Neurobiological and Lifestyle Contributions to Word-Finding Abilities in Healthy Ageing

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A thesis submitted for the degree of

Doctor of Philosophy

July 4, 2024

Contents

Declaration

I declare that the work presented in this thesis is, to the best of my knowledge and belief, original and my own work. The material has not been submitted, either in whole or in part, for a degree at this, or any other university. This thesis does not exceed the maximum permitted word length of 80,000 words including tables, figures, and footnotes, but excluding the thesis abstract, bibliography, and appendices.

Name: Elise Jisca Oosterhuis

Date: July 4, 2024

Acknowledgements

This PhD thesis would not have been possible without the help of my amazing supervisors. Helen Nuttall, Patrick May, and Kate Slade, I'm so very grateful for all your help and guidance. Helen, you've always supported and encouraged me on a professional and personal level. Through your motivation and enthusiasm, you've guided me through the ups and downs. Patrick, your wisdom and enthusiasm were invaluable for my research endeavours. Kate, as my supervisor, colleague, and friend, thank you for our coffees, cakes, and walks in Williamson's Park. Your passion for research and hard work are a real inspiration to me.

To the members of the NoSA lab, thank you for the fun lab meetings and support. I also had the pleasure of meeting many great participants who offered their time and clean hair to volunteer in my research studies. Thank you Neil Bailey for your expertise and guidance on advanced EEG analyses. Peter Tovee and Barrie Usherwood, thank you for all your technical and programming help. Thanks to my fellow PhD friends, some are already doctors and some will be a doctor very soon. To Kim Hudspeth and Charlotte Rothwell, thank you for all our office chats, our laughs, and the thesis writing support. To Didar Karadağ, it was a pleasure to start our PhD time together. I will miss our coffee and chats. To Rachael Cheung, thank you for your encouragement and our continued friendship. Thank you all, I hope all your dreams for academia and beyond will come through. A special thanks to Frank Sierra. I greatly appreciate your support and encouragement during the last phase of my PhD and the transition to a job in data science.

To my parents Harry and Esther, my sister Maureen, and Sjoerd. Thank you for your love and everlasting encouragement. To Ian, for your love and bearing with me in my emotional ups and downs. I'm ever so grateful to all of you. To the rest of my family, thank you for always showing your interest and for encouraging me. A special thanks to Gert and Jennifer, for our engaging and encouraging chats, and for opening up your home. In memory of my opa Henk, whom I greatly miss. I know you would've been so proud of me.

Lastly, to my friends, Nanneke Boxall, Micky Clancy, Nikki Choong, and Maddie Donnelly. Thank you for many chats, laughs, adventures, and for making me feel loved for the past few years. I love you all. To James and Ellis, for opening up your house when my internet was failing me and for teaching me some British banter. Thank you Pete and Esther Carrington, Malcolm and Debbie Robinson, and my CCL family, for supporting and loving me, and for being my family during my time in Lancaster. I'd like to thank Ross Miller, Nathan Price, Matt Woodrow, and Dom Sulston for our continued friendships, our "easy" hikes, our laughs, and our chats. To Valeriya Tolkacheva, моя дорогая подруга, even though we're so far away, I'm so grateful for our friendship.

But most importantly, I thank God for giving me the strength, patience, and energy. *I can do all things through Christ who strengthens me* (Philippians 4:13).

"The brain is more than an assemblage of autonomous modules, each crucial for a specific mental function. Every one of these functionally specialized areas must interact with dozens or hundreds of others, their total integration creating something like a vastly complicated orchestra with thousands of instruments, an orchestra that conducts itself, with an ever-changing score and repertoire."

Oliver Sacks (2007). *Musicophilia: Tales of Music and the Brain.*

Abstract

Neurobiological and Lifestyle Contributions to Word-Finding Abilities in Healthy Ageing

Elise Jisca Oosterhuis, MSc

Cognitive ageing is a highly complex and individualised process influenced by underlying neurobiology and lifestyle factors, where the latter also influences the former. Currently, the literature lacks clarity on factors influencing healthy cognitive ageing, particularly concerning word-finding difficulties, which are a primary challenge associated with ageing. This thesis aimed to investigate the neurobiological and lifestyle contributions to word-finding in healthy ageing.

Chapter 2 reviewed the revisited Scaffolding Theory of Aging and Cognition and Cognitive Reserve (CR) theory. Chapters 3 and 4 investigated the relationship between CR and word-finding across the lifespan and in Parkinson's disease (PD). The findings revealed that education, occupation, and current lifestyle choices support word-finding in middle-aged but not in older adults or PD. Contrary to previous literature, CR did not have a positive impact in older adults or PD but did mitigate word-finding difficulties in middle age.

Chapter 4 investigated the link between action language and motor ability in PD. We demonstrated a relationship between motor and word-finding ability in both individuals with and without PD, suggesting a potential shared neuronal circuit. Chapters 5 and 6 aimed to investigate the role of neural coherence in word-finding among younger and older adults using electroencephalography. Chapter 5 revealed a link between word-finding difficulties and functional brain networks, especially in the delta band. Finally, Chapter 6 demonstrated greater frontocentral phase coherence in older adults during action word comprehension, with greater frontocentral phase coherence being related to faster action word processing in both younger and older

adults.

Overall, this thesis provided evidence for lifestyle contributions to word-finding abilities in middle-aged but not in older adults. The findings also emphasised the significance of neurobiological factors, especially phase coherence, in maintaining word-finding abilities across the lifespan. The final chapter of this thesis will discuss implications, limitations, and suggestions for future research.

"I am writing this with my left hand, although I am strongly right-handed. I had surgery to my right shoulder a month ago (. . .) and am not capable of use of the right arm at this time. I write slowly, awkwardly - but more easily, more naturally, with each passing day. I am adapting, learning, all the while - not merely this left-handed writing, but a dozen other left-handed skills as well: I have also become very adept, prehensile, with my toes, to compensate for having one arm in a sling. (. . .) I am developing different patterns, different habits. . . a different identity, one might say. There must be changes going on with some of the programs and circuits in my brain - altering synaptic weights and connectivities and signals (though our methods of brain imaging are too crude to show these).(. . .)

Defects, disorders, diseases, in this sense, can play a paradoxical role, by bringing out latent powers, developments, evolutions, forms of life, that might never be seen, or even be imaginable, in their absence. (...)

Thus while one may be horrified of the ravages of developmental disorder or disease, one may sometimes see them as creative toon- for if they destroy particular paths, they may force the nervous system into making other paths and ways, force on it an unexpected growth and evolution. This other side of development or disease is something I see, potentially, in almost every patient; and it is this, here, which I am especially concerned to describe.(. . .)

Oliver Sacks (1993). *An anthropologist on Mars: seven paradoxical tales.*

Chapter 1

Introduction

To promote well-being in healthy ageing, it is important to promote an individual's mental and physical abilities, along with their environment and the interactions between these different factors (World Health Organization, 2020). Of the mental abilities, older adults recognise word-finding difficulties as the most prominent problem with ageing (Condret-Santi et al., 2013). This thesis focused on the neurobiological and lifestyle contributions of word-finding abilities in healthy cognitive ageing. We investigated the impact of lifestyle choices (e.g., engaging in cognitively stimulating activities) and lifetime experiences (e.g., education) on word-finding abilities across the lifespan. Moreover, the thesis focused on word-finding ability in relation to action words (i.e., words that describe physical actions, such as "*throwing*"). The investigation into action word-finding is approached from a healthy ageing perspective, as well as from a neurodegenerative perspective concerning Parkinson's disease. Finally, this thesis employed both behavioural and neurobiological methods to investigate word-finding ability.

1.1 An Ageing Population

Due to increases in life expectancy, 10% of the world population is currently aged 65 years or older, and this number is expected to increase to 16% by 2050 (United Nations, 2022). Normal age-related cognitive changes are linked to age-related

changes in both brain structure and function (Damoiseaux, 2017). Some cognitive functions, such as processing speed and working memory, are more affected by the healthy ageing process than, for example, general knowledge (Salthouse, 2009). The most prominent cognitive problem older adults experience is that of age-related word-finding difficulties (Burke & Shafto, 2004; Condret-Santi et al., 2013). When cognitive changes surpass that of healthy ageing, dementia may develop in some people. Understanding the mechanisms of healthy ageing is one of the main goals of the World Health Organization (WHO), to enable the development of evidence-based intervention and prevention strategies to combat dementia (World Health Organization, 2020). Age is the main risk factor for neurodegenerative diseases, such as Alzheimer's and Parkinson's disease (PD), with PD being the second-most common neurodegenerative disease worldwide (Parkinson's UK, 2018). The increasing incidence of PD in the worldwide population is closely associated with the general trend of an ageing population we see in the world (Ou et al., 2021). Therefore, it is crucial to understand the lifestyle and neurobiological contributions to healthy cognitive ageing, which could help slow down the transition to dementia (World Health Organization, 2022).

1.2 Healthy Cognitive Ageing

Two of the big questions in ageing and dementia research are 1) what factors are involved in healthy cognitive ageing? and 2) why do some people develop dementia whilst others do not? When investigating the mechanisms of healthy cognitive ageing, researchers have focused on external factors, such as lifestyle and lifetime experiences, as well as internal factors, that is, age-related brain changes and neuronal processes to maintain cognitive performance. The following subsections will discuss the lifestyle and neurobiological factors involved in healthy cognitive ageing.

Lifestyle Contributions to Cognitive Ageing

Lifestyle factors, such as physical exercise and engagement in leisure and cognitively stimulating activities, and lifetime experiences, such as greater educational and occupational attainment, have repeatedly been linked to better cognitive functioning in older age (Berggren et al., 2018; Köhncke et al., 2018; Lavrencic et al., 2018). Moreover, education in late life, physical exercise, and higher occupational attainment could delay the onset of dementia, but studies indicate that this may only be the case in people who have a genetic predisposition for dementia (Beckett et al., 2015; McKenzie et al., 2020; Rodriguez et al., 2021; Seeman et al., 2005; Shih et al., 2016; Shih et al., 2018). Hence, when evaluating the lifestyle contributions to cognitive ageing, it is important to consider individual differences and individual ageing trajectories. Such individual differences could be caused by the different positive and negative factors we experience during our lifetime, such as the education we receive or the stress we experience (Livingston et al., 2020).

Two prominent frameworks, Cognitive Reserve (CR) theory (Stern et al., 2020) and the revised Scaffolding Theory of Aging and Cognition (STAC-r; Reuter-Lorenz & Park, 2014), could explain individual differences in cognitive ageing trajectories. These theories have been proposed to explain the complex mechanisms and factors involved in cognitive ageing. Chapter 2 contains a critical literature review on CR and STAC-r. The review discusses evidence for the cognitive ageing mechanisms proposed by either theory, where the two theories overlap, and further outlines the strengths and shortcomings of both theories. The theory touches briefly on other cognitive ageing theories and theories of age-related brain changes, and how such theories relate to CR and STAC-r.

Several studies have investigated the effects of lifestyle choices and lifetime experiences on cognitive domains, such as executive functioning and memory (see Chapter 2). However, research on whether a combination of different lifestyle choices and lifetime experiences might attenuate word-finding abilities across the lifespan is currently lacking. Hence, Chapter 3 reports an empirical study, investigating

whether CR has a positive effect on word-finding ability in younger, middle-aged, and older adults.

Neurobiological Contributions to Cognitive Ageing

Longitudinal studies indicated that maintained cognitive ability in older age was related to better white matter micro-structure (i.e., structural connections between brain areas), less brain atrophy, and fewer white matter hyperintensities (i.e., tiny brain lesions; Corley et al., 2018; Cox et al., 2021). Hence, deterioration of brain structure might lead to cognitive difficulties in older adults. However, it is currently unclear why some people are still able to maintain cognitive performance despite age-related deterioration of the brain. One reason for this may be linked to compensatory neuronal changes that counteract deterioration (Reuter-Lorenz & Park, 2014; Stern, 2009).

Deterioration of brain status is called "neural decline" and can be counteracted by "neural enhancement", a process of increasing neural resources, such as the genesis of new neurons or changes in brain function (Cabeza et al., 2018). Both CR and STAC-r, as will be discussed in Chapter 2, propose that individuals can compensate for "neural decline" (i.e., deterioration of brain status) by recruiting additional or alternative brain regions and neuronal networks (Reuter-Lorenz & Park, 2014; Stern, 2009). Several researchers have provided hypotheses about the kind of functional brain changes we could observe in older adults, reflecting compensatory processes for age-related brain pathology to maintain cognition (see Table 1 in Chapter 2 for a description of these hypotheses). Moreover, both CR and STAC-r posit that the ability to compensate for pathology-induced cognitive decline is enabled through lifestyle factors and lifetime experiences, as discussed in Section 1.2. Multiple methodological techniques to measure brain functioning have been implemented to investigate age-related changes in brain functioning. However, further research is required regarding the neuronal mechanisms underpinning age-related word-finding difficulties. Therefore, Chapter

5 used secondary electroencephalography (EEG) data to investigate the relationship between changes in brain segregation and integration measures and word-finding ability in younger and older adults. Chapter 6 describes an in-person EEG study, which investigated whether action word-finding ability declines with age or remains relatively preserved.

1.3 A Theoretical Model Explaining Word-Finding

This thesis focused on neurobiological and lifestyle contributions to age-related changes in word-finding ability. Therefore, the following sections will review a theoretical model of word-finding as well as the word-finding difficulties observed in healthy ageing.

Word retrieval, also called "lexical access", is a cognitive process during which words are retrieved from long-term memory (Levelt et al., 1999). In this thesis, word-finding ability or lexical access means the activation (i.e., retrieval) of words in our long-term memory and the higher-order cognitive processes involved (Pisoni et al., 1985). Over the years, several psycholinguistic models have been proposed to explain word-retrieval processes. Most models focused either on word production or comprehension, such as the Parallel-Distributed-Processing (Seidenberg & McClelland, 1989), Dual Route Cascaded Model (Coltheart et al., 2001), Dell's Interactive Two-step Model (Dell et al., 1997), and the Logogen model (Morton, 1969). The current thesis does not aim to provide evidence for these models. However, to give the reader a theoretical overview of how words are accessed from our memory in single-word production and comprehension, we will discuss the WEAVER++ model in more detail in the next section (Levelt et al., 1999; Roelofs, 2005, 2014).

The WEAVER++ Model of Single Word Production and Comprehension

The WEAVER++ model presents word production and comprehension as a staged process. Figure 1.1 provides a schematic overview of the word production and comprehension stages proposed by the WEAVER++ model. The first stage is the conceptualisation stage during which the concept or idea is generated. In the case of a picture-naming task, the concept is generated by recognising the visual object presented via the picture (Levelt et al., 1998). For verbal fluency tasks, the ideas or concepts are generated through a verbal prompt that has been given to the participant. The model can also be used for written word comprehension (e.g., lexical decision; Roelofs, 2023). However, during written word comprehension, the lemma retrieval stage or word-form encoding stage is immediately accessed, bypassing the conceptualisation stage (Indefrey & Levelt, 2004; Roelofs, 2023). After the lexical concept has been generated, the word with its semantic and syntactic properties (i.e., lemma) is selected among other lexical competitors (Levelt et al., 1999).

The next two stages involve the encoding of the word form, which includes morphological, phonological, including the metric or syllable structure of the phonological word form, and phonetic encoding. Finally, the motor speech commands necessary to orally produce the word, such as that of the vocal tract, are generated, and the word is articulated and presented as a sound wave during the articulation stage. Importantly, the model also includes "self-monitoring", during which the speaker hears themselves speak (either overtly/externally or covertly/internally). Self-monitoring enables the detection of any errors or disfluencies in the speech.

Recently, the WEAVER++ model was updated using behavioural, neuroimaging, and clinical evidence, into the WEAVER++/ARC model (Roelofs, 2014). Importantly, the WEAVER++/ARC makes a distinction between declarative and procedural

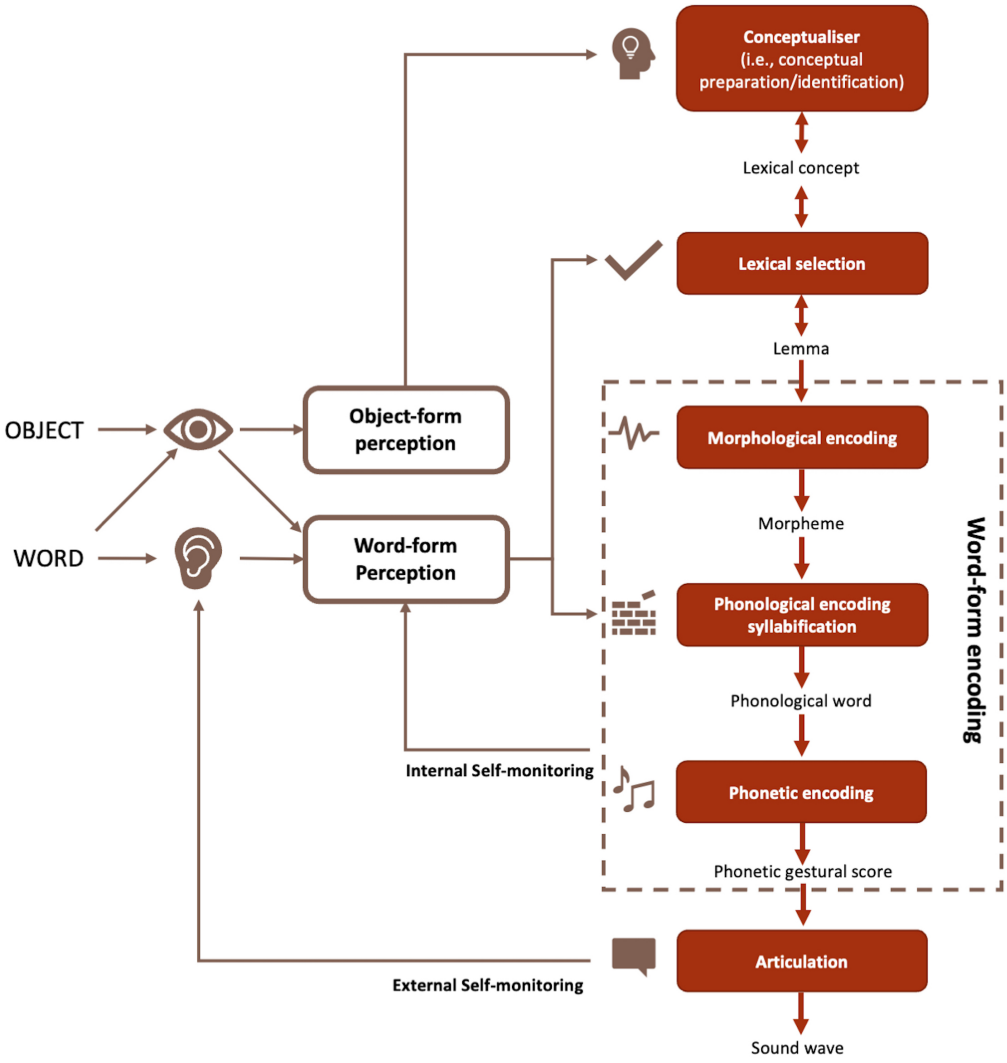

Figure 1.1. The WEAVER++ model of single-word production. Adapted from Levelt and colleagues Levelt et al. (1999) and Roelofs (2005)

memory for word processing. That is, in the lexical system, declarative memory includes memory for word meaning, form, and category, whilst procedural memory involves lexical grammar, such as word inflections, and phonological rules (Ullman, 2004). The lexical network, including declarative and procedural memory, is subserved by a broad network of neuronal connections and brain regions.

To summarise, this section discussed a theoretical model for spoken and written word-finding. However, we have not yet discussed how ageing can affect these

processes. We will, therefore, discuss the effect of age on word-finding in the next subsection.

