe dementia, residential care |
| Parkinson's group | 11 | Parkinson's disease | 68 | 2003 | 29 | 7 | dementia | n/a | Short-term memory can be a problem. Noticable word finding difficulties during conversation with some circumlocution, complains of this. |
| | 12 | Parkinson's disease | 66 | 2003 | 25 | 6 | dementia | n/a | Complains of short-term and prospective memory problems, but long-term memory preverved. |
| | 13 | Parkinson's disease | 48 | 2003 | 30 | 3 | dementia | n/a | Cognisant but slight deterioration in short-term memory. |

* Recent brain scan shows that this patient now has severve atrophy to approximately 25% of the frontal cortex. The location and nature of this extensive degeneration corresponds to a head injury sustained when this patient was aged 57 years (baton attack which forced retirement).

**Models:** EM = eye movement variables; NP = neuropsychological assessments



8 Predicting Dementia

### 8.4.3.1 Mild Cognitive Impairment

The MCI patients represented an interesting test for each model as these patients were assessed as not having dementia, the outcomes are summarised as follows:

**Case 1**: This patient first attended the memory clinic at Lytham Hospital with a very mild memory deficit. Certainly, the clinical rating scale scores for this patient at this time (baseline) - high SMMSE score of 28 (out of 30) and normal EADAScog score of 9 - demonstrated that there were no obvious signs of dementia. However, when the patient's antisaccade error rates were entered into the saccadic eye movement model, the model predicted that this MCI patient as having (or perhaps would develop) early dementia. Surprisingly, the other model using a reduced set of neuropsychological assessments, did not classify this patient as having early dementia. Interestingly, this patient's scores had deteriorated somewhat at the 18 month test session (final), the SMMSE score falling by 3 points to 25 and the EADAScog increasing to 11, which suggests that the patient's deficits had become more severe. Some four years on from the initial test date, the present status of this patient at the time of writing this thesis, indicated that the patient appears to have clear signs of dementing illness, becoming easily confused when confronted with day-to-day tasks and only vaguely remembering having taken part in any type of study. Therefore, the eye movement model appears to have correctly predicted that the patient had early dementia in this case, a deficit that was apparently too subtle for initial psychological tests and clinical rating scales to detect efficiently.

**Case 2**: This patient was referred to the memory clinic following mild problems with prospective memory. Early cognitive tests indicated that further clinical evaluation was advisable. However, supplementary tests were found to be unremarkable. On entering the baseline scores of this patient into the saccadic eye movement model, the model classified the

patient as having early dementia, whereas the model using a reduced set of neuropsychological assessment scores did not predict dementia for this case. By the final test session at 18 months, the clinical rating scale scores for this patient had worsened (SMMSE = 26, EADAScog 16), showing a subtle decline in cognition over time. On following this case up at three years post baseline test, the patient was found to have obvious signs of mild dementia, with severe memory impairment, circumlocution and confusion. The patient has no recollection whatsoever of having taken part in the study and does not remember the researcher (despite having had a close rapport during the study). Thus, the saccadic eye movement model predicted dementia from the initial antisaccade error components for this patient, whereas the neuropsychological assessment model did not (Table 8.10). However, it should be stressed that the initial clinical rating scale scores for this patient did draw attention to the case. Importantly, as mentioned above however, further psychological assessment results were found to be unremarkable and inconclusive.

**Case 3**: This case was referred to the memory clinic following mild problems with prospective memory. Early cognitive tests were fairly normal as indicated in Table 8.10. However, this patient's memory continued to deteriorate over time and the patient no longer remembers having participated in the study and of particular note, she has no memory of the investigator with whom a good rapport was established. Puzzlingly, both regression models failed to predict dementia for this case, with the implication that memory may be dysfunctional in some patients, whilst inhibitory control and psychomotor ability remain preserved.

### *8.4.3.2 Vascular Dementia and Mixed Dementia*

The cases with vascular dementia and also those with mixed dementia, where diagnosed as having a dementing illness, on entering the present study. However, as displayed in Table 8.10, both models were insufficiently sensitive to predict dementia for all these cases.

The eye movement model predicted dementia correctly in five out of the seven cases, whereas the neuropsychological assessment model predicted only four out of the seven cases correctly.

Case number 8 has emerged as an interesting patient over time. The saccadic eye movement model classified this case as normal, whilst conversely, the neuropsychological assessment model correctly predicted dementia. This patient sustained a head injury some 25 years ago (1980), it is therefore possible to argue that this patient's dementia actually stems from the *head injury*. Indeed, this is the conclusion recently suggested by consultants, following an MRI scan of the patient's brain. The scan revealed extensive atrophy of frontal cortical areas, which correspond with the location of the head injury. Therefore, the location of the head injury may explain the nature of the outcomes from various cognitive tests. The patient was found to have good inhibitory control in the antisaccade task at each test session of the longitudinal study, however, the clinical rating scale scores were somewhat fluctuant. Whilst the SMMSE score remained unchanged over time (baseline = 24, 18 months = 24), the EADAScog score improved from a high score of 25 to a much lower score of 12. Psychomotor ability was well preserved in this patient (Trail Making and Gibson Spiral Maze scores were found to be no different to those of the EC group), however, working memory performance was poor, which resulted in a classification of dementia for this patient by the neuropsychological assessment model. This is another interesting case, where it seems apparent that working memory can be impaired, whilst inhibitory control is well preserved.

#### *8.4.3.3 Parkinson's Disease*

The saccadic eye movement model was applied to the Parkinson's disease patients, and interestingly, three of the patients were classified as having dementia. Unfortunately, the neuropsychological assessment model could not be applied to the PD patients, as the full range of neuropsychological assessment tests were not conducted with this group. Interestingly, on following up the three cases predicted as having dementia, patients 11 and 12 were found to

have developed some cognitive problems, including short-term and prospective memory deficits (Table 8.10). Patient 13 has also demonstrated a subtle decline in short-term memory performance. Of course, without a comprehensive follow-up of all the other PD patients, to verify as to whether they have also developed memory difficulties, these results remain inconclusive.

### 8.4.4 The Saccadic Eye Movement Model in the Prediction of Dementia

One of the most striking observations of the present study was the ability of the saccadic eye movement model to detect apparently subtle deficits of inhibitory control early on in dementing illness. Of particular interest here, was the finding that two MCI patients were predicted as having early dementia by the model, which now transpires to be the case, as the patients display clear signs of having developed dementia. Furthermore, the model was able to classify mixed and vascular dementia cases with a high success rate. It may be the case that the key to the success of the model is that inhibitory control is a sensitive marker of early dementia i.e. a disturbance of inhibitory control and error correction is characteristic of dementia. Many batteries of psychological tests do not assess inhibitory control but instead concentrate to a large extent on the assessment of various types of short-term memory, orientation and psychomotor ability. This would explain why the MCI patients were not found to have dementia early on in the course of their disease.

Of practical interest, is the fact that this model was derived from patients with probable AD of mild to moderate dementia severity, i.e. the patients were recruited to the study in the early stages of disease. The main implication for the results is that a small set of variables from just one antisaccade task was able to distinguish between patients with early dementia and control participants with impressive sensitivity and specificity. Thus, there is a good argument in favour of the antisaccade gap task as and aid to diagnosis of early dementia. The antisaccade task is easy to administer and takes less time than an extensive battery of

neuropsychological assessments. Specificity was high, i.e. the test produced very low false positives (3.1%), whereas sensitivity was good, which means that the test generated few false negatives (17.6%). However, there is thus a risk in the applied setting, that approximately 17% patients in the mild stages of dementia may test negative, when in fact, the are positive (i.e. they have dementia). Nevertheless, it is possible that the antisaccade task could be refined, by adjusting the temporal parameters of the visual stimuli and developing the test further by validating the model on many more patients considered to have early dementia. Thus, further research is needed to establish the test as a model paradigm. However, it is clear that the antisaccade gap paradigm can reliably dissociate between dementia patients and other groups, and that regression models have the capacity to reliably predict dementia from saccadic variables. Moreover, the data suggest that uncorrected errors are specific to dementia, as other groups (including clinical) have been shown to have high inhibition error correction rates.

Although the analysis in the present project was somewhat limited due to the low number of dementia patients and with regard to the relatively small number of neuropsychological assessments included in the test battery, it is important to note that the patients were also clinically evaluated prior to test and final diagnosis. Therefore, it is reasonable to claim that the classification of cases by each model provides a reliable prediction of dementia, which could potentially reduce the degree of extensive testing that is presently associated with the diagnosis of dementia (and specifically AD) in Health Service Trusts with limited resources.

## 8.5 Conclusions

- ✧ The present study has demonstrated that error components of the antisaccade gap task, specifically corrected errors, uncorrected errors and omissions, provide a sensitive indicator of early dementia. These variables can be successfully included in a logistic regression model that can be used to predict dementia.

- High proportions of uncorrected errors are specific to dementia as other groups retain the capacity to spontaneously correct errors of inhibition.

- Although working memory and inhibitory control are closely associated, some patients appear to have a deficit of one more than the other.

- A reduced set of neuropsychological assessments can reliably predict dementia with somewhat higher sensitivity than that of the saccadic eye movement model. However, the saccadic eye movement model requires only one short test from which three sensitive variables can be derived. The neuropsychological assessment model on the other hand requires three separate tests.

- Combined with a clinical rating scale test, a refined antisaccade task that produces high sensitivity and specificity, has the potential to provide a test that is a sensitive marker of early dementia, thereby facilitating early diagnosis and treatment with modern drugs that may provide prophylactic benefit for dementia patients and ease the burden of care for carers.

## 8.6 Limitations of the Study

- The number of patients in the initial study was too small. Validation of the present models would require a study designed with power analyses and a greater number of patients to both replicate the existing observations and extend the findings further.

- The final regression models were only tested on a small number of dementia patients of other types than AD. The models should be applied to data gathered from a greater number of dementia patients, recruited randomly from various locations widely ranging around the United Kingdom.

# Chapter Nine

# General Discussion

## 9.1 Introduction

The primary aim of the present thesis was to investigate the potential for sensitive oculomotor markers in the detection of dementia, specifically, AD given the findings of extensive previous research into AD, which has indicated working memory and attention deficits, in addition to eye movement abnormalities. Voluntary and involuntary saccade paradigms were utilized in an attempt to probe these cognitive deficits, which were described in the earlier chapters of the present thesis. In particular, the antisaccade task was employed, as this model paradigm has proved advantageous in previous studies (Broerse et al., 2001; Hutton et al., 2002; Monsell & Driver, 2000). This final chapter will endeavour to draw together the findings from each of the studies in this thesis.

## 9.2 A Longitudinal Analysis of Cognitive and Eye Movement Deficits in Alzheimer's Disease

The present thesis explored a range of oculomotor tasks specifically employed to investigate the dynamics and behavioural characteristics of saccadic eye movements. Additionally, a battery of neuropsychological assessments and clinical rating scales were used to assist in the diagnosis of AD and to provide a range of cognitive measures.

A number of areas provided the focus of interest for the study, which included inhibitory control for attention and the FOE. Error correction was also investigated and each of these areas was examined to distinguish the effects of healthy aging from dementia.

Furthermore, additional tests sessions were conducted longitudinally, in an attempt to look closely at the progression of disease over time by an extensive analysis of cognitive and eye movement tests.

### 9.2.1 Voluntary Saccade Tasks and Inhibitory Control

In the case of inhibitory control generally, it was hypothesized that as working memory is dysfunctional in AD diminished working memory resources would result in AD patient performance decreasing linearly across voluntary saccade tasks, depending on the cognitive load (i.e. task demand) for a given task. As working memory resources become more taxed, task goals are insufficiently activated and the requirement to inhibit prepotent responses would result in errors of inhibition. Therefore, a task that places low demands on working memory resources would result in lower errors of inhibition, as the level of activation for task goals remains sufficient to facilitate attentional processing. Conversely, a task that taxes working memory resources highly would result in a higher proportion of inhibition errors. The control groups should obviously produce less inhibition errors than AD patients, as working memory in these groups is relatively well preserved or intact. Thus, controls are endowed with more efficient online processing for a given task and ultimately greater capacity to manipulate task instructions and thereby inhibit prepotent response.

### 9.2.2 The Fixation Offset Effect

AD patients have been found to present with a disengagement deficit from an attended stimulus, when required to disengage the attended stimulus and attend an alternative target. Correspondingly, for the FOE the general hypothesis was therefore that AD patients would present with an FOE of greater magnitude than that of controls. Thus, as a result of attentional capture by the central fixation point and a disruption in the ability to disengage this point, the latency of the primary saccade to the peripheral target in overlap tasks would be prolonged.

## 9.3 Discussion of Findings

### 9.3.1 Inhibition Errors

A number of analyses were carried out on inhibition error rates in an attempt to investigate thoroughly the sensitivity of this measure to the effects of disease. These analyses included the following:-

- Comparison of inhibitory error across voluntary saccade tasks
- Analysis of corrected and uncorrected errors

#### 9.3.1.1 Inhibitory Errors Across Voluntary Saccade Tasks

The main findings from this analysis were that dementia patients as a whole and at the sub-group level of AD and DOT, committed higher proportions of inhibition errors than the EC group on each voluntary saccade task, as predicted (Study I). However, there was no significant difference between sub-groups (i.e. between ADs and DOTs). Furthermore, data from PDs and YCs in Study III, revealed that these effects were able to distinguish between dementia and the effects of normal aging and moreover, PD. Importantly, a linear trend was also found in the data, relating to the demands of the voluntary saccade task, supporting the hypothesis that error rates would increase linearly in accord with task demand: The No-Go task, placing least demand on working memory resources, through antisaccade gap task and the Go/No-Go task taxing working memory resources to the highest degree. The results from the present study are consistent with a depletion of working memory resources, as found in AD may be explained in terms of poor inhibitory control and thus the generation of inhibitory errors.

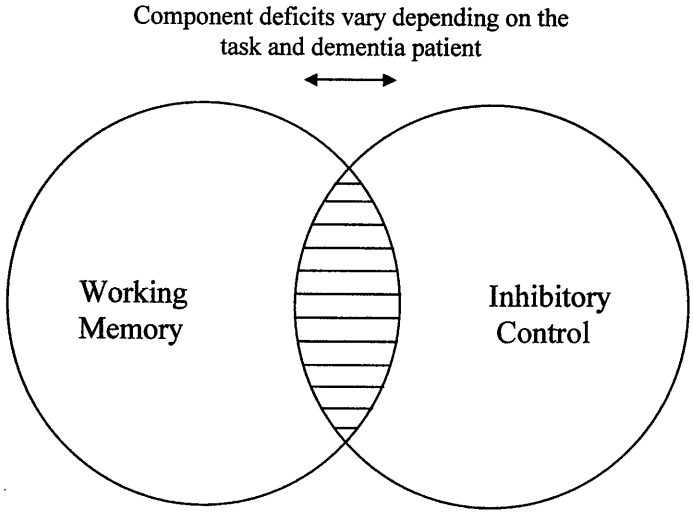
As previously discussed in Section 3.1, there is healthy debate concerning the primary mechanism by which inhibition is delivered. Hasher and Zacks (1988) for example, postulated that inhibitory mechanisms are less efficient with age, as task-irrelevant information becomes

more active in working memory. Along a similar trend of thought, other researchers hypothesise that errors of inhibition in eye movement tasks can be explained as a consequence of depleted working memory resources and with effective inhibition and attentional processing requiring that task goals be sufficiently activated in working memory.

The findings outlined above support the results from previous research in healthy individuals and schizophrenic patients which investigated the antisaccade task and variously, the consequences of varying task demands or secondary tasks on working memory resources (Eenshuistra, Ridderinkhof & van der Molen, 2004; Hutton et al., 2002; Mitchell et al., 2002; Roberts et al., 1994; Stuyven et al., 2000; Walker et al., 1998). However, in the present thesis correlations between AD group voluntary saccade inhibition error rates and cognitive tasks that require working memory, were found to be varied in size from weak to only moderate strength. In fact, only the antisaccade gap task was moderately correlated with Spatial Span Reverse, Digit Span Reverse and Trail Making Form A.

How can the lack of correlation between the more demanding Go/No-Go task inhibition error rate and cognitive tasks that place demands on working memory resources be explained? One possible alternative explanation is that there was a high variance in the scores of individual participants on the different tests, hence the weak correlations. However, there is a further plausible explanation that corresponds with the pattern of results and this is that working memory and inhibitory control could feasibly operate as individual parallel systems, the performance of which will co-vary depending on the nature of a given task (Figure 9.1).

**Figure 9.1** The Components of Working Memory and Inhibitory Control Co-vary Depending on the Nature of a Given Task




Crucially, for the present thesis, working memory and inhibitory control could co-vary according to the AD patient. Therefore, some patients may have good working memory and poor inhibitory control, and the converse of this situation could conceivably be the case for other patients, whilst some patients have more of an even performance between the two components. This notion would also support the idea of a competition between two parallel programmes as discussed in Section 3.1, the reflexive automatically generated programme and the endogenously generated voluntary saccade programme each competing to execute a saccade (Massen, 2004; Mockler & Fischer, 1999). Attention and inhibition can be viewed as two sides of the same coin and when task goals are sufficiently activated in working memory (Miller & Cohen, 2001; Nieuwenhuis et al., 2004), the attentional biasing is sufficiently activated to attend to the task appropriately.

