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Distinguishing between impairments of working memory and inhibitory control in cases of early dementia

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Abstract:

Dementia (most notably, Alzheimer's Disease) is often associated with impairments of both working memory and inhibitory control. However, it is unclear whether these are functionally distinct impairments. We addressed the issue of whether working memory and inhibitory control can be dissociated, using data from a sample of patients who were recruited in a longitudinal study (Crawford et al. 2013, 2015). The first case revealed a preserved working memory capacity together with poor inhibitory control in the anti-saccade task. A longitudinal follow-up revealed that the defective inhibitory control emerged 12-months before the dementia was evident on the mini-mental state examination assessment. A second case revealed a poor working memory together with a well-preserved level of inhibitory control. The dissociation of working memory and inhibitory control was confirmed statistically in 7 additional cases. These findings yield converging evidence that working memory and inhibitory control are distinct cognitive operations and challenges the Kimberg and Farah (2000) cognitive model of working memory.

Keywords: Working memory, Inhibitory control, anti-saccade task, dementia, Alzheimer's disease, attention

1. Introduction:

Dementia can emerge from various disorders and etiologies, the most common of which are Alzheimer's disease and vascular dementia. There is growing evidence that eye-tracking tasks offer a sensitive and well-tolerated measure of cognitive impairment in people with early dementia (Boxer et al. 2006; Crawford et al, 2005; 2013; 2015; Currie et al 1991; Garbutt et al. 2008; Kaufman et al. 2012; Shafiq-Antonacci et al. 2003). The rapid gaze shifts, known as saccadic eye movements, are controlled by a network of cortical and subcortical connections that are also involved in the regulation of complex cognitive operations, including working (WM) and inhibitory control (IC). Eye-tracking provides a convenient and promising biological marker of cognitive impairment in people with psychological and neurological disorders (Crawford et al, 2013; Leigh & Kennard, 2004), which may aid in the early diagnosis and long-term monitoring of the disease.

The antisaccade task (AST) (Hallet, 1978; Crawford et al, 2011) is one of the most-widely used paradigms of IC in both healthy individuals and clinical disorders (Hutton & Ettinger 2006; Broerse et al, 2001). When a novel object comes into view, there is a strong and natural impulse to move your eyes to view the object. The AST requires that the observer looks away from the object, in the opposite direction. The AST offers a convenient way to capture IC, both within and outside the research laboratory. However, the underlying cognitive operations of this deceptively simple task are unclear. There is little doubt that top-down control is required to guide the eye away from the visual target in the AST. However, it is argued that this top-down control of the eye requires the resources of WM (Crawford et al., 2011; Conway and Engle 1996). According to one influential theory, high order cognitive operations, such as WM have a direct influence on IC, although much of the evidence is based on a dual-task methodology (Roberts et al. 1994; Mitchell et al. 2002; Eenshuistra et al. 2004, 2007; Kimberg & Farah, 2000). The AST also includes a central inhibitory component, as witnessed by the high proportion of corrective eye movements that normally follow the inhibition failures (Crawford et al., 1995a,b; Crawford et al., 2013). However, these corrections are much less frequent in people with Alzheimer's disease (Crawford et al., 2013). Do the inhibition failures and the reduction in the capacity of WM emerge from a common source? Are they in fact one and the same thing?

It is worth distinguishing between a ‘moderate’ form and the ‘extreme’ variant of the WM theory of IC. The ‘moderate’ form acknowledges that a high-level ‘cognitive control’ process is important for inhibitory control; in the AST an endogenous saccade must be activated to trigger the eye movement away from the stimulus. However, this cognitive control can be distinguished from WM. Miller and Cohen (2001) stated, ‘‘It may also be important to distinguish the capacity limits of cognitive control from those of short-term storage of item information (e.g. verbal or visual short-term memory) (Miller 1956; Baddeley 1986). The limited capacity of short-term memory may involve mechanisms (e.g. articulatory rehearsal) and structures (e.g. sustained activity in the posterior cortical areas) that are not central to cognitive control and that may or may not rely on PFC function. Here the ability to inhibit an irrelevant action is not to be conflated with the short-term memory capacity that is required to store memory representations.”

Kimberg and Farah, (2000) support the ‘extreme’ variant. According to their model the failure of cognitive inhibition is simply an emergent property of a weak or limited working memory. They stated, ‘prefrontal cortex sub-serves working memory, and does not implement inhibition as a distinct functional element of the cognitive architecture of the task’. No specific inhibitory mechanism was included in their model, as they argued that such a dedicated mechanism was not needed to account for “disinhibited” behaviour. Working memory alone was able to account for the disinhibited behaviour that for example, is linked with damage to the prefrontal cortex (Kimberg and Farah, 2000).

So far the eye-tracking studies of IC have relied heavily on studies that are based on the average scores from groups that were tested at a given time point. Group studies can reveal evidence for generalizable patterns of behavior, but they have not been able to determine for example, whether changes in IC are evident **before** the substantive deterioration of WM, or vice versa. A detailed assessment of individual cases can address questions in relation to the dissociation of cognitive operations, which cannot be resolved by the average scores from a group of diverse patients (Shallice, 1988). If IC and WM are separate cognitive functions, then it should be possible for a patient to retain WM, and at the same time manifest a deficiency in IC. The converse should also be possible; a patient should be able to manifest a deficient working memory, while IC is preserved. Here, we explore whether WM is dissociable from IC (‘independence hypothesis’), using empirical evidence from single case analyses of people in the early stages of the Alzheimer’s disease, vascular and mixed

dementia. It is worth noting that there are various dementia disorders and etiologies, thus not all will have an impact on IC or WM in the early stages of the disease.

Summary of the key findings:

We first demonstrate the double dissociation in our first 2 patients who consented to take part in a comprehensive longitudinal assessment. Poor IC was discovered in one patient with dementia at the same time as a well-preserved WM span. The impairment of IC was revealed several months before the dementia was detected using conventional tests. A second patient showed the converse pattern of well-preserved IC with a poor WM. We summarize and confirm the dissociation of WM and IC with statistical evidence in a further 7 patients from the sample (Crawford et al, 2013). Apparently, impairments of IC and WM can emerge separately in people with dementia.

2. Methods

2.1 Participants:

Dementia group

Patients were recruited as part of the Lytham longitudinal dementia study (see Crawford et al, 2013). This sample included 6 mild-to-moderate patients with Alzheimer's disease, 2 patients with vascular dementia and a patient with mixed dementia (age range = 70-81; mean = 76.6; SD = 3.67; 8 males). Patients with Alzheimer's disease fulfilled the criteria for probable Alzheimer's Disease according to the American Psychiatric Association's DSM IV (American Psychiatric Association, 2000) and the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS). All underwent a detailed clinical history, physical/neurological examination and routine investigations: hemoglobin, full blood count, erythrocyte sedimentation rate, urea and electrolytes, liver function tests, blood glucose, thyroid function tests, serum vitamin B12 and folate, serology for syphilis and urinalysis.