Word-Finding Difficulties in Healthy Ageing

Word-finding difficulties have been demonstrated in healthy cognitive ageing (Marini & Andreetta, 2016; Mortensen et al., 2006). Word-finding difficulties typically occur around the age of 40 or 50 years (Kavé & Knafo-Noam, 2015). Word-finding ability can be measured through picture-naming and verbal fluency or "word generation" tasks (Whiteside et al., 2016). In a verbal fluency task, the participant is given a fixed time limit, typically one or two minutes, to generate as many words as possible belonging to a certain semantic category (i.e., semantic fluency; e.g., *"animals"*) or starting with a certain letter (i.e., letter fluency; e.g., */s*). Studies on semantic- and letter-fluency tasks have revealed an age-related decrease in the number of generated words, with an earlier onset and faster decline for semantic fluency compared to letter fluency (Gordon et al., 2018; Kavé & Knafo-Noam, 2015; McDowd et al., 2011). Another way of measuring word-finding ability is through naming pictures of objects and actions (Mortensen et al., 2006), which is found to be more difficult for older than younger adults (e.g., Connor et al., 2004; Kavé et al., 2010; Mackay et al., 2002). In this thesis, Chapters 3 - 5 investigated word-finding ability through verbal fluency and picture-naming tasks, assessing word production.

In word comprehension studies, lexical-decision tasks have been used to assess word-finding abilities (Seidenberg & McClelland, 1989). Lexical decision requires an individual to decide whether a string of letters represents a word or a non-word by pressing a button. Whilst the accuracy of lexical decisions remains high across the lifespan, reaction times slow down with age (Davies et al., 2017; Ratcliff et al., 2004). In contrast, studies have revealed an asymmetry between word production and comprehension in that age-related declines in word comprehension seem to be very subtle if not absent whilst word production is more affected by age (James & MacKay, 2007). Hence, for a more complete picture of the age-related effects

on word-finding ability, it is important to investigate both word production and comprehension. Therefore, Chapter 6 focused on word comprehension, using a lexical-decision task.

1.4 Neurobiology of Word-Finding

The Neuroanatomy and Neurophysiology of Word-Finding

Years of neuroimaging and electrophysiological studies have revealed a widespread network of brain regions involved in word-finding. Following the scope of the thesis, this section will be limited to discussing the neurobiology of spoken word production and written word comprehension, with an emphasis on lexical access. This section will review the brain regions underlying word-finding following MRI studies as well as its time course, based on electroencephalography (EEG) and magnetoencephalography (MEG) studies. Because the time course of word-finding processes is partly based on event-related potentials (ERPs) components, we will also briefly discuss the ERP components involved in lexical access.

The first stage, conceptual preparation, starts 150-200ms after stimulus onset (Indefrey & Levelt, 2004; Indefrey, 2011). Semantic concepts activate partly overlapping brain regions, mostly left-lateralised, during single-word production and comprehension (Binder et al., 2009; Price, 2010, 2012). Regions include the angular gyrus, lateral and ventral temporal cortex (e.g., middle temporal gyrus), ventral medial and dorsomedial prefrontal cortex, inferior frontal gyrus, and posterior cingulate gyrus (see Figure 1.2).

Furthermore, researchers largely agreed that linguistic concepts encompass action, perception, and emotion features, activating brain regions underlying such features (Kemmerer, 2019). For example, the word *"hammer"* would activate brain regions linked to the action of hammering. Perception involves what the hammer feels, looks, and sounds like, while emotion involves the emotions an individual associates with *"hammer"*, for example, the pain of hitting one's thumb.

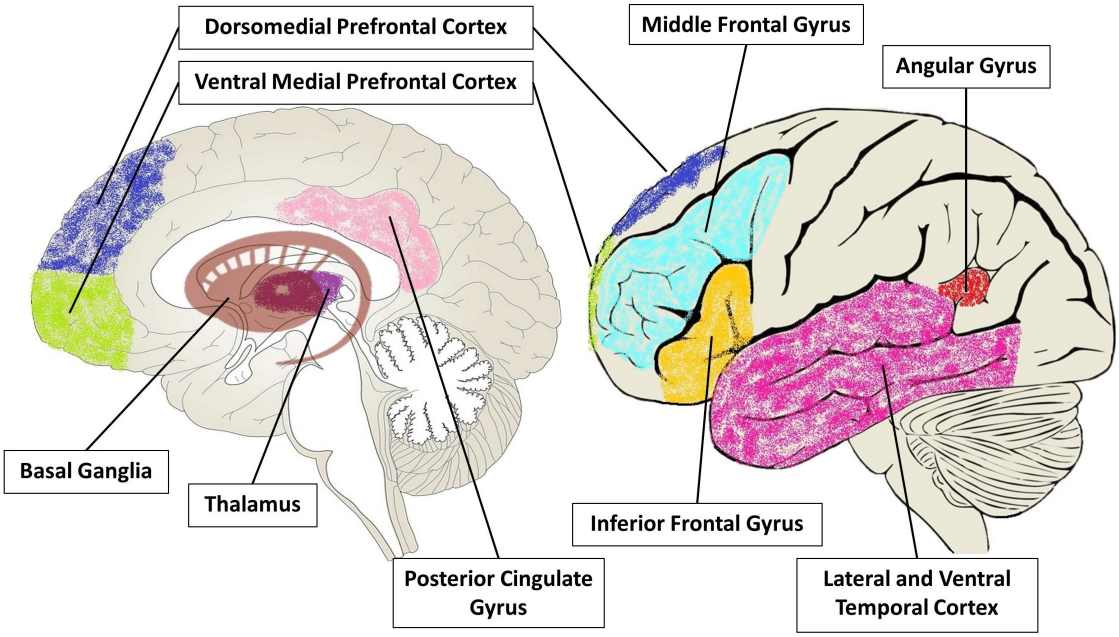

Figure 1.2. Brain regions involved during the lexical access stage of word-finding.

These features are then combined in a multimodal hub region, often believed to be comprised of the anterior temporal lobes, which is involved in the conceptual processing of both written words and pictures (Rice et al., 2015; Visser et al., 2010). Cortical thinning of the anterior temporal lobes may lead to impairments in naming performance (Domoto-Reilly et al., 2012).

The lemma retrieval process starts around 200ms after stimulus onset and takes approximately 75ms. For written word comprehension, lexical access starts around 200ms after the word has been presented. However, during written word comprehension, lexical access relies on the written word form rather than a conceptual meaning. Morphophonological encoding starts around 275ms after stimulus onset and takes about 80ms (Indefrey & Levelt, 2004; Indefrey, 2011). Both conceptual preparation and morphophonological encoding processes continue during the next stage. The left (posterior) middle temporal gyrus and the left middle frontal gyrus (see Figure 1.2) likely underlie lexical access (Kemmerer, 2019; Lau et al., 2008; Piai & Eikelboom, 2023; Price, 2010). More specifically, the left middle temporal gyrus is mainly activated during the retrieval of object nouns (Kemmerer,

2019). In contrast to object nouns, action verbs might be supported by different brain regions (discussed in section 1.5). During lemma retrieval, the inferior frontal gyrus and the anterior cingulate gyrus are thought to underlie cognitive control mechanisms, such as inhibition and attention (Haber, 2016; Kemmerer, 2019).

Regarding the ERP components involved in lexical access, the N200/N250 component (i.e., a negative peak around 200-300ms post-onset) is thought to reflect early lexical access processes, reflecting the retrieval of written word forms (Grainger & Holcomb, 2009). In addition, the N400 is an important ERP component underlying word-finding ability and takes place within a time window of 200-600ms, with a negative peak around 300-400ms post-stimulus-onset (Kutas & Federmeier, 2011). The N400 might reflect semantic processing and facilitated lexical access (de Zubicaray & Schiller, 2019; Kutas & Federmeier, 2011; Lau et al., 2008). Moreover, the N400 has been proposed to indicate lexical competition during written word comprehension (Meade et al., 2018).

Phonological encoding (i.e., syllabification) starts around 355ms and takes on average 235ms, however, the duration is dependent on the number of phonemes and syllables the word contains (Indefrey & Levelt, 2004; Indefrey, 2011). The next stage, phonological form retrieval processes during speech production, takes place in the left posterior superior and middle temporal gyri (i.e., Wernicke's area; Indefrey & Levelt, 2004; Kemmerer, 2019; Price, 2012). Syllabification processes activate the left posterior inferior frontal gyrus (i.e., Broca's area; Indefrey & Levelt, 2004; Indefrey, 2011; Kemmerer, 2019).

Finally, it is difficult to entangle the phonetic encoding and articulation stages due to overlapping cognitive processes (Indefrey & Levelt, 2004). The phonetic encoding stage starts around 455ms but might start earlier, once the first syllable has been phonologically encoded. This stage ends when the articulation of the word starts. Neuroanatomical studies have indicated the left ventral pars opercularis (i.e., inferior frontal gyrus) and left ventral premotor cortex as the brain regions responsible for phonetic encoding (Kemmerer, 2019; Price, 2012). Several motor and

pre-motor areas, among others, are involved during articulatory processes (Price, 2010).

Hence, when investigating age-related changes in word-finding ability, it is important to take into account the neurobiological contributions to word-finding ability with ageing. In this thesis, we specifically focused on neuronal coherence, an aspect of neurophysiology, which will be discussed in the next subsection.

Neuronal Coherence

At a micro level, our brain is capable of rapidly synchronising neuronal activity across different groups of neurons, enabling fast information processing between brain regions. This synchronisation of neuronal activity is also called coherence and subserves higher-order cognitive functions and cognitive flexibility (Fries, 2005, 2015; Uhlhaas et al., 2009). The 'neuronal communication through neuronal coherence' hypothesis states that groups of neurons communicate by aligning or synchronising their oscillatory fluctuations, both their frequencies and phase, with other groups of neurons (i.e., coherence; Fries, 2005). Frequency is the speed of brain oscillations (in Hertz) and phase is the position of the oscillation at a certain point in time (Cohen, 2014). Cognitive demands can also shape the dynamics of neuronal communication. Following Fries' (2005) hypothesis, neuronal coherence could subserve word-finding ability and other related cognitive processes. Moreover, changes in oscillatory activity might indicate age-related cognitive decline and decline following neurodegenerative disease (Courtney & Hinault, 2021). More specifically, increases and decreases in neuronal coherence as a consequence of healthy or pathological ageing can signal compensatory and maladaptive neuroplasticity. The exact neurophysiological mechanisms underlying age-related word-finding difficulties are still unclear. Investigating how neuronal coherence supports word-finding ability in older age could provide further insights into the processes underlying word-finding.

Methods to Investigate Neuronal Coherence

Neuronal coherence can be investigated in several ways. It can be quantified by determining functional connectivity, which measures the statistical dependencies (i.e., correlations) between different neuronal populations (Friston, 1994; Sporns et al., 2004). Neuronal coherence can also be measured through inter-trial phase coherence (ITPC), which measures the synchrony between phases (i.e., the consistency between phases) that are time-locked to specific events or stimuli (Delorme & Makeig, 2004).

In the current thesis, functional brain connectivity during rest (i.e., in the absence of a task) was evaluated to investigate whether functional brain connectivity is related to word-finding difficulties in older age. Resting-state EEG analyses hold significance due to the ease and speed of administering resting-state EEG recordings. Such analyses offer valuable insights into cognitive functioning, as well as the potential for diagnosing and treating neurodegenerative diseases (Ishii et al., 2017; O'Neill et al., 2018; Rosazza & Minati, 2011; van Diessen et al., 2015). One kind of resting-state analysis employs graph theory, which can be used to map and describe functional brain networks. In functional brain networks, the nodes represent brain regions or EEG electrode positions, and the edges represent the neuronal coherence between the nodes (Bullmore & Sporns, 2009; Sporns et al., 2004).

Through the identification of functional brain networks via EEG, we can investigate the effects of physiological ageing and identify biomarkers for age-related pathology, including dementia (Valizadeh et al., 2019; Vecchio et al., 2020). Next, we can derive measures of functional connectivity from functional brain networks, such as the strength of neuronal coherence or the organisation of the brain network. Such measures can give an indication of the brain's efficiency or strength of information transfer between different brain regions (Bullmore & Sporns, 2009; Fries, 2005). We can link functional connectivity measures to behaviour, enabling the investigation of neuronal mechanisms underlying age-related cognitive changes. Therefore, Chapter 5 takes a graph theoretical approach, using secondary EEG data to investigate

the relationship between changes in functional brain networks and word-finding ability in younger and older adults. By increasing our understanding of how functional brain networks change with age and what effect this has on word-finding ability, intervention techniques could be developed that are aimed at maintaining or optimising functional brain networks that support word-finding ability in older age.

Another measure, ITPC, is quantified using time-frequency-based analysis. The phase consistency obtained through ITPC has been suggested to reflect the synchronisation of neuronal activity across neuronal populations (Cohen, 2014). Few studies have investigated the relationship between age and ITPC. These studies showed that theta band ITPC might increase from childhood into adulthood and decrease again in older age, possibly reflecting increases and decreases in cognitive control (Papenberg et al., 2013). Increased theta band ITPC in younger compared to older adults might also reflect early attention processes related to working memory (Ho et al., 2012). ITPC has been argued to reflect neuroplasticity with age (in younger adults vs. children; Yordanova & Kolev, 2009) and brain reorganisation after stroke (Gyulai et al., 2021). Therefore, investigating age-related changes in ITPC underlying word-finding can provide us with insights into the brain mechanisms underlying age-related word-finding abilities.

Subcortical Involvement in Word-Finding

Not only cortical but also subcortical areas are involved in word-finding. According to the WEAVER++/ARC model, the basal ganglia and thalamus underpin the procedural memory system in the lexical network (Roelofs, 2014). The thalamus has been proposed to control and adapt the connectivity between cortical areas, due to the connections between the thalamus and cortical areas, including Broca's area (Bohsali et al., 2015; Klostermann et al., 2013). That is, the thalamus might be involved in language processing by enabling communication and information exchange between thalamocortical neurons (Klostermann et al., 2013). Moreover, the thalamus has been proposed to act as a "gatekeeper" in cognition, including

language, by selectively filtering and passing on information to different brain areas (Moustafa et al., 2017). For word-finding specifically, the cortico-thalamic connections may enable the binding of multiple perceptual features of words, such as action features, during language production and comprehension (Bohsali et al., 2015).

Another subcortical structure involved in word-finding is the basal ganglia (see Figure 1.2). In conjunction with the basal ganglia, the thalamus may be involved in the process of mapping a semantic concept onto an appropriate word whereby the basal ganglia reduces the probability of error during the word-finding processes (Crosson, 2021). The basal ganglia might also play a domain-general role in the controlled selection and inhibition of words during language production and comprehension (Copland et al., 2021). Furthermore, the basal ganglia have connections to the cortex, including frontal and motor areas, which form cortico-basal ganglia pathways (see Section 1.6 and Figure 1.3; Alexander et al., 1986). Several of such pathways seem to play a role in cognition and language (for a review, see Copland et al., 2021). Specifically, the pathway between the basal ganglia and the frontal cortex (i.e., the frontostriatal pathway) seems involved in combining motor/action and linguistic information (Birba et al., 2017; Ullman, 2004). Consequently, certain subcortical brain regions, like the basal ganglia, could have a specific role in accessing and integrating motor aspects of words. As a result, we will discuss the neurobiological differences between action and object words in the following section.

1.5 Action versus Object Words

Word-finding involves both nouns and verbs. Different but partially overlapping brain regions and networks seem to be involved depending on whether our brain processes a noun or verb. Therefore, the empirical study in Chapter 3 distinguishes between object and action word-finding ability and, additionally, considers the effect

of age-related changes in general cognitive processing. Lesion studies showed that noun deficits follow from damage of the temporal cortices while verb deficits can occur after a lesion in a variety of different brain regions, including the frontal lobe or basal ganglia (Mätzig et al., 2009). However, some authors argued that the different brain patterns are caused by semantics (i.e., object vs. actions) and not grammatical class (Moseley & Pulvermüller, 2014, i.e., nouns vs. verbs). This argument falls within the embodied cognition framework and is based on the idea that different conceptual features, such as motor and perceptual features, are grounded in corresponding brain regions (e.g., those involved in motor processing; Barsalou, 1999; Kiefer & Pulvermüller, 2012; Lakoff & Johnson, 1980). Indeed, knowledge of objects and actions seems to be represented in the left inferior temporal cortices and prefrontal cortex, respectively, but such distinction was not found for grammatical class (Vigliocco et al., 2011). Action words are words that describe physical action, such as the word *"throwing"*. Action verb naming involves brain regions in the precentral gyrus (or primary motor cortex), inferior frontal gyrus, and basal ganglia (Akinina et al., 2019). Hence, action verbs seem to activate motor-related brain regions. Not only verbs but also nouns can possess motor/action features (e,g., how manipulable an object is), such as the word *"hammer"* and other tools (Kellenbach et al., 2003). Evidence comes from aphasia and dementia studies, which found that high-manipulable words were more impaired in individuals with aphasia and dementia, irrespective of the word's grammatical class (Arévalo et al., 2007; Bak & Hodges, 2003).

Both older and younger adults seem to rely on different types of mental representations, using sensory knowledge among others, to process language (Burke, 2006). Activation of motor-related brain regions might facilitate word-finding (Akinina et al., 2019). Degradation of these brain regions with age, possibly as a result of neural dedifferentiation (see Chapter 2) could lead to a decrease in the link between perceptual/motor systems and cognition (Baltes & Lindenberger, 1997; Costello & Bloesch, 2017). Regarding word-finding, some researchers argued

that action word-finding is relatively preserved with age (Reifegerste et al., 2021) whilst others argued that action language declines in older adults (Bidet-Ildei et al., 2020). Activation of intact motor-related brain regions might facilitate word-finding in older age to maintain performance. In addition, age-related declines in motor-related brain regions could be related to action language declines in older adults. Both ideas imply that the preservation of motor brain regions might be important in maintaining action word-finding in older age. However, research into the effects of age on the neuronal mechanisms underlying action language is currently sparse. Therefore, Chapter 6 describes an in-person EEG study to investigate whether action language declines with age or whether action word-finding ability remains relatively preserved. More specifically, ITPC in the frontocentral brain region was investigated as a neuronal signature of action language and whether there is a difference in ITPC between younger and older adults. In addition, the study distinguished between high- and low-action content of words but not between nouns and verbs.

1.6 Parkinson's Disease as a Neurodegenerative Model for Word-Finding

Word-finding difficulties are also present in individuals with Parkinson's disease (PD; Henry & Crawford, 2004). In particular, action language seems to be affected in PD (e.g., Bocanegra et al., 2017; Cotelli et al., 2007; Herrera, Rodríguez-Ferreiro, et al., 2012). Therefore, action word-finding difficulties in PD are especially of interest when investigating the neurobiological contributions of word-finding. This paragraph will discuss the neural system affected in individuals with PD, mainly that of the basal ganglia, and how pathology-related changes in the neural system relate to action language.

Basal Ganglia Dysfunction

The classical basal ganglia model includes a "direct" and an "indirect" pathway (see Figure 1.3; Albin et al., 1989; Alexander & Crutcher, 1990). The direct pathway is comprised of striatal neurons projecting to output basal ganglia structures (the globus pallidus internus (GPi) and substantia nigra pars reticulata), allowing motor initiation by disinhibiting the thalamus. The indirect pathway involves striatal neurons projecting to output basal ganglia structures through the globus pallidus externus (GPe) and the subthalamic nucleus (STN), suppressing movement by inhibiting the thalamus. The "hyperdirect" pathway connects the cortex (inferior frontal gyrus and pre-supplementary motor area) to the STN, bypassing the striatum, enabling swift modulation of basal ganglia outputs (Nambu et al., 2002). This pathway is important for stopping movements that have already been initiated, based on stop- and conflict signals (Aron et al., 2016; Chen et al., 2020).