Longitudinally, inhibition error rates were not found to change significantly for either group over time, the 18 month period of testing reflecting little change in the progression of AD, although a non-significant increase was observed overall in each task. However, it is possible to argue these results are somewhat complicated by the fact that medication with acetylcholinesterase inhibitors may have produced a subtle improvement (reduction) in the error rates for each task at the 6 month test session.

#### 9.3.1.2 Error Correction

On committing saccadic errors, the majority of healthy individuals frequently generate a spontaneous corrective saccade so as to position the eye to the correct location in accordance with task instructions. By far the most prominent observation in the analysis of inhibition errors for the present thesis was the low corrective error rate of AD patients. This was examined in the first instance during Studies I and III (Chapters 3 and 5 respectively) where the factor correctness of performance was found to reveal a profile that was different to that of the other groups. Specifically, the antisaccade gap task variables for the proportions of correct saccades, corrected errors and uncorrected errors were found to have a flat profile for the AD group. However, the data for each of the other groups consistently produced a profile with a linear trend across these three variables. Therefore, this profile is able to distinguish between the effects of normal aging and also between disease effects for AD and PD. These findings highlight the potential for error correction rates as a possible sensitive diagnostic marker for AD, and the plausibility of their inclusion in some sort of predictive model. The profile for correctness of performance was chosen as it incorporates the data from all participants in the study, thereby providing an account of performance for the whole group. This is in contrast to the error correction rate that was utilised in the discussion section (8.4.2) of Chapter 8, which only includes participants that have generated errors (corrected errors/inhibition errors x100). The vital component for either analysis was observed to be the uncorrected error rate for the AD patients. An additional analysis from the present project in a recently published article, showed that the corrected errors were just as common in the second half of the task as in the first half (Crawford et al., 2005a). Thus, this result confirms that the corrected error rate does actually indicate that patients have understood the task instructions and furthermore, that spontaneity of error correction is intermittent in AD. This finding is important as it demonstrates that patients understood the demands of the task, following training with the clinical antisaccade task and subsequent practice trials prior to commencing the task.

Moreover, it also shows that uncorrected errors in AD are *not* the result of patients having forgotten the task instructions, due to memory deficit. Previous research showed that individuals are likely to modify behavioural responses on detecting errors, facilitating a decrease in further errors (Rabbitt, 1967). However, it is evident that this is not the case for the AD patients in the present thesis, who demonstrate a sporadic dysfunction in error monitoring, as errors occurred intermittently during the antisaccade task. These findings suggest that the AD patients in the present study have a dysfunction of error monitoring that is distinct from control participants and two other clinical groups, PD and as described in Chapter 8, schizophrenia. A significant increase in the uncorrected error rate for the AD group was also observed to occur longitudinally, between the 6 and 18 months test sessions indicating that this measure is sensitive to the progression of AD over time.

Recent studies have found evidence to suggest that the neural substrates involved in error correction and self-monitoring include the ACC and DLPFC (Section 1.4.2.3). In particular the ACC is believed to be specifically involved in error processing (Garavan et al., 2002; Ito et al., 2003; Menon et al., 2001), whereas the DLPFC is involved in response inhibition and monitoring competition between tasks (Gaymard et al., 2003; Matsuda et al., 2000; Menon et al., 2001; Pierrot-Deseilligny et al., 2004). Alternative explanations to account for sporadic uncorrected errors in AD antisaccade performance, could involve a dysfunction of working memory, which corresponds with the ideas set out in Section 9.3.1.1. A further explanation could involve a fixation disengagement deficit. Thus, once a reflexive saccade has been generated inappropriately by the VGR in response to the peripheral stimulus in the antisaccade gap task, the AD patient has difficulty disengaging fixation from the already attended target location and thus there is a generating a saccade to an empty location. This observation may be specific to the antisaccade task and possibly involve a disturbance of working memory.

### 9.3.2 The Fixation Offset Effect for Reflexive Saccades

As hypothesized, the reflexive saccade FOE was found to be of a significantly greater magnitude for the AD group at baseline compared with that of the EC, PD and YC groups[23]. Although the magnitude of FOE for the AD group was also greater than that of the DOT group, this difference was non-significant. Surprisingly, the magnitude of this measure did not *increase* over time as hypothesized. Conversely, the magnitude of FOE actually *decreased* over the following test sessions from baseline through 18 months. Study V (Section 7.4.6) offered two possible explanations for the decrease of FOE over time. The first explanation suggested that the decrease over time in reflexive saccade overlap task latency could be the result of deterioration in the fixation system. This idea is supported by Bylsma et al. (1995) study, which found that intrusive saccades interrupt fixation longitudinally in AD. Therefore, this notion would correspond with a dysfunction of inhibitory control overtime, as found in the antisaccade gap task (uncorrected errors). However, a plausible alternative explanation for the reduction of FOE was also postulated in Study V (in Chapter 7), and suggested that early on in the course of the disease, it is possible that patients tended to apply compensation strategies to counter a dysfunctional fixation system (commensurate with the attentional deficits reported in previous AD research (Parasuraman & Haxby, 1993; Perry & Hodges, 1999). However, this fixation dysfunction may be such that the AD patients *over compensate* when attending the central fixation point. It is feasible that this adaptive behaviour manifests as the observed increase in latency during the reflexive overlap task, when the central fixation point overlaps temporally with the appearance of the peripheral target in contrast to the gap task, where following offset of the central fixation point, a temporal gap of 200 msecs. elapses prior to onset of the peripheral target. Over compensation could have the effect of exaggerating the FOE. However, the phenomenon could diminish over time, as dementia severity worsens and patients no longer over compensate so that the FOE settles down to a lower magnitude, but a

[23] The PD and YC groups were only analysed in Chapter 5. Longitudinal data was not gathered from the PD and YC groups, i.e. these two groups are not included in Chapter 7.

magnitude that is nonetheless larger than that of the EC group, as indicated by the longitudinal results.

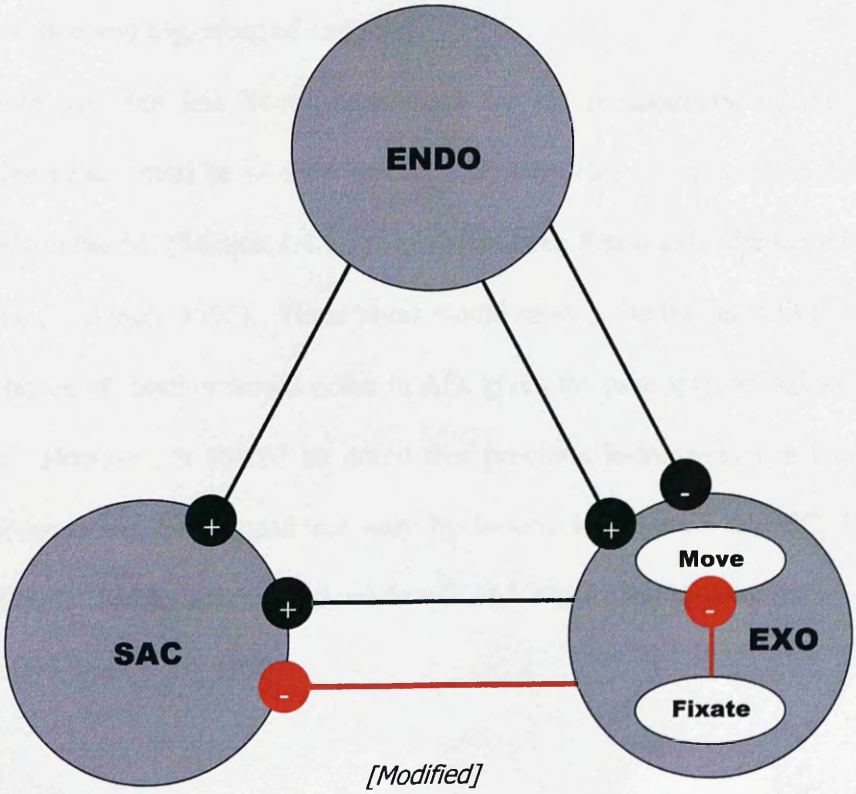
This notion corresponds with mild dementia, which was the severity rating for the majority of the cases at baseline. Furthermore, volitional control was a faculty that remained reasonably functional at this stage of illness. Note, that these patients were able to participate successfully in the voluntary saccade tasks, having completed the No-Go, Go/No-Go and antisaccade paradigms (*following* the reflexive tasks). Moreover, notwithstanding that the AD patients commit an abnormal proportion of inhibition errors on the voluntary saccade tasks (compared to the EC group), it is important to remember that they were also *able* to correct inhibition errors to some degree (baseline mean antisaccade gap task = 27.2 % of trials). A further interesting point, is that the mean latency for the AD group in the reflexive saccade overlap task was 293 msecs., which is actually not very much shorter than the antisaccade gap task latency of the EC participants (304 msecs.) and AD participants (336 msecs.). Antisaccade gap task amplitude ($4.3^{o}$) for the AD group also indicates fair accuracy for target location, further confirming task understanding. Taken together, these observations offer good support for the view that the AD patients could have been using volitional compensation in an attempt to comply with the task instructions for the reflexive saccade overlap task and counteract disturbance of the visual fixation system. In essence, it is reasonable to suggest that perhaps the AD patients performed the task along the lines of a voluntary saccade task, rather than a reflexive task, however, the simplicity of the task resulted in saccades of shorter latency than in the antisaccade task. However, by the end of the longitudinal study the volitional compensation had deteriorated somewhat, leaving a FOE of magnitude that was only subtly larger than that of the EC group - which for the AD group, is the manifestation of the putative fixation disengagement deficit. This deterioration of voluntary control would also correspond with the progressive degeneration found in AD, of frontal cortex and the limbic system. Furthermore, the reduction in voluntary control is also consistent with the increase reported in

Chapter 7 for the proportion of antisaccade uncorrected errors by the final test session at 18 months of longitudinal study.

The neural basis for the fixation disengagement deficit in AD can be envisaged in terms of the Forbes and Klein model, which was discussed in Study II (Section 4.1, Chapter 4). Figure 9.2 is a modified version of Figure 4.1, and highlights the proposed areas for the model that result in the fixation disengagement deficit in AD.

In healthy individuals, the ENDO and EXO systems both receive stimulation for reflexive saccades, however, VGR foveation is assisted by saccadic parameters and commands that are mostly generated by the EXO system. When a fixation point is presented, the fixation cells of the SC provide a brake by inhibiting movement cells in the SC and providing excitatory stimulation of the inhibitory omnipause neurons in the SAC system. By removing the fixation point, the systems are disinhibited and saccade latency reduced.

**Figure 9.2** The Forbes & Klein Model Illustrating the Functional Activity Between Endogenous (ENDO) and Exogenous (EXO) Systems in the Control of Saccade (SAC) Generation. Modified to Highlight the Theorised Neurodegenerative Links for Alzheimers' Disease




*[Modified]*

Source: Forbes & Klein (1996)

In Figure 9.2 certain links in the Forbes and Klein model have been highlighted in red to indicate where in the model, the putative disruption of the fixation system occurs in AD. The present thesis draws the conclusion that the disruption occurs in elements of the EXO system, corresponding with reflexive saccades or using terminology from the Forbes and Klein model, exogenously generated saccades. Here, according to the model, the neural substrates involved in the generation exogenous saccades involve the SC and the parietal cortex. The parietal lobe is reported to have reciprocal connections with the FEF, which is also known to possess fixation and movement cells, thus, the parietal lobe, in particular the PEF provides an important interface with brainstem nuclei. As latency in the reflexive saccade gap task was found to be normal for the AD group, it is probable that the SAC system and perhaps the SC component of the EXO system are functioning normally. However, when the fixation point remains illuminated in the reflexive overlap task, it is hypothesized here, that latency is subtly prolonged by comparison to that of the EC group, due to dysfunction of the fixation cells or movement cells in the FEF or PEF in the parietal lobe. Note that Section 1.4.2.2 emphasized the vital importance of the PEF in coding for particular objects of interest in spatial coordinates and in the generation and triggering of saccades.

An alternative, but less likely explanation for the prolongation of saccades in the reflexive overlap task, would be to draw attention sub-cortically, to a possible disturbance of the fixation cells in the SC (Section 1.4.1.2) which has been found to be the neural correlate of the FOE (Dorris & Munoz, 1995). These areas would seem to be the most likely locations in which a disturbance of fixation would occur in AD, given the neuropsychological background of the disease. However, it should be noted that previous lesion evidence has found that fixation impairments can be induced not only by lesions to the FEF and SC, but also the cerebellum, DLPFC, SMA, inferior parietal lobule and basal ganglia (Anderson et al., 1994; Leigh & Zee, 1999; Petit et al., 1999).

### 9.3.3 Neuropsychological Assessment

In Chapter 7, an extensive and thorough examination of neuropsychological assessment and clinical rating scale scores was conducted on longitudinal data gathered from four test sessions spanning a period of 18 months at 6 monthly intervals. With the exception of the Digit Span Forwards test, all neuropsychological assessment tests and clinical rating scales were found to result in poorer performance scores for dementia patients as a whole and the AD patient sub-group, when compared with the scores of EC participants. Thus, the Digit Span Forwards test, which assesses short-term auditory memory and can also be considered as an index of attention or concentration, was insufficiently sensitive to detect the subtle short-term memory problems symptomatic of all dementia patients in the study.

However, this broad analysis revealed that with the exception test of the Digit Span Reverse test, none of neuropsychological assessments were sufficiently sensitive to the progression of AD (within-groups) over the period of 18 months. These results demonstrate that although the tests are sensitive in detecting the difference between mild dementia and healthy control participants, having poor temporal resolution they detect little by way of change overtime. The range of tests comprising the present battery is also rather limited by comparison with the number tests contained in some of the more extensive test batteries that are in use (see Chapter 8). Thus, it is a plausible argument, to suggest that in many memory clinics the number of tests involved in the assessment for the diagnosis of AD is almost certainly too high, as clinicians try to ensure high sensitivity in an attempt not to miss any patients (however, a counter argument might suggest that it is important to establish a deficit remains, even if that deficit has not changed over time). Therefore, it would be advantageous to the clinician to be able to reduce the number of tests in a battery when it is appropriate to do so, thereby reducing the labour intensity of diagnosis, potential for test duplication and the possibility of unnecessary fatigue for patients. The aim of Study VI in Chapter 8, was to investigate the range of eye movement test variables and neuropsychological assessments, in

an attempt to find a sensitive set of regressors that would successfully predict dementia. This approach is discussed in the following section.

## 9.4 Predicting Dementia

In Study VI of the present thesis, the saccadic eye movement variables and neuropsychological assessments found to be of salient value in distinguishing between groups in the earlier studies of the thesis were evaluated to establish their ability to predict dementia. The rationale behind this study was to attempt to find a model that could predict dementia efficiently with the least set of predictors as possible. The benefit of such a model would be that patients with early dementia could be diagnosed effectively with a minimum number of tests, perhaps along with the SMMSE or EADAScog. Additionally, if patients could be diagnosed as having dementia with some certainty at the earliest opportunity, then there is potential for early treatment or prophylactic action from modern anti-dementia drugs, such as the acetylcholinesterase inhibitors.

Two models were achieved in the study using logistic regression for the prediction of dementia using the AD group of patients. The first model used a reduced set of neuropsychological assessments, the most efficient of which was found to combine Spatial Span Reverse, Trail Making Form A and the Gibson Spiral Maze test as predictors. Prediction success was impressive in this model, with 93.8% of dementia patients and 93.8% of EC participants, correctly predicted. Thus, the model reached an overall success rate of 93.8%. The variables in this model were also able to account for a large amount of variance in disease status, having a high $R^2$ of .876. Therefore, both sensitivity and specificity were very good in this model, the model performing with few false negatives or false positives.

The second model incorporated saccadic eye movement predictors and found that the solution for the best model included antisaccade gap task variables. The best predictors of dementia in this model were found to be corrected errors, uncorrected errors and omission

errors. Interestingly, omission errors emerged as a good predictor of dementia, but were analysed in Study I without finding statistical significance. The reason for this earlier non-significant finding was that the statistical procedure employed in the study used *age* as a covariate (i.e. to control for age as a precautionary measure) and this almost certainly removed some of the treatment effect, reducing the likelihood of obtaining a significant result. For this model, 82.4.0% of dementia patients and 96.9% of EC participants were correctly predicted and the overall success rate was 91.8%. A strong level of variance was accounted for in disease status by this model with the $R^2$ value reaching .683. Sensitivity for this model was not quite as high, indicating the chance of higher false negatives in application, however, specificity was slightly higher than the neuropsychological assessment model showing that fewer false positives would be generated when applying the model to cases.

A further model was attempted, in an effort to obtain a superior model by combining neuropsychological predictors with saccadic eye movement predictors, but to no avail. Therefore, no benefit was found by combining measures from saccadic eye movement variables with neuropsychological assessment scores.

In comparing the detectibility of the two models using ROC analysis, both models performed impressively showing that the area under the curve was > 0.9 in each model. Thus, the trade-off between true positives and false negatives was shown to be negligible for each model and with that there would be no significant difference between the two models.