Case history AP11: (Mixed Dementia)

This 81-year old patient lived alone, having lost a spouse several years previously. She had become concerned about her memory, for example she was unable to find things that she had put away for safety. Her daughter described her as an intelligent person who had always used her mind a great deal and who continued many interests such as crosswords, but she had noticed that AP11 had become forgetful in the last few months. At initial assessment she was taking Fluoxetine for depression, and was under consideration for further treatment with anti dementia medication. In recent weeks she and her daughter had seen a noticeable improvement in memory. Apart from diabetes, controlled by diet, she was in good physical health. She had good eye contact and was able to establish a good rapport with people. Her speech was appropriate, normal rate and volume with good verbal fluency. Her mood was subjectively and objectively euthymic and the patient presented no preoccupation of thought. There was no evidence of perceptual abnormality and she showed good topographical orientation. Appetite, sleep and concentration were undisturbed. On cognitive examination her MMSE score was 30/30.

Case history AP18. (Vascular Dementia)

This 79-year-old patient (AP18) reported increasing problems with his memory over the previous five years, which had declined over the last year, and had become a daily problem. He forgot names of his friends and things that his wife had said to him only a few moments before. He demonstrated a good memory for remote events, but revealed a poor short-term memory. He complained of low mood, poor appetite, weight loss and sleep disturbance with nocturia. He also complained of poor topographical orientation. On cognitive examination the MMSE score was 24/30. The neurological examination revealed no abnormality of note. He was seen again in six months later, and complained of low mood, reduced appetite, poor concentration and reduced levels of energy and motivation. Sleep was also disturbed. His memory had deteriorated and he was now unable to recognize the voices of his children over the telephone.

Control group

The control group were 24 elderly volunteers from the local community (mean age 70.6, SD = 6.1, range 58-85 years; males=13, females=21). Participants were excluded if the SMMSE was in the sub-normal range (<23/30). All participants were right-handed, with normal or corrected Snellen chart visual acuity. No participant demonstrated visual neglect on the

line bisection task (Schenkenberg et al. 1980). Patient's scores were expressed as a z-score ($z = \frac{(\bar{x} - x)}{SD}$) in relation to the mean control scores for all the measures on the eye-tracking and cognitive test batteries. Written informed consent was obtained from all the participants. The study was approved by the Blackpool, Wyre and Fylde Local Research Ethics Committee.

2.2 Neuropsychological Assessment

All participants were tested with the following battery of cognitive and neuropsychological assessments:

Dementia & Psychopathology: Standardized Mini Mental State Examination (SMMSE), (Molloy et al, 1991) – brief screening instrument for dementia; European version of the Alzheimer's Disease Assessment Scale Cognitive Sub-Test (EADAScog) (Dahalke et al., 1992; Rosen, Mohs & Davis, 1984). Clinical Dementia Rating Scale (CDR), (Hughes et al, 1982); Neuropsychiatric Inventory (NPI) (Cummings et al, 1994); Alzheimer's Disease Functional Assessment and Change Scale (ADFACS) (Galasko et al, 1997; identifies difficulties in everyday living, practical skills and personal care based on carer interview); Geriatric Depression Scale (Yesavage et al, 1983).

Premorbid IQ: National Adult Reading Test (NART) (Nelson, 1982):

Executive Function & Verbal ability: Trail Making (Reitan, 1958) both parts, A & B; Verbal Fluency (Storandt et al, 1984); Day/Night Response Inhibition Test (Gerstadt at al, 1994). Motor Perseveration – tapping (Luria 1973 see above ref); Gibson Spiral Maze (Gibson, 1965)

Verbal & Spatial WM & memory Span: Digit Span, forward and reversed (Wechsler Adult Intelligence Scale III; Wechsler, 1997a); Spatial Span, forward and reversed (Wechsler Memory Scale III; Wechsler, 1997b). Note that the forwards test provides a measure of passive memory span. The reverse memory test imposes an additional demand on working memory, because the sequence of the items is manipulated whilst the spatial and verbal representations are maintained in short-term memory.

2.3 Eye Tracking: APPARATUS & PROCEDURES

Saccadic eye movements were recorded monocularly using the 'ExpressEye' (Optom, Freiburg, Germany) infra-red, scleral reflection system. Samples were taken at 1000 Hz with a spatial resolution of 0.1°. The system is linear over 15° of the visual field. The central

fixation light was presented within an unfilled 0.75°x 0.75° empty square marker; the target was a red 0.4° spot, which was projected left and right horizontally. A head-mounted laser projected these stimuli onto a white tangential screen at 57 cm. The laser output was 0.2mW, with a wavelength of 635 nm with a luminance of 66.37 cd/m2.

Figure 1 about here: Pro & Anti Saccade diagram

2.3.1 Prosaccade task (PST):

At the start of each trial the central fixation light was presented for 1,000 ms. The target for the eye was presented at ±4° for 2000 ms; the direction was randomized to avoid predictive saccades. Participants' were given two versions of this task: (i) In the prosaccade 'gap' condition the central fixation light was removed 200 ms before the target was presented. (ii) In the prosaccade 'overlap' condition the target was presented while the fixation light remained on. Thus there was a 200ms 'overlap' period when both the fixation light and the target were on at the same time. Finally, the target was turned off for 1,200 ms, when only the central square was visible. In this condition the transfer of attention from the fixation light to the target is normally slowed, relative to the prosaccade 'gap' condition, yielding slower overall reaction times in the overlap tasks (see Figure 1).

2.3.2 Saccadic Inhibition Go-No-Go tasks:

GO/NO-GO Paradigm: At the start of each trial a central fixation light was illuminated for 1000ms. This central light was then switched off, followed by a 200 ms 'gap'. At the termination of the 'gap' period a target was presented at ±4° for 700 ms, while the central fixation light remained off. We varied the levels of inhibition and complexity in 3 versions of this task. i) No-Go: Participants were instructed to ignore the target and to maintain fixation at the centre of the screen for the entire duration of the trial. This simple task required little attention to the target, and no switching between initiation ii) Go-RIGHT/No-Go-LEFT: Participants were instructed to 'look' at the target that appeared in the right visual field, but to prevent eye movements to the target when it was on the left side of the screen iii) Go-LEFT/No-Go-RIGHT: Participants were instructed to 'look' at the target if it was presented in the left field but to prevent eye movements to the target if it appeared on the right side of the screen. These Go-No-Go

tasks required more complex, trial-by-trial monitoring and switching control between the Go and No-go demands.