In PD, dopaminergic neurons in the substantia nigra pars compacta degenerate, resulting in dopamine loss (Jellinger, 2012; Postuma et al., 2015). This loss impacts basal ganglia structures, thalamus, and neuronal pathways between the basal ganglia and cortical areas. It increases the activity of the indirect pathway while reducing direct pathway activity. Consequently, the thalamus gets excessively inhibited via heightened GPe inhibition, increased STN activity, and intensified GPi influence on the thalamus (McGregor & Nelson, 2019). Basal ganglia dysfunction in PD, but also in Huntington's disease, small vessel disease, and basal ganglia strokes, can cause difficulties in word-finding ability (Camerino et al., 2022).

Action Language in Parkinson's Disease

Dysfunction of the frontostriatal pathway could lead to difficulties with action language in PD (Auclair-Ouellet et al., 2017; Birba et al., 2017). Language impairments may even indicate frontostriatal pathway dysfunction in the early stages of PD (Auclair-Ouellet et al., 2017). Since the core clinical characteristics of PD are

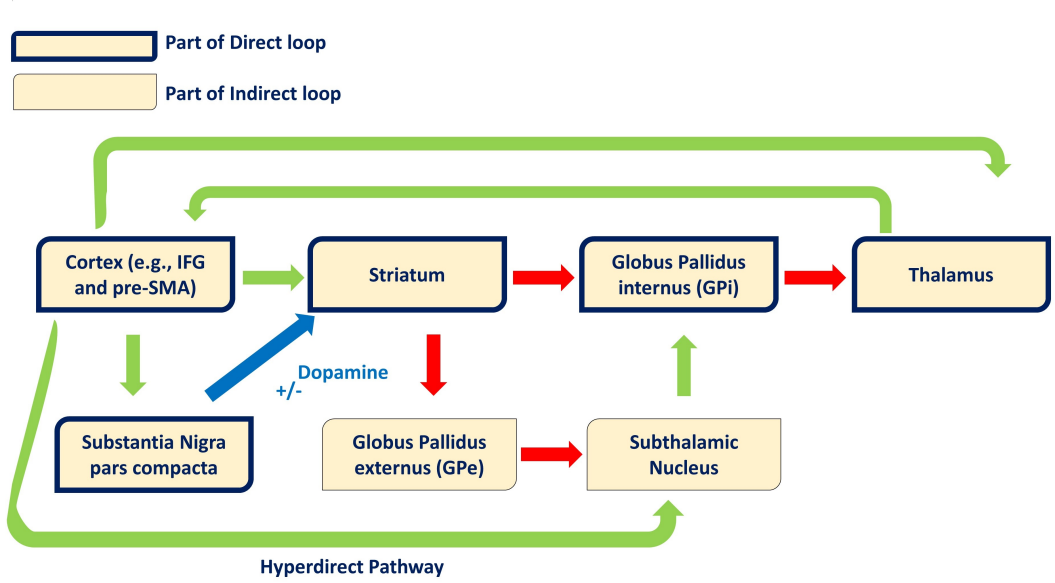

Figure 1.3. Classic Basal Ganglia model with the direct, indirect, and hyperdirect pathways. Green arrows indicate excitatory pathways whilst red arrows indicate inhibitory pathways. Movement is suppressed by stronger inhibition of the thalamus whilst disinhibition of the thalamus allows movement initiation. Dopamine is important to increase (more dopamine) or decrease inhibition (less dopamine) of the striatum. Dopamine loss in Parkinson's increases the disinhibition of the striatum and increases thalamus inhibition, which hinders motor initiation.

motor symptoms, such as bradykinesia (Postuma et al., 2015), investigating action word-finding abilities in PD offers a valuable opportunity to provide further insights into the neurocognitive systems underlying action language.

Studies suggested that difficulties in action language might stem from the involvement of the brain's motor systems, including the basal ganglia (i.e., action language being "grounded" in motor systems; Birba et al., 2017; Bocanegra et al., 2015; Gallese & Cuccio, 2018). That is, brain motor systems support action word-finding, but PD-related dysfunction of such systems may result in action word-finding difficulties (Boulenger et al., 2008). If action language is indeed grounded in the brain's motor systems, we would expect a relationship between action language and motor ability as both skills rely on similar neuronal systems. However, most

studies provided evidence against such a relationship (Bocanegra et al., 2017; Johari et al., 2019).

Evidence for such a relationship comes from a study by Roberts et al. (2017), showing that greater upper-limb impairment (i.e., that of the hand and arm) was related to slower processing of verbs describing upper-limb actions in PD. However, whether motor ability and action language of specific body parts, such as the upper limbs, are also related in individuals without PD has not been investigated yet. Hence, individuals without PD might also reveal a relationship between upper-limb action words and upper-limb motor ability. If this is the case, such a relationship will have implications for the idea of grounded action language in both unimpaired and clinical populations. Therefore, Chapter 4 reports an empirical study in people with and without Parkinson's disease. The chapter specifically investigated the relationship between upper-limb motor ability and the production of words (both nouns and verbs) that describe upper-limb actions.

1.7 Summary and Thesis Outline

Cognitive ageing is a complex process, and it is currently unclear what lifestyle and neurobiological factors exactly contribute to healthy cognitive ageing and, more specifically, word-finding ability. Hence, the overall aim of this thesis was to investigate both lifestyle and neurobiological contributions to word-finding abilities in healthy ageing. Therefore, the first part of this thesis focused on lifestyle factors involved in healthy cognitive ageing and its effect on word-finding abilities.

First, this thesis evaluated ageing theories on the mechanisms of healthy cognitive ageing (Chapter 2) and the relationship between word-finding difficulties lifestyle choices and lifetime experiences across the lifespan (Chapter 3). Secondly, the thesis investigated how action language difficulties are linked to motor impairments in Parkinson's disease as a neurodegenerative model (Chapter 4).

Investigating neuronal coherence using EEG data has the potential to illuminate

age-related changes in brain function, and could be used as a method to detect changes beyond that of normal ageing and potentially to predict dementia and track disease progression. Therefore, the second part of the thesis focused on the neurophysiological underpinnings of age-related changes in word-finding abilities. More specifically, the thesis aimed to answer how functional brain networks are linked to age-related word-finding difficulties (Chapter 5). In addition, the thesis aimed to investigate a neuronal signature (i.e., ITPC) underlying action-word comprehension in younger and older adults and whether ITPC underlying action-word comprehension declines with age (Chapter 6). Finally, Chapter 7 provides a general discussion of the findings and limitations of the four empirical studies (Chapters 3 - 6), and outlines directions for future research.

Rationale for Alternative Format

Chapters 2 - 6 in this thesis are written in publishable manuscript format. The review paper in Chapter 2 and the empirical study in Chapter 3 have both been published (Chapter 2: *The Journals of Gerontology Series B: Psychological Sciences*; Chapter 3: *PLOS ONE*). The empirical studies in Chapters 4 - 6 will be submitted for peer review and are therefore presented in publishable manuscript format. The secondary data analysis in Chapter 5 is being prepared for submission to *Neurobiology of Language*. The different chapters in this thesis cover different but important aspects of cognitive ageing, including both behavioural and neurocognitive aspects. Although the chapters contain distinct papers, the topics and findings discussed in these papers are interlinked and provide a logical and unified narrative regarding lifestyle and neurobiological contributions to age-related changes in word-finding ability.

My Contributions to the Research

For all the studies presented in this thesis, I was responsible for the conceptualisation, study design, data collection, data analyses, and the writing and revision of the

manuscripts, under the supervision of Dr Helen Nuttall, Dr Patrick May, and Dr Kate Slade. For Chapter 5, however, secondary data from the "Leipzig Study for Mind-Body-Emotion Interactions" database was analysed due to COVID-19 pandemic restrictions. In addition, the data in Chapters 3 and 4 were collected online, using Teams conference calls and the Gorilla Experiment Builder, due to COVID-19 pandemic restrictions. For Chapters 5 and 6, we collaborated with Dr Neil Bailey (Monash University, Australia), who provided his expertise on complex EEG data analyses (i.e., functional connectivity and ITPC analyses).

Chapter 2

Toward an Understanding of Healthy Cognitive Aging: The Importance of Lifestyle in Cognitive Reserve and the Scaffolding Theory of Aging and Cognition

This chapter reviews two prominent theories of healthy cognitive ageing, Cognitive Reserve (CR) theory and the revised Scaffolding Theory of Aging and Cognition (STAC-r). In particular, we will discuss the mechanisms that contribute to cognitive ageing supported by relevant literature. Such mechanisms include lifestyle choices and lifetime experiences (e.g., physical activity and education), as well as brain function, which are themes discussed throughout this thesis.

Author Note: *This paper was accepted for publication in December 2022 and was produced in collaboration with Dr. Kate Slade, Dr. Patrick May, and Dr. Helen Nuttall as co-authors. It is available as a published paper at:* Oosterhuis, E. J., Slade, K., May, P. J. C., & Nuttall, H. E. (2022). Toward an Understanding of Healthy Cognitive Aging: The Importance of Lifestyle in Cognitive Reserve and the Scaffolding Theory of Aging and Cognition. *The Journals of Gerontology: Series B, gbac197.* https://doi.org/10.1093/geronb/gbac197

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Journals of Gerontology: Psychological Sciences
cite as: *J Gerontol B Psychol Sci Soc Sci*, 2023, Vol. 78, No. 5, 777–788
https://doi.org/10.1093/geronb/gbac197
Advance Access publication December 21, 2022

OXFORD

New Directions in Aging

Toward an Understanding of Healthy Cognitive Aging: The Importance of Lifestyle in Cognitive Reserve and the Scaffolding Theory of Aging and Cognition

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Received: July 1, 2022; Editorial Decision Date: December 8, 2022

Decision Editor: Vanessa Taler, PhD

Abstract

The World Health Organization (WHO) aims to improve our understanding of the factors that promote healthy cognitive aging and combat dementia. Aging theories that consider individual aging trajectories are of paramount importance to meet the WHO's aim. Both the revised Scaffolding Theory of Aging and Cognition (STAC-r) and Cognitive Reserve theory (CR) offer theoretical frameworks for the mechanisms of cognitive aging and the positive influence of an engaged lifestyle. STAC-r additionally considers adverse factors, such as depression. The two theories explain different though partly overlapping aspects of cognitive aging. Currently, it is unclear where the theories agree and differ and what compensation mechanism of age-related cognitive decline might be better explained by either STAC-r, CR, or by both. This review provides an essential discussion of the similarities and differences between these prominent cognitive aging theories, their implications for intervention methods and neurodegenerative disease, and significant shortcomings that have not yet been addressed. This review will direct researchers to common insights in the field and to intervention targets and testable hypotheses for future research. Future research should investigate the potential use of STAC-r in neurodegenerative diseases and provide clarity as to what combination of factors build CR, including their relative importance and when in life they are most effective.

Keywords: Compensatory mechanisms, Intervention, Neurodegenerative disease, Shortcomings

Examining the Mechanisms of Cognitive Decline

The global population over age 65 is expected to increase by 120% between 2019 and 2050 (United Nations et al., 2020). With a rapidly aging population, dementia also becomes more prevalent. Mild cognitive changes are an inevitable part of healthy aging. However, declines in cognitive function beyond the expected age-related changes may signal a transition into dementia. The World Health Organization emphasizes the importance of understanding mechanisms of healthy aging to create evidence-based intervention and prevention strategies to combat dementia (World Health Organization, 2020). Therefore, it is crucial to investigate what factors promote healthy cognitive aging and slow down the transition to dementia.

Approximately 40% of dementia cases can be delayed or prevented through a healthy lifestyle that reduces risk factors, such as physical inactivity, low education, and social isolation (Livingston et al., 2020). Such risk factors contribute to heterogenous aging trajectories, in which

some people age better than others (Daskalopoulou et al., 2019). Why certain subsections of the population, such as centenarians, are able to maintain cognitive functioning at very old age (e.g., Beker et al., 2021) is unclear. Hence, there is a need for aging theories that consider individual trajectories of cognitive aging.

Currently, there are several aging theories that demonstrate some overlap in their constructs, such as changes in brain activity patterns with age (for a review, see Barulli & Stern, 2013). Attempts have been made to form a consensus of terminology and constructs (Cabeza et al., 2018; Stern et al., 2020). Previous reviews have mainly focused on finding common ground between different cognitive aging theories (Barulli & Stern, 2013). However, determining both similarities and differences between theories of cognitive aging will allow us to identify what cognitive aging mechanisms are agreed upon and what mechanisms need clarification.

Several cognitive aging theories, such as the hemispheric asymmetry reduction in older adults (HAROLD; Cabeza, 2002; see Table 1 for an overview of these theories), aim to explain the mechanisms underlying cognitive decline. However, they might not be comprehensive enough to fully explain the complex mechanism involved in cognitive aging (Festini et al., 2018). In contrast, the revised Scaffolding Theory of Aging and Cognition (STAC-r; Reuter-Lorenz & Park, 2014) and the theory of Cognitive Reserve (CR; Stern et al., 2020) present important viewpoints on the underpinnings of healthy cognitive aging by taking a multifaceted approach. The theories have both similarities and important differences. This review aims to evaluate which aspects of cognitive aging might be explained best by either theory. We will focus on the effect of lifestyle factors and brain health on cognitive decline and discuss how the two theories could serve as models in predicting dementia. Through critical comparison, we will direct researchers to common insights in the field and to intervention targets and testable hypotheses for future research. We first review current theories of cognitive aging and contrast these theories with CR and STAC-r. We then discuss the similarities and differences between CR and STAC-r, and their implications for intervention methods and neurodegenerative disease. Finally, for both theories, we identify significant shortcomings that have not yet been addressed and provide directions for future research.

Theories of Age-Related Cognitive Decline

Cognitive aging theories, such as the compensation-related utilization of neural circuits hypothesis (CRUNCH; Reuter-Lorenz & Cappell, 2008), HAROLD (Cabeza, 2002), and posterior–anterior shift in aging (PASA; Davis et al., 2008), explain age-related changes in cognitive functioning through modulations in brain activation patterns. However, HAROLD and PASA might not explain why some individuals are better able to compensate for age-related cognitive decline than others. A strong point of CRUNCH is that it considers the effect of external factors, such as exercise or genetic disadvantages, on successful compensation. A weakness is that CRUNCH may not be applicable to every cognitive domain, such as visuospatial working memory, as the crunch point cannot always be found in older adults despite high task loads and increases in brain activity (e.g., Jamadar, 2020). In addition, HAROLD proposes that age-related changes in brain activity may reflect neural dedifferentiation, wherein brain activation patterns become less specific (Cabeza, 2002; Li et al., 2001). However, the relationship between cognition and neural dedifferentiation can also be demonstrated in younger adults (see Koen & Rugg, 2019). Hence, it can be hypothesized that neural dedifferentiation might not underlie age-related declines in all cognitive domains. Moreover, the effects of lifestyle choices

Table 1. Description of the Main Theories on Age-Related Cognitive Decline

Cognitive Aging Theory	Description
Compensation-related utilization of neural circuits hypothesis (Reuter-Lorenz & Cappell, 2008)	• As task demands increase, the brain recruits more neural resources to maintain task performance • When task demands are too high, the brain is not able to effectively compensate for the increase in load (i.e., crunch point) • Older adults experience this crunch point sooner than younger adults and age-related decreases in cognitive task performance become apparent • Compensatory processes benefit from, for example, cognitive training and exercise, and are influenced negatively by genetic disadvantages
Hemispheric asymmetry reduction in older adults (Cabeza, 2002)	• Older adults recruit bilateral prefrontal cortices during cognitive tasks to maintain task performance • Younger adults show more unilateral brain activity
Posterior–anterior shift in aging (Davis et al., 2008)	• Older adults maintain optimal task performance despite brain activity decreases in posterior brain regions due to brain activity increases in anterior regions
Neural dedifferentiation hypothesis (Li et al., 2001)	• With age, brain regions and networks become less functionally specific to certain perceptual inputs or cognitive processes • Brain activation will become more widespread in older compared to younger adults

on neural dedifferentiation are not accounted for and are currently unknown (Koen & Rugg, 2019).

External factors could explain why some individuals are better able to compensate for age- and disease-related cognitive difficulties than others. CR (Stern et al., 2020) states that cognitive "reserve" is accumulated through lifestyle choices and lifetime experiences, such as social activities and education (Figure 1). To measure CR, researchers use individual or combinations of proxies, including years of education, IQ, and engagement in leisure, social, or physical activities. The accumulated CR increases cognitive and neural flexibility by enabling the use of cognitive strategies, strengthening existing brain networks, or recruiting alternative brain networks. To illustrate, if two individuals have similar age-related structural brain changes, one individual could still be able to maintain cognitive performance due to higher CR levels while the performance of the other individual falters. The person who maintains cognitive performance has higher CR levels that enable the use of alternative cognitive strategies and functional brain networks. Stern and colleagues hypothesized that CR proxies predict both cognitive performance and the rate of cognitive decline, and that high CR slows down disease-related cognitive decline and delays the onset of dementia (Stern et al., 2020).