Both models were tested on the data from the DOT patients and also, on the PD patients from Study III. For the DOT patients, the saccadic eye movement model predicted seven out of ten cases correctly, whereas the neuropsychological assessment model correctly predicted only four out of ten cases (Table 8.10). It is interesting to note that the eye movement model predicted two MCI patients as having dementia and that these two cases have now deteriorated into a demented state (which the neuropsychological

assessment model *failed* to do). However, one of the MCI patients now has an extremely severe memory deficit, but unfortunately neither model predicted dementia with this patient's data. Three PD patients were classified as having dementia by the saccadic eye movement model[24] and post-test follow-up suggested a significant deterioration in cognition for these patients, particularly for two of the patients who appeared to have developed prospective and short-term memory deficits (one of the patients presenting with word finding difficulties with circumlocution). It is of course possible that these patients are in the process of developing Parkinson's dementia. However, without following up the rest of the PD group to assess their mental status, it is impossible to conclude precisely how well the model has performed on these patients i.e. some of the patients who the model classified as not having dementia (who were omitted from Table 8.10) may now have some dysfunction.

A crucial difference between the two models is that the saccadic eye movement model requires three predictors that are derived from only one short antisaccade task, which takes only a matter of minutes to train, set-up and conduct the test with the patient. However, the neuropsychological assessment tests take substantially longer to conduct and are possibly more susceptible to problems of conformity with the patient, who may not wish to comply with memory tasks, computer based tasks or pencil and paper tests. During the course of the study, none of the patients complained of the eye movement tasks, but occasionally became fatigued or annoyed with neuropsychological assessment despite having developed a good rapport with the researcher.

The present results of the antisaccade dementia prediction model are promising and if developed, has the potential to form a useful aid to assist in the prediction of early dementia perhaps when incorporated with the SMMSE and EADAScog.

[24] Unfortunately PD patients were not tested with the full range of neuropsychological assessments.

## 9.5 Methodological Considerations

Study IV assessed the baseline data of medicated and non-medicated patients, in an attempt to eliminate medication with acetylcholinesterase inhibitors as a confounding variable at that stage of the study (as medicated patients had only commenced medication shortly – in the majority of cases – prior to baseline test). Although the study concluded that there were no medication effects for that stage, all but one of the patients were on medication throughout the test sessions following baseline measurement and as the data demonstrate, there appear to be some subtle medication effects. However, this study was not a clinical trial and at no time was it under consideration that patients should be deprived from medical treatment that had the potential to improve quality of life. Therefore, with regard to the longitudinal data, there are a number of points that should be noted regarding dementia patients treated with acetylcholinesterase inhibitors, which are as follows:

- Patients may respond differently to each drug.
- It is not clearly established which dementia patients derive benefit from which drug.
- No all patients derive benefit from medication with acetylcholinesterase inhibitors.
- Some patients suffer side effects from acetylcholinesterase inhibitors, including sickness and diarrhoea, which may affect performance at test.
- Neuropsychiatric presentation in dementia patients fluctuates.

Therefore, in view of these observations care should be taken when interpreting longitudinal data.

A further point of interest concerns the equipment used for the present study. Although the headset was fairly lightweight, any research in relation to the development of the prediction model would benefit from a '*headset free*' system, to minimize the potential for fatigue in patients. Without the headset, it is possible that the number of trials could be increased to 40 (from 24) per block, thereby improving the reliability of the data. The present Express Eye headset system has a sample rate of 500 Hz, if future development of the prediction model only required the analysis of saccade behavioural characteristics i.e. the saccadic errors of the

present prediction model and not saccade dynamics, then a sample rate of 250 Hz or less would be quite sufficient and considerably cheaper than a head set free 500 Hz system.

The results of the present thesis were weakened somewhat, by the low number of dementia patients that were available for participation. Findings for the study would have been much more robust, had the study been able to include more patients. Future study will endeavour to increase numbers to between eighty and one hundred patients to rectify this situation.

## 9.6 Future Research

The present thesis has drawn attention to a number of potential areas for future research. Firstly, studies in the future should consider validating the error correction rate as a diagnostic marker for dementia. This should be carried out with considerably more participants than took part in the present study. The antisaccade model to predict dementia could be applied to these data. An additional element of the study could manipulate temporal, spatial and luminance characteristics of targets in the antisaccade gap task, in an attempt to ascertain the structure of the uncorrected error in dementia, particularly AD. Can error-correction be assisted in dementia patients by manipulating target features, or any of the characteristics mentioned previously? As outlined in Chapter 2 for example, previous studies have indicated that target luminance has a direct effect on saccade latency (Crawford, 1996; Reuter-Lorenz et al., 1991). The time-course of the uncorrected error could feasibly be plotted, by changing the central fixation offset and target SOA through a range of temporal gaps.

It would also be interesting to investigate the FOE for reflexive saccades in greater depth on AD patients. The SOA for this task could also be manipulated to plot the time course of the reflexive saccade FOE, perhaps using SOAs of 0, 100, 200, 300 and 400 msecs. If volitional compensation strategies were being adopted by mild dementia patients in the present thesis, resulting in the large magnitude of FOE at baseline, then an intermediate SOA may

remove the capacity to compensate. Additionally, manipulating target eccentricity many also have an effect on volitional compensation.

Further research could explore the inhibitory effect of a recent distractor (Crawford, Hill & Higham, 2005b) in AD patients. It is postulated that visuomotor centres are linked areas of the brain that identify the spatial location of a distractor. This information is used by the visual system to inhibit eye movements to that location. This task is possibly a somewhat simpler alternative task to the antisaccade task, for AD patients to participate in. The participant simply has to ignore distractors that appear on screen simultaneously with targets. Therefore, in a large study high success and reliability rates could be anticipated. The task comprises two target screens, the first with a target and a distractor and the second with a target only, which can appear at the same location as the target in the previous screen, the location of the distractor in the previous screen, or a new location altogether (three conditions). Error-correction rates could be derived from inhibition errors to target screen one and the latency for saccades to screen two following errors in screen one could also be monitored. For successful trials where the target was located successfully in screen one (and the distractor inhibited) the primary saccade latency for the saccade in target screen two would be the key measure compared across the three experimental conditions. To reiterate, the task should be is easier for patients to do, but similar information to the antisaccade task could be derived with minimal training.

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**INFORMATION SHEET - Eye Movement and Memory Study**

You are being invited to take part in a research study. Before you decide, it is important that you understand why the study is being done and what it will involve. Please take time to read the following information carefully and discuss it with anyone you wish. Please ask if there is anything that is not clear, or if you want more information. Take your time to decide whether or not you want to take part.

**BACKGROUND**

We have recently started a research project looking at memory and concentration. The aim of the study is to look at whether eye movement tests can help us in the assessment of patients with this type of difficulty. A team of local hospital and university researchers have decided to undertake this research to try to help us understand if abnormal eye movements are related to early memory problems. We hope that in the long term this research will help to improve our understanding of diseases associated with memory problems.

**WHAT IS INVOLVED ?**

The research project involves tests looking at how fast and accurately your eyes move in response to the movement of a small target. In order to record your eye movements a small helmet will be placed on your head, and you will be asked to track the target whilst your eye movements are monitored.
Normally the eye movement tests will last for approximately 25 minutes but you can rest at any time if you would like a break.

We will also need to conduct some specific memory tests. This will involve the researcher talking to you and asking you some questions. This will enable us to understand how eye movements are related to memory. These tests may be conducted over several sessions and will take approximately 2 hours to administer. You may rest at any time during the study if you wish.

Your decision on whether to participate in the study will have no bearing on your treatment. You will be free to withdraw from the study at any time should you so wish. Should you choose do so this will have no effect on your treatment or management.

**CONSENT FORM : Eye Movement and Memory Study**

1. **Please read this carefully.**
2. **If there is anything that you do not understand about the information sheet or consent form or you want to ask any questions; please speak to Steve Higham whose number and address is at the bottom of the Information sheet attached.**
3. **Please check that all the information is correct. If it is and you understand the information please tick the boxes ☐ below and sign the form.**

☐ I have read and received a copy of the Research Information Sheet.

☐ I have had the opportunity to ask questions and discuss the study.

☐ I have received enough information about the study.

☐ I have spoken to someone involved in the research.

☐ I understand that I am free to withdraw from the study at any time without giving a reason and without it affecting the future care of either myself or a relative/friend.

☐ I have had enough time to think about the study, talk to relatives and friends about it and to decide, without pressure, if I want to take part.

☐ I agree to take part in the research study.

Name (BLOCK CAPITALS please).....

Signature..... Date.....

Name of witness (BLOCK CAPITALS please).....

Signature of witness.....

RMO (BLOCK CAPITALS please).....

Signature of RMO.....

**Participant History**

Participant: ..... Date: .....

DOB: .....Place of birth: .....

History:.....

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Siblings: None ☐ Brother(s) ☐ Sister(s) ☐ Retirement Age ☐

Single ☐ Married ☐ Widowed ☐ Divorced ☐ Children: None ☐ Boy(s) ☐ Girl(s) ☐

Familial dementia:

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Education:- Primary: Yes ☐ No ☐ Senior: Secondary ☐ Grammar ☐

Starting age ☐ Other ☐

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Left school aged:

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Health:.....

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Medication: .....

Smoking: .....

Alcohol: .....

**Snellen Chart**

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**APPENDIX 5**

# Clinical Dementia Rating Scale

**CDR**

| Category | Healthy CDR 0 | Questionable dementia CDR 0.5 | Mild dementia CDR 1 | Moderate dementia CDR 2 | Severe dementia CDR 3 |
|---|---|---|---|---|---|
| Memory | No memory loss or slight inconstant forgetfulness | Mild consistent forgetfulness; partial recollection of events; 'benign' forgetfulness | Moderate memory loss, more marked for recent events; defect interferes with everyday activities | Severe memory loss; only highly learned material retained; new material rapidly lost | Severe memory loss; only fragments remain |
| Orientation | Fully oriented | | Some difficulty with time relationships; oriented for place and person at examination but may have geographic disorientation | Usually disoriented in time, often to place | Orientation to person only |
| Judgment + problem solving | Solves every day problems well; judgment good in relation to past performance | Only doubtful impairment in solving problems, similarities, differences | Moderate difficulty in handling complex problems; social judgment usually maintained | Severely impaired in handling problems, similarities, differences; social judgment usually impaired | Unable to make judgments or solve problems |
| Community affairs | Independent function at usual level in job, shopping, business and financial affairs, volunteer and social groups | Only doubtful or mild impairment, if any, in these activities | Unable to function independently at these activities though may still be engaged in some; may still appear normal to casual inspection | No pretence of independent function outside home | |
| Home + hobbies | Life at home, hobbies, intellectual interests well maintained | Life at home, hobbies, intellectual interests well maintained or only slightly impaired | Mild but definite impairment of function at home; more difficult chores abandoned; more complicated hobbies and interests abandoned | Only simple chores preserved; very restricted interests, poorly sustained | No significant function in home outside of own room |
| Personal care | Fully capable of self care | | Needs occasional prompting | Requires assistance in dressing, hygiene, keeping of personal effects | Requires much help with personal care; often incontinent |
| Score using box overleaf. Score as 0, 0.5, 1, 2, 3 only if impairement is due to cognitive loss. | | | | | |

Hughes CP *et al.*, *Br J Psychiatry* 1982; 140: 566-572.

# Clinical Dementia Rating Scale cont'd

**CDR**

## ASSIGNING THE CLINICAL DEMENTIA RATING

There are two methods of combining the domain scores to give the overall CDR. The domain scores can either be summed to give the CDR-SB (Sum of Boxes) score, or an algorithm can be used as follows:

The global CDR score is derived from the scores in each of the six categories. Memory (M) is considered the primary category and all others are secondary. CDR = M if at least three secondary categories are given the same score as memory. Whenever three or more secondary categories are given a score greater or less than the memory score, CDR equals the score of the majority of secondary categories that are on whichever side of M has the greatest number of secondary categories. If there are ties in the secondary categories on one side of M, the CDR score closest to M is chosen.

When M = 0.5, CDR = 1 if at least three of the other categories are scored one or greater. If M = 0.5, CDR cannot be 0; it can only be 0.5 or 1. If M = 0, CDR = 0 unless there is questionable impairment in two or more secondary categories, in which case CDR = 0.5.

| Score | 0 | 0.5 | 1 | 2 | 3 |
|---|---|---|---|---|---|
| M | | | | | |
| O | | | | | |
| JPS | | | | | |
| C | | | | | |
| HH | | | | | |
| PC | | | | | |

Mark in only one box for each category. To assign the CDR, see grids on the right. Shaded areas indicate defined range within which the scores of individual subjects must fall to be assigned a given CDR.

**Clinical Dementia Rating** ☐

**CDR 0 – No Dementia**

| Score | 0 | 0.5 | 1 | 2 | 3 |
|---|---|---|---|---|---|
| M | ■ | | | | |
| O | ■ | | | | |
| JPS | ■ | ■ | | | |
| C | ■ | ■ | | | |
| HH | ■ | ■ | | | |
| PC | ■ | | | | |

**CDR 0.5 – Questionable Dementia**

| Score | 0 | 0.5 | 1 | 2 | 3 |
|---|---|---|---|---|---|
| M | | ■ | | | |
| O | ■ | ■ | ■ | | |
| JPS | ■ | ■ | ■ | | |
| C | ■ | ■ | | | |
| HH | ■ | ■ | ■ | | |
| PC | ■ | ■ | | | |

**CDR 1 – Mild Dementia**

| Score | 0 | 0.5 | 1 | 2 | 3 |
|---|---|---|---|---|---|
| M | | | ■ | | |
| O | | | ■ | | |
| JPS | | | ■ | | |
| C | | ■ | ■ | ■ | |
| HH | | ■ | ■ | ■ | |
| PC | ■ | ■ | ■ | ■ | |

**CDR 2 – Moderate Dementia**

| Score | 0 | 0.5 | 1 | 2 | 3 |
|---|---|---|---|---|---|
| M | | | | ■ | |
| O | | | | ■ | |
| JPS | | | ■ | ■ | ■ |
| C | | | | ■ | ■ |
| HH | | | | ■ | ■ |
| PC | | | | ■ | |

**CDR 3 – Severe Dementia**

| Score | 0 | 0.5 | 1 | 2 | 3 |
|---|---|---|---|---|---|
| M | | | | | ■ |
| O | | | | | ■ |
| JPS | | | | | ■ |
| C | | | | | ■ |
| HH | | | | | ■ |
| PC | | | | | ■ |

## Participation Record

Sheet Number:

| No | Surname | First Name(s) | Sex | DOB | Handedness | Occupation | Group (CP/AP) | Snellen L | Snellen R | Eye Movement Tests: Tested | Date | Time | Duration (mins) | Location | Complete | Neuropsychological Ass.: Wisconsin card sorting | Day/Night: Inhibition | Trail Making | Digit Span | Gibson Spiral Maze | Line bisection | Spatial Span | Verbal fluency | Clinical eye movement | Clinical Rating Scales: MMSE | E ADAS-Cog | NART | GDS | CDR | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
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Key: LG = Lytham Greendale Unit / LL = Lytham Lab. / CP = Clinical Psychology / RH = Residential home

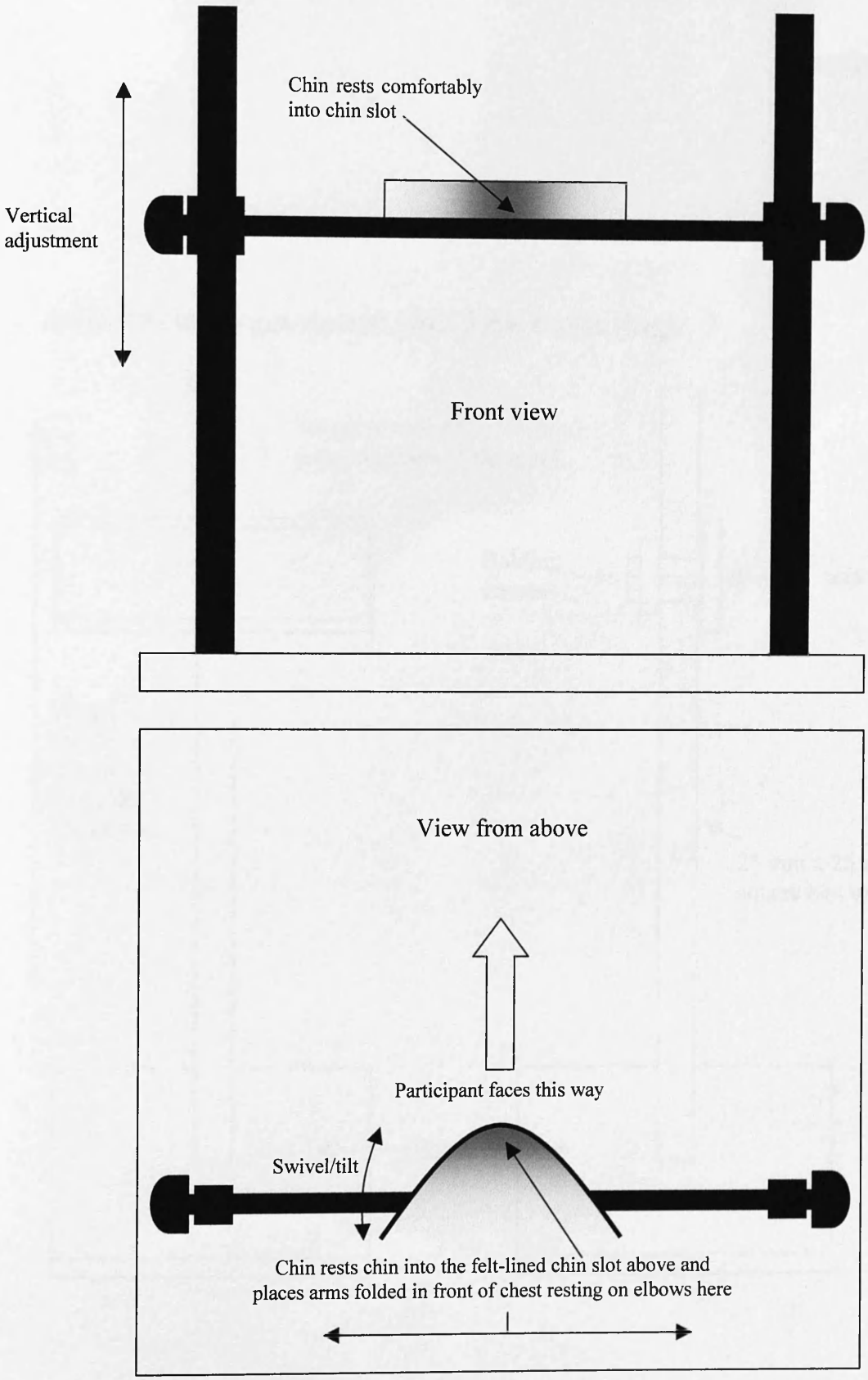
## Clinical antisaccade test report

Name: ..... Stage: ..... Date: .....