2.3.3. **Antisaccade Task (AST):**
The format of the target presentations was identical to the prosaccade 'gap' and prosaccade 'overlap' conditions, only the instructions to the participants changed. In this condition participants were instructed to direct their gaze in the opposite direction to the target, i.e. to the mirror-image location. As in the case of the PST, 2 versions of this test were used. (ii) In the 'gap' condition the central fixation light was removed 200ms before the target was presented. (i) In the 'overlap' condition the fixation light 'overlapped' with the target for 200ms (see Fig. 1).

Figures 2 about here: Saccadic Characteristics

2.3.4 Measurement of saccadic parameters
The start and end of a saccade was detected when the eye velocity crossed a 30°/s threshold. These saccadic measurements include: the amplitude and reaction time of the primary saccade that was generated towards or away from the target; proportion of correctly directed saccades (or errors) towards or away from the target; the amplitude and latency of corrective saccades, the final eye positions (see Fig. 2). Tests for homogeneity of variance were conducted using IBM SPSS Statistics 21.

Figures 3a-b: AP11 & AP18 Eye-tracking & cognitive measures

Figures 4a-b: AP11 Baseline, 12 & 18 months

3. Results

Figs. 3a-b show the normalized saccadic eye movement and neuropsychological and z-score charts for AP11 and AP18. AP11 with the maximum score (MMSE = 30), revealed no apparent dementia at the time of the initial assessment (see Fig. 3c). Her verbal recall and recognition scores on the ADAS Cog were preserved in comparison to controls. Digit and spatial span were within the control range (see Fig. 3c). In contrast, the mean score for her

inhibitory control errors in the ‘gap’ AST was over 3 standard deviations above the control mean (Fig. 3a), although she was able to generate spontaneous error corrections. There was a clear contrast between her preserved WM and her high level of inhibition failures. The high correction rate following the inhibition errors provided a reassuring indicator that she was compliant, well motivated and retained the memory representation of the task goal. Her errors were substantially impaired on the overlap and Go No-Go tests at baseline (see Fig. 3b). This inhibitory impairment was not generalized to the verbal and motor tapping tasks. She scored 20/20 on the verbal day/night inhibition task. On the motor tapping task (‘When I tap once, you tap twice’ and vice versa) she obtained the maximum score (5/5). No lines were omitted on the line bisection task. A complete cognitive and eye-tracking re-assessment was conducted at 12 and 18 months follow-up (Fig. 4a-b). Ten months after the completion of the final assessments at 18-months AP11 continued to deteriorate. The MMSE score had fallen substantially to 14/30 and she was now quite disorientated. She was now expressing violence towards members of the family, and was placed into the care of a local nursing home.

Fig. 4a shows the evolution over 18-months of AP11 dementia in relation to eye-movements. Her subjective cognitive complaints were not reflected in the traditional cognitive assessments at baseline (see Fig. 4b). However, whilst these cognitive assessments scores were apparently well preserved, there was a pronounced impairment of IC in the AST at the baseline assessment (see Fig. 4a). Fig. 4b shows that by 12-months the MMSE was signalling a descent towards dementia. Her dementia continued to worsen and was now clearly apparent in the MMSE at 18-months (see Fig. 4b). Note that the AST inhibitory impairment was evident throughout. Fig. 4a revealed that the AST detected cognitive impairment, some 12 months earlier than the MMSE, while the other cognitive measures failed to reveal the mental deterioration.

Figs. 3a-c shows the normalized neuropsychological and saccadic profile for AP18 in contrast to AP11. He revealed mild cognitive impairment (MMSE = 24, and 25; ADAS Cog= 25). The verbal recognition, verbal recall, digit and spatial span tests revealed significant widespread impairment of WM (Fig. 3c). Inhibition errors were rare (gap AST = 2%; overlap AST = 0%, Fig. 3a). However, he was outstanding on both the gap and overlap AST, yielding no secondary corrective saccades. The contrast of Figs. 3a with Fig. 3c reveals a clear dissociation of memory impairment and inhibitory control.

Table 1 about here

3.1 Statistical test of the dissociation of cognitive operations:

Tests for the dissociations of inhibitory control and working memory were conducted with reference to the control sample using the revised standardized difference tests with statistical package developed by Crawford & Garthwaite (2005). AP11 errors on inhibitory control on the AST were reliably higher in comparison to control sample (z= -3.415, t=-3.347, p=0.0014, df=23), whilst working memory score was preserved (t=-0.637, p=0.2625, df=23). Conversely, for AP18 inhibitory errors on the AST were preserved (z = 1.151, t=1.128, p = 0. 0.1355, df = 23) whilst scores on working memory were significantly lower than the control sample (z = -2.317, t=-2.270, p = 0.01645, df=23).

It is important to determine whether the dissociation of cognitive operations was unique in this sample of patients. Table 1 reveals that 4 patients from the original sample (N=18) met the Crawford & Garthwaite (2005) statistical criteria for a "strong" dissociation; 4 additional cases met the criteria for a "classical" dissociation; 4 patients (not shown) revealed a significant t-test difference compared to the control group on either inhibitory control or working memory, but did not satisfy all the Crawford & Garthwaite (2005) criteria for a dissociation of function. Four patients revealed no dissociation, and there was missing data from 1 patient. Apparently, the dissociation of working memory and inhibitory control is not at all uncommon in patients with early dementia.

4. Discussion

Single case analyses provide an opportunity to gather converging evidence to explore theories of cognition. However, there have been very few studies that have examined the cognitive relationship of IC and WM with evidence from single case studies of people with dementia. Together AP11 and AP18 revealed a double dissociation of WM and inhibitory control. Patient AP11 had preserved features of WM alongside low IC in the AST. AP18 showed poor WM with no impairment in the AST. Impaired WM can co-exist with an intact IC and this provides evidence that inhibition and WM are isolable systems. The dissociation of was confirmed in 7 further patients from our sample (Crawford et al, 2013) and so was not uncommon. This has theoretical significance for models of cognition (e.g. Kimberg and

Farah, 2000), although it is important to recognize that for many people with dementia the two cognitive operations may be disrupted at the same time. The findings from AP11 show that cognitive impairment on formal neuropsychological tests is not a necessary precursor of inhibitory impairment. That inhibition effects showed up first, thus it may be that inhibitory failures leave the individual vulnerable to later cognitive impairment. These data also confirm that IC is not a unitary construct. Our patients generally showed a clear dissociation between inhibitory errors in the AST and preserved inhibition in the day/night and inhibitory tapping tasks.