An important limitation of CR is that, despite attempts and the use of neural proxies (e.g., blood flow), no explicit neural basis has been proposed. Instead, brain reserve and brain maintenance are often discussed in conjunction with cognitive reserve (Barulli & Stern, 2013). Brain reserve reflects the brain's anatomical resources (e.g., the number of neurons) and is fixed because it cannot be altered by life experiences (Stern et al., 2020). Individuals with more brain reserve would be better able to cope with pathology, delaying the manifestation of cognitive changes. Quantitative measurements of brain structure, which reflect brain reserve, can predict when cognitive disfunction occurs. Although brain reserve and cognitive reserve are

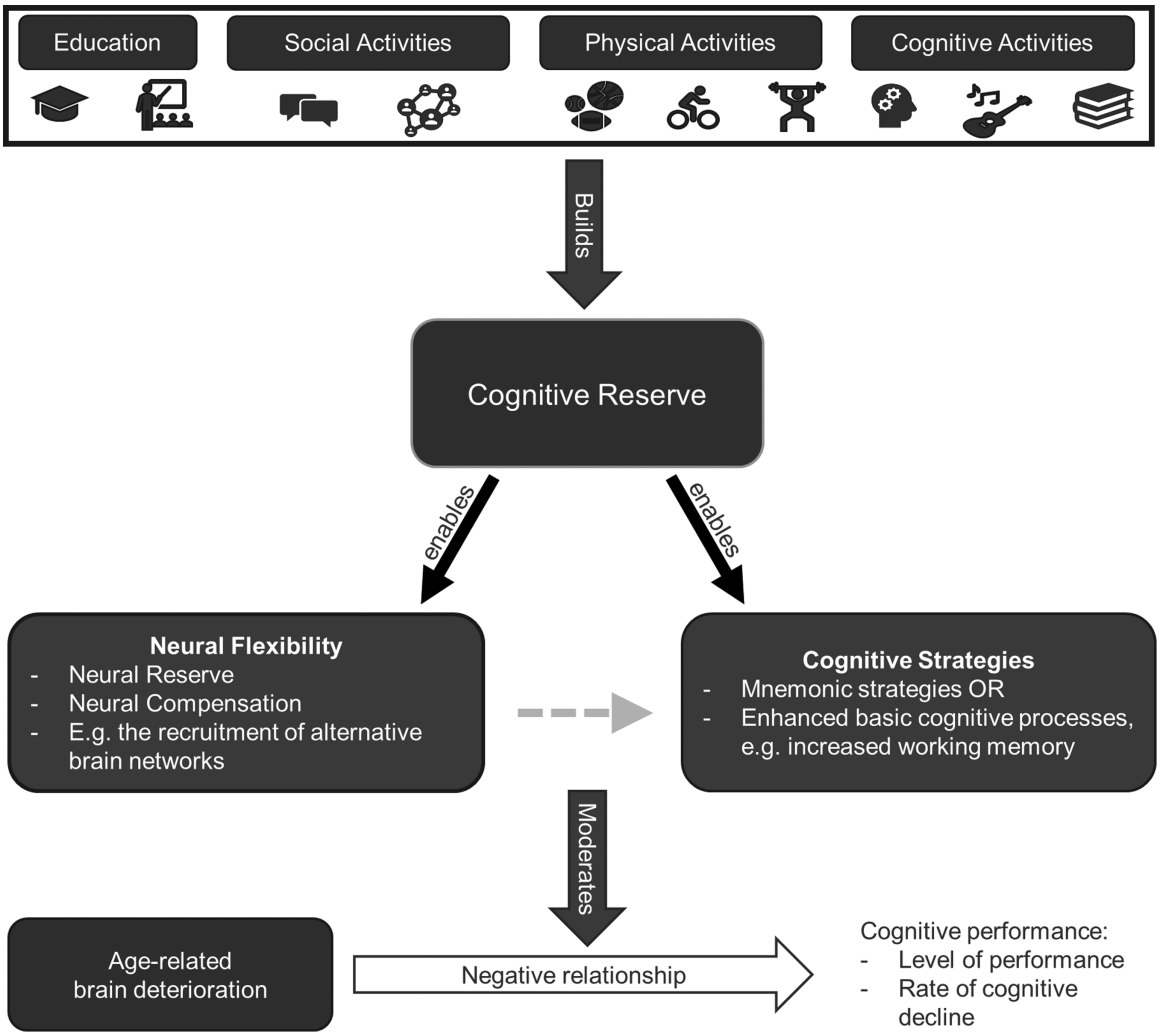

Figure 1. A schematic representation of Cognitive Reserve theory. Cognitive Reserve enables Neural Flexibility and Cognitive Strategies, which both moderate the negative influence of age-related brain deterioration on cognitive performance. The gray dashed arrow indicates that the neuronal processes inevitably influence cognitive processes.

discussed as separate concepts, Cabeza and colleagues (2018) argued that the concepts should be merged under the umbrella term "reserve" because cognition is based in the brain. Brain maintenance refers to the mechanisms of repair and plasticity that can protect against structural decline of the brain. Lifestyle choices and genetics feed into brain maintenance, and can delay the development of brain pathology and increase the brain reserve threshold for cognitive decline. To summarize, brain reserve protects against the effects of brain pathology but cannot be altered by life experiences. Brain maintenance protects the brain against the development of pathology and is modulated through genetics and life experiences. Finally, CR explains individual differences in the ability to cope with cognitive difficulties resulting from brain pathology through differences in life experiences. Recently, researchers started to use the umbrella term of "resilience" to describe the ameliorating effect of CR, brain reserve, and brain maintenance on slowing down age-related brain changes and pathology (Stern et al., 2020).

However, the different concepts of reserve have not yet been integrated into a single model. A comprehensive model is needed where such concepts are linked clearly to make specific predictions about the complex mechanisms of cognitive aging. Moreover, whilst CR does predict lower cognition and faster cognitive decline in people with low CR, it does not include adverse factors, such as depression. STAC-r offers a multifaceted framework that includes adverse life factors (Figure 2; Reuter-Lorenz & Park, 2014). According to STAC-r, cognitive decline is caused by age-related deterioration of brain structure and function, such as a reduction in brain volume and functional brain connectivity. "Scaffolding," which is essentially a form of neuroplasticity, enables people to compensate for age-related cognitive decline through the recruitment of alternative brain regions or the generation of new brain cells.

Life-course experiences influence how well someone can "scaffold" (Reuter-Lorenz & Park, 2014). Similar to CR, scaffolding is boosted by lifestyle choices and lifetime experiences, such as education and the engagement in cognitively stimulating activities, which is termed "neural resource enrichment." Unlike CR, however, STAC-r also considers the effects of adverse life events, such as depression,

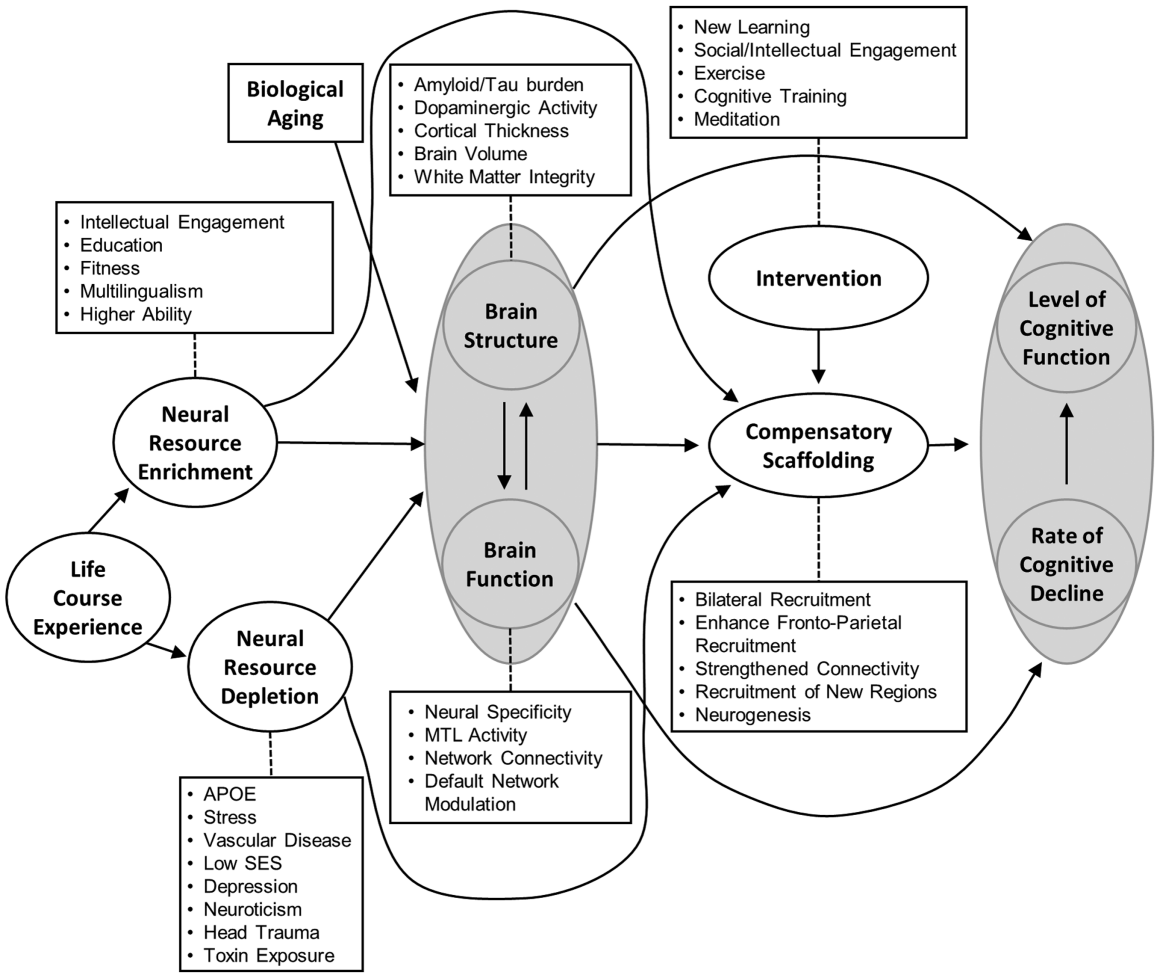

Figure 2. A conceptual model of the Scaffolding Theory of Aging and Cognition—revised. The arrows indicate the influence of one model's component over another. Adapted from Reuter-Lorenz and Park (2014).

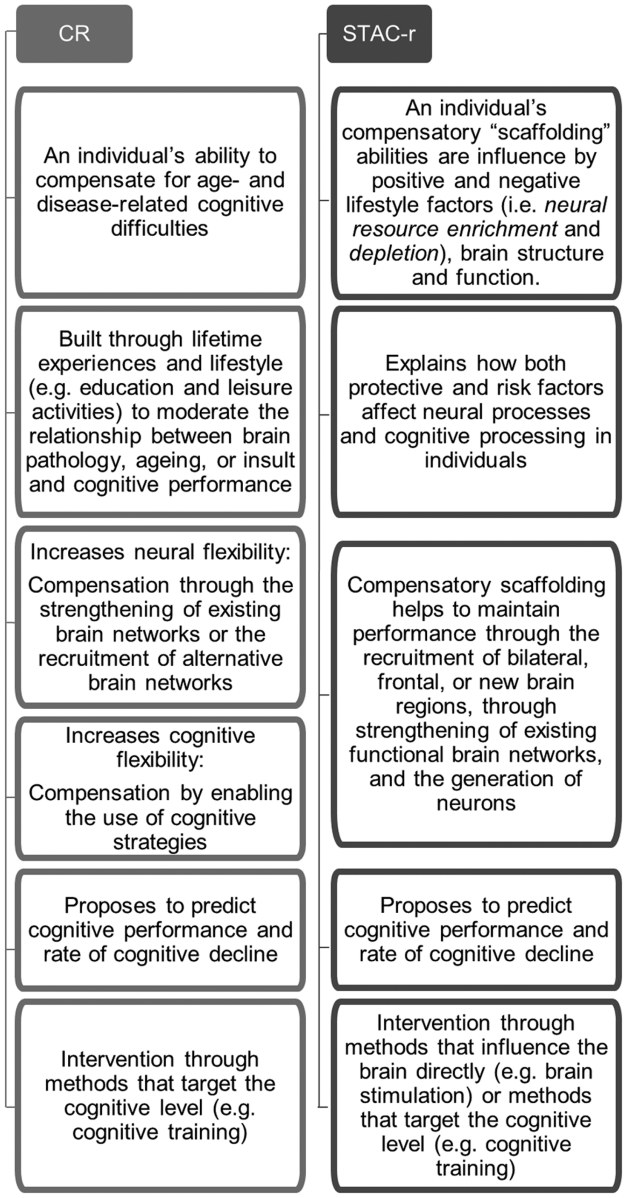

Figure 3. A schematic representation of the main ideas proposed by Cognitive Reserve CR) theory and Scaffolding Theory of Aging and Cognition—revised (STAC-r). Ideas of the two theories about the same theme (e.g., intervention) are aligned to allow for more direct comparison.

vascular disease, and head trauma. These events fall under the "neural resource depletion" construct and weaken scaffolding abilities. Aging and neural resource enrichment and depletion contribute to maintaining overall brain status (i.e., the brain's structure and functional processes). Neural resource enrichment can positively influence the structure and function of the brain, whereas depletion can have a negative influence. Brain structure can be influenced by neuropathology, such as amyloid/tau burden, which would indicate that dementia-related pathology can influence cognitive aging. Brain function can decrease in efficiency (i.e., speed and quality of neural processing) due to changes in, for example, functional brain networks. Brain structure and function are interlinked through the beneficial and adverse influences of neuroplasticity (e.g., neurogenesis and cortical thinning). Moreover, brain structure and function directly contribute to people's scaffolding abilities.

In the initial STAC model, the concept of neural dedifferentiation was suggested as a cause of functional deterioration (Park & Reuter-Lorenz, 2009). In the revised STAC model, the concept has been replaced by "neural specificity," which indicates that neural specificity can decrease with age and through adverse life events but that it can also increase through neural resource enrichment factors (Reuter-Lorenz & Park, 2014). This term corresponds to that of "neural selectivity" proposed by Koen and Rugg (2019). Neural selectivity refers both to reduced brain activity in the brain area underlying a certain cognitive function and to increased brain activity in brain areas that normally do not underly that cognitive function. Furthermore, STAC-r posits that scaffolding ability can improve through intervention, such as through learning and cognitive training as well as through social, physical, and cognitively stimulating activities. The level of cognitive function and the rate of cognitive decline can be predicted through measures of neural resource enrichment and depletion, through observations of brain structure and function, and through compensatory abilities of an individual. Figure 3 compares the proposed mechanisms of STAC-r and CR.

Overlapping Constructs: The Positive Effects of a Healthy Lifestyle

Both STAC-r and CR agree on the positive effects of a healthy, cognitively stimulating lifestyle. Recent research in healthy older adults demonstrates the positive effects of education and IQ on a wide range of cognitive domains, such as executive functioning, memory, and language (Berggren et al., 2018; Caballero et al., 2021; Lavrencic et al., 2018; Thow et al., 2018). In centenarians, maintaining performance in several cognitive domains was related to higher education and IQ (Beker et al., 2021). Although higher education and IQ might not benefit all cognitive domains equally (Lavrencic et al., 2018; Mungas et al., 2021; Thow et al., 2018), higher education in early life (before the age of 45) has been identified as an important factor in reducing dementia risk in older age (Livingston et al., 2020).

Participation in leisure, social, and cognitively stimulating activities has also been shown to predict cognitive ability in older age (Chan et al., 2018; Grotz et al., 2017). Physical activity, such as aerobic and strength exercise, at different life stages might also improve cognitive functioning in older age (Reas et al., 2019; Sprague et al., 2019) and in centenarians (Beker et al., 2021). A recent meta-analysis indicated that the effect on cognition might depend on the nature of the physical activity (Sprague et al., 2019). For example, aerobic exercise might improve cognitive

flexibility, whilst strength training could improve cognitive inhibition. Better cognitive performance in, for example, executive functioning and memory could be due to the generation of nerve cells promoted by physical exercise (Reas et al., 2019).

Because of the positive effects of lifestyle on cognition, both STAC-r and CR propose that the mechanisms compensating for the effects of aging (i.e., scaffolding and reserve) can be enhanced through intervention programs (Klobušiaková et al., 2019; Kocagoncu et al., 2020; Reuter-Lorenz & Park, 2014; Stern, 2013). That is, compensation abilities and reserve can be increased through programs that promote further education and a healthy lifestyle. Furthermore, a healthy lifestyle and interventions, such as cognitive training, can modulate the flexibility of functional brain processes, which is in line with both scaffolding and CR (Reuter-Lorenz & Park, 2014; Stern et al., 2020).

Where the Theories Part

STAC-r: Better Capture of the Complexity of Cognitive Aging

Unlike CR, STAC-r incorporates "neural resource depletion," which includes factors, such as vascular (e.g., smoking) and genetic ones, that negatively influence brain health and compensatory abilities (Reuter-Lorenz & Park, 2014). Brain measures and health factors, such as cortical thinning and high body mass index (BMI), have already been linked to cognitive decline. For example, greater dopamine generation capacity was related to greater cortical thinning in older adults (Ciampa et al., 2021). In this study, cortical thinning was related to decreased working memory performance, but only in people with lower dopamine generation capacity. The relationship between brain function and structure has been demonstrated through studies showing that patterns of functional brain connectivity can change depending on the magnitude and locus of brain tissue deterioration (Vieira et al., 2020), as is predicted by STAC-r (Reuter-Lorenz & Park, 2014). Furthermore, older adults (aged 60–80 years) with similar memory performance to younger adults (aged 18–35 years) exhibit comparable youth-like brain connectivity, indicating the influence of brain function on maintaining cognitive performance (Zhang et al., 2020). However, future studies need to clarify the interplay between neural resource enrichment and depletion factors, intervention, and the bidirectional relationship between brain structure and function.

There is an established relationship between various health measures and cognitive functioning (Caballero et al., 2021; Sebastiani et al., 2020). Specifically, the prevalence of the APOE genotype (i.e., a dementia genetic risk factor), stroke incident, and alcohol abuse predict faster decline of cognitive processing speed, episodic memory (Sebastiani et al., 2020), and executive functioning (Caballero et al., 2021) with age. In centenarians, education and cognitive activities, but not dementia-related brain pathology or genetic risk, were related to cognitive performance (Beker et al., 2021). Hence, compensation mechanisms might stabilize or diverge at very old age, stressing the need for a dynamic model of cognitive aging. STAC-r includes a wider variety of protective and risk factors of cognitive decline, and hence might be more successful than CR in capturing the complex mechanisms involved in cognitive aging.

Time Course of Compensation Mechanisms

Both STAC-r and CR describe compensation mechanisms (i.e., scaffolding and CR) as dynamic, changing over time due to modulations in overall brain status and in environmental factors, such as lifestyle choices (Reuter-Lorenz & Park, 2014; Stern et al., 2020). STAC-r specifically states that neural resource depletion, enrichment factors, and overall brain status continually contribute to compensation mechanisms, such as neural reorganization and repair (Reuter-Lorenz & Park, 2014). Stern and colleagues (2020) argue that CR is dynamic as lifestyle choices and events change throughout the life span, for example, with education often taking place in early life and professional occupation happening later in life (Stern et al., 2020). However, it is unclear whether CR can be accumulated throughout the life span (Grotz et al., 2017), or whether CR can only be acquired before a certain age (Chan et al., 2018). Finally, CR does not specify whether CR levels decline with age or how long it takes for accumulated CR to increase cognitive and neural flexibility. Hence, future studies should clarify the time course of CR across the life span.

Rate of Cognitive Decline

The purpose of STAC-r and CR is to predict both age-related cognitive performance and the rate of cognitive decline (Reuter-Lorenz & Park, 2014; Stern, 2013). The association between the proposed constructs of STAC-r and the rate of age-related cognitive decline is supported by several studies. Cognitive decline can be slowed down by factors such as education (Caballero et al., 2021; Sebastiani et al., 2020; but see McKenzie et al., 2020: only in people at genetic risk for dementia), participation in physical activities, and engagement in cognitive activities, such as completing tax forms (Caballero et al., 2021; Reas et al., 2019). However, stroke or cardiovascular risk (Caballero et al., 2021; Sebastiani et al., 2020), dementia genotypes and inflammation (Sebastiani et al., 2020), as well as health risk factors, such as smoking and high BMI (Caballero et al., 2021; Sebastiani et al., 2020), can speed up cognitive decline.

Although CR can help maintain level of cognitive performance, healthy-aging studies do not seem to support that CR slows down cognitive decline (Beker et al., 2021; Berggren et al., 2018; Lavrencic et al., 2018). Moreover, it

has been argued that education is not an important proxy for CR in healthy older adults, as it does not predict cognitive change on its own. Rather, brain structure needs also to be considered (Mungas et al., 2021). In contrast, several dementia studies demonstrated slower decline in people with high CR, quantified as the difference between observed and expected (based on structural brain measures and demographics) memory performance, despite the presence of dementia-related pathology (e.g., McKenzie et al., 2020). Warranting further investigation, the effect of CR on the rate of cognitive decline might only become apparent when a certain level of brain pathology is reached.

CR: Compensation Through Cognitive Strategies

STAC-r proposes that scaffolding happens at a neural level, and that it is stimulated by interventions and cognitive engagement. In contrast, CR posits that compensation through high CR happens at a cognitive level by increasing the efficiency or flexibility of cognitive processes to counter cognitive decline (Stern et al., 2020). However, it is currently unclear what cognitive strategies CR enables. One explanation is that CR allows for faster cognitive processing or that it counteracts the age-related depletion of attentional or working memory resources (Lojo-Seoane et al., 2020). Several aging theories have already proposed that age-related decreases in basic cognitive processes, such as working memory and processing speed, underlie declines in more complex cognitive functions, such as language or decision-making (Hasher & Zacks, 1988; Salthouse, 1990, 1996). That is, poorer performance in older compared to younger adults could be due to slower information processing. However, it could also be caused by a reduction in attentional resources or working memory capacity caused by, for example, difficulties in suppressing irrelevant information. High CR could enhance processing speed, inhibitory control, or attention, which then positively influences other cognitive processes (Lojo-Seoane et al., 2020).