**Test sequence:**

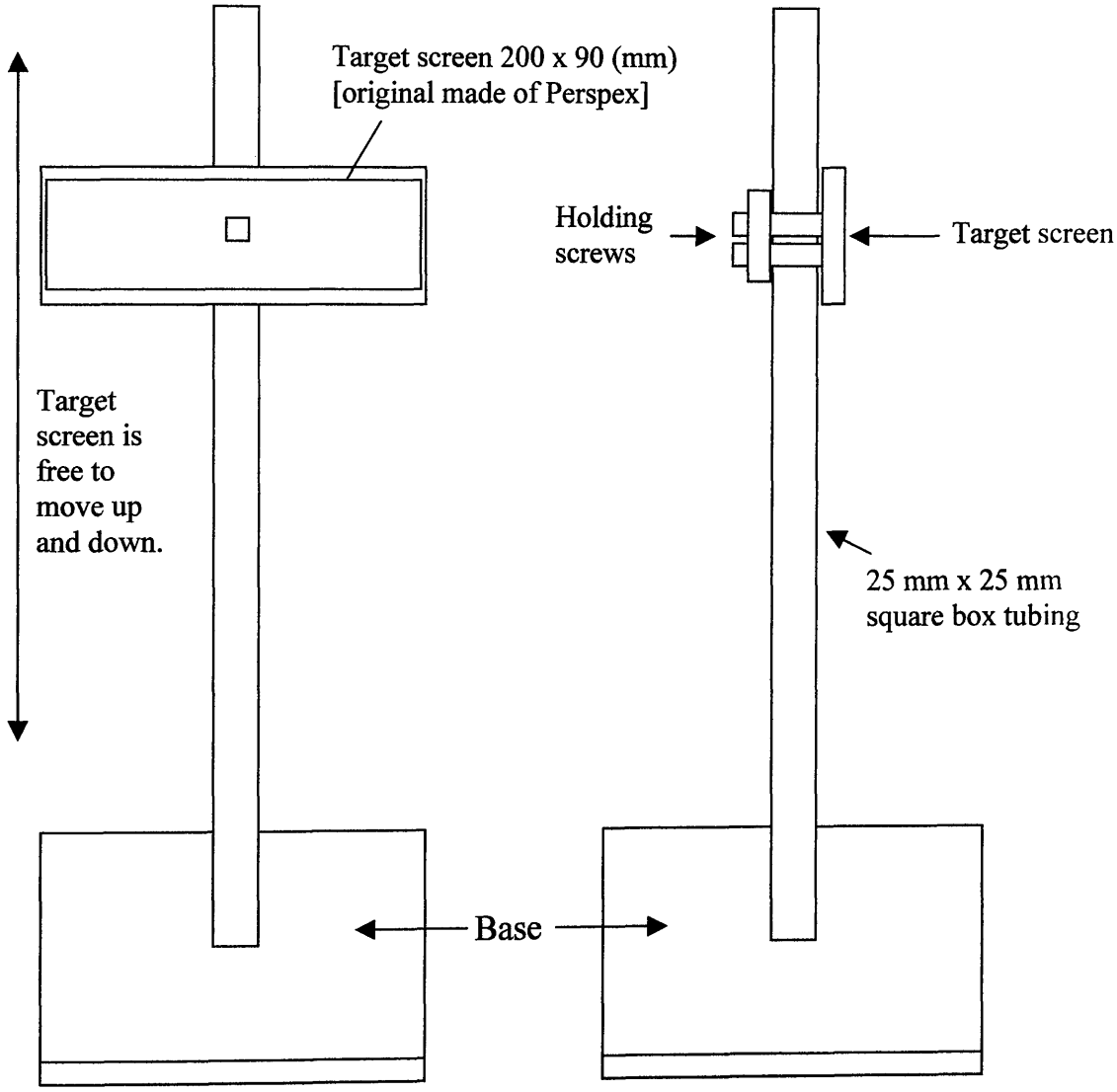
| Trial | | Correct Primary | Corrected error | Uncorrected error |
|---|---|---|---|---|
| 1. | Anti saccade Right (Inhibit left) | | | |
| 2. | Anti saccade Right (Inhibit left) | | | |
| 3. | Anti saccade Left (Inhibit right) | | | |
| 4. | Anti saccade Right (Inhibit left) | | | |
| 5. | Anti saccade Left (Inhibit right) | | | |
| 6. | Anti saccade Left (Inhibit right) | | | |
| 7. | Anti saccade Right (Inhibit left) | | | |
| 8. | Anti saccade Left (Inhibit right) | | | |
| 9. | Anti saccade Right (Inhibit left) | | | |
| 10. | Anti saccade Right (Inhibit left) | | | |
| 11. | Anti saccade Left (Inhibit right) | | | |
| 12. | Anti saccade Left (Inhibit right) | | | |

| | Score | Proportion |
|---|---|---|
| **Correct Primary** = | | |
| **Corrected errors** = | | |
| **Uncorrected errors** = | | |


Chin rests comfortably
into chin slot
Vertical
adjustment
Front view
View from above
Participant faces this way
Swivel/tilt
Chin rests chin into the felt-lined chin slot above and
places arms folded in front of chest resting on elbows here

**Chin Rest**

# Adjustable target screen (for desk mounting)



## Experimental Procedure: Infra-red Oculography

**1 Reflex Saccade Gap** - look at the lights as quickly and accurately as you can

Explain
calibration
Instructions
5 practice trials - stop
24 experimental trials
R/L 50%

Central fixation: 1000ms duration
Target onset: 1200ms; 1798ms duration
Target offset: 2998ms
SRT start: 1200ms
Pause: 1200ms Trial end: 2998ms

**2 Reflex Saccade Overlap** - Look at the lights as quickly and accurately as you can

Explain
calibration
Instructions
5 practice trials - stop
24 experimental trials
R/L 50%

Central fixation: 2998ms duration
Target onset: 1200ms; 1798ms duration
Target offset: 2998ms
SRT start: 1000ms
Pause: 1200ms Trial end: 2998ms

**3 Inhibition of VGR: NO-GO** Look at the central target and ignore the targets that appear to the Right or Left.

Explain
calibration
10 trials
R/L 50%

Central fixation: 1000ms duration
Target onset: 1200ms; 700 ms duration
Target offset: 1900ms
SRT start: 1200ms
Pause: 1000ms Trial end: 1900ms

**4 (GO-Left / NO-GO-Right)** I'm going to give you a rule; If the target appears to the **Right,** I want you to **ignore** it and keep looking straight ahead. But if the target appears on the **Left then look at it.**

Explain
calibration
Instructions
5 practice trials - stop
10 experimental trials
R/L 50%

Central fixation: 1000ms duration
Target onset: 1200ms; 700 ms duration
Target offset: 1900ms
SRT start: 1200ms
Pause: 1000ms Trial end: 1900ms
**Repeat with converse instruction.**
**(GO-Right / NO-GO-Left)**

**5 Anti Saccade: Gap** - Direct your gaze towards a position in space equally distant but in the opposite direction from the target, as quickly and accuratley as you can

Explain
calibration
Instructions
5 practice trials - stop
24 experimental trials
R/L 50%

Central fixation: 1000ms duration
Target onset: 1200ms; 1798ms duration
Target offset: 2998ms
SRT start: 1200ms
Pause: 1200ms Trial end: 2998ms

**6 Anti Saccade: Overlap** - Direct your gaze towards a position in space equally distant but in the opposite direction from the target, as quickly and accuratley as you can

Explain
calibration
Instructions
5 practice trials - stop
24 experimental trials
R/L 50%

Central fixation: 2998ms duration
Target onset: 1200ms; 1798ms duration
Target offset: 2998ms
SRT start: 1000ms
Pause: 1200ms Trial end: 2998ms

# Data input template spreadsheet

**APPENDIX 12**

## Antisaccade: Gap Paradigm

Corrective Error
Uncorrected Error
Anticipatory Saccade

**Participant:** CP33 D4

| Trial | Target Dir | Num Sacs | Primary Lat | Errors | Dur Prim. | Max Vel Prim. | Primary Amp | 2nd Latency | Dur 2nd sac | 2nd Max Vel | 2nd Amp | Amp correction | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 1 | 2 | 326 | Corrected error | 59 | -114.2 | -3.87 | 651 | 98 | 262.2 | 12.95 | 9.1 | Corrected error |
| 2 | 1 | 1 | 295 | Correct | 75 | 115.6 | 4.29 | | | | | | Correct |
| 3 | 1 | 2 | 223 | Correct | 69 | 168.9 | 6.4 | 383 | 45 | -93.3 | -2.69 | 3.7 | Correct |
| 4 | 1 | 2 | 146 | Corrected error | 58 | -122.3 | -4.16 | 374 | 81 | 150.9 | 7.07 | 2.9 | Corrected error |
| 5 | 1 | 2 | 234 | Correct | 77 | 128.9 | 5.12 | 424 | 34 | -75.6 | -1.25 | 3.9 | Correct |
| 6 | 1 | 1 | 257 | Correct | 64 | 106.7 | 4.15 | | | | | | Correct |
| 7 | 1 | 1 | 286 | Correct | 65 | 116.3 | 4.57 | | | | | | Correct |
| 8 | 1 | 1 | 272 | Correct | 71 | 80 | 2.91 | | | | | | Correct |
| 9 | 1 | 1 | 244 | Correct | 75 | 102.2 | 3.49 | | | | | | Correct |
| 10 | 1 | 2 | 256 | Correct | 85 | 160 | 7.92 | 365 | 76 | -155.6 | -5.97 | 2.0 | Correct |
| 11 | 1 | 1 | 217 | Correct | 77 | 84.4 | 3.26 | | | | | | Correct |
| 12 | 1 | 2 | 340 | Correct | 64 | 120 | 4.69 | 497 | 34 | -62.2 | -1.52 | 3.2 | Correct |

| Target Direction Left | Rate | Latency | Err Latency | Dur Prim. | Max Vel Prim. | amplitude | Latency Sec | | | 2nd Amp | Secondary FFP |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Correct Primary | 10 | 262.4 | | 72.2 | 118.3 | 4.7 | | | | | |
| Corrective errors | 2 | | 236.0 | | | -4.0 | 512.5 | | | 10.0 | 6.0 |
| Uncorrected errors | 0 | | #DIV/0! | | | #DIV/0! | | | | | |
| Un/Cor error means | | | #DIV/0! | | | #DIV/0! | | | | | |
| No Saccade | 0 | | | | | | | | | | |
| Anticip Sacs. | 0 | | | | | | | | | | |
| Error Sub-total L | 2 | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 13 | 2 | 2 | 77 | Anticipatory | 61 | 62.2 | 2.19 | 286 | 78 | -191.6 | -7.28 | -5.1 | Anticipatory |
| 14 | 2 | 2 | 205 | Correct | 72 | -154.9 | -5.76 | 629 | 48 | 48.9 | 1.52 | -4.2 | Correct |
| 15 | 2 | 2 | 311 | Correct | 76 | -163.1 | -6.34 | 523 | 57 | 61.2 | 1.88 | -4.5 | Correct |
| 16 | 2 | 2 | 185 | Corrected error | 60 | 111.1 | 3.82 | 408 | 100 | -191.6 | -8.37 | -4.6 | Corrected error |
| 17 | 2 | 3 | 108 | Correct | 39 | -65.2 | -1.66 | 169 | 16 | 32.6 | 0.34 | -1.3 | Correct |
| 18 | 2 | 2 | 260 | Correct | 70 | -163.1 | -5.99 | 636 | 35 | 48.9 | 1.15 | -4.8 | Correct |
| 19 | 2 | 2 | 255 | Correct | 80 | -146.8 | -6.23 | 579 | 46 | 57.1 | 1.66 | -4.6 | Correct |
| 20 | 2 | 2 | 147 | Corrected error | 45 | 71.1 | 2.11 | 455 | 91 | -183.5 | -8.03 | -5.9 | Corrected error |
| 21 | 2 | 2 | 157 | Correct | 84 | -146.8 | -5.87 | 562 | 36 | 44.9 | 1.15 | -4.7 | Correct |
| 22 | 2 | 2 | 169 | Corrected error | 79 | 106.7 | 4.27 | 445 | 99 | -181.9 | -7.88 | -3.6 | Corrected error |
| 23 | 2 | 2 | 241 | Correct | 86 | -154.9 | -6.8 | 565 | 52 | 46.9 | 1.44 | -5.4 | Correct |
| 24 | 2 | 2 | 219 | Correct | 79 | -203.9 | -8.76 | 368 | 67 | 114.2 | 3.94 | -4.8 | Correct |

| Target Direction Right | Rate | Latency | Err Latency | Dur Prim. | Max Vel Prim. | amplitude | Latency Sec | | | 2nd Amp | Secondary FFP |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Correct Primary | 8 | 219.5 | | 73.3 | -149.8 | -5.9 | | | | | |
| Corrective errors | 3 | | 167.0 | | | 3.4 | 436.0 | | | -8.1 | -4.7 |
| Uncorrected errors | 0 | | #DIV/0! | | | #DIV/0! | | | | | |
| Un/Cor error means | | | #DIV/0! | | | #DIV/0! | | | | | |
| No Saccade | 0 | | | | | | | | | | |
| Anticip Sacs. | 1 | | | | | | | | | | |
| Error Sub-total R | 3 | | | | | | | | | | |

| | |
|---|---|
| Total Correct Primary Saccades | 18 |
| Total Errors (L+R) | 5 |
| Total Corrective Errors | 5 |
| Total Uncorrected Errors | 0 |
| Total No Saccade | 0 |
| Total Anticip Sacs. | 1 |
| Mean Corrective details | |
| Total Trials | 24 |

| | | |
|---|---|---|
| | 474.3 | |
| | 9.1 | 5.3 |

# Standardised Mini-Mental State Examination (SMMSE)

*I am going to ask you some questions and give you some problems to solve. Please try to answer as best you can.*

| | | Max Score |
|---|---|---|
| 1. | (Allow 10 seconds for each reply) | |
| a) | *What year is this?* (accept exact answer only) | **1** |
| b) | *What season is this?* (during last week of the old season or first week of new season, accept either season) | **1** |
| c) | *What month of the year is this?* (on the first day of new month, or last day of the previous month, accept either) | **1** |
| d) | *What is today's date?* (accept previous or next date, e.g. on the 7th accept the 6th or 8th) | **1** |
| e) | *What day of the week is this?* (accept exact answer only) | **1** |
| 2. | (Allow 10 seconds for each reply) | |
| a) | *What country are we in?* (accept exact answer only) | **1** |
| b) | *What province / state / country are we in?* (accept exact answer only) | **1** |
| c) | *What city / town are we in?* (accept exact answer only) | **1** |
| d) | **(In clinic)** *What is the name of this hospital / building?* (accept exact name of hospital or institution only) | **1** |
| | **(In home)** *What is the street address of this house?* (accept exact name of hospital or institution only) | **1** |
| e) | **(In clinic)** *What floor of the building are we on?* (accept exact answer only) | **1** |
| | **(In home)** *What room are we in?* (accept exact only) | **1** |

| | | Max Score |
|---|---|---|
| 3. | *I am going to name 3 objects. After I have said all three objects, I want you to repeat them. Remember what they are because I am going to ask you to name them again in a few minutes.* | **3** |

(say them slowly at approximately 1 second intervals)

**Ball** **Car** **Man**

**For repeated use:**

| | | |
|---|---|---|
| **Bell** | **Jar** | **Fan** |
| **Bill** | **Tar** | **Can** |
| **Bull** | **War** | **Pan** |

*Please repeat the 3 items for me.*
(score 1 point for each correct reply on the first attempt)

Allow 20 seconds for reply, if subject did not repeat all 3, repeat until they are learned or upto a maximum of 5 times.

**4.** *Spell the word **WORLD**.* **5**
(you may help subject to spell world correctly)

Say: *now spell it backwards please.* Allow 30 seconds to spell backwards.
(If the subject cannot spell world even with assistance – score 0)

**5.** *Now what were the three objects that I asked you to remember?* **3**

**Ball** **Car** **Man**

Score 1 point for each correct response regardless of Order, allow 10 seconds.