The central issue here is the extent to which IC is necessary, or sufficient, to maintain the capacity of WM. An alternative way to phrase this issue is to consider whether in principal it would be possible to protect WM by strengthening IC? Case studies of people with dementia offer a useful approach to this question, and a critical test bed for the WM theories of IC (Kimberg and Farah, 2000). If the strong form of the WM theory is correct, then its dysfunction should not co-exist with the preservation of IC, and vice versa. The fact that abnormal IC can occur with the preservation of WM is consistent with the independence hypothesis; that these are distinct cognitive operations. The Kimberg and Farah (2000) theory is not fatally weakened by this dissociation *per se*, as it could be argued that the impairment of IC is also modulated by a variety of factors, independent of WM. However, it is difficult to see how to reconcile Kimberg and Farah's (2000) stance on this issue when the combined evidence from the dissociations evident in these patients are considered together.

One possible account for the poor performance was a difficulty in task comprehension, lack of motivation or other non-specific factors in relation to the AST. However, the analyses of the corrective eye movements (e.g. Fig. 4a) revealed that AP11 understood the task, and was motivated to perform well. The saccadic profile of AP11 revealed that the mean spontaneous error correction rate, the mean corrective latency, and the mean final eye position were all equivalent to, or more efficient than, the equivalent characteristics of the control group.

Cognitive inhibition has an important relationship with high-level cognitive operations. According to one popular theory proposed by Hasher and Zacks (1999) IC has an essential function in preserving the contents of WM from various sources of potential interference that would affect cognitive processing. IC is therefore important for working memory, but can be dissociated from it. A defect in the ability to inhibit irrelevant information is likely to impede

memory function given the importance of attention in the encoding, storage and retrieval of items from memory. The evidence of high levels of distractibility of saccadic eye movements in the early stages of AD, together with the spontaneous correction of errors suggests that the disorder of inhibition is not simply an end stage consequence of memory impairment (Boxer et al. 2006; Crawford et al, 2005; 2013; Currie et al 1991; Garbutt et al. 2008; Kaufman et al. 2012; Shafiq-Antonacci et al. 2003).

5. Conclusions

Valid inferences on the dissociation of cognitive operations are heavily constrained when we rely exclusively on the average scores from individuals with brain damage (Shallice, 1988). Here we examined the relationship of IC and WM in a sample of people who were referred to an outpatient memory clinic. Inhibitory control in the AST and WM was clearly dissociated in several cases. This was clearly illustrated by contrasting AP11 and AP18. AP18 revealed an impairment of general cognition and WM, together with good IC. AP11 revealed preserved cognitive function, together with poor IC. The dissociation of IC and WM was detected in 7 further patients from our sample (Crawford et al., 2013). These data demonstrate that, in principal, IC and WM are distinct cognitive operations, and thus are a challenge to a central feature of the Kimberg and Farah (2000) model.

Clearly, the eye movement and cognitive z-score charts were more informative than the mean statistic from a single task. This approach has a number of attractive properties. (1) The candidate eye-tracking features that are impaired or well preserved are readily apparent. (2) These eye movement data are recorded relatively quickly (a few minutes) with relatively few trials. (3) The technology is affordable, and in principal could be implemented in a primary care setting. (4) Finally, the methods are objective and repeatable.

These findings also have clinical implications. It is often assumed that people with dementia suffer primarily from a deficit of WM. However, there is increasing evidence that people with early Alzheimer's disease have subtle impairments in cognitive IC that are often undetected by traditional cognitive assessments. We suggest that this inhibitory impairment should be a focus of treatment, disease monitoring and assessment in pharmacological drug trials.

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Table 1

Results showing patient with dissociations of inhibitory control and working memory using revised standardized difference tests (Crawford & Garthwaite, 2005).

Pat	Task	t (2-tail)	p	Z-score	t (1-tail)	p	df	C&G (2005) Criteria
AP2 vs CS	IC			-3.147	-3.083	0.00262*		
	WM			-2.317	-2.270	0.01645*		
	IC vs. WM	-2.926	0.0076*				23	Strong
AP3 vs CS	IC			-2.682	-2.629	0.0075*		
	WM			-4.817	-4.719	0.00005*		
	IC vs. WM	-2.278	0.03232*				23	Strong
AP6 vs CS	IC			-3.8	-3.723	0.00056*		
	WM			-3.15	-3.086	0.00262*		
	IC vs. WM	-3.506	0.0019*				23	Strong
AP9 vs CS	IC			-3.066	-3.004	0.00317*		
	WM			-3.983	-3.903	0.000036*		
	IC vs. WM	-2.719	0.01224*				23	Strong
AP11 vs CS	IC			-3.415	-3.347	0.0014*		
	WM			-0.65	-0.637	0.26525		
	IC vs. WM	3.318	0.003*				23	Classical
AP13 vs CS	IC			-4.532	-4.44	0.00009*		
	WM			-1.483	-1.453	0.07982		
	IC vs. WM	- 4.355	0.00023*				23	Classical
AP14 vs CS	IC			-3.416	- 3.347	0.0014*		
	WM			- 1.483	- 1.453	0.07982		
	IC vs. WM	- 3.255	0.00349*				23	Classical
AP17 vs CS	IC			-3.148	- 3.084	0.00262*		
	WM			-1.483	- 1.453	0.07982*		
	IC vs. WM	- 2.990	0.00654*				23	Classical
AP18 vs CS	IC			1.151	1.128	0.1355		
	WM			-2.317	-2.27	0.01645*		
	IC vs. WM	- 1.311	0.20266				23	

Pat- patient: CS - Control sample: IC – inhibitory control in antisaccade task. **WM**- working memory in reversed spatial span test. **C&G (2005)** criteria - Crawford & Garthwaite (2005) criteria for classic and strong single dissociation between cognitive operations. Classical criteria are satisfied when " 1. Patient's score on Task X significantly lower than that of controls ($p < .05$, one-tailed) on Crawford & Howell's (1998) test; that is, score meets the criterion for an impairment. 2. Patient's score on Task Y not significantly lower than that of controls ($p > .05$, one tailed) on Crawford & Howell's test; that is, score fails to meet criterion for an impairment and is therefore considered to be within normal limits. 3. Patient's score on Task X significantly lower ($p < .05$, two-tailed) than patient's score on Task Y with the use of the RSDT. The test is two-tailed to allow for the fact that the data are examined before deciding which task is X and which is Y." Crawford & Garthwaite strong criteria are satisfied when