CR can positively influence working memory performance, which then benefits complex cognitive functioning in middle-aged and older adults (Cansino et al., 2020; Lojo-Seoane et al., 2020). That is, there are two explanations for the positive relationship between CR and working memory in older age. Higher CR either leads to better cognition by enhancing working memory directly (Lojo-Seoane et al., 2020), or it serves as an additional resource when working memory resources reach a threshold of depletion (Cansino et al., 2020). Thus, CR could benefit or serve as an additional cognitive resource to the basic cognitive functions described in aging theories, such as theories of limited cognitive resources (Salthouse, 1990). Future research should investigate whether the brain changes that underlie compensatory mechanisms are detectable and what types of neuroplasticity accompany each cognitive change facilitated by CR.

Compensation at the Level of the Brain

According to STAC-r, to maintain cognitive performance, scaffolding is reflected as an increase in brain activity, recruitment of alternative brain regions, and the generation of neurons (Reuter-Lorenz & Park, 2014). The relationship between brain structure and brain function is well documented (Zahodne et al., 2019). For example, brain structural measures, such as the volume of myelinated content of white matter tracts, predict cognitive processing speed across a wide age range (Chopra et al., 2018). Moreover, compensatory scaffolding can occur in response to brain atrophy by either supporting affected brain areas or recruiting support from less affected brain areas (Vieira et al., 2020). These results indicate that it is possible to characterize brain function without reference to the cognitive level, which is in line with STAC-r.

Stern and colleagues propose that CR ameliorates the effect of brain deterioration on cognition by increasing the efficiency or flexibility of functional brain networks (Stern et al., 2020). That is, brain networks that are more efficient will need less brain activation during cognitive tasks. Flexibility concerns the recruitment of alternative brain networks to maintain cognitive performance. As an example, gray matter loss would have less impact on cognition in people who engage in midlife activities and, hence, have high CR levels (Chan et al., 2018). Recent studies found a positive link between the level of CR and increased efficiency and flexibility of functional brain networks (e.g., Conti et al., 2021). People with low CR measured through educational and occupational attainment, and leisure activity, exhibited similar functional connectivity patterns as was found in a study with people with mild cognitive impairment (MCI; Buldú et al., 2011). Such studies indicate an important role of interventions aimed at increasing CR levels, such as cognitive training, to enable protective mechanisms at the level of functional brain networks.

STAC-r and CR: Differences in Intervention Methods

STAC-r and CR claim that interventions increase compensatory scaffolding and CR levels, respectively. Intervention programs, such as through brain stimulation or cognitive training, aim at enhancing scaffolding and could improve functional brain processing (Reuter-Lorenz & Park, 2014). Specifically, STAC-r proposes that interventions using brain stimulation could influence brain structure and function directly by enhancing functional connectivity. In line with this proposal, a recent study demonstrated that brain stimulation interventions enabled better cognitive performance in explicit learning, but only in people with low baseline performance (Perceval et al., 2020). That is, brain stimulation could enable compensatory brain mechanisms and improve performance in healthy older adults with suboptimal cognitive performance pre-stimulation. In contrast, executive

functioning in older adults might not improve after brain stimulation (Yu et al., 2020). Therefore, future brain stimulation studies might need to consider baseline cognitive performance to detect any beneficial effects of stimulation on cognitive performance.

In addition to brain stimulation, STAC-r proposes that interventions at a cognitive level, such as cognitive training and engagement in cognitive and physical activities, can increase compensatory scaffolding abilities (Reuter-Lorenz & Park, 2014). Brain structure and function could also directly influence compensatory scaffolding abilities (Reuter-Lorenz & Park, 2014). Indeed, the strength of functional connectivity can predict the outcomes of cognitive training. That is, stronger functional connectivity leads to higher training gains in certain cognitive functions (Faraza et al., 2021). Hence, the effect of intervention on compensatory scaffolding could be dependent on brain status. In contrast, CR proposes that interventions should happen at a cognitive level (Stern, 2013). That is, interventions are based on proposed CR proxies, such as cognitive or physical activity, and do not directly increase neuroplasticity through brain stimulation. Such interventions then lead to changes which can be observed both at the cognitive and the neuronal level. For instance, cognitive training, such as learning new skills, was shown to enhance functional connectivity (van Balkom et al., 2020), in line with both STAC-r and CR.

Relevance of STAC-r and CR to Neurodegenerative Diseases

STAC-r is primarily concerned with age-related cognitive decline but could also be applied to neurodegenerative diseases. The role of STAC-r in neurodegenerative disease is indicated by the influence of neuropathology (e.g., amyloid/tau burden), on brain structure (Reuter-Lorenz & Park, 2014). Factors such as stroke incident, years of education, and brain atrophy could be used as predictors for the risk of and transition into MCI or neurodegenerative diseases (Xu et al., 2020). Furthermore, the relationship between deterioration of brain structure, changes in functional brain networks, and subsequent cognitive decline has been demonstrated in dementia (Klobušiaková et al., 2019; Kocagoncu et al., 2020). For example, tau burden (i.e., that of proteins in nerve cells) in Alzheimer's disease is associated with changes in functional brain networks, which can lead to the worsening of cognitive functions (Kocagoncu et al., 2020). The efficiency of functional brain networks as measured through resting-state functional neuroimaging analyses has been linked to MCI and neurodegenerative diseases (Klobušiaková et al., 2019). These studies show that, compared to healthy adults, people with MCI, Alzheimer's disease, or Parkinson's disease show a reduction in brain efficiency, which correlates with the severity of cognitive impairments. In Parkinson's disease specifically, reductions in brain efficiency may indicate pre-onset cognitive dysfunction (Klobušiaková et al., 2019). Post-onset cognitive dysfunction in people with Parkinson's disease with MCI might be related to increased brain efficiency, potentially indicating a compensatory mechanism for their cognitive impairment in response to changes in brain status.

High CR can delay the onset of dementia (Stern, 2013; Stern et al., 2020; Xu et al., 2020) and lessen the impact of this disease on cognitive functioning (Stern et al., 2020). At later stages of neurodegenerative diseases, CR might not be enough to compensate for the negative impact of brain pathology (Stern et al., 2020). Consequently, there is an acceleration in the rate of cognitive decline (Zahodne et al., 2019). CR could decrease the negative impact on cognition caused by age-related brain pathology, such as white matter hyperintensities (Zahodne et al., 2019), and might delay the onset of dementia symptoms by optimizing functional brain networks and increasing the brain's efficiency of information transfer (Li et al., 2021).

Taken together, both STAC-r and CR could be useful in predicting dementia risk, onset, and disease progression. Although STAC-r has not often been discussed specifically in light of neurodegenerative diseases, STAC-r could lead to more accurate predictions as it considers both the positive effects of lifestyle and the influence of adverse health factors. How the different components of STAC-r interact with each other to explain disease-related cognitive impairments warrants further research. Finally, the protective effects of CR might be reduced when someone is at a genetic risk for dementia (Li et al., 2021). Alternatively, CR might mitigate genetic risk factors of dementia (Beker et al., 2021). These findings stress the importance of a comprehensive model that also considers adverse health factors.

Concluding Remarks and Future Perspectives

In this review, we have discussed two frameworks that can explain the mechanisms that compensate for cognitive decline in healthy aging and neurodegenerative diseases. Both scaffolding and CR involve increased neural efficiency, and the ability to scaffold or compensate can be influenced by lifestyle factors and interventions. While CR provides a framework for the effects of an enriching lifestyle on late-life cognition, STAC-r offers a more multifaceted approach that better encompasses the complex mechanisms of age- and dementia-related cognitive decline. Recent research supports the interaction of neural resource enrichment and depletion (e.g., healthy lifestyle and APOE genotype respectively; Caballero et al., 2021; Sebastiani et al., 2020). Hence, future studies would benefit from considering not only healthy lifestyle factors, but also factors that negatively influence cognitive aging. Indeed, researchers have argued that both models could be combined in that resilience (i.e., cognitive reserve, and brain reserve and maintenance) might contribute to compensatory mechanisms to maintain cognition (Cabeza et al., 2018).

Table 2. Identified Strengths and Shortcomings of STAC-r and CR

Shortcomings	Strengths
STAC-r	
• The role of STAC-r in neurodegenerative diseases is underspecified	• STAC-r might be able to predict the onset and rate of cognitive decline brought on by neurodegenerative diseases (see, e.g., Kocagoncu et al., 2020) • STAC-r might be more suitable for predicting the rate of cognitive decline as opposed to CR • STAC-r proposes a specific link between brain processes and compensation/resilience through scaffolding
CR	
• CR does not clearly explain the relationship between cognitive, brain, and functional reserve, making it difficult to test the theory • No neural basis for CR has been proposed. Hence, it is unclear what specifically underlies CR • There is still no consensus on whether each CR proxy weighs equally when estimating CR (Borgeest et al., 2020) or whether some proxies, such as education, are more important than others, such as engaging in leisure activities (Chan et al., 2018; Grotz et al., 2017) • It is currently unclear whether CR can be accumulated throughout the life span (Grotz et al., 2017), as proposed by CR (Stern et al., 2020), or whether there is a "critical period" for building CR (Chan et al., 2018), for example, before very old age (i.e., the age of 100 years; Beker et al., 2021) • CR proxies can predict cognitive performance, but the rate of decline is altered by factors other than CR proxies. Predicting the rate of cognitive decline is paramount for identifying detrimental cognitive problems at an early stage	• In contrast to STAC-r, CR offers a simpler framework that might be easier to use for designing focused intervention programs • CR contributes to understanding the onset and progression of dementia symptoms. Therefore, CR might better apply to cognitive decline in dementia than STAC-r

Note: CR = Cognitive reserve; STAC-r = Strengths of the Scaffolding Theory of Aging and Cognition—revised.

Both STAC-r and CR suffer from shortcomings in their explanations of age- and disease-related cognitive decline (Table 2). Hence, future studies should aim to address the weaknesses of both theories in pursuing evidence-based intervention and prevention strategies against dementia. Neurodegenerative diseases exhibit distinct profiles, including disease-related changes of functional brain networks (Klobušiaková et al., 2019). STAC-r could potentially be developed into disease-specific submodels for generating prognoses of cognitive decline, which could serve as a tool for predicting the onset and progression of dementia. Regarding CR, it is important to clarify the time window for building CR, so that intervention programs can be implemented at the right age. Finally, more research is needed to understand the importance of different CR proxies and their influence on different cognitive domains to determine what combination of proxies should be targeted in interventions.

As the mean age of the global world population increases rapidly and dementia becomes more prevalent in our societies, it is of paramount importance to develop our understanding of the mechanisms that allow for healthy cognitive aging. Therefore, we need to develop a better understanding of the mechanisms that compensate for dementia-related cognitive decline and slows the onset of the disease. Both STAC-r and CR provide promising explanations for cognitive decline with age and in neurodegenerative diseases. They both identify a range of factors that predict healthy cognitive aging, and STAC-r also specifies factors that predict the rate of cognitive decline. It is likely that these predictive qualities can be boosted using machine-learning algorithms, which could provide a set of tools that would allow for early intervention, improved compensatory abilities, and delay in the onset of dementia symptoms.

Funding

This work was supported by a Faculty of Science & Technology scholarship from Lancaster University awarded to EJO, and the Biotechnology and Biological Science Research Council (grant number BB/S008527/1) awarded to HEN which supported KS.

Conflict of Interest

None declared.

Acknowledgments

A special thanks to the members of the Neuroscience Speech and Action laboratory for their support and to Tom Beesley for his reflections during the annual review panel meeting.

Author Contributions

E. J. Oosterhuis: Conceptualization; investigation; writing—original draft; writing—review and editing; visualization. P. J. C. May: Conceptualization; writing—review and editing; supervision. K. Slade: Conceptualization; writing—review and editing; supervision; visualization. H. E. Nuttall: Conceptualization; writing—review and editing; supervision; project administration.

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Chapter 3

Getting the Brain Into Gear: An Online Study Investigating Cognitive Reserve and Word-Finding Abilities in Healthy Ageing

In the previous chapter, we reviewed CR and STAC-r, two prominent cognitive ageing theories, and outlined the strengths and shortcomings of both theories. In Chapter 3, we investigated the relationship between CR and word-finding ability in younger, middle-aged, and older adults. To overcome one of the current shortcomings of CR, we took a more comprehensive measure, including engagement in leisure, cognitively stimulating, and physical activities, as well as educational and occupational attainment. We also investigated whether general cognitive ability could explain any of the effects. Because the study took place during the COVID-19 pandemic, all data was collected online.

Author Note: *This paper was published in April 2023 and was produced in collaboration with Dr. Kate Slade, Dr. Patrick May, and Dr. Helen Nuttall as co-authors. It is available as a published paper at:* Oosterhuis, E. J., Slade, K., Smith, E., May, P. J. C., & Nuttall, H. E. (2023). Getting the brain into gear: An online study investigating cognitive reserve and word-finding abilities in healthy ageing. *PLOS ONE, 18*(4), e0280566. https://doi.org/10.1371/journal.pone.0280566

PLOS ONE

RESEARCH ARTICLE

Getting the brain into gear: An online study investigating cognitive reserve and word-finding abilities in healthy ageing

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OPEN ACCESS

Citation: Oosterhuis EJ, Slade K, Smith E, May PJC, Nuttall HE (2023) Getting the brain into gear: An online study investigating cognitive reserve and word-finding abilities in healthy ageing. PLoS ONE 18(4): e0280566. https://doi.org/10.1371/journal.pone.0280566

Editor: Katya Numbers, University of New South Wales, AUSTRALIA

Received: August 22, 2022

Accepted: January 2, 2023

Published: April 20, 2023

Peer Review History: PLOS recognizes the benefits of transparency in the peer review process; therefore, we enable the publication of all of the content of peer review and author responses alongside final, published articles. The editorial history of this article is available here: https://doi.org/10.1371/journal.pone.0280566

Data Availability Statement: The minimal anonymised datasets have been uploaded to the PURE repository and have the following DOIs: - Picture naming actions: https://doi.org/10.17635/

Abstract

Lifetime experiences and lifestyle, such as education and engaging in leisure activities, contribute to cognitive reserve (CR), which delays the onset of age-related cognitive decline. Word-finding difficulties have been identified as the most prominent cognitive problem in older age. Whether CR mitigates age-related word-finding difficulties is currently unknown. Using picture-naming and verbal fluency tasks, this online study aimed to investigate the effect of CR on word-finding ability in younger, middle-aged, and older adults. All participants were right-handed, monolingual speakers of British English. CR for both the period preceding and coinciding with the COVID-19 pandemic was measured through years of education and questionnaires concerning the frequency of engagement in cognitive, leisure, and physical activities. Linear mixed-effect models demonstrated that older adults were less accurate at action and object naming than middle-aged and younger adults. Higher CR in middle age predicted higher accuracies for action and object naming. Hence, high CR might not only be beneficial in older age, but also in middle age. This benefit will depend on multiple factors: the underlying cognitive processes, individual general cognitive processing abilities, and whether task demands are high. Moreover, younger and middle-aged adults displayed faster object naming compared to older adults. There were no differences between CR scores for the period preceding and coinciding with the pandemic. However, the effect of the COVID-19 pandemic on CR and, subsequently, on word-finding ability might only become apparent in the long term. This article discusses the implications of CR in healthy ageing as well as suggestions for conducting language production studies online.

Introduction

The population around the world is ageing rapidly. Ageing is accompanied by cognitive decline, which starts in early adulthood [1]. Positive lifestyle choices and lifetime experiences, such as engaging in leisure activities and higher education, might delay the onset of cognitive decline and slow down its progression in healthy ageing, and could decrease the risk of dementia [2–4]. According to Cognitive Reserve (CR) theory, positive lifestyle choices and lifetime experiences build up a "cognitive reserve", which enables individuals to maintain cognitive

lancaster/researchdata/586 - Picture naming objects: https://doi.org/10.17635/lancaster/researchdata/587 - Verbal fluency actions: https://doi.org/10.17635/lancaster/researchdata/583 - Verbal fluency semantic: https://doi.org/10.17635/lancaster/researchdata/588 - Verbal fluency letter: https://doi.org/10.17635/lancaster/researchdata/585 The study's GitHub repository (available on https://github.com/EliseJis/GBG-Online-Study) contains R Markdown files with the analysis code and analysis output.

Funding: H.E.N. received a grant from the Biotechnology and Biological Science Research Council (grant number BB/S008527/1). https://www.ukri.org/councils/bbsrc/. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. E.J.O. received a Faculty of Science & Technology PhD scholarship from Lancaster University. https://www.lancaster.ac.uk/sci-tech/. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: The authors have declared that no competing interests exist.

performance despite age-related brain changes or pathology. Greater CR can enable the use of cognitive strategies (e.g., mnemonics), strengthen existing brain networks, and facilitate the recruitment of additional brain networks to support cognitive performance [5, 6]. Brain reserve is another concept often discussed in conjunction with CR. Brain reserve reflects the brain's anatomical resources, such as number of neurons, and individuals with greater 'brain reserve' (i.e., more neurons) are thought to be better able to tolerate neurological attrition before it becomes pathophysiological [6]. Indeed, through 'brain maintenance' some individuals maintain their brains more so than others, for example, through life experience and genetics. Such brain maintenance is thought to increase brain reserve [6]. Brain reserve differs from CR in that CR explains individual differences in the ability to cope with cognitive difficulties through differences in lifestyle choices and life experiences.

Of the cognitive difficulties older adults experience, word-finding difficulties are considered as the most prominent problem associated with ageing [7]. Word-finding difficulties can extend beyond the difficulties associated with healthy ageing, which could signal the onset of dementia [8, 9]. However, CR can delay the onset of age- and dementia-related cognitive decline [6]. The effect of CR on age-related word-finding difficulties is currently unknown. Because word-finding difficulties have also been associated with both healthy ageing and dementia, it would be important to investigate the link between CR and age-related word-finding difficulties. This would also help us understand why some adults develop dementia whilst others stay cognitively healthy [3, 10]. Therefore, this study aimed to investigate age-related declines in word-finding abilities and how lifestyle factors might affect this decline. The results of this study will inform us whether CR has a mitigating effect on age-related word-finding difficulties.

Word-finding difficulties can be detected through picture-naming and verbal fluency tasks [11, 12]. In picture-naming tasks, action naming has been identified as more difficult than object naming in younger adults, possibly because different cognitive processes underly object and action naming. More cognitive resources are needed for action naming, resulting in slower processing times for action compared to object naming [13]. Compared to younger adults, older adults have more difficulties in picture naming [14–18]. Age-related declines are also found in verbal fluency [19–21], with an earlier onset and greater decline in semantic fluency than in letter fluency [19, 20]. Moreover, older adults generate more common words (i.e., high-frequency words) in verbal fluency tasks than younger adults, which can reflect difficulties in lexical access whereby highly frequent words are the easiest to access from memory [19]. Dementia can add to the difficulties with verbal fluency tasks that are already associated with healthy ageing [8, 9]. Therefore, verbal fluency performance could serve as an early neuropsychological marker of dementia [22, 23].

Variability in cognitive performance across individuals increases with age (e.g. [18, 24]. Currently, there is no consensus on the age when picture-naming ability starts to decline. Some studies indicate that the start of decline begins as early as at 30 [14] or 50 years of age [17, 18, 25]. Yet others found that decline starts at 75 years of age, possibly because an increase in vocabulary with age masks early word-finding difficulties [15]. The different ages of onset might be explained by individual differences in cognitive ageing trajectories.