**6.** Show wrist watch. Ask: *What is this called?* **1**

Score 1 point for correct response. Accept "wristwatch" or "Watch".
Do not accept "clock", "time", etc. (allow 10 seconds)

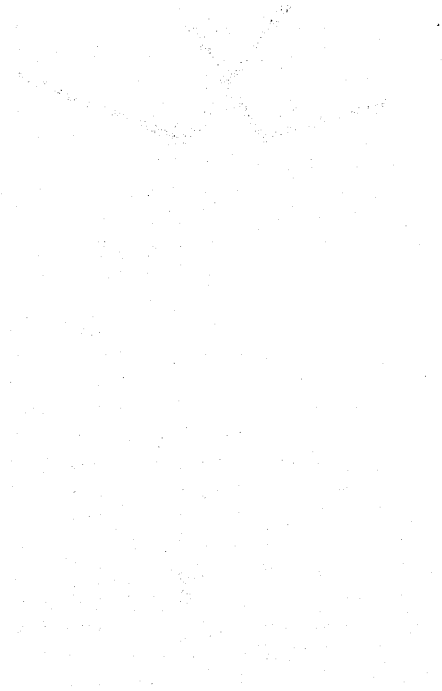
7. Show pencil. Ask: *What is this called?* **1**

Score 1 point for correct response. Accept "pencil" only,
score 0 for pen.

8. *I'd like you to repeat a phrase after me: "no if's, and's or but's".* **1**
(allow 10 seconds for response. Score one point for a correct repetition.
Must be **exact**, e.g. *"no if's or but's"* – score 0)

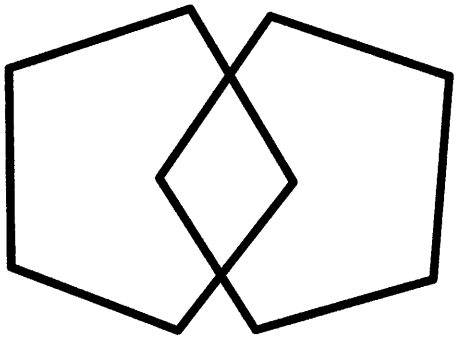
| | | Max Score |
|---|---|---|
| 9. | *Read the words on this page and do what it says:*<br><br>Hand the subject the sheet of paper with CLOSE YOUR EYES on it.<br><br>**CLOSE YOUR EYES**<br><br>If subject just reads and does not then close eyes – you may repeat: *read the words on this page and then do what it says* to a maximum of 3 times. Allow 10 seconds, score 1 point **only** if subject closes eyes. Subject does not have to read aloud. | **1** |
| **10.** | Ask if the subject is right or left handed. Alternate right/left hand in statement, e.g. if the subject is right-handed say *Take this paper in your left hand...* Take a piece of paper – hold it up in front of subject and say the following:<br><br>*"Take this paper in your right/left hand, fold the paper in half once with both hands and put the paper down on the floor."*<br><br>Takes paper in correct hand<br>Folds paper in half<br>Puts it on the floor<br><br>Allow 30 seconds. Score 1 point for each instruction correctly executed. | **3**<br><br>**1**<br>**1**<br>**1** |
| **11.** | Hand subject a pencil and paper.<br><br>*Write any complete sentence on that piece of paper.*<br><br>Allow 30 seconds. Score 1 point. The sentence should make Sense. Ignore spelling errors. | **1** |
| **12.** | Place design, pencil, eraser and paper in front of the subject.<br><br>Say: *"Copy this design please."*<br><br>Allow multiple tries until the patient is finished and hands it back. Score 1 point for correctly copied diagram. The subject must have drawn a 4-sided figure between two 5-sided figures. Maximum time – 1 minute. | **1** |
| | **Total Test Score** | **30** |

# CLOSE YOUR EYES



Writing:

Copy design:



# European Alzheimer's Disease Assessment Scale
# Cognitive sub-test

**Participant:** ..... **Date:** .....

Euro-ADAS

**1 Word-recall task**

SCORE ❑
(average number incorrect)

The patient reads 10 high-imagery words exposed for 2 seconds each. The patient then recalls the words aloud. One trail of reading and recall is given. The score equals the number of words not recalled (maximum - 10).

| TRIAL 1 | | |
|---|---|---|
| **WORD** | **Yes** | **No** |
| BOTTLE | | |
| POTATO | | |
| GIRL | | |
| TEMPLE | | |
| STAR | | |
| ANIMAL | | |
| FOREST | | |
| LAKE | | |
| CLOCK | | |
| OFFICER | | |
| **TOTAL INCORRECT (TOTAL "NO")** | | |

# Euro-ADAS

## 2. Commands

Receptive speech is assessed on the patient's ability to carry out one-to-five-step commands (1). The command may be repeated once in its entirety. Check each command successfully completed by the patient.

| Response Correct? YES | NO | |
|---|---|---|
| | | 1. Make a **fist** (one-step command) |
| | | 2. Point to the **ceiling**, then to the **floor** (two-step command) |

Line up a pencil, watch and card, in that order, on a table in front of the patient.

| Response Correct? YES | NO | |
|---|---|---|
| | | 3. Put the **pencil on top of the card**, then **put it back** (three-step command) |
| | | 4. Put the **watch on the other side of the pencil** and then **turn over the card** (four-step command) |
| | | 5 **Tap each shoulder twice** with **two fingers**, keeping your **eyes shut** (five-step command) |

Each command scored is as a whole. Check the rating corresponding to the highest number of commands correctly performed. Record the number corresponding with that rating as the SCORE.

- ❑ 0 = Five commands correct
- ❑ 1 = Four commands correct
- ❑ 2 = Three commands correct
- ❑ 3 = Two commands correct
- ❑ 4 = One command correct
- ❑ 5 = All commands incorrect

SCORE ❑

# Euro-ADAS

## 3 Naming finger/objects

a. The patient is asked to name the fingers of his/her dominant hand. Check "Yes" or "No" per patient response.

| Finger | Response Correct? | |
|---|---|---|
| | Yes | No |
| Thumb<br>Middle<br>Ring | | |

| Finger | Response Correct? | |
|---|---|---|
| | Yes | No |
| Index<br>Pinky or little finger | | |

| | |
|---|---|
| 3a. Number incorrectly named | |

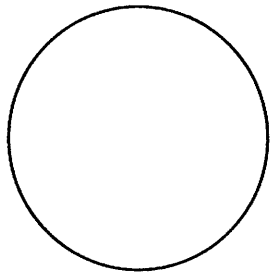
b. The patient is then asked to name 12 randomly presented real objects, whose frequency values* are: high, medium and low. Standard clues may be used to assist those patients having difficulty. The objects and their clues are listed below.

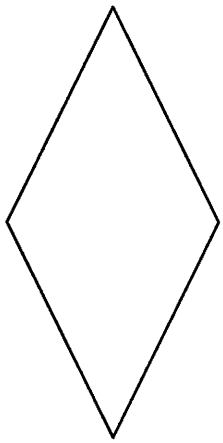
| Object-Clue | Response Correct? | |
|---|---|---|
| | Yes | No |
| Whistle - makes sound when blown<br>Comb - used on hair<br>Tweezers - use to pick up small objects<br>Flower (plastic) - grows in garden<br>Mask - hides your face<br>Wallet - holds your money<br>Bed - (doll house furniture) - used for sleeping<br>Scissors - cuts paper<br>Harmonica - a musical instrument<br>Pencil - used for writing<br>Rattle - a baby's toy<br>Stethoscope - doctor uses it to listen to your heart | | |

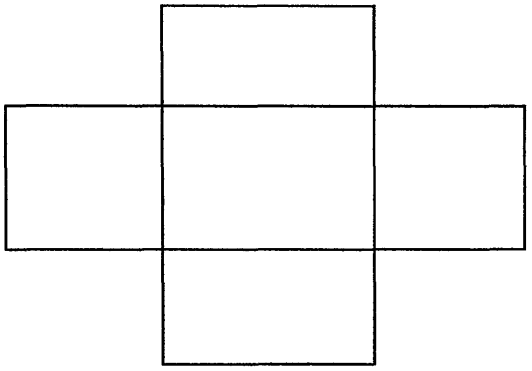
| | |
|---|---|
| 3b. Number incorrectly named | |

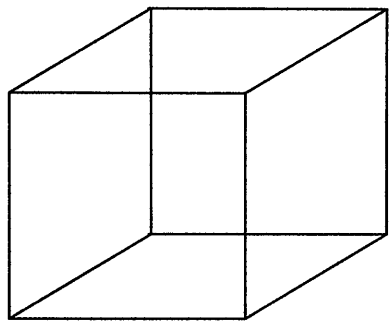
Check the rating corresponding to the number of items (objects and/or fingers) named incorrectly (3a & 3b)

- ☐ 0 = 0-2 items incorrect
- ☐ 1 = 3-5 items incorrect
- ☐ 2 = 6-8 items incorrect
- ☐ 3 = 9-11 items incorrect
- ☐ 4 = 12-14 items incorrect
- ☐ 5 = 15-17 items incorrect









4. **Drawing**

## GEOMETRIC DESIGNS SCORESHEET

| | |
|---|---|
| All four drawings correct | = 0 |
| One drawing incorrect | = 1 |
| Two drawings incorrect | = 2 |
| Three drawings incorrect | = 3 |
| Four drawings incorrect | = 4 |
| No drawing attempted | = 5 |

**TOTAL SCORE FOR GEOMETRIC DESIGN** ❑

# Euro-ADAS

## 5. Ideational Praxis

SCORE ❑

The patient is given an 8★ x 11' sheet of paper and a long envelope. The patient is instructed to pretend to send the letter to himself/herself. The patient is told to put the paper into the envelope, seal it, address it to himself/herself, and indicate where to place the stamp. If the patient forges part of the task, re-instruction is given, one task at a time. Impairment on this item should reflect dysfunction in executing an over learned task only and not recall difficulty.

| TASK | Completed Correctly? | |
|---|---|---|
| | Yes | No |
| Fold letter<br>Put letter in envelope<br>Seal envelope<br>Addressing of envelope<br>Put stamp on envelope | | |
| Number Incorrect ("No") | | |

Check the rating which describes the patient's performance on this exercise. Record the number associated with that description as the SCORE.

- ❑ 0 = all task completed successfully
- ❑ 1 = difficulty or failure to perform 1 task
- ❑ 2 = difficulty or failure to perform 2 tasks
- ❑ 3 = difficulty or failure to perform 3 tasks
- ❑ 4 = difficulty or failure to perform 4 tasks
- ❑ 5 = difficulty or failure to perform 5 tasks

## 6. Orientation

SCORE ❑

The components of orientation and the acceptable range of answers for each component are given below. Enter the total number of incorrect responses are the SCORE for this section.

| ITEM | Response Correct? | |
|---|---|---|
| | Yes | No |
| Person (self, full name)<br>Date (day's date ± 1 day)<br>Month (current month)<br>Year (current year)<br>Day of the Week (current day)<br>Season (current season or within 1 week of upcoming season or within 2 weeks of previous season)<br>Time of the day (current time ± 1 hour)<br>Place (partial or full name of site) | | |
| **Total Number Incorrect Responses ("No")** | | |

# Euro-ADAS

## 7 Word-recognition task

SCORE ❑

The patient reads aloud 12 high-imagery words. These are then randomly mixed with 12 words the patient has not seen. The patient indicates whether or not the word was shown previously. The score equals the number of incorrect responses (maximum score allowed = 12). Place a mark next to the work if instructions repeated.

List words are LARGE and BOLD, and new words are SMALL and ITALIC.

| TRIAL 1 | | |
|---|---|---|
| **WORD** | **Answer Correct?** | |
| | **Yes** | **No** |
| **COST** | | |
| *NATION* | | |
| **CHIMNEY** | | |
| *SPARROW* | | |
| **DAMAGES** | | |
| *TRAFFIC* | | |
| **SANDWICH** | | |
| *SERVICE* | | |
| *SHELL* | | |
| **SOLUTION** | | |
| *YARD* | | |
| **TUBE** | | |
| *BODY* | | |
| *GROUND* | | |
| *STICK* | | |
| **ENGINE** | | |
| **RICHES** | | |
| **GRAVITY** | | |
| *SUMMER* | | |
| *WISDOM* | | |
| *MAN* | | |
| **MEAL** | | |
| **PASSENGER** | | |
| **ACID** | | |
| **Number Incorrect** | | |

# Euro-ADAS

8. **Spoken-language ability** (check the box which best describes the patient's capabilities. Record the number associated with that description as the SCORE).

SCORE ❑

This is a global rating of the quality of speech, ie. clarity and ease or difficulty in making oneself understood. Quality is not rated on this item.

- ❑ 0 = none; patient speaks clearly and/or is understandable
- ❑ 1 = very mild; one instance of lack of understandability
- ❑ 2 = mild; subject has difficulty < 25% of the time
- ❑ 3 = moderate; subject has difficulty 25-50% of the time
- ❑ 4 = moderately severe; subject has difficulty ≥ 50% of the time
- ❑ 5 = severe; one or two word utterances; fluent, but empty speech; mute

9. **Comprehension of spoken language** (check the box which best describes the patient's capabilities. Record the number associated with the description as the SCORE.

SCORE ❑

This rating evaluates the patient's ability to understand speech. Do not include responses to commands.

- ❑ 0 = none; patient understands
- ❑ 1 = very mild; one instance of misunderstanding
- ❑ 2 = mild; 3-5 instances of misunderstanding
- ❑ 3 = moderate; requires several repetitions and rephrasing
- ❑ 4 = moderately severe; patient only occasionally responds correctly, ie. yes/no questions
- ❑ 5 = severe; patient rarely responds to questions appropriately, not due to poverty of speech

# Euro-ADAS

10. **Remembering test instructions** (check the box which best describes the patient's capabilities. Record the number associated with that description as the SCORE.

SCORE ❑

The patient's ability to remember the requirements of the Word-recognition task (task #7) is evaluated. On each recognition trail, the patient is asked prior to presentation of the first two words, "Did you see this work before or is this a new word?" For the third word, the patient is asked, "How about this one?" If the patient responds appropriately, ie, "yes" or "no", then recall of instructions is accurate. If the patient fails to respond, this signifies that the instructions have been forgotten. Then instruction is repeated. The procedure used for the third word is repeated for words 4-24. Each instance of recall failure is noted.

- ❑ 0 = none; patient remembers instructions
- ❑ 1 = very mild; forgets once
- ❑ 2 = mild; must be reminded 2 times
- ❑ 3 = moderate; must be reminded 3 or 4 times
- ❑ 4 = moderately severe; must be reminded 5 or 6 times
- ❑ 5 = severe; must be reminded 7 or more times

11. **Word-finding difficulty in spontaneous speech** (check the box which best describes the patient's capabilities. Record the number associated with that description as the SCORE.