"1. Patient's score on Task X significantly lower than that of controls ($p < .05$, one-tailed) on Crawford & Howell's test; that is, score meets the criterion for an impairment. 2. Patient's score on Task Y is also significantly lower than that of controls ($p < .05$, one-tailed) on Crawford & Howell's test; that is, score meets the criterion for an impairment. 3. Patient's score on Task X significantly lower ($p < .05$, two-tailed) than patient's score on Task Y with the use of the RSDT. " Crawford & Garthwaite (2005), p326

Legends

Figure 1

An illustration of the (A) prosaccade and (B) antisaccade 'gap' and overlap tasks. In (A) participants were required to 'look' quickly and accurately towards the red light. In (B) the task was to 'look' away form the red light to opposite side of the screen. In the gap task the fixation point is withdrawn prior to the presentation of the peripheral target. In the Overlap paradigm the fixation remains on at the onset of the target. In addition there were three 'Go No-Go' tasks'. In the 'No-Go' (NG) task participants were asked to inhibit all saccades to the targets and to 'look' at the centre of the screen throughout the test. In the 'Go No-Go' tasks (GNG) participants were asked to 'look' towards the target when it appeared, for example, on the left (or the right) but to maintain fixation when the target appeared on the right (or the left).

Figure 2

An saccadic error in the antisaccade task followed by a corrective eye movement. A – error saccade amplitude; B – error saccade latency; C – saccadic inhibitory error; D- Corrective saccade; E- corrective error latency; F – corrective saccade amplitude; G – Final eye position.

Figure 3a, b show the z-scores for the saccadic eye movement parameters in the Anti Gap and Anti overlap (Fig 3a), prosaccade gap and prosaccade overlap (Fig 3b). The charts represent standardized (standard deviation) scores with reference to the mean of the control group (0-line). AP11 (black filled bars) shows a high frequency of inhibition errors in the AST (gap and overlap) relative to the controls (0-line). Inhibitory errors were evident in the gap, overlap AST, Go and No-Go tasks. Several anti saccade error parameters are absence for AP18 (striped bars), due to the paucity of saccadic inhibitory errors and eye movements with no corrective (secondary) saccades in the AST.

NG – No-Go task ; GLNR- Go Left, No Go Right in the Go-No-Go task; GRNL – Go Right, No Go Left in the Go-No-Go task; R- right; L-Left; NG-Err – frequency of direction errors in direction of the target; Go-L corr – frequency of correct saccades toward the target in the Go-No task; Amp – saccade amplitude; Lat – saccade latency; Err – saccade direction errors.

Figure 3c show the z-scores for the cognitive assessments for AP11 (black filled bars) and AP18 (striped bars). AP11 showed a relatively preserved working memory. AP18 revealed high dementia scores (SMMSE & EADASCog) together with low scores on WM, particularly on the forward and reverse spatial span tasks. VF 'F' – Verbal fluency –letter F; VF 'P' – Verbal fluency – letter P; EADAS Rec - Recall subtest; EADAS Recog- Recognition subtest; Nart predicted FSIQ – NART full scale IQ; Trails A&B - Trail making mean (A&B); DS – Digit Span; SS – Spatial span;

Figure 4a-b show the eye tracking measures (Figure 4a) and cognitive scores (Figure 4b) assessed at baseline (Empty white bars), 12-months (filled backward slash (\\) and 18-months (filled forward slash (//).

Figure 1

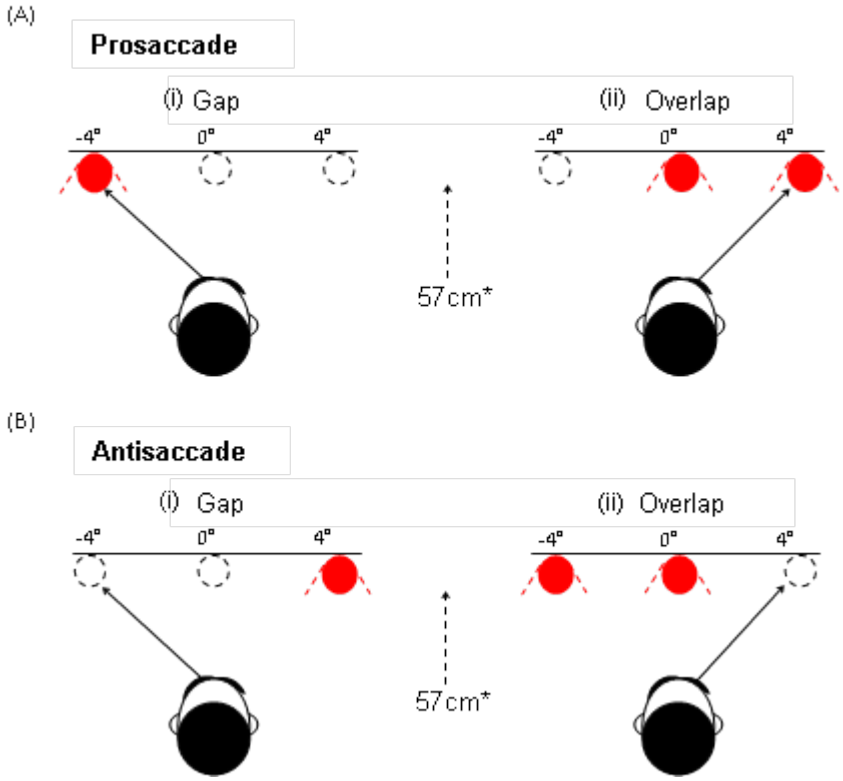

(A)
Prosaccade
(i) Gap
(ii) Overlap
-4°
0°
4°
-4°
0°
4°
57 cm*
(B)
Antisaccade
(i) Gap
(ii) Overlap
-4°
0°
4°
-4°
0°
4°
57 cm*

Figure 2.