Differences in CR across individuals might account for the individual differences in ageing trajectories as CR might delay the onset and decrease the rate of age-related cognitive decline [2–4]. CR, measured through the proxy of the number of years of education, has a positive effect on verbal and source memory [26, 27] and might modulate the effect of age on letter fluency [28]. In addition, CR might not only benefit cognitive performance at older age but also in middle-aged adults [29]. Therefore, high CR might ameliorate age-related word-finding difficulties in both middle and older age. To reduce the effect of age on word finding, CR might

strengthen the connections between brain areas involved in language processing (e.g., between the left frontal and temporal gyri) and increase bilateral activity between frontal brain regions, which enables the use of more general cognitive processes (e.g., executive functioning) to support word finding. One possibility is that participating in leisure activities and higher educational and occupational attainment train our word-finding abilities (e.g., through social interactions) and increases the efficiency of brain areas underlying word-finding [30]. However, the effect of CR on word-finding abilities across younger, middle, and older age has not yet been investigated.

The current study aimed to investigate the relationship between word-finding ability and levels of CR in young, middle-aged, and older adult participants. We hypothesised that cognitive reserve modulates age-related declines in lexical access so that higher CR predicts better performance in picture-naming and verbal fluency tasks. Furthermore, in testing this hypothesis, we first sought to replicate the results of previous studies showing that older adults have difficulties with word-finding compared to middle-aged and younger adults. Specifically, we expected an age-related decline in accuracy and reaction time for both object and action naming [16], and a decrease in the number of words produced on a verbal fluency task [18, 20]. Secondly, we expected that older adults produce more high-frequency words on verbal fluency tasks compared to younger adults [19]. In addition, because social isolation during the COVID-19 pandemic can negatively affect cognition even over a short period of time [31], we also explored whether a decrease in social and leisure activities due to the COVID-19 pandemic had an effect on CR scores and the performance of the behavioural tasks.

Material and methods

Participants

A total of 90 healthy, right-handed, monolingual speakers of British English participated in this study. To control for variance in word-finding speed between monolinguals and bi-/multilinguals [32], only monolingual speakers of British English were included in this study. The sample size was based on a-priori power analysis using an online sample size calculator (https://clincalc.com/stats/samplesize.aspx; [33, 34]). The anticipated means, equating to approximately medium to large effect sizes, were based on previous literature on word-finding ability in healthy ageing [20, 21, 35–37]. The outcome variable was set as *continuous (means)*. Power was set at 80% and the alpha level at .05 to obtain a large effect size (Cohen's $f = 0.40$). This resulted in a sample size of 30 participants per age group. The participants were grouped into 30 younger (aged 18–30; 23 females), 30 middle-aged (aged 40–55; 22 females), and 30 older adults (aged 65–80; 17 females). The age bands were based on previous literature [e.g., 21, 25, 38, 39] and the 10-year age gap between the groups was introduced to increase the sensitivity to detect age-related effects.

Participants reported no history of or current neurological (e.g., stroke or epilepsy), psychiatric (e.g., schizophrenia or bipolar), speech, or language disorders. All participants had self-reported normal or corrected-to-normal hearing and vision. All participants had a score of 19 or less on the Beck Depression Inventory-II (BDI-II; [40]) and, hence, did not suffer from depression. In addition, all participants had a score of less than 3.6 on the Informant Questionnaire on Cognitive Decline Self-Report (IQCODE-SR; [41]), reflecting absence of cognitive difficulties. Years of education, occupational score, and frequency of leisure activity can be found in Table 1. The study was approved by the Research Ethics Committee of the Faculty of Science and Technology of Lancaster University. Participants gave digital consent to take part in the study.

Table 1. Descriptive statistics of the measures to compute cognitive reserve for the periods preceding and coinciding with the COVID-19 pandemic separately.

Age Group	Education (in years)	Occupational Attainment[a]	General Activities[b]		Cognitive Activities[b]		Social Activities[b]		Productive Activities[b]		Physical Activities[b]	
			Pre	During	Pre	During	Pre	During	Pre	During	Pre	During
Younger	15.1 (1.6)	9.5 (3.5)	25.3 (8.3)	21 (6.9)	8.5 (3.5)	7.7 (3.8)	10.4 (2.9)	5.7 (2.9)	6.4 (3.6)	7.6 (2.9)	3679.4 (3988.4)	2163 (1998.8)
Middle-Aged	17 (3.1)	4.9 (2.7)	27.5 (6.8)	23.1 (6.4)	8.9 (3.1)	8.9 (3.6)	10 (2.5)	4.5 (2.2)	8.6 (3)	9.7 (3.3)	2418 (2068.1)	2446.9 (1884.6)
Older	18.4 (4.3)	4.3 (1.9)	33.7 (6.9)	26.2 (6.8)	13.2 (4.4)	11.8 (4.1)	9.9 (2.5)	3.7 (2.6)	10.6 (2.6)	10.7 (3)	2872 (1849.7)	2149.2 (1268.3)

[a]Lower scores on occupational attainment reflect higher socioeconomic status. NAs were present for younger (15), middle-aged (3), and older adults (9). The higher number of missing values for younger adults is due to their student status. Some older adults reported retirement status and, hence, their occupational attainment could not be calculated.

[b]Higher scores on the activities represent higher frequency of engagement in these activities.

https://doi.org/10.1371/journal.pone.0280566.t001

Materials

The BDI-II, the short IQCODE-SR, a demographics questionnaire, and the CR questionnaire were completed online via the Qualtrics XM Platform (Qualtrics, Provo, UT). The behavioural tasks for assessing word-finding ability (i.e., picture naming and verbal fluency) and general cognitive functions (i.e., cognitive processing speed, working memory, and inhibitory control) were completed online via the Gorilla Experiment Builder [42].

Cognitive reserve

CR was quantified through a General Activities Questionnaire comprising questions about social/leisure, intellectually stimulating, and productive activities. The questions were adopted from previously published studies [43, 44] and adapted where necessary by merging, adding, or modifying questionnaire items. The frequency of participation was rated on a 4-point scale from never (0) to every day (3). In addition, physical activity was measured through the Global Activity Questionnaire [45]. The CR questionnaire was split into two parts. The first part required participants to report the frequency of their activities for the period preceding the COVID-19 pandemic. That is, the participants were asked to report the frequency of their activities retrospectively. The second part of the CR questionnaire required participants to report the frequency of their activities for the period coinciding with the COVID-19 pandemic. Occupational attainment was obtained by computing the occupational scores using the UK Standard Occupational Classification system [46]. Internal consistency was calculated using Cronbach's Alpha [47] and was $\alpha = .59$ for all items used to compute CR. Years of education, occupational attainment, and scores for the General Activities Questionnaire and Global Activity Questionnaire were converted into *z*-scores within each age group. Following the method by Soldan and colleagues (2013), a fixed composite score for CR per individual was obtained by averaging over these standardised scores [48], for the periods preceding and coinciding with the COVID-19 pandemic separately. By averaging over the *z*-scores, education, occupational attainment, and general and physical activities were given equal weight when computing CR. This resulted in two CR composite scores per individual, one for the period preceding the COVID-19 pandemic and one for the period coinciding with the pandemic.

Picture naming

Pictures were obtained from the Center for Research in Language International Picture-Naming Project [49], and were carefully selected and balanced for word frequency (actions:

M = 3.3, *SD* = 1.8; objects: *M* = 3.1, *SD* = 1.7), age of acquisition of the words (actions: *M* = 5.2, *SD* = 1.7; objects: *M* = 4.8, *SD* = 1.4), and had high picture-name agreement across individuals (actions: 91%, objects: 99%). Action and object words were not matched for word length. However, this should not affect our results as word length is unlikely to influence naming speed [50]. In addition, we did not directly compare naming speed between object and action naming. The final set contained 79 pictures of actions and 70 pictures of objects. For action naming, the items "vacuum", "somersault", "wait", and "talk" were excluded as these items resulted in low accuracy or name agreement in this study. The item "cut" was excluded as this item was also used in a practice trial. For object naming, the items "football" and "skunk" were excluded as these items resulted in low name agreement across participants.

The picture naming tasks were presented in a blocked manner. That is, participants first completed the object naming task after which they completed the action naming task. Both the object and action picture-naming task started with four practice trials. The participant read the instructions on the computer screen and was instructed to name the pictures as quickly and accurately as possible. The participant first tested their microphone. Next, the participant completed four practice trials, which were recorded and played back to the participant. After the practice trials, the actual experiment started. All trials started with a fixation cross with a 500 ms duration, followed by a blank screen for 700 ms. After this, the picture was presented for 3000 ms. Differences in microphones used by the participants and the lags in audio recordings caused timing variability between participants and trials. Therefore, in order to indicate the start of the picture and measure timing variability, a trigger sound was added. The trigger sound enabled the experimenter to calculate the verbal reaction time more accurately. The stimuli were never repeated to avoid practice effects and were presented in a pseudo-random order, with the trials being randomised for frequency, age of acquisition, number of syllables in the picture names, and name agreement. Picture names starting with the same letter never followed each other. Both accuracy and reaction time were obtained using CheckVocal [51].

Verbal fluency

The verbal fluency task comprised tasks measuring semantic, action, and letter fluency. Participants completed the letter fluency task after the semantic and action fluency task so as to avoid the use of any cued strategies. For semantic fluency, the category prompts were: "animals", "vehicles", "fruits and vegetables", "fluids", and "writing utensils". The action fluency task was prompted by "things people can do" and "things you can do to an egg". Lastly, the letter fluency task included the letter prompts "S", "M", and "P". The verbal fluency prompts were based on previous studies, which also have validated the use of these prompts [20, 21, 52, 53]. The participant had 60 seconds to produce aloud as many words as possible for each of the verbal fluency prompts. The responses were recorded and later transcribed by two transcribers in order to assess the interrater reliability. Composite scores for each of the three verbal fluency tasks were created to reduce the number of multiple comparisons. To obtain a composite score for the semantic, action, and letter fluency tasks separately, scores were standardised within age groups per verbal fluency prompt. The standardised scores were then averaged for each of the three verbal fluency tasks. This resulted in three different verbal fluency composite scores: one for semantic fluency, one for action fluency, and one for letter fluency.

Control tasks

In order to control for the influences of more general processing difficulties in ageing [54, 55], tasks for inhibitory control, working memory, and cognitive processing speed were assessed. The control tasks were counterbalanced and presented visually and, thus, did not require

auditory processing. For all three tasks, scores were transformed into *z*-scores within age groups to create an average score per participant which reflects general cognitive processing ability. To investigate inhibitory control, a spatial Stroop task was used [56]. In this task, an arrow appeared on either the left or right side of the screen and the participant had to press the button corresponding to the direction the arrow was pointing. In incongruent trials (e.g., arrow pointing to the left but appearing on the right side of the screen), the participant had to inhibit the tendency to respond to the location of the arrow to select the correct response (i.e., the direction the arrow pointed to).

Working memory was assessed using a computerised visual adaptation of the Digit Ordering Test [56–58]. The participant was presented visually with a sequence of digits, ranging from 4 to 7 digits. Each digit in the sequence was presented for 700 ms with a 300 ms blank screen between the digits. After the sequence was presented, the participant had to type the sequence of digits in ascending order.

Finally, cognitive processing speed was assessed using the Deary-Liewald task [59], which included both Simple and Choice Reaction Time tasks. In the Simple Reaction Time task, the participant had to press the spacebar each time an X appeared in a square in the middle of the screen. In the Choice Reaction Time task, four empty squares were presented next to each other, and the X could appear in one of the four squares. The participant had to press the key corresponding to the square in which the stimulus appeared. A composite score for cognitive processing speed was created by averaging over the standardised scores of the Simple Reaction Time and Choice Reaction Time task [59]. Computerised versions of these three control tasks are widely used and even implemented in and validated for cognitive testing batteries such as the Cambridge Neuropsychological Test Automated Battery (CANTAB; [60]).

Procedure

The participant was first assessed for their eligibility via email, after which they logged onto the Gorilla Experiment Builder. After providing digital consent, the participant was directed to Qualtrics XM Platform to complete the demographics and CR questionnaires, which included the General Activities Questionnaire and the Global Activity Questionnaire. Next, the participant was redirected to the Gorilla Experiment builder to complete the behavioural tasks. The participant started with either the three control tasks or with the language production tasks, in a counterbalanced order. For the language production tasks, the participant started first with the verbal fluency task, after which they completed the picture-naming tasks. This order was fixed to avoid priming effects of picture naming on verbal fluency performance. At the end of the experiment, the participant was debriefed and thanked for their participation. Each participant completed the CR questionnaires and the behavioural tasks only once.

Statistical analysis

Data pre-processing and data analysis were done in R [61]. For data pre-processing, we used the package *tidyverse* [62]. For the analysis of the picture-naming data, linear mixed-effect models (LMMs) were employed, using the *lme4* package [63]. The outcome variables were 1) reaction time of correct trials for object and action naming separately and 2) accuracy for object and action naming separately. As accuracy is a binomial variable, we used generalised linear mixed-models (GLMMs) as these are well-suited for binomial data [64]. Moreover, because the accuracy data in this study is binary (1 for correct or 0 for incorrect) with a highly skewed distribution (asymmetric distribution where there are more 1's than 0's), a binomial family with a complementary log-log (cloglog) link function was chosen [65] with a "Nelder Mead" optimiser [66]. Multiple linear regression was conducted on the verbal fluency data as

there were no repeated measures. The outcome variables were 1) number of correctly produced words and 2) average frequency of the correctly produced words.

Following the preregistration, the data was trimmed using *z*-scores to reduce the probability of Type-II errors [67]. The dependent variables were transformed into *z*-scores within each age-group and outliers were identified as being above and below 2.5 *SD*. That is, picture-naming reaction times above or below 2.5 *SD* were considered outliers and subsequently removed (object naming: 4.4%, action naming: 7.9%). For verbal fluency, values for the number of correctly produced words and average frequency of the produced words above or below 2.5 *SD* were considered outliers. These were removed from the data before calculating the number of correctly produced words (semantic: 2.6%, letter: 2.9%, action: 1.7%) and average frequency of the produced words (semantic: 2.2%, letter: 2.6%, action: 2.2%). CR composite scores and scores on each of the three control measures were considered outliers if they had a value of 2.5 *SD* below or above the mean of each age group. Because there were no repeated measures for these scores and because they were important predictors in our analysis, the detected outliers were winsorised at +/- 2.5 *SD*. This allowed for the scores to remain on the extreme side of the distribution without loss of data. CR scores were missing for two participants and part of the CR scores was missing for three participants. For the control tasks, two participants had missing data for cognitive processing speed and three had missing data for working memory. Missing data was replaced using single imputation, where the mean per age group was imputed. This was done before creating any composite scores.

The predictor variables for all models were Age with three levels (younger adults aged 18–30; middle-aged adults aged 40–55; and older adults aged 65–80), the standardised CR composite score (continuous predictor), and an interaction between Age and CR composite score. The categorical variable Age was coded using Helmert contrasts such that the first contrast reflects the difference between middle-aged and younger adults, and the second contrast reflects the difference between older adults and the mean of the younger and middle-aged adult groups. The package *emmeans* was used to conduct post-hoc comparisons between age groups, including the Tukey Multiple Comparison test to obtain adjusted p-values [68]. Furthermore, we compared the models with the CR scores for the period preceding and coinciding with the COVID-19 pandemic. This was done to test whether CR scores for the period preceding or coinciding with the COVID-19 pandemic explained current word-finding ability better. Standardised scores for the general cognitive processing composite variable were added to the model as covariates.

For the picture-naming data, random effects for Item ID (i.e., variance caused by between-item variability) and Participant ID (i.e., variance caused by between-subject variability) were included [69]. To justify the inclusion of both random effects in our model, we compared the Akaike Information Criterion (AIC; [70]) values of the model with and without random effects. A lower AIC value indicates a better fit. For action naming reaction time, the AIC for inclusion of both random effects was substantially lower than the null model without random effects (32.9 and 2095.4 respectively). For object naming reaction time, the model which included both random effects resulted in a substantially lower AIC value compared to the null model without random effects (-796.3 and 1403.3 respectively). For action naming accuracy, the AIC for the model with both random effects was lower than the null model without random effects (2771.5 and 2994.4 respectively). For the model with both random effects for object naming accuracy, the AIC was also lower than the null model without random effects (1012.50 and 1070.89 respectively).

To assess goodness of fit, the assumptions of the different statistical models were investigated, and the AIC was compared against a null model. In addition, we reported the conditional and marginal R-squared (R^2) for all models using the function "r2_nakagawa" of the

package *performance* [71] for the LMMs and the function "r.squaredGLMM" of the package *MuMIn* for the GLMMs [72]. Moreover, goodness of fit of the GLMMs was assessed by testing for overdispersion, using "testDispersion" function of the *DHARMa* package [73]. Concordance and Somer's D were calculated using the "somers2" function of the *Hmisc* package to assess the predictive power of the GLMMs [74].

Data availability

The study hypotheses, design, and statistical analyses were preregistered on aspredicted.org (https://aspredicted.org/b6we4.pdf). R code, Cognitive Reserve questionnaires, picture names, and additional online materials are openly available at the project's GitHub repository (https://github.com/EliseJis/GBG-Online-Study). The dataset will be openly available via Lancaster University's Pure repository. The dataset's DOI will be made available after acceptance.

Results

Picture naming reaction time data

The reaction times for action and object naming were analysed separately. Mean reaction times per age group were calculated for accurate items only. The mean reaction time for action naming was 1063.9 ms (*SD* = 348.3 ms) for younger adults, 1006.6 ms (*SD* = 312.4 ms) for middle-aged adults, and 1071.2 ms (*SD* = 326.8 ms) for older adults. The mean reaction time for object naming was 763.6 ms (*SD* = 183.2 ms), 792.9 ms (*SD* = 222.4 ms), and 881.0 ms (*SD* = 246.9 ms) for younger, middle-aged, and older adults, respectively.

The full model for both action and object naming with main predictors (Age and CR), the interaction term (Age*CR) and the covariates (the control tasks) converged without the need for optimisers. The assumptions for linearity and homoscedasticity were both met. To obtain normality of residuals, the outcome variable (reaction time) was log transformed.

Model formulas and results are reported in Tables 2 and 3 for action and object naming respectively. For action naming reaction time, none of the predictors were significant. For object naming reaction time, we found a main effect of age ($\beta = 0.05$, $t(87.99) = 3.83$), such that older adults were significantly slower than both younger (adjusted $p = .003$) and middle-aged adults (adjusted $p = .001$). The interaction between CR and Age did not reach significance.

For action naming, approximately 16.2% and 16.8% of the variance not explained by our fixed effects was explained by the random effects for Participant ID and Item ID respectively. Marginal and conditional R^2 were calculated as a measure of model fit. Fixed effects explained 1.4% of the variance in the data (marginal $R^2 = .014$), whilst 34.0% of the variance was explained by the full model, including random effects (conditional $R^2 = .340$). For object naming, 24.3% and 9.2% of the variance not explained by our fixed effects was explained by the random effects for Participant ID and Item ID, respectively. Fixed effects explained 5.9% of the variance in the data (marginal $R^2 = .059$), whilst 37.4% of the variance was explained by the full model, including random effects (conditional $R^2 = .374$).

Picture naming accuracy data

Accuracy data for object and action naming was analysed separately. Mean accuracy for action naming was 94.7% for younger adults (*SD* = 22.4%), 95.4% for middle-aged adults (*SD* = 20.9%), and 93.5% for older adults (SD 24.7%). For object naming, the respective mean accuracies were 99% (*SD* = 10%), 98.7% (*SD* = 11.3%), and 97.3% (*SD* = 16.1%).

Table 2. Results of the fixed effects for action naming reaction time.