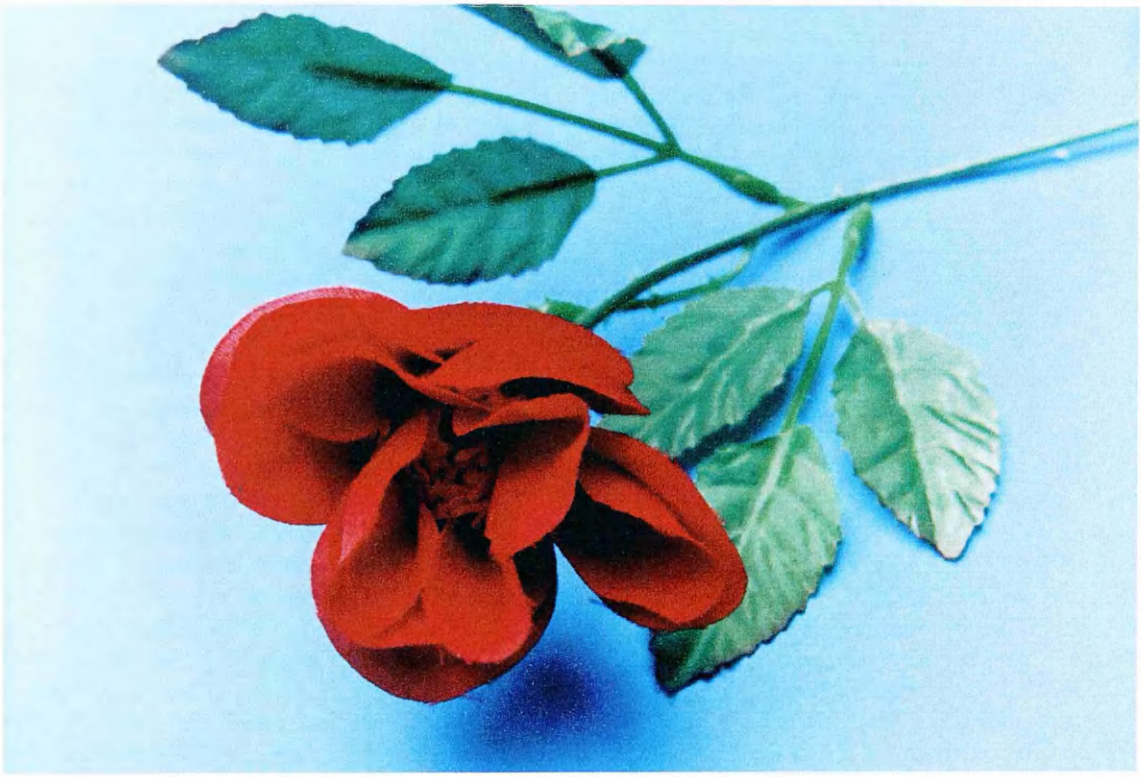
SCORE ❑

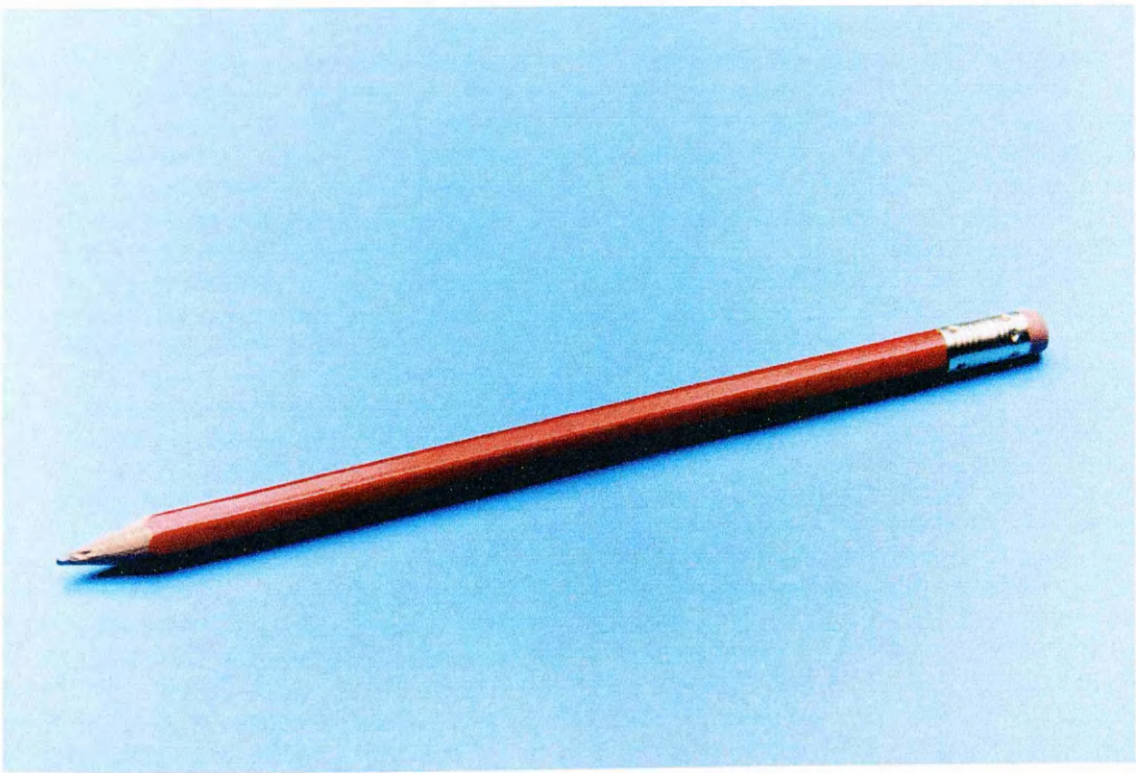
Determines the level of difficulty the patient has in finding the desired word in spontaneous speech. The problem may be overcome by circumlocution, ie, giving explanatory phrases or nearly satisfactory synonyms. Do not include finger and object naming in this rating.

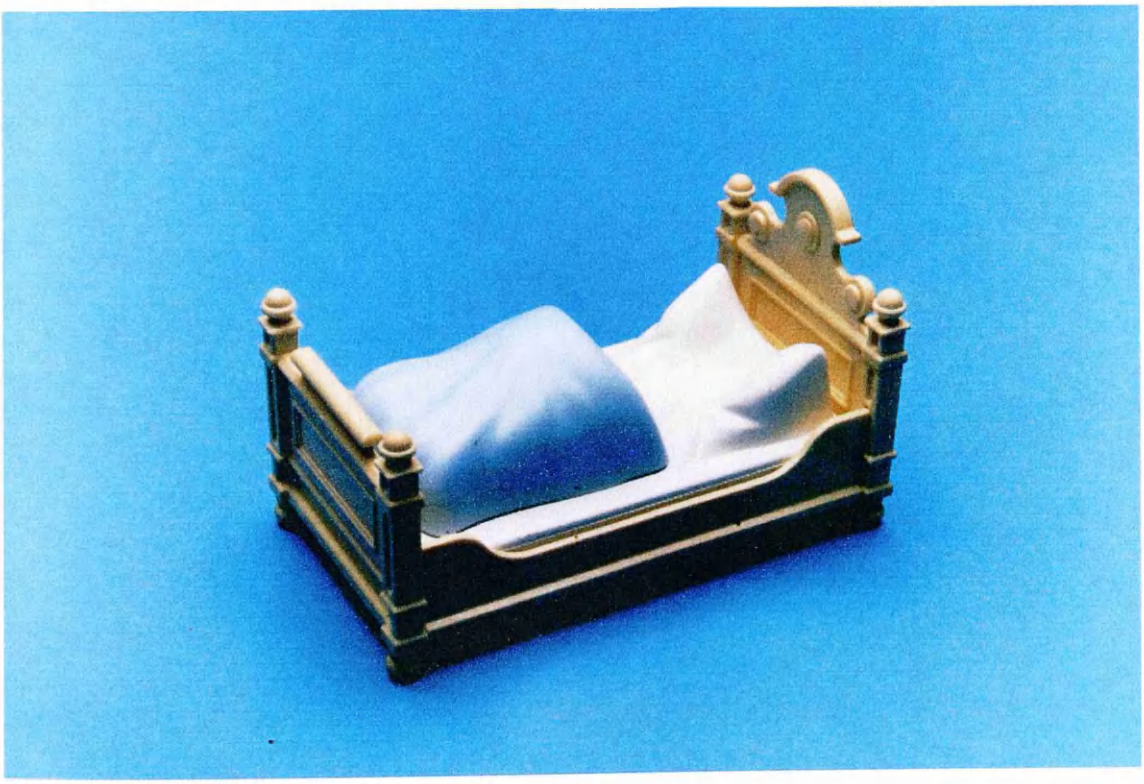
- ❑ 0 = none; no instances of difficulty
- ❑ 1 = very mild; one or two instances, not clinically significant
- ❑ 2 = mild; noticeable circumlocution or synonym substitution
- ❑ 3 = moderate; loss or word without compensation on occasion
- ❑ 4 = moderately severe; frequent loss or words without compensation
- ❑ 5 = severe; nearly total loss of content words; speech sounds empty; one- or two- word utterances

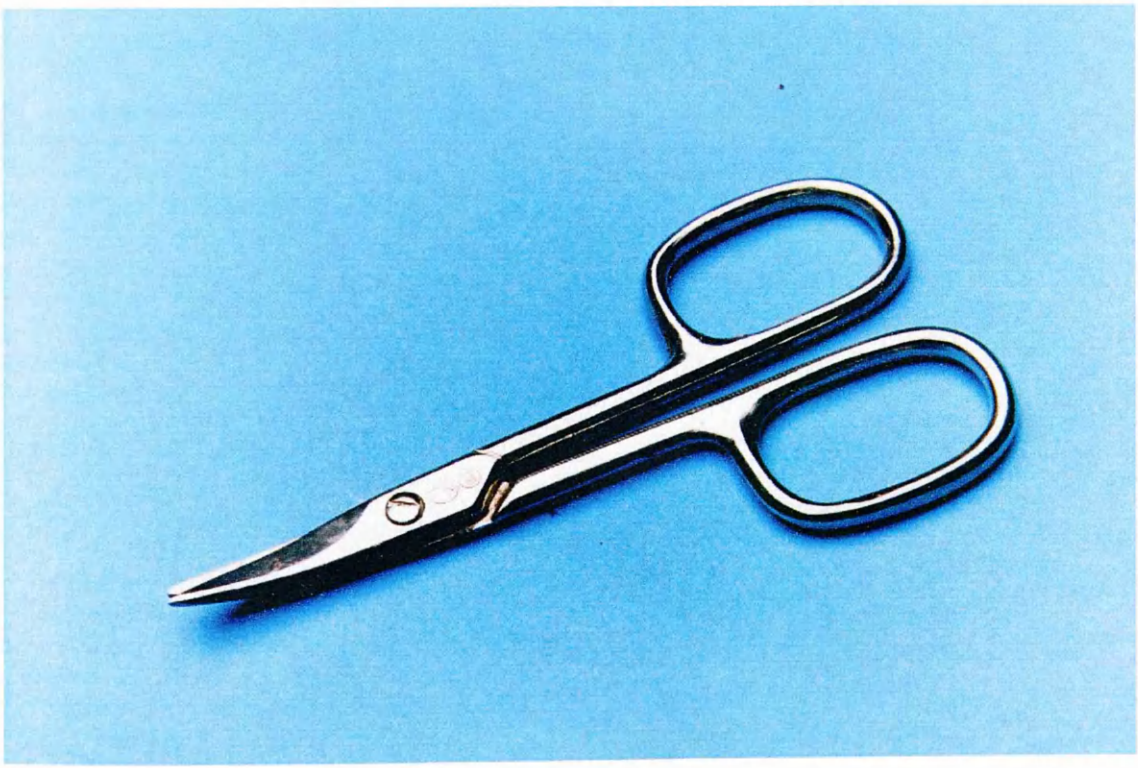
## Euro-ADAScog: Visual Stimuli for Object Naming Task

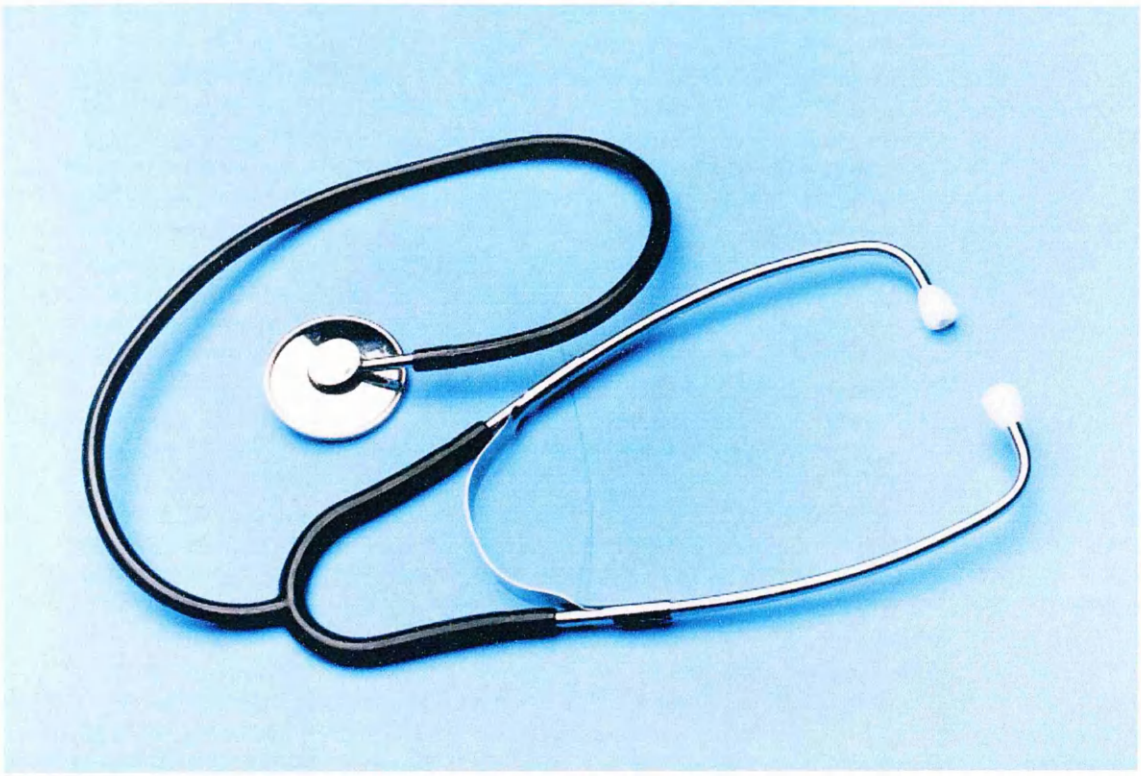
## Euro-ADAScog: Visual Stimuli for Object Naming Task

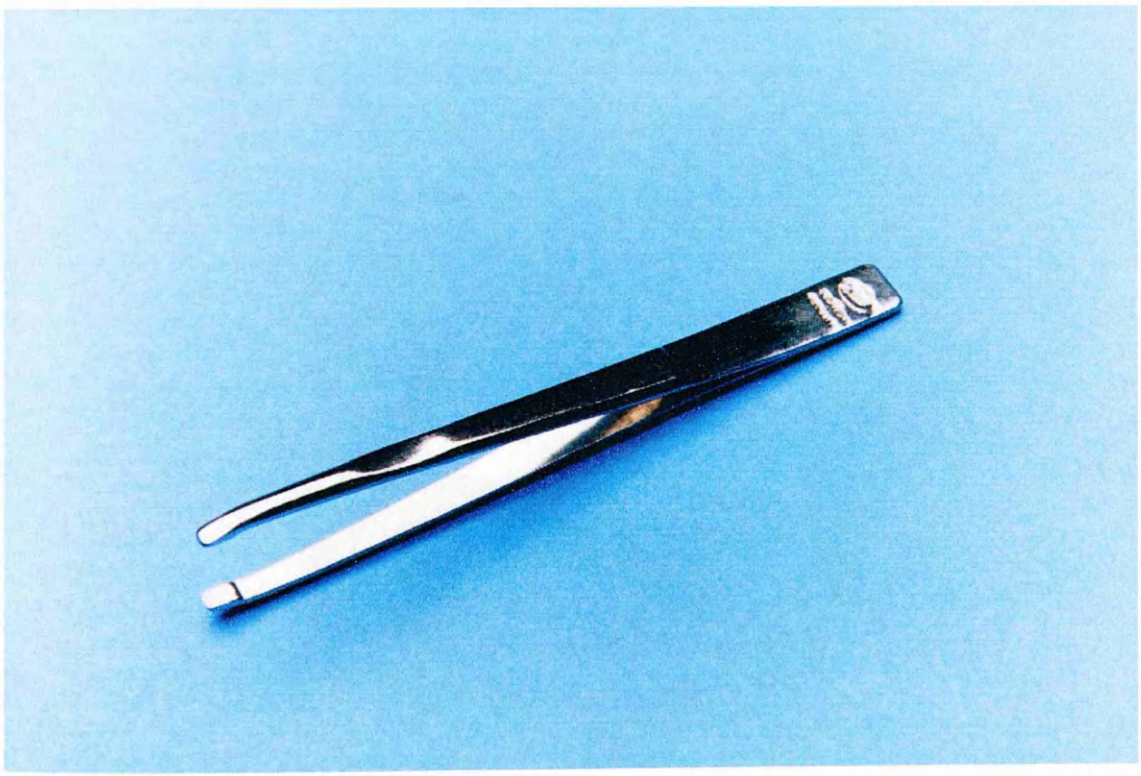




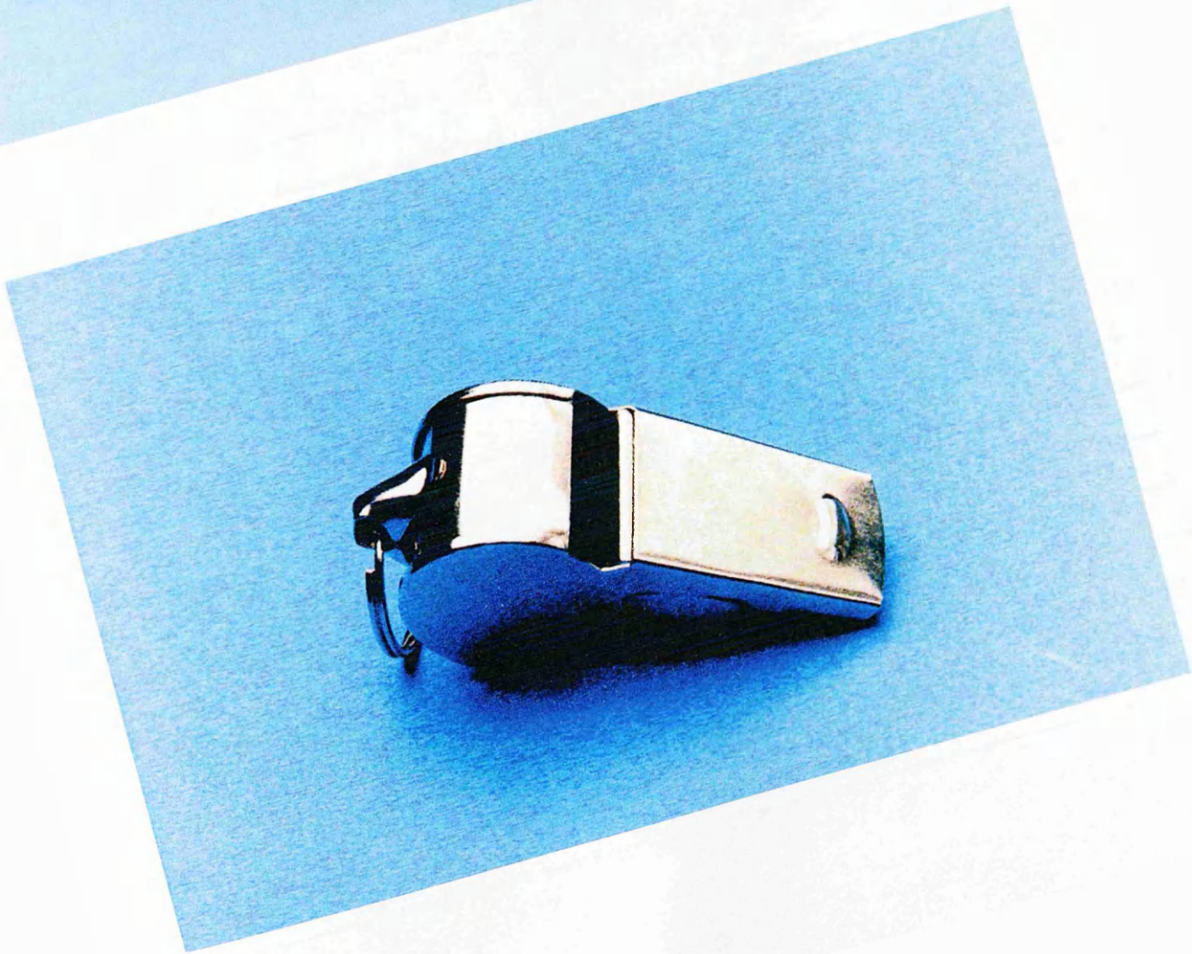








# APPENDIX 14.1

# National Adult Reading Test (NART)

**Response Sheet**

**Name:** ..... **Date:** .....

| | Errors |
|---|---|
| CHORD | |
| ACHE | |
| DEPOT | |
| AISLE | |
| BOUQUET | |
| PSALM | |
| CAPON | |
| DENY | |
| NAUSEA | |
| DEBT | |
| COURTEOUS | |
| RAREFY | |
| EQUIVOCAL | |
| NAIVE | |
| CATACOMB | |
| GAOLED | |
| THYME | |
| HEIR | |
| RADIX | |
| ASSIGNATE | |
| HIATUS | |
| SUBTLE | |
| PROCREATE | |
| GIST | |
| GOUGE | |

| | Errors |
|---|---|
| SUPERFLUOUS | |
| SIMILE | |
| BANAL | |
| QUADRUPED | |
| CELLIST | |
| FACADE | |
| ZEALOT | |
| DRACHM | |
| AEON | |
| PLACEBO | |
| ABSTEMIOUS | |
| DETENTE | |
| IDYLL | |
| PUERPERAL | |
| AVER | |
| GAUCHE | |
| TOPIARY | |
| LEVIATHAN | |
| BEATIFY | |
| PRELATE | |
| SIDEREAL | |
| DEMESNE | |
| SYNCOPE | |
| LABILE | |
| CAMPANILE | |