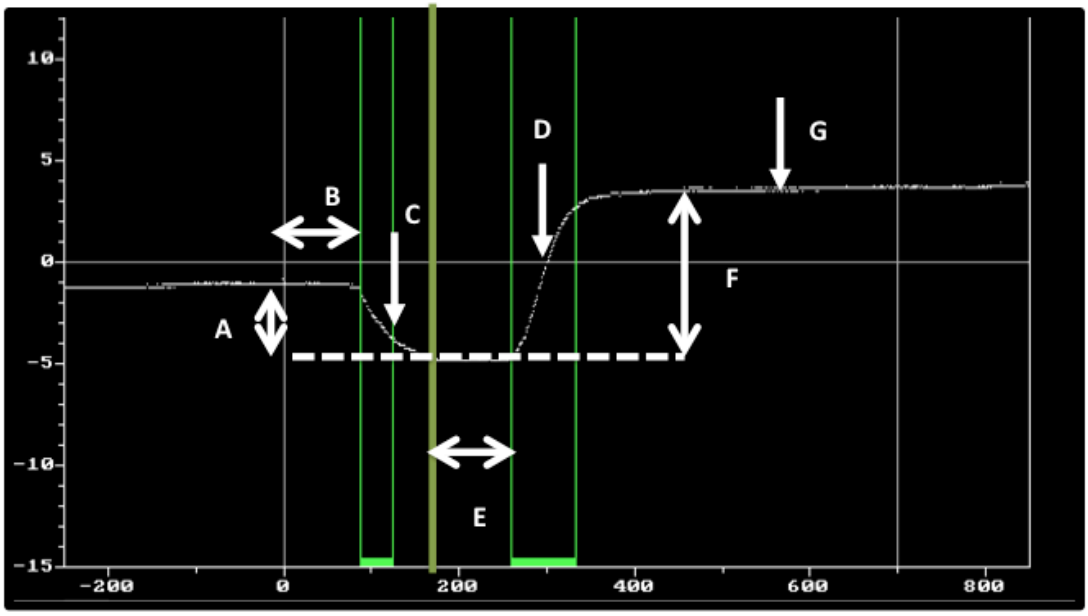


Fig 3a

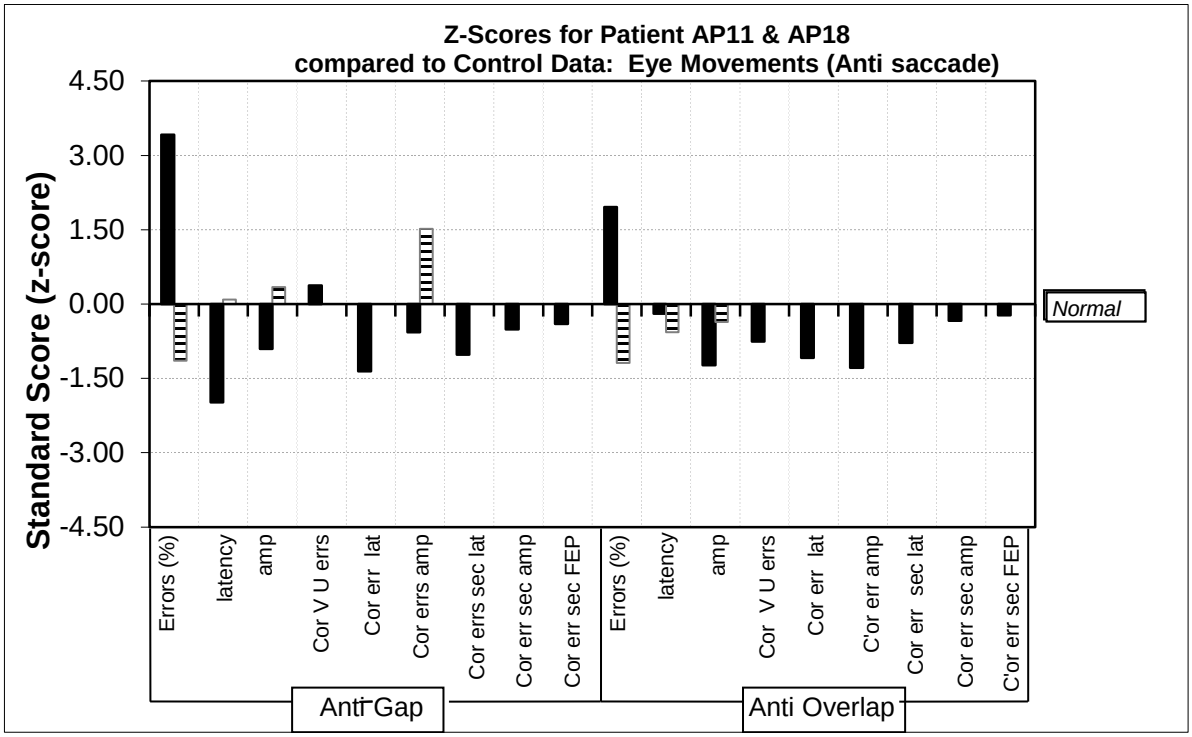

Z-Scores for Patient AP11 & AP18
compared to Control Data: Eye Movements (Anti saccade)
Standard Score (z-score)
4.50
3.00
1.50
0.00
-1.50
-3.00
-4.50
Normal
Errors (%)
latency
amp
Cor V U errs
Cor err lat
Cor errs amp
Cor errs sec lat
Cor err sec amp
Cor err sec FEP
Errors (%)
latency
amp
Cor V U errs
Cor err lat
C'or err amp
Cor err sec lat
Cor err sec amp
C'or err sec FEP
Anti-Gap
Anti Overlap