Model	log(RT) ~ Age Group*CR score + General Cognitive Processing + (1|Participant ID) + (1|Item ID)						
Effect	Estimate	SE[d]	t value	df[e]	p value	CI[f] Low	CI[f] High
Intercept	6.904	0.018	381.321	155.999	.000***	6.868	6.940
MA[a] vs. YA[b]	0.019	0.016	1.156	89.661	.251	-0.013	0.051
OA[c] vs. MA[a] / YA[b]	0.015	0.010	1.434	89.638	.155	-0.006	0.035
CR[g] Score	-0.006	0.013	-0.436	89.726	.664	-0.031	0.020
MA[a] vs. YA[b] * CR[g] Score	0.012	0.016	0.742	89.670	.460	-0.019	0.042
OA[c] vs. (MA[a] / YA[b]) * CR[g] Score	-0.014	0.009	1.555	89.859	.124	-0.032	0.004
Covariates							
General Cognitive Processing	-0.009	0.029	-0.310	88.582	.757	-0.066	0.048

[a]MA = middle-aged adults
[b]YA = younger adults
[c]OA = older adults
[d]SE = standard error
[e]df = degrees of freedom
[f]CI = 95% Confidence Intervals
[g]CR = Cognitive Reserve
*$p < .05$
**$p < .01$
***$p < .001$.

https://doi.org/10.1371/journal.pone.0280566.t002

Model formulas and the results of both models are reported in Tables 4 and 5 for action and object naming respectively. For both models, there was a main effect for Age, in that older adults were less accurate in action and object naming than middle-aged adults (action naming:

Table 3. Results of the fixed effects for object naming reaction time.

Model	log(RT) ~ Age Group*CR score + General Cognitive Processing + (1|Participant ID) + (1|Item ID)						
Effect	Estimate	SE[d]	t value	df[e]	p value	CI[f] Low	CI[f] High
Intercept	6.679	0.017	388.170	141.602	.000	6.586	6.690
MA[a] vs. YA[b]	-0.004	0.019	-0.207	87.845	.837	-0.082	0.067
OA[c] vs. MA[a] / YA[b]	0.045	0.012	3.834	87.952	< .001***	0.058	0.202
CR[g] Score	-0.005	0.015	-0.369	87.953	.713	-0.062	0.036
MA[a] vs. YA[b] * CR[g] Score	0.024	0.018	1.332	87.887	.186	-0.024	0.119
OA[c] vs. (MA[a] / YA[b]) * CR[c] Score	-0.016	0.010	-1.595	88.018	.114	-0.095	0.045
Covariates							
General Cognitive Processing	0.019	0.033	0.578	87.924	.564	-0.010	0.085

[a]MA = middle-aged adults
[b]YA = younger adults
[c]OA = older adults
[d]SE = standard error
[e]df = degrees of freedom
[f]CI = 95% Confidence Intervals
[g]CR = Cognitive Reserve
*$p < .05$
**$p < .01$
***$p < .001$.

https://doi.org/10.1371/journal.pone.0280566.t003

Table 4. Results of the fixed effects for action naming accuracy.

Model	Accuracy ~ Age Group*CR score + General Cognitive Processing + (1|Participant ID) +(1|Item ID), family = binomial (link = "cloglog")					
Effect	Estimate	SE[d]	*z* value	*p* value	CI[e] Low	CI[e] High
Intercept	1.255	0.053	23.826	.000	1.152	1.358
MA[a] vs. YA[b]	-0.037	0.035	-1.083	.279	-0.105	0.030
OA[c] vs. MA[a] / YA[b]	-0.053	0.021	-2.259	.011*	-0.094	-0.012
CR[f] Score	0.023	0.027	0.864	.387	-0.029	0.076
MA[a] vs. YA[b] * CR[f] Score	-0.113	0.033	-3.379	< .001***	-0.178	-0.047
OA[c] vs. (MA[a] / YA[b]) * CR[f] Score	-0.007	0.019	-0.363	.716	-0.043	0.030
Covariates						
General Cognitive Processing	-0.021	0.059	-0.360	.718	-0.138	0.095

[a]MA = middle-aged adults
[b]YA = younger adults
[c]OA = older adults
[d]SE = standard error
[e]CI = 95% Confidence Intervals
fCR = Cognitive Reserve
*$p < .05$
**$p < .01$
***$p < .001$.

https://doi.org/10.1371/journal.pone.0280566.t004

β = 0.20, z = 2.92, adjusted p = .010; object naming: β = -0.19, z = 2.33, adjusted p = .05) and less accurate in object naming than younger adults (β = 0.25, z = 2.53, adjusted p = .03). For action naming accuracy, the interaction between Age and CR reached statistical significance in

Table 5. Results of the fixed effects for object naming accuracy.

Model	Accuracy ~Age Group*CR score + General Cognitive Processing + (1|Participant ID)+ (1|Item ID), family = binomial (link = "cloglog")					
Effect	Estimate	SE[d]	*z* value	*p* value	CI[e] Low	CI[e] High
Intercept	1.630	0.069	23.781	.000	1.499	1.768
MA[a] vs. YA[b]	0.031	0.048	0.653	.514	-0.062	0.125
OA[c] vs. MA[a] / YA[b]	-0.074	0.026	-2.846	.004**	-0.125	-0.023
CR[g] Score	-0.013	0.034	-0.385	.701	-0.079	0.053
MAa vs. YA[b] * CR[f] Score	-0.106	0.045	-2.368	.018*	-0.193	-0.018
OA[c] vs. (MA[a] / YA[b]) * CRf Score	0.011	0.022	0.503	.615	-0.032	0.054
Covariates						
General Cognitive Processing	0.047	0.073	0.644	.520	-0.096	0.189

[a]MA = middle-aged adults
[b]YA = younger adults
[c]OA = older adults
[d]SE = standard error
[e]CI = 95% Confidence Intervals
fCR = Cognitive Reserve
*$p < .05$
**$p < .01$
***$p < .001$.

https://doi.org/10.1371/journal.pone.0280566.t005

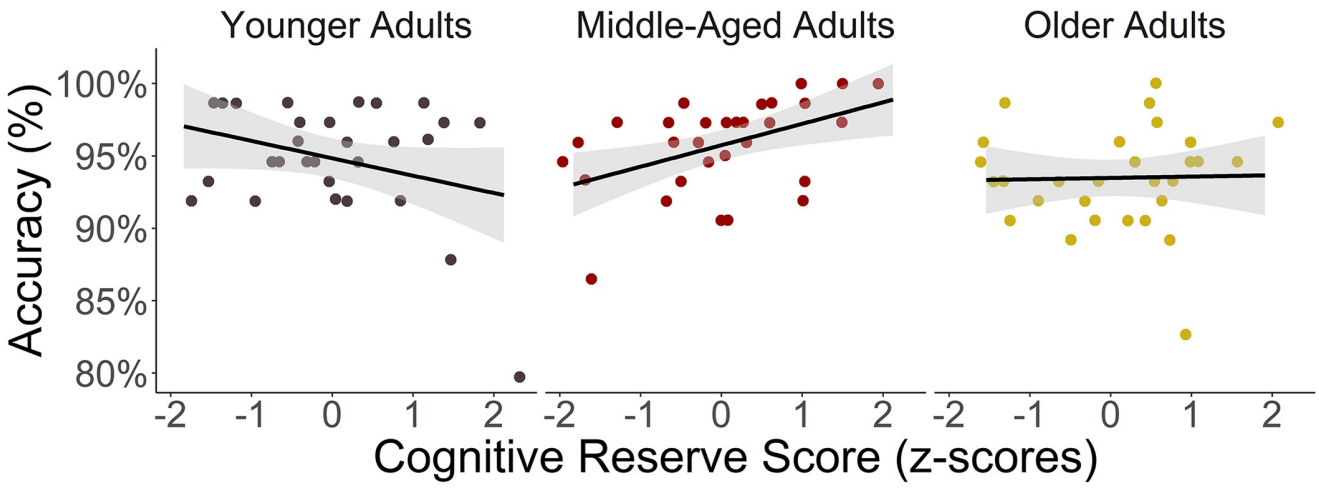

Fig 1. The relationship between Cognitive Reserve (CR) and action naming accuracy per age group. The Effect of CR is Significant in Middle-Aged Adults.

https://doi.org/10.1371/journal.pone.0280566.g001

middle-aged adults (see Fig 1). That is, CR had a positive effect on action naming accuracy (β = -0.11, z = -3.38, $p < .001$). Post-hoc comparisons revealed that the interaction was significant in middle-aged compared to younger adults (adjusted p = .002). For object naming accuracy, we found an interaction effect between Age and CR (β = -0.11, z = -2.37, p = .020). Post-hoc comparisons revealed that the interaction was significant in middle-aged compared to younger adults (adjusted p = .047; see Fig 2).

Both the models for object and action naming showed a good fit for picture-naming accuracy and there was no overdispersion. For action naming, Concordance and Somer's D were .82 and .65, respectively. For object naming, the respective values were .89 and .78. In addition, marginal and conditional R^2 for binomial distributions were calculated. Marginal R^2 was .008 for action naming and .012 for object naming. Conditional R^2 was .096 for action naming and .078 for object naming. However, logistic models often lead to low R^2 values [75] and low R^2 values are not an indication of poor model fit but could indicate a wider spread of data points instead [76, 77].

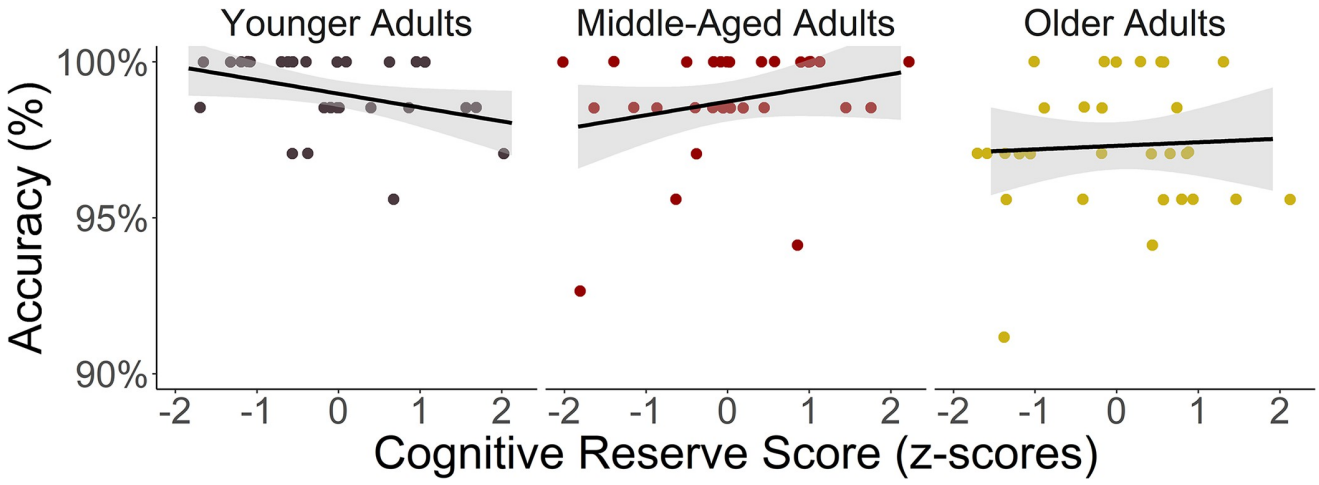

Fig 2. The relationship between Cognitive Reserve (CR) and action naming accuracy per age group. The Effect of CR is Significant in Middle-Aged Adults.

https://doi.org/10.1371/journal.pone.0280566.g002

Table 6. Descriptive statistics of the verbal fluency tasks (i.e., semantic, letter, and action fluency) per age group.

Age Group	Measure	Task[b]		
		Semantic	Letter	Action
Younger adults	N words total[a]	88 (19)	48 (14)	36 (7)
	Average Frequency	3.96 (0.16)	4.22 (2.64)	4.20 (0.17)
Middle-aged adults	N words total	94 (18)	54 (18)	36 (9)
	Average Frequency	4.40 (2.99)	4.08 (0.26)	4.21 (0.16)
Older adults	N words total	85 (14)	51 (20)	33 (6)
	Average Frequency	4.23 (2.05)	4.92 (0.24)	4.32 (0.88)

[a]N words total is the total number of correctly produced words.

[b]Values reflect means (SD)

https://doi.org/10.1371/journal.pone.0280566.t006

Verbal fluency data

Table 6 summarises the descriptive statistics of the verbal fluency tasks. For the models with the number of correctly produced words as the outcome variable, General Cognitive Processing was a significant predictor for action fluency only (β = 0.42, $t(83)$ = 2.25, p = .03). None of the other predictors were significant. This was the case for all three verbal fluency variables (i.e., semantic, action, and letter fluency). For semantic fluency, Age was a significant predictor of average frequency of the produced words (β = -0.06, $t(83)$ = 2.31), but the effect disappeared after correcting for multiple comparisons (p = .11). Moreover, none of the models predicted the data well, as was assessed through model fit diagnostics, including a non-significant overall model fit.

The effect of COVID-19 on CR and subsequent task performance

It is possible that social isolation due to the COVID-19 pandemic led to changes in CR scores, which could impact current word-finding ability. Table 1 provides the descriptive statistics per age group for the CR scores preceding and coinciding the COVID-19 pandemic. To investigate whether changes in CR scores due to the COVID-19 pandemic affected behavioural performance, we performed an exploratory analysis whereby we ran all models again with the CR scores measured during the pandemic. Next, ANOVA for model comparisons and AIC were used to compare the models with CR scores preceding the COVID-19 pandemic to that with the CR scores coinciding with the pandemic for all picture-naming and verbal fluency models separately. The ANOVAs for model comparisons and AIC values revealed no differences between the models with CR scores preceding the COVID-19 pandemic and those with CR scores coinciding the pandemic.

Discussion

This study investigated the relationship between CR and age-related word-finding difficulties, and explored the impact of the COVID-19 pandemic on CR. To our knowledge, this is the first study investigating these relationships. We hypothesised that CR modulates age-related declines in word finding. We quantified word-finding difficulties through picture-naming and verbal fluency tasks, and CR through a comprehensive questionnaire on lifestyle. We found that age predicts word-finding ability: Older adults had lower accuracy of action and object naming compared to middle-aged adults, and they had lower accuracy of object naming compared to younger adults. Both middle-aged and younger adults displayed faster reaction times for object naming compared to older adults. We found no age effect on action naming reaction

time nor on any of the verbal fluency measures. In addition, middle-aged adults with higher CR scores reached higher accuracies for both action and object naming. CR did not modulate action or object naming reaction times, nor did it modulate verbal fluency performance in any of the age groups. Finally, CR scores preceding the COVID-19 pandemic did not explain behavioural scores any differently than CR scores coinciding with the pandemic.

We found that older adults achieved lower accuracy for action and object naming and were slower in object naming, which is in line with previous studies showing a decrease in word-finding ability in older age [25, 36]. Older age did not predict reaction times for action naming. A recent study showed that action naming was less affected by age, possibly because action and object naming rely on different neural networks [78]. In addition, research suggests that action naming is a slower process compared to object naming because more cognitive resources are needed [13]. Hence, the speed of accessing action words may be relatively preserved in older adults, due to already slower processes involved and because of different underlying neural networks.

Our study did not reveal an effect of general cognitive processing on picture-naming performance. Some ageing theories state that cognitive deficits are caused by a shrinking of cognitive resources, such as a slowing down of cognitive processing speed [55] or a reduction of working memory capacity [54]. If the above-mentioned theories are correct, an age-related reduction in cognitive resources would explain the variance in the reaction times for action and object naming in the current study. Note this point holds true only under the assumption that the measures employed are good measures for capturing the aforementioned constructs. However, pure measures of complex psychological constructs, such as cognitive processing speed, are difficult to capture because measures can be influenced by multiple factors in addition to the construct itself [79]. However, general cognitive processing scores did not predict word finding in the current study. Hence, the age-related word-finding difficulties during the picture-naming task could not be explained by a reduction in cognitive resources. Future research should investigate the influence of general cognitive processes in relation to CR on word finding abilities.

We found no interactions between age and CR for reaction times nor for accuracies of action and object naming in older adults, which is in contrast with studies showing a modulatory effect of CR on cognitive functioning in older age [2]. There may be two possible reasons for this discrepancy. Firstly, previous studies showed that CR does not benefit all cognitive domains equally [26, 79]. In these studies, whilst CR was associated with better verbal memory and crystallised intelligence in older adults, CR did not enhance performance on a finger tapping, cognitive processing speed, or executive functioning task. Hence, CR might not mitigate word-finding difficulties in older age. Alternatively, CR might increase performance when task demands are high by enhancing general cognitive processes (for a discussion, see [80]). Hence, the effects from CR might become too subtle to detect whilst the beneficial effects on word finding from other cognitive processes becomes apparent.

In contrast to the findings in older adults, our results revealed an interaction between CR and age for action and object naming accuracy in middle-aged adults, with a stronger effect for action than object naming. Previous studies have reported that CR, quantified through years of education, modulates the performance of verbal memory and semantic memory [26, 27]. To our knowledge, the current study is the first to demonstrate that middle-aged people with high CR achieve higher action naming accuracy than those with low CR. Action naming is more challenging than object naming and the two processes are quite different from one another because of the different underlying cognitive processes and brain regions [13]. Hence, if CR is drawn upon when task demands are high and additional resources are needed, for example due to slower cognitive processes underlying action-word finding ability [5], it would benefit action naming more than object naming.

Moreover, the modulating effect of CR in middle-aged adults is in line with the findings of Cansino and others [29], who found that CR only contributes to source memory performance in middle age but not in older age. In middle age, high CR might be necessary as an additional resource when task demands are high [5], whilst in younger and older adults, different cognitive strategies are necessary to tackle difficult tasks [29]. Therefore, middle-aged adults might draw upon CR resources to support their word-finding abilities whilst older adults might enhance their word-finding abilities by tapping into other cognitive processes, such as cognitive processing speed, working memory, or vocabulary, that might be more beneficial [29]. A cautionary note should be given as it is currently unclear whether there is a causal link between CR and cognitive functioning. Several factors can influence cognitive ageing that have not been measured here, such as hearing loss [81], smoking, and high blood pressure [82], to name a few. Such factors have not been considered in the current study but could in theory have exerted influence on the relationship between CR and word-finding abilities. Longitudinal studies that control for such factors and investigate the causal role of CR interventions on cognition would provide critical information regarding the causal link between CR and cognition.

Furthermore, we observed that older adults experienced greater word-finding difficulties relative to both younger and middle-aged adults. Currently, there is no consensus on the age when word-finding difficulties become apparent. The results of this study indicate that subtle word-finding abilities can be detected from the age of 65 years old. This is in line with previous studies suggesting that a decline in word-finding abilities starts at 75 years of age [15]. Some studies suggested that word-finding difficulties already become apparent at the age of 30 years old [14] or as early as 50 years of age [17, 18, 25]. In contrast, we did not find differences in word-finding abilities between younger and middle-aged adults. Hence, it is likely that subtle word-finding difficulties can commence from the age of 65, depending on the individual.

The COVID-19 pandemic might have led to changes in CR scores, which could have immediately impacted word-finding ability. The current study investigated whether the level of CR coinciding with the COVID-19 pandemic would explain the data better than the CR levels preceding the pandemic. The current study showed that CR scores for the period coinciding with the COVID-19 pandemic did not explain behavioural performance better than CR scores for the period preceding the pandemic. Assuming that the pandemic resulted in short-term changes in CR levels, these changes do not seem to influence behaviour. One explanation is that there is a "critical period" for accumulating CR [83]. Therefore, CR accumulated early in life might be more important for word-finding ability than CR accrued later. As a result, changes in CR in older age would not modulate age-related declines in word-finding ability. However, several studies demonstrate that increasing CR levels at older age, for example through late-life education, increases cognitive performance [4, 79]. Moreover, the current study measured CR in both early (i.e., education) and later life (i.e., current engagement in leisure, cognitive, and psychical activities), and showed that CR modulated performance in middle and older age. Alternatively, the effects of lower CR on word-finding ability might be delayed and only become apparent later on. If reductions in CR scores result in lower cognitive performance in the long term, this could have an enormous impact on healthy brain function later in life. Therefore, it is of paramount importance that future studies investigate the long-term effects of changes in CR due to the COVID-19 pandemic on cognition.