**Verbal Fluency** **Date: ..... Participant No: .....**

The test requires the participant to produce as many words as possible beginning with the letters 'S' and 'P' each within a one minute time period.

Say: *"I am going to say a letter from the alphabet and I want you to name as many words as you can that begin with the letter, calling the words out loud as fast as you can. But you have not to use numbers or the names of places and people. For example, if I say the letter 'A' you could say: apple, able or attic. Can you think of any other words that begin with the letter 'A'?"*

Wait for the participant to give 2 examples, if successful indicate that the responses were correct and proceed with the test. If inappropriate words or replies are given, or failure to respond, repeat the instructions.

When satisfied begin the task:

Say: *"That is fine. Now I would like you to name as many words as you can beginning with another letter, the letter 'S'. You will have one minute and I want you to tell me all the words you can think of beginning with 'S' in one minute".*
*"Are you ready, begin."*

**S (60 secs.)**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |

Total:
Intrusions:

**Reneat test this time with the letter 'P'**

**P (60 secs.)**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |

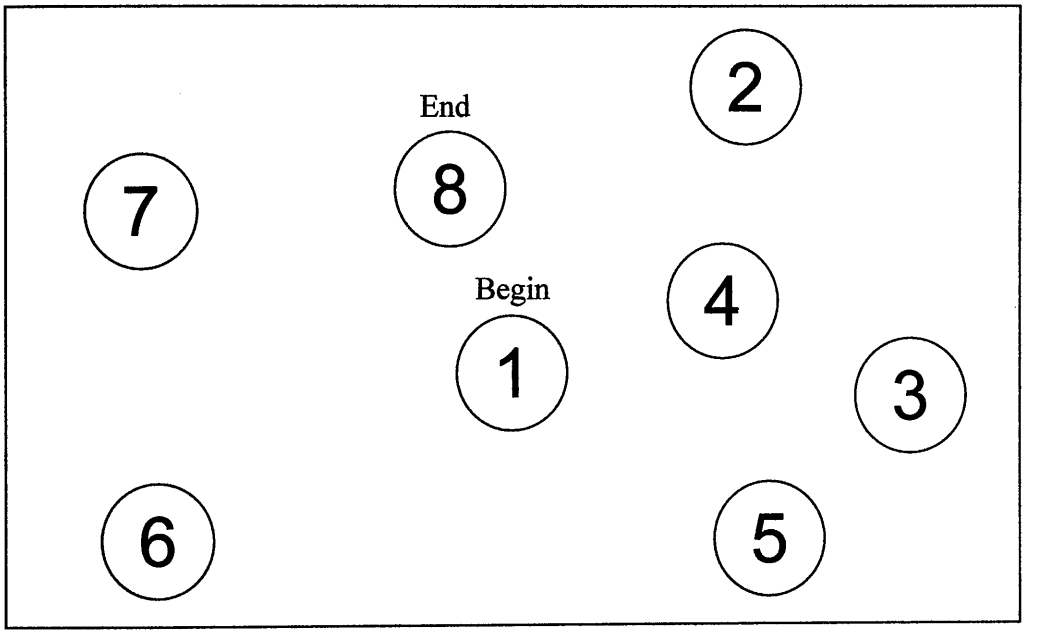
Total:
Intrusions:

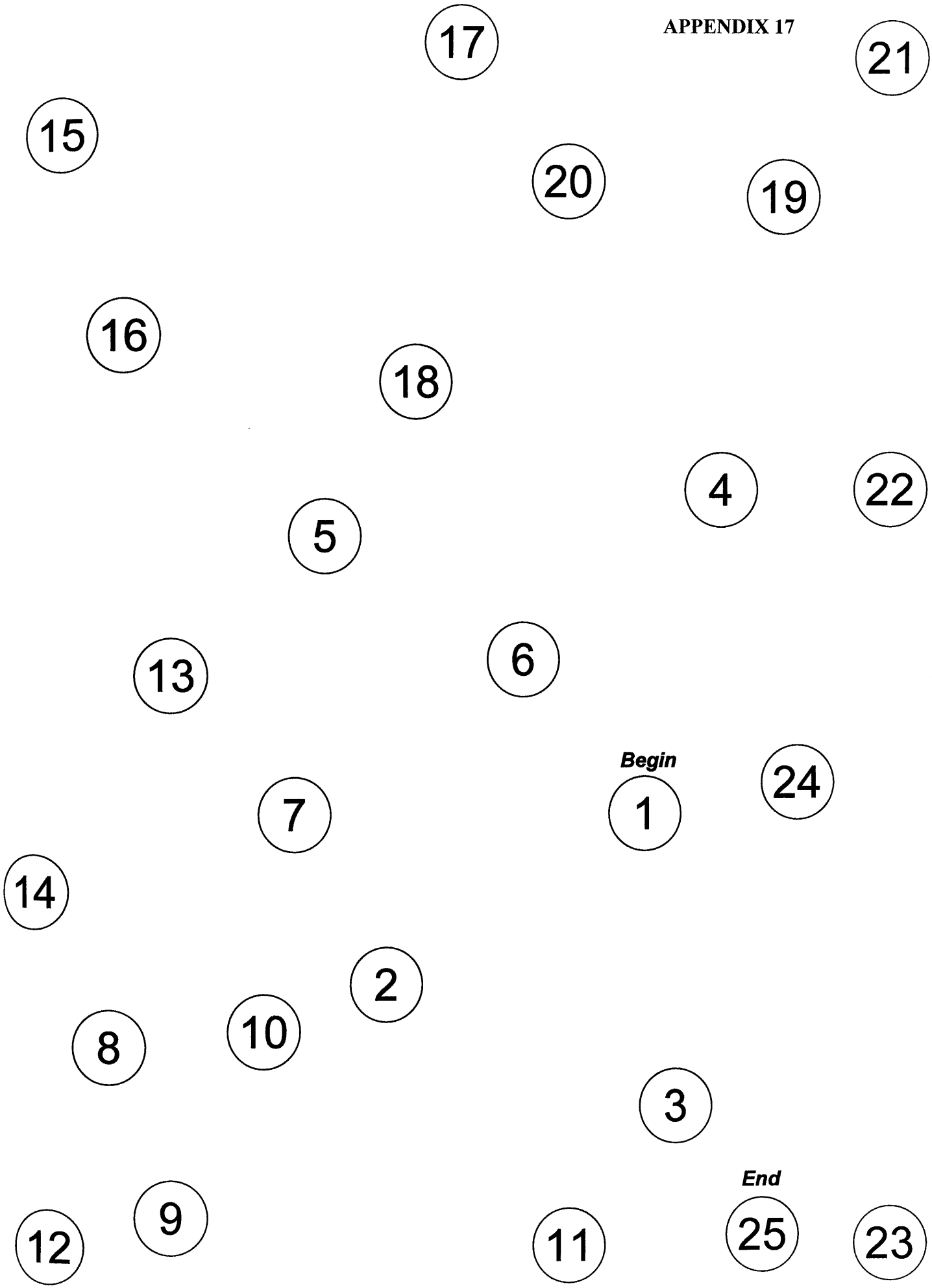
Grand Mean:

# TRAIL MAKING

## Form A

SAMPLE

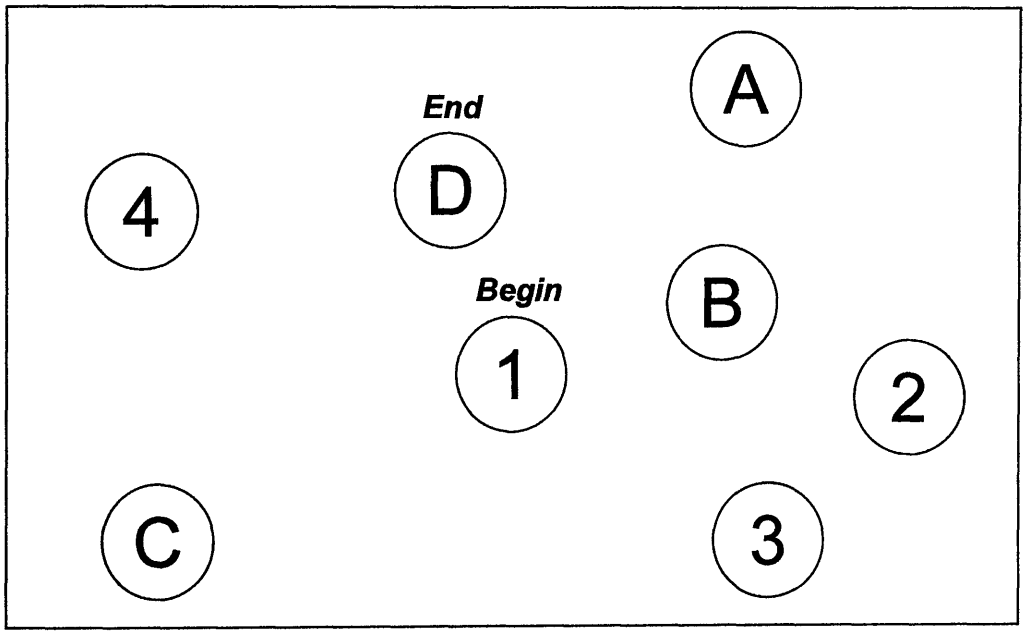


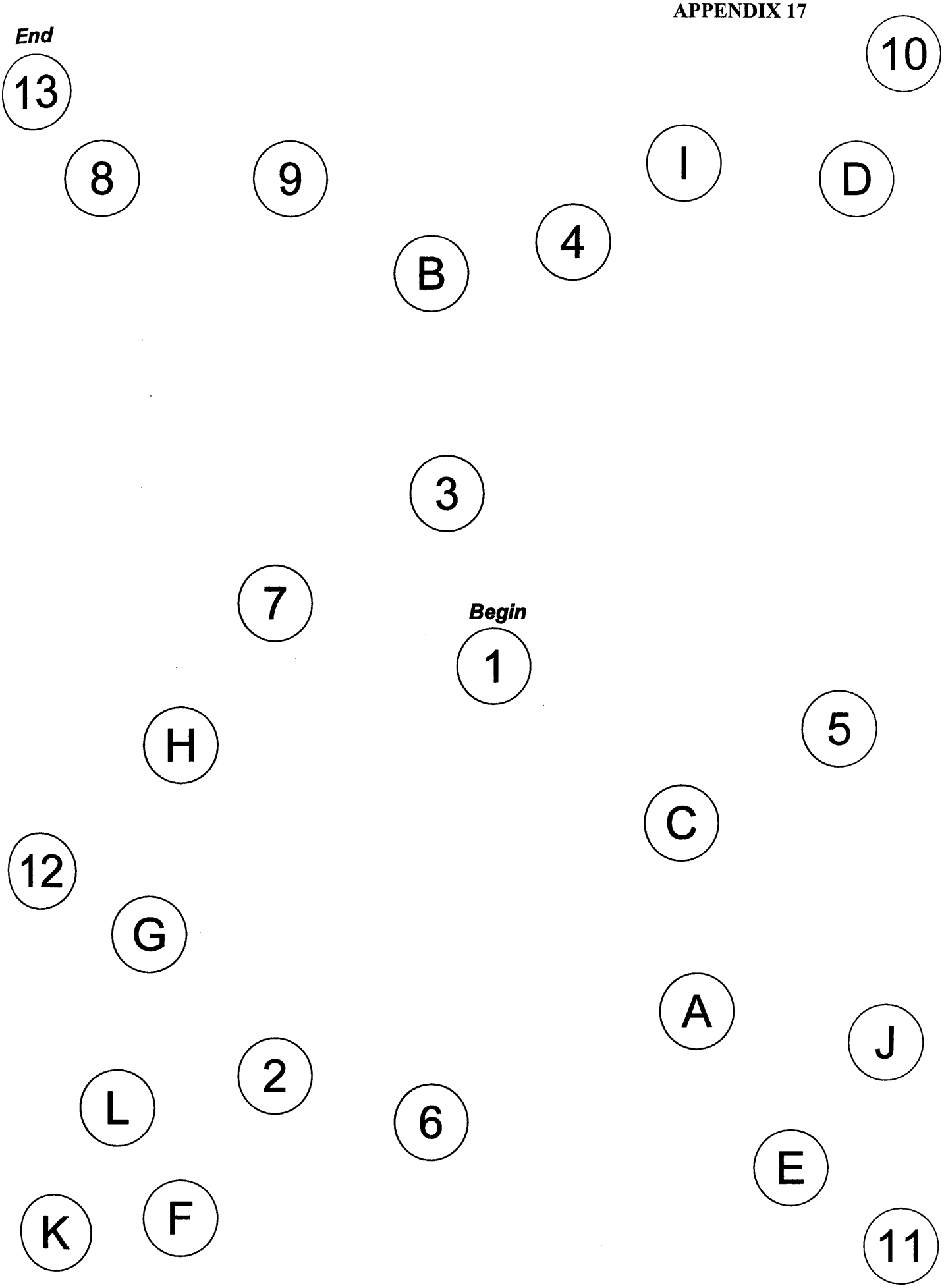

17
21
15
20
19
16
18
4
22
5
6
13
Begin
24
7
1
14
2
10
8
3
End
9
12
11
25
23

# TRAIL MAKING

## Form B

SAMPLE




End
13
10
8
9
I
D
4
B
3
7
Begin
1
5
H
C
12
G
A
J
2
L
6
E
K
F
11

| CREDITS FOR TRAIL MAKING | | | |
|---|---|---|---|
| FORM A | | FORM B | |
| Time in Seconds | Credits | Time in Seconds | Credits |
| 0 – 38 | 10 | 0 – 43 | 10 |
| 39 – 44 | 9 | 44 – 50 | 9 |
| 45 – 49 | 8 | 51 – 56 | 8 |
| 50 – 58 | 7 | 57 – 63 | 7 |
| 59 – 65 | 6 | 64 – 71 | 6 |
| 66 – 72 | 5 | 72 – 78 | 5 |
| 73 – 82 | 4 | 79 – 88 | 4 |
| 83 – 97 | 3 | 89 – 99 | 3 |
| 98 – 110 | 2 | 100 – 145 | 2 |
| 111 and over | 1 | 146 and over | 1 |

# Digit Span

Discontinue Rule

Digits Forward and Backward: Score of 0 on both trials of any item. For both Digits Forward and Backward, administer both trials of each item even if trial 1 is passed. Administer Digits Backward even if examinee scores 0 on Digits Forward