Fig 3b

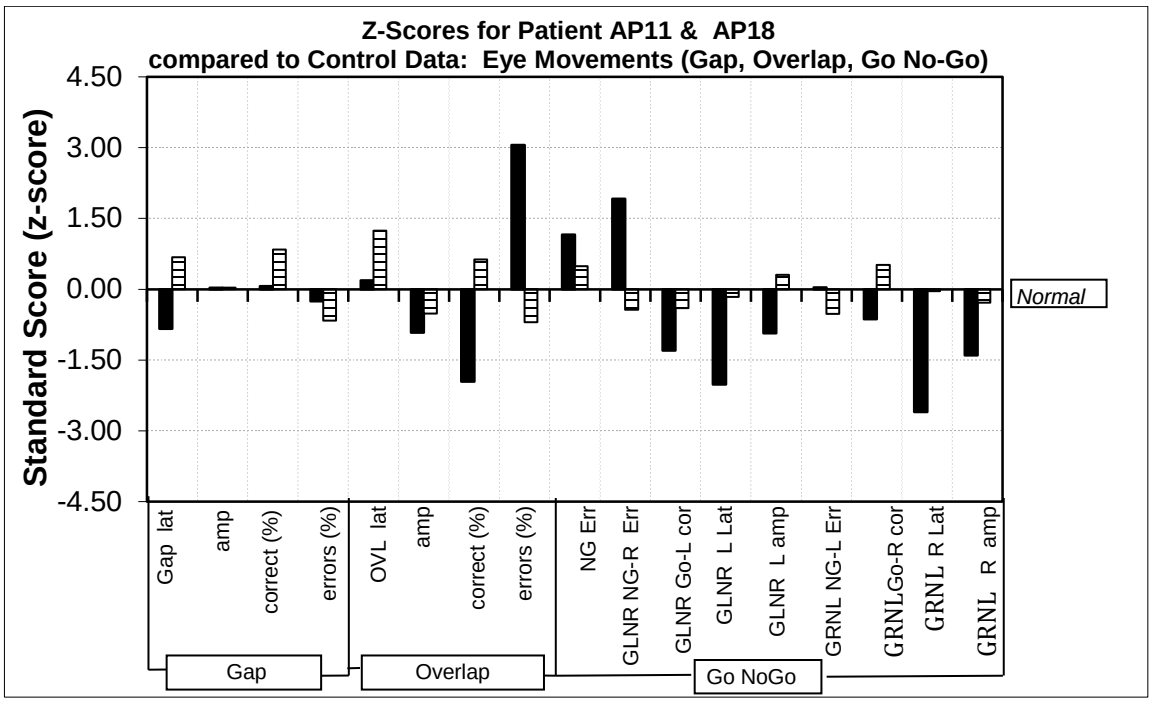

Z-Scores for Patient AP11 & AP18
compared to Control Data: Eye Movements (Gap, Overlap, Go No-Go)
Standard Score (z-score)
4.50
3.00
1.50
0.00
-1.50
-3.00
-4.50
Normal
Gap lat
amp
correct (%)
errors (%)
OVL lat
amp
correct (%)
errors (%)
NG Err
GLNR NG-R Err
GLNR Go-L cor
GLNR L Lat
GLNR L amp
GRNL NG-L Err
GRNLGo-R cor
GRNL R Lat
GRNL R amp
Gap
Overlap
Go NoGo

Fig 3c

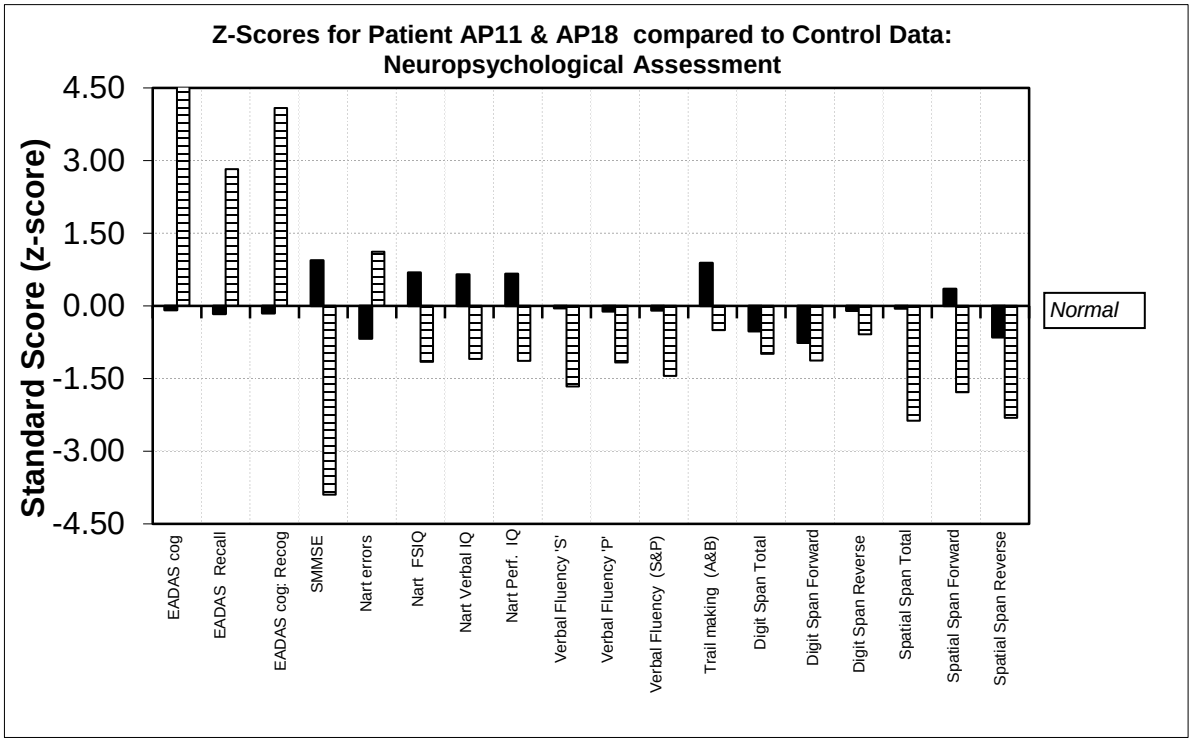

Z-Scores for Patient AP11 & AP18 compared to Control Data:
Neuropsychological Assessment
Standard Score (z-score)
4.50
3.00
1.50
0.00
-1.50
-3.00
-4.50
EADAS cog
EADAS Recall
EADAS cog: Recog
SMMSE
Nart errors
Nart FSIQ
Nart Verbal IQ
Nart Perf. IQ
Verbal Fluency 'S'
Verbal Fluency 'P'
Verbal Fluency (S&P)
Trail making (A&B)
Digit Span Total
Digit Span Forward
Digit Span Reverse
Spatial Span Total
Spatial Span Forward
Spatial Span Reverse
Normal

Fig 4a

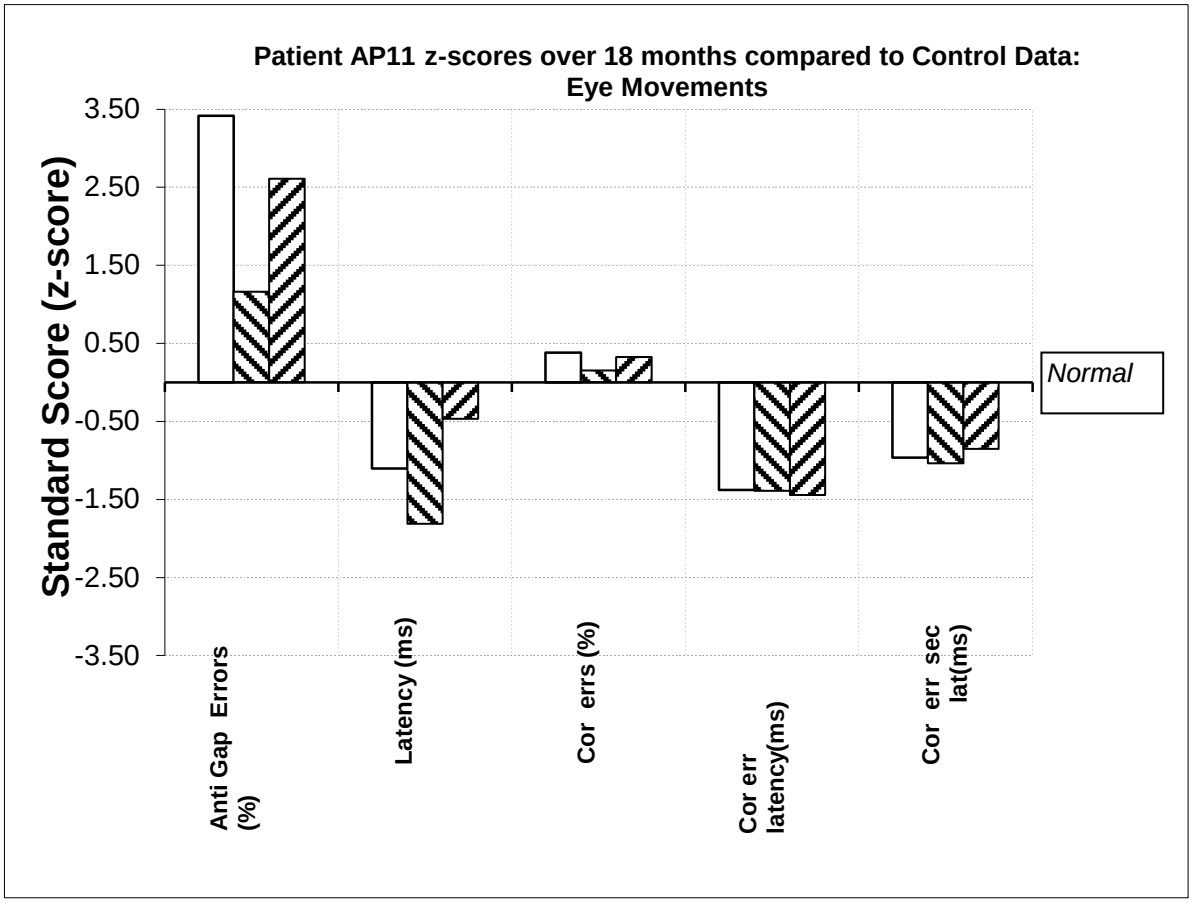
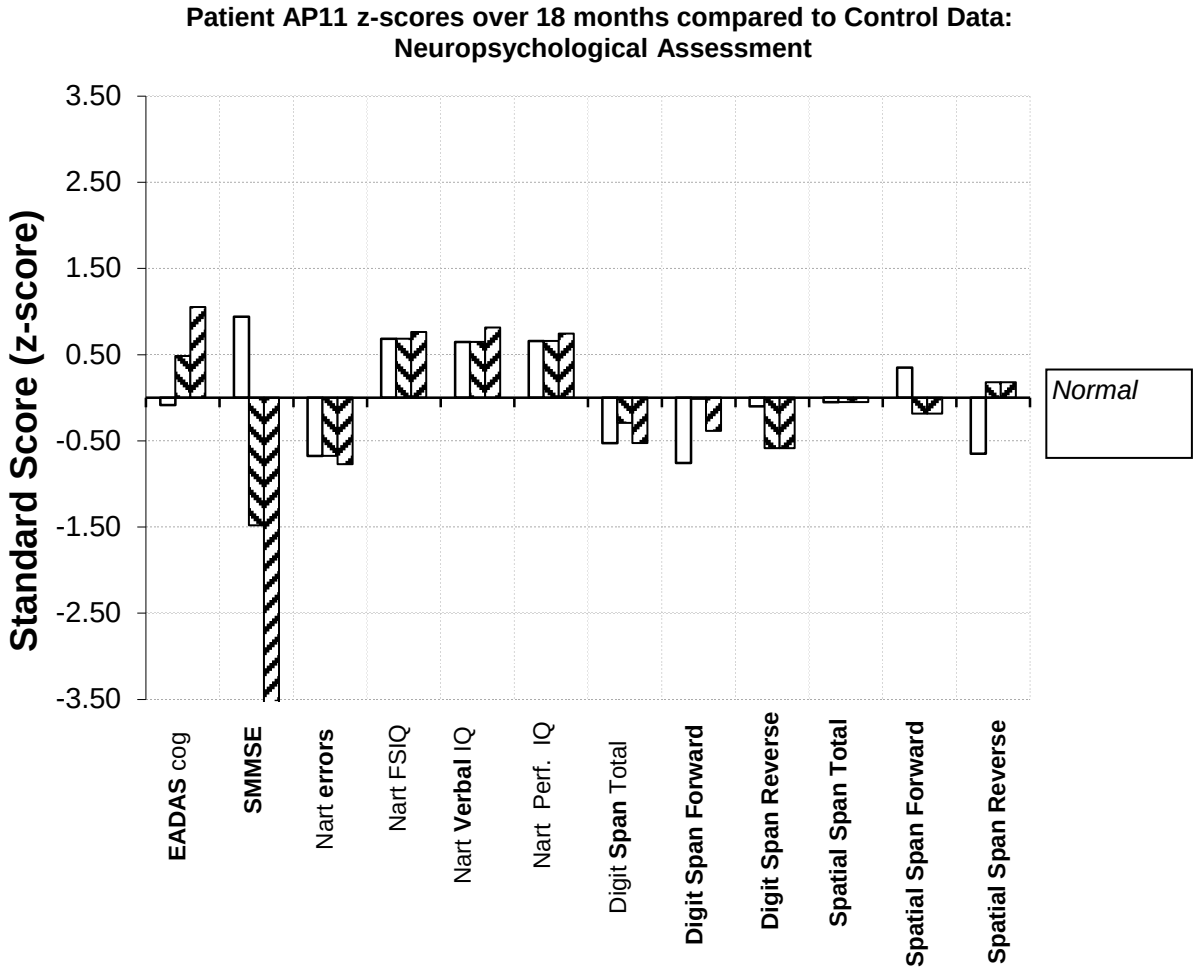

Patient AP11 z-scores over 18 months compared to Control Data:
Eye Movements
Standard Score (z-score)
3.50
2.50
1.50
0.50
-0.50
-1.50
-2.50
-3.50
Anti Gap Errors (%)
Latency (ms)
Cor errs (%)
Cor err latency(ms)
Cor err sec lat(ms)
Normal

Fig 4b


Patient AP11 z-scores over 18 months compared to Control Data: Neuropsychological Assessment
Standard Score (z-score)
3.50
2.50
1.50
0.50
-0.50
-1.50
-2.50
-3.50
EADAS cog
SMMSE
Nart errors
Nart FSIQ
Nart Verbal IQ
Nart Perf. IQ
Digit Span Total
Digit Span Forward
Digit Span Reverse
Spatial Span Total
Spatial Span Forward
Spatial Span Reverse
Normal