Scoring Rule

Each Trial: 0 or 1 point for each response
Item score = Trial 1 + Trial 2

| Digits Forward | | | Trial score | Item score (0 or 1) |
|---|---|---|---|---|
| Trial | | Item/Response | | |
| 1. | 1 | 1 - 7 | | |
| | 2 | 6 - 3 | | |
| 2. | 1 | 5 - 8 - 2 | | |
| | 2 | 6 - 9 - 4 | | |
| 3. | 1 | 6 - 4 - 3 - 9 | | |
| | 2 | 7 - 2 - 8 - 6 | | |
| 4. | 1 | 4 - 2 - 7 - 3 - 1 | | |
| | 2 | 7 - 5 - 8 - 3 - 6 | | |
| 5. | 1 | 6 - 1 - 9 - 4 - 7 - 3 | | |
| | 2 | 3 - 9 - 2 - 4 - 8 - 7 | | |
| 6. | 1 | 5 - 9 - 1 - 7 - 4 - 2 - 8 | | |
| | 2 | 4 - 1 - 7 - 9 - 3 - 8 - 6 | | |
| 7. | 1 | 5 - 8 - 1 - 9 - 2 - 6 - 4 - 7 | | |
| | 2 | 3 - 8 - 2 - 9 - 5 - 1 - 7 - 4 | | |
| 8. | 1 | 2 - 7 - 5 - 8 - 6 - 2 - 5 - 8 - 4 | | |
| | 2 | 7 - 1 - 3 - 9 - 4 - 2 - 5 - 6 - 8 | | |
| | | Digits Forward Total Score (Maximum = 16) | | |

| Digits Backward | | | Trial score | Item score (0 or 1) |
|---|---|---|---|---|
| Trial | | Item/Response | | |
| 1. | 1 | 2 - 4 | | |
| | 2 | 5 - 7 | | |
| 2. | 1 | 6 - 2 - 9 | | |
| | 2 | 4 - 1 - 5 | | |
| 3. | 1 | 3 - 2 - 7 - 9 | | |
| | 2 | 4 - 9 - 6 - 8 | | |
| 4. | 1 | 1 - 5 - 2 - 8 - 6 | | |
| | 2 | 6 - 1 - 8 - 4 - 3 | | |
| 5. | 1 | 5 - 3 - 9 - 4 - 1 - 8 | | |
| | 2 | 7 - 2 - 4 - 8 - 5 - 6 | | |
| 5. | 1 | 8 - 1 - 2 - 9 - 3 - 6 - 5 | | |
| | 2 | 4 - 7 - 3 - 9 - 1 - 2 - 8 | | |
| 7. | 1 | 9 - 4 - 3 - 7 - 6 - 2 - 5 - 8 | | |
| | 2 | 7 - 2 - 8 - 1 - 9 - 6 - 5 - 3 | | |
| | | Digits Backward Total Score (Maximum = 14) | | |

| Forward | + | Backward | = | (Maximum = 30) |
|---|---|---|---|---|
| | | | | |

**Response Inhibition Tests** Date: Participant:

**Day/Night Test**

| Trial | Control | Correct | Incorrect | Inhibition | Correct | Incorrect |
|---|---|---|---|---|---|---|
| 1 | D | | | N | | |
| 2 | D | | | N | | |
| 3 | N | | | D | | |
| 4 | D | | | N | | |
| 5 | N | | | D | | |
| 6 | N | | | N | | |
| 7 | D | | | N | | |
| 8 | N | | | N | | |
| 9 | D | | | D | | |
| 10 | N | | | D | | |
| 11 | D | | | N | | |
| 12 | D | | | D | | |
| 13 | N | | | N | | |
| 14 | D | | | D | | |
| 15 | N | | | D | | |
| 16 | N | | | D | | |
| 17 | D | | | N | | |
| 18 | N | | | N | | |
| 19 | D | | | D | | |
| 20 | N | | | D | | |

Score

**Motor Perseveration - Tapping**



Say: 'I'm gong to give you a rule. When I tap on the table once, you tap twice; and when I tap twice, you tap once'.

Give **three practice runs** - correcting the participant as necessary and then follow on with the test sequence; **DO NOT CORRECT THE PARTICIPANT DURING THE TEST !**

| Trial | Task | Correct | Incorrect |
|---|---|---|---|
| Practice 1 | - | - | - |
| Practice 2 | - | - | - |
| Practice 3 | - | - | - |
| 1 | Tap twice | once | |
| 2 | Tap once | twice | |
| 3 | Tap once | twice | |
| 4 | Tap twice | once | |
| 5 | Tap once | twice | |

Score

THE GIBSON SPIRAL MAZE



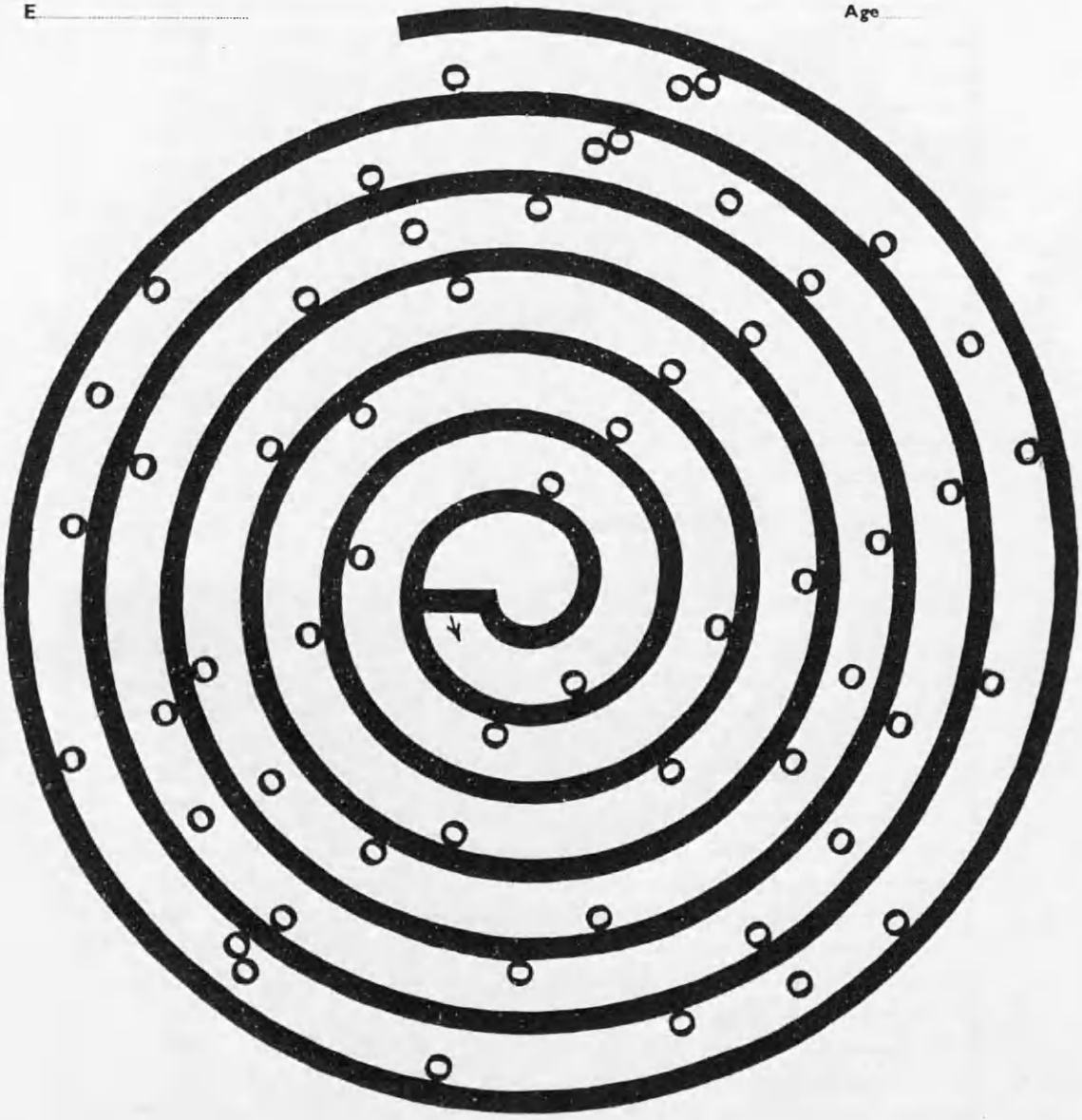
*Twenty-second impression 1998*

T.....

E.....

Name.....

Age.....



Hodder & Stoughton 338 Euston Road, London NW1 3BH

(Reduced to 65% of actual size)

## Spatial Span

Discontinue Rule:
After scores of 0 on both trials of any item. For both Spatial Span Forward and Spatial Span Backward, administer both trials of each item even if trial 1 is passed.

Scoring Rule:
0 - 1 point for each trial

**Spatial Span Forward**

| Item/Trial | | Response | Score (0 or 1) |
|---|---|---|---|
| 1. | Trial 1 | 3 - 10 | |
| | Trial 2 | 7 - 4 | |
| 2. | Trial 1 | 1 - 9 - 3 | |
| | Trial 2 | 8 - 2 - 7 | |
| 3. | Trial 1 | 4 - 9 - 1 - 6 | |
| | Trial 2 | 10 - 6 - 2 - 7 | |
| 4. | Trial 1 | 6 - 5 - 1 - 4 - 8 | |
| | Trial 2 | 5 - 7 - 9 - 8 - 2 | |
| 5. | Trial 1 | 4 - 1 - 9 - 3 - 8 - 10 | |
| | Trial 2 | 9 - 2 - 6 - 7 - 3 - 5 | |
| 6. | Trial 1 | 10 - 1 - 6 - 4 - 8 - 5 - 7 | |
| | Trial 2 | 2 - 6 - 3 - 8 - 2 - 10 - 1 | |
| 7. | Trial 1 | 7 - 3 - 10 - 5 - 7 - 8 - 4 - 9 | |
| | Trial 2 | 6 - 9 - 3 - 2 - 1 - 7 - 10 - 5 | |
| 8. | Trial 1 | 5 - 8 - 4 - 10 - 7 - 3 - 1 - 9 - 6 | |
| | Trial 2 | 8 - 2 - 6 - 1 - 10 - 3 - 7 - 4 - 9 | |

**Forward Total Score** ____

(Range = 0 to 16

**Spatial Span Backward**

| Item/Trial | | (Correct Response)/Response | Score (0 or 1) |
|---|---|---|---|
| 1. | Trial 1 | 7 - 4 (4 - 7) | |
| | Trial 2 | 3 - 10 (10 - 3) | |
| 2. | Trial 1 | 8 - 2 - 7 (7 - 2 - 8) | |
| | Trial 2 | 1 - 9 - 3 (3 - 9 - 1) | |
| 3. | Trial 1 | 10 - 6 - 2 - 7 (7 - 2 - 6 - 10) | |
| | Trial 2 | 4 - 9 - 1 - 6 (6 - 1 - 9 - 4) | |
| 4. | Trial 1 | 5 - 7 - 9 - 8 - 2 (2 - 8 - 9 - 7 - 5) | |
| | Trial 2 | 6 - 5 - 1 - 4 - 8 (8 - 4 - 1 - 5 - 6) | |
| 5. | Trial 1 | 9 - 2 - 6 - 7 - 3 - 5 (5 - 3 - 7 - 6 - 2 - 9) | |
| | Trial 2 | 4 - 1 - 9 - 3 - 8 - 10 (10 - 8 - 3 - 9 - 1 - 4) | |
| 6. | Trial 1 | 2 - 6 - 3 - 8 - 2 - 10 - 1 (1 - 10 - 2 - 8 - 3 - 6 - 2) | |
| | Trial 2 | 10 - 1 - 6 - 4 - 8 - 5 - 7 (7 - 5 - 8 - 4 - 6 - 1 - 10) | |
| 7. | Trial 1 | 6 - 9 - 3 - 2 - 1 - 7 - 10 - 5 (5 - 10 - 7 - 1 - 2 - 3 - 9 - 6) | |
| | Trial 2 | 7 - 3 - 10 - 5 - 7 - 8 - 4 - 9 (9 - 4 - 8 - 7 - 5 - 10 - 3 - 7) | |
| 8. | Trial 1 | 8 - 2 - 6 - 1 - 10 - 3 - 7 - 4 - 9 (9 - 4 - 7 - 3 - 10 -1 - 6 - 2 - 8) | |
| | Trial 2 | 5 - 8 - 4 - 10 - 7 - 3 - 1 - 9 - 6 (6 - 9 - 1 - 3 - 7 - 10 - 4 - 8 - 5) | |

**Backward Total Score** ____

Range = 0 to 16)

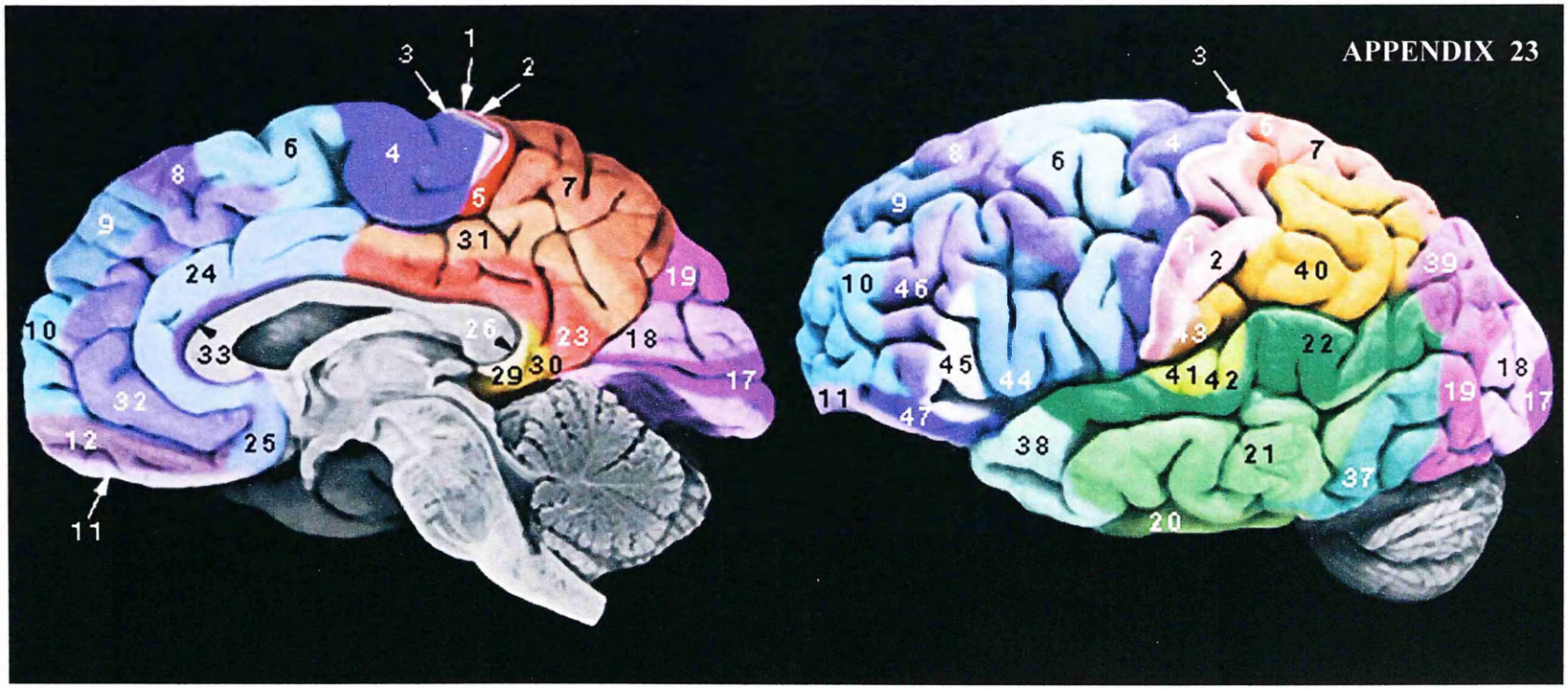
**Total Score** ____

Range = 0 to 32)

# Geriatric Depression Scale
# (Short form)

Please answer all the following questions by ringing "Yes" or "No".

1. Are you basically satisfied with your life? Yes / No
2. Have you dropped many of your activities and interests? Yes / No
3. Do you feel that your life is empty Yes / No
4. Do you often get bored? Yes / No
5. Are you in good spirits most of the time? Yes / No
6. Are you afraid that something bad is going to happen to you? Yes / No
7. Do you feel happy most of the time? Yes / No
8. Do you often feel helpless? Yes / No
9. Do you prefer to stay at home, rather than going out and doing new things? Yes / No
10. Do you feel you have more problems with your memory than most? Yes / No
11. Do you think it is wonderful to be alive now? Yes / No
12. Do you feel pretty worthless the way you are now? Yes / No
13. Do you feel full of energy? Yes / No
14. Do you feel that your situation is hopeless? Yes / No
15. Do you think that most people are better off than you are? Yes / No




**Brodmanns Areas**

Hoehn and Yahr: Parkinson's disease motor function assessment

**Stage One**
1. Signs and symptoms on one side only
2. Symptoms mild
3. Symptoms inconvenient but not disabling
4. Usually presents with tremor of one limb
5. Friends have noticed changes in posture, locomotion and facial expression

**Stage Two**
1. Symptoms are bilateral
2. Minimal disability
3. Posture and gait affected

**Stage Three**
1. Significant slowing of body movements
2. Early impairment of equilibrium on walking or standing
3. Generalized dysfunction that is moderately severe

**Stage Four**
1. Severe symptoms
2. Can still walk to a limited extent
3. Rigidity and bradykinesia
4. No longer able to live alone
5. Tremor may be less than earlier stages

**Stage Five**
1. Cachectic stage
2. Invalidism complete
3. Cannot stand or walk
4. Requires constant nursing care