Regarding verbal fluency, we found no effect of age or CR. In contrast, previous studies reported age-related decreases in verbal fluency performance [19–21] and a modulatory effect of CR on letter fluency [28]. The study was conducted online (because of the COVID-19 pandemic) and as such, participants had no opportunity to ask the researcher directly for clarification of the instructions. Because verbal fluency tasks are normally conducted in-person,

administering this task via an online platform without the researcher being present might have resulted in null results for verbal fluency in this study.

The optimal way to quantify CR is currently unclear as there are several proxies that can contribute to CR [6]. However, using a single proxy for CR, such as years of education, might not fully capture CR. In order to obtain a score that reflects CR across the lifespan, the current study implemented a more comprehensive measure by creating a composite score from the frequency of leisure, social, and cognitively stimulating activities in addition to educational and occupational attainment.

Lastly, we found that quite a large proportion of the variance in the picture naming reaction time data was explained by the additional random effects for between-individual and between-trial variability (when comparing conditional vs. marginal R^2). Previous studies showed that ageing trajectories are very person-specific and the deviation in performance increases with age [18, 24]. Hence, the large between-individual variability highlights the importance of controlling for individual differences in ageing research.

Limitations

The online nature of the study meant that the participants were not in a controlled environment. We tried to control the study through initial screening, providing clear instructions with example pictures, giving the opportunity to test the microphone, and by asking the participants to complete the study in a quiet environment with as few distractions as possible. Future online studies would benefit from a researcher attending the session via a conference call whilst the participant is completing the study to increase participant-researcher interaction. Furthermore, the current study was restricted to a sample of monolingual speakers of British English to reduce the variance in word-finding speed, which can be affected by language background [32]. Hence, the results of this study cannot be generalised to multilingual speakers. Future studies should investigate this question using groups of speakers with varied language backgrounds to expand on the relationships between CR and word-finding abilities across the lifespan. Such future research will increase our understanding of the effects observed in the current study, which has a restricted sample.

In the current study, we transformed the picture-naming reaction times and the number of correctly produced words on the verbal fluency tasks into *z*-scores within each participant group. We then classified any score above or below 2.5 *SD* as an outlier, which was subsequently removed. It is theoretically possible that trimming data, including the above-mentioned method, can lead to distortions of the data set [84, 85]. However, recent research suggests that not excluding outliers leads to a greater negative bias [67]. That is, the probability of Type-II errors increases when the data is not trimmed. Using the *z*-score method mentioned in this study leads to the smallest bias. With increasing age, standard deviations in cognitive tasks increase, meaning more variance within older than younger samples. Hence, trimming the data, especially in older adults, may lead to masking of deviation effects. In the current study, we chose to trim the data within each of the age groups, reducing the chance of masking such deviations. In addition, it is likely that trimming the data using *z*-scores has led to lower bias than not trimming the data at all (see [83]).

We also note that the study was powered for a medium-large effect size, so any smaller effects sizes may have been missed. Future work could use the data collected here to inform data simulations or power calculations associated with specific statistical tests. For LMMs, Hox proposes to use the rule of thumb of 30 groups with 30 observations [86]. The current study has 30 participants per group and over 70 trials per participants, and, hence, would comply with Hox's suggestion, so it is likely that the study is adequately powered.

The internal consistency of the CR questionnaire was poor (α = .59), indicating that the items in the questionnaire are multidimensional [87]. The low internal consistency score could be due to few questionnaire items or because they do not measure the same underlying construct. CR is a concept that is believed to be built up by lifestyle choices and lifetime experiences, such as physical activity and education [6]. Hence, CR in itself is a multidimensional construct and this multidimensionality might be reflected through the low Cronbach's Alpha score. However, there is currently no consensus as to what lifestyle choices and lifetime experiences must be included to compute an individual's CR level (for a discussion, please see [80]). To better capture CR, the current study included a range of CR proxies, including years of education, frequency of cognitively stimulating activities, and physical activities. Hence, the low Cronbach Alpha score may be a trade-off of using a more comprehensive CR measure.

Moreover, the use of different operating systems, browsers, and differences in microphone setup could have increased the variability in scores between participants. To reduce the timing variability in the audio recordings for the picture-naming tasks, the start of each trial was indicated with a trigger sound. To increase the reliability of the estimate of reaction time, we subtracted the trigger onset from voice onset. However, we could not control for the distance between participant and microphone, and this could have increased reaction time variability across participants and even across trials. We recommend that future online studies provide instructions on the distance between the participant and the computer (e.g., the participant should sit at arm's length).

Lastly, the current study did not investigate the effect of vocabulary on picture-naming performance in older adults. Previous studies showed that vocabulary positively modulated word-finding ability in older adults [29] and that an increase in vocabulary masks subtle declines in word-finding ability [38, 88]. However, we found age-related declines in word-finding ability in older adults. This participant group was slower in object naming and achieved lower accuracy for action and object naming than younger and middle-aged adults. Because word-finding difficulties in older age were present in the current study, vocabulary could not have masked word-finding difficulties. However, future studies on CR need to clarify the effect of both vocabulary and CR on word finding across the lifespan to provide a clearer picture as to what resources are necessary in maintaining word-finding in older age.

Conclusions

Lower action and object naming accuracy, and slower object naming reaction times, are associated with older age. These results suggest the presence of subtle word-finding difficulties in older age. Moreover, the results showed that high CR is associated with more accurate action and object naming in middle age. Hence, high CR might not always be beneficial in older age, but also in middle age, and this benefit will depend on multiple factors: the underlying cognitive processes, whether task demands are high, and individual differences in general cognitive processing abilities. Future studies should clarify at which life stages CR is most beneficial and whether this depends on the cognitive function being investigated. Finally, changes in CR due to the COVID-19 pandemic did not affect word-finding abilities. However, such effects might become apparent only after several years, and future studies should investigate the long-term effects of the COVID-19 pandemic on CR and subsequent cognitive functioning. If changes in CR negatively affects cognitive functioning, timely interventions are necessary to counteract the negative consequences and increased risk of dementia by, for example, increasing late-life CR. Such interventions can include cognitive training, education later in life, and promoting healthy lifestyle choices throughout the lifespan (for a discussion on interventions, please see [80]).

Acknowledgments

We would like to thank the members of the Neuroscience of Speech and Action laboratory for their support. We thank Peter Tovee and Barrie Usherwood for their advice on setting up a language production study using online platforms. Lastly, we would like to thank all the participants for their time and efforts.

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Chapter 4

Motor Ability Relates to Word-Finding in Both Individuals With and Without Parkinson's Disease

Linking Statement:

The first chapter reviewed the neurobiology and lifestyle contributions to healthy cognitive ageing. The second chapter provided an investigation into the lifestyle contributions to age-related word-finding difficulties. Parkinson's disease (PD) is the second-most common neurodegenerative disease (Parkinson's UK, 2018). PD has been associated with word-finding difficulties, specifically with words related to physical actions (Bocanegra et al., 2017; Henry & Crawford, 2004). Therefore, PD could serve as a neurodegenerative model to investigate the neurobiological mechanisms contributing to word-finding difficulties. This chapter investigated PD-related difficulties in words associated with upper-limb actions. In addition, we explored whether positive lifestyle factors might mitigate the negative effects of PD on word-finding ability. The discussion section discussed the neurobiological and neuropsychological implications of the findings.

Author Note:

The study hypotheses, design, and statistical analyses were preregistered on the

Open Science Framework (https://osf.io/u872g).

This paper has been prepared in collaboration with Dr. Kate Slade, Dr. Patrick May, and Dr. Helen Nuttall as co-authors.

4.1 Abstract

Parkinson's disease (PD) is characterised by motor symptoms and cognitive deficits, including action language difficulties, which have been linked to disruptions of the frontostriatal brain pathway. Few studies have differentiated between body parts and the amount of physical activity associated with a word (i.e., actionality) when investigating action language in PD. Additionally, an engaging lifestyle contributing to higher Cognitive Reserve (CR) may mitigate cognitive decline in PD, but its impact on action language impairments is unclear. This study aimed to investigate upper-limb action-word finding abilities in individuals with and without PD, considering word actionality and the impact of CR. Forty native-British speakers with idiopathic PD and 40 matched older adults without PD participated. Action-word finding was assessed via picture-naming and verbal fluency tasks. Upper-limb motor ability was assessed through a keyboard-tapping task. CR was measured through years of education, occupational attainment, and questionnaires concerning the frequency of engagement in cognitive, leisure, and physical activities. Linear mixed-effects models demonstrated that in both groups, participants with better motor ability skills named pictures faster. Multiple linear regression revealed a similar relationship between motor ability and the number of generated words on the verbal fluency task. These findings suggest a shared neuronal circuit underlying both word-finding and motor ability. The study revealed no distinct upper-limb action word impairment in individuals with PD compared to controls nor did CR or the actionality of the words affect word-finding. This study discusses the relationship between motor and word-finding ability, study limitations, and future directions.

Keywords: action language; Parkinson's disease; word-finding ability; motor ability.

4.2 Introduction

Parkinson's disease (PD) is the second most common brain disease, which affects over 145,000 people in the United Kingdom. This number is expected to increase by 18% in 2025 (Parkinson's UK, 2018). Motor symptoms, such as tremors and bradykinesia, are core criteria to clinically diagnose PD (Kalia & Lang, 2015; Postuma et al., 2015). However, individuals with PD also suffer from cognitive deficits, including language impairments (Aarsland et al., 2021; Camerino et al., 2022; Goldman & Litvan, 2011; Pagonabarraga & Kulisevsky, 2012; Verbaan et al., 2007). More specifically, individuals with PD show a selective deficit in producing verbs compared to nouns (Auclair-Ouellet et al., 2017). Words describing physical action may be most sensitive in PD due to PD-related dopamine depletion disrupting the frontostriatal brain pathway that combines linguistic and motor information (Birba et al., 2017; Ullman, 2004). Accordingly, action language capabilities could potentially be used to predict disease progression or contribute to the diagnosis of PD (Smith & Caplan, 2018). Whilst Parkinson's has many negative consequences for cognition, among which language, researchers have shown that an engaging lifestyle could potentially mediate the negative impact of Parkinson's on cognition (Ciccarelli et al., 2021). Therefore, an engaging lifestyle could alleviate PD-related action language problems.

In PD, dopamine neurons in the substantia nigra pars compacta degenerate, resulting in dopamine loss and dysfunction in the basal ganglia and thalamus (Jellinger, 2012; Postuma et al., 2015). At the onset of motor symptoms, 50-70% of the dopaminergic cells have already been lost (Fearnley & Lees, 1991). The basal ganglia play a vital role in the programming and control of movement (Alexander et al., 1986). The basal ganglia have connections to the cortex, forming pathways that include the primary motor cortex, and parts of the premotor, oculomotor, prefrontal, and inferotemporal cortical areas (Alexander et al., 1986; Middleton & Strick, 2000). It has been suggested that the frontostriatal pathway (i.e., the

pathway between frontal brain areas and the striatum) plays a role in combining linguistic and motor information (Birba et al., 2017; Ullman, 2008; Ullman, 2004). Disruption of this pathway could lead to difficulties in producing action words (e.g., *"to run"*) but not object words (e.g., *"book"*) in individuals with PD (Birba et al., 2017; Zgaljardic et al., 2003), demonstrated through action fluency and action naming impairments (Bocanegra et al., 2015; Herrera, Rodríguez-Ferreiro, et al., 2012; McDowd et al., 2011; Rodríguez-Ferreiro et al., 2009; Salmazo-Silva et al., 2017). Additionally, neuropsychiatric symptoms, such as apathy and depression, are common in PD and could influence word-finding ability (Aarsland et al., 2007; Cohen et al., 2015; D'Iorio et al., 2018; Dujardin et al., 2009; Fernandez et al., 2009; Ng et al., 2015).

Most studies differentiate between nouns and verbs when investigating action-word production difficulties in PD (e.g., Bertella et al., 2002; Herrera, Rodríguez-Ferreiro, et al., 2012; Salmazo-Silva et al., 2017), although nouns can also possess action-related features (Mahon & Caramazza, 2009). To further understanding, PD research has started to differentiate between words that are high or low in action content, measured through the amount of physical movement associated with the word (Auclair-Ouellet et al., 2021; Bocanegra et al., 2017; Herrera, Rodríguez-Ferreiro, et al., 2012; Rodríguez-Ferreiro et al., 2009; Salmazo-Silva et al., 2017). For example, the word *"screwdriver"* has high action content, while *"tree"* has low action content. Studies demonstrated that naming manipulable objects (i.e., high in action content), such as *"hammer"*, is more impaired in PD than naming non-manipulable objects (e.g., *"house"*; Auclair-Ouellet et al., 2017; Bocanegra et al., 2017; Cotelli et al., 2007; Johari et al., 2019). The dissociation between the naming of words with high versus low action content has not been observed in individuals without PD (Herrera, Rodríguez-Ferreiro, et al., 2012).

As bradykinesia has been associated with worse semantic fluency, processing speed, and executive functioning (Siokas et al., 2022), studies have also explored the relationship between action language and PD-related motor impairment but found

no association between action language and overall motor impairment (Bocanegra et al., 2017; Johari et al., 2019; Signorini & Volpato, 2006). However, studies may need to consider different body parts associated with action words (Roberts et al., 2017). Specifically, individuals with PD with an upper-limb motor impairment showed slower processing of upper-limb dominant verbs compared to lower-limb dominant verbs. Previous studies on action language in PD have yet to explore the specific relationship between upper-limb motor impairment and upper-limb action language using picture naming or action fluency.

Interestingly, certain lifestyle factors, such as engaging in social activities or education, can protect against or compensate for the consequences of PD (Ciccarelli et al., 2021; Hindle et al., 2016; Oosterhuis et al., 2022; Shih et al., 2016). Cognitive Reserve theory states that people can compensate for age- or disease-related cognitive impairments through a cognitive reserve (CR; Stern et al., 2020). CR is built up through lifetime experiences, such as education, and lifestyle, such as engaging in social and cognitive activities. Studies have demonstrated higher cognitive functioning in individuals with PD who have higher levels of CR (Guzzetti et al., 2019; Hindle et al., 2016; Rouillard et al., 2017). More specifically, individuals with PD who have high CR levels demonstrated less severe motor and general cognitive impairment (Guzzetti et al., 2019), and better semantic fluency performance than individuals with PD who have low CR levels (Ciccarelli et al., 2018). Although CR might be beneficial during the early stages of Parkinson's, it might not suffice to compensate for the negative impact of brain pathology as the disease progresses (Guzzetti et al., 2019; Stern et al., 2020). Currently, research on the effect of cognitive and leisure activities on cognition in PD is sparse (Nag & Jelinek, 2019) and it is unclear whether lifestyle choices can mitigate action language impairments in individuals with PD (Aarsland et al., 2021).

The primary aim of this study was to investigate whether upper-limb action language (i.e., words that express actions performed with the hand and arm, such as *"throwing"*) can be used to distinguish individuals with PD from healthy controls.

This is the first study to investigate PD-related impairments in action language using picture naming, with a primary focus on the action content of both nouns and verbs as a continuous predictor. We formulated the following hypotheses:

1. Individuals with PD show greater difficulty in producing words that describe upper-limb actions (e.g., *"throwing"*) compared to words associated with actions involving less upper-limb movement, when compared to individuals without PD.

2. In individuals with PD, there is a positive correlation between the ability to produce upper-limb action words and their upper-limb motor ability, measured by a keyboard tapping task.

As a secondary aim, the effects of CR, such as engaging in social activities, on action language were investigated. Lifestyle choices, such as physical activity, higher education, and social contact, could decrease the risk of dementia (Livingston et al., 2020). Hence, we hypothesised:

3. An engaging lifestyle, indicated by engaging in social and cognitively stimulating activities, physical activity, and higher education, is positively associated with better performance in producing action words in individuals with and without PD.

The hypotheses, predictions, and experimental design were preregistered on the Open Science Framework website at https://osf.io/u872g.

4.3 Method

Participants

To determine the sample size with adequate power, we conducted an a-priori power analysis using the *samplesize_mixed* function of the "sjstats" package in R (Lüdecke, 2021), setting the power at .80 and alpha level at .05. The power analysis resulted

in a sample size of 33 participants per group (total $N = 66$) to detect a moderate to large effect size (Cohen's $d = 0.7$). Because the study was run online, we expected some data loss due to technical difficulties, such as problems with audio recordings. Therefore, we set the maximum sample size at 80 participants (40 participants with PD and 40 control participants), with this maximum limited by time and monetary resources.

A total of 40 participants with PD (17 females; Mage=63.5) and 40 matched control participants (17 females; Mage = 64.7) took part in this study. All participants were native speakers of British English and reported normal or corrected-to-normal vision and hearing, no history of language or speech disorders, and no current psychiatric disorders that can be directly related to PD, such as compulsive behaviour (Han et al., 2018). Participants with a score of 4 or higher on the Informant Questionnaire on Cognitive Decline Self-Report (Jansen et al., 2008, IQCODE-SR), reflecting cognitive difficulties, were excluded. Following this exclusion criterion, one individual with PD was removed from the analysis. The control group reported no neurological disorders and was matched to the PD group for age ($t(78)$ = -0.58, p = .560), sex ($t(78)$ = -0.67, p = .508), and handedness ($t(78)$ = 1.18, p = .241). Table 4.1 shows the demographic characteristics of both participant groups. All participants gave digital consent before participating. The study was approved by the Research Ethics Committee of the Faculty of Science and Technology of Lancaster University.

All participants with PD self-reported a diagnosis of idiopathic PD. None of the participants with PD had other parkinsonisms, such as vascular parkinsonism or multiple system atrophy. All 39 PD participants were taking their prescribed PD medication as normal. Of the PD participants, 37 participants were taking combination drugs (e.g., containing levodopa and decarboxylase inhibitors, such as madopar), 28 participants were taking a dopamine agonist (e.g., pramipexole), and 16 participants were taking a monoamine oxidase inhibitor (e.g., rasagiline). Parkinsonian motor and non-motor symptoms were assessed with the Movement

Table 4.1. *Demographics and Medical Characteristics Mean (SD; range) for the Parkinson's Disease and Control Groups.*

Group	**PD**	**Controls**
Age (years)	64.94 (6.16; 51-77)	66.22 (7.88; 50-79)
Education (years)	4.89 (3.68; 0-20)	5.73 (5.21; 0-32)
BDI-II	9.83 (5.49; 1-26)	7.08 (6.59; 0-30)
SAS	11.08 (5.05; 3-22)	8.97 (4.27; 1-18)
IQCODE-SR	3.26 (0.21; 3-3.81)	3.14 (0.20; 2.81-3.81)
Years since onset	8.36 (4.67; 2-22)	
Years since diagnosis	6.51 (3.58; 1.25-18)	
Years on medication	6.69 (5.20; 1.25-30)	
Time since last dosage of medication (min)	157.50 (110.57; 20-610)	
MDS-UPDRS Part 1[a]	11.81 (5.32; 3-26)	
MDS-UPDRS Part 2[b]	10.81 (4.88; 4-25)	
MDS-UPDRS Part 3[c]	6.08 (4.44; 1-20)	
MDS-UPDRS Part 4[d]	4.11 (3.84; 0-11)	
MDS-UPDRS upper-limb bradykinesia[e]	3.67 (2.85; 0-12)	
MDS-UPDRS upper-limb tremor[f]	1.92 (2.21; 0-9)	
Levodopa Equivalent Daily Dose (mg)	615.56 (309.27; 262-1950)	

[a]Non-motor experiences of daily living; [b]motor experiences of daily living; [c]motor examination (condensed version, only items 3.4–3.6, 3.15, 3.16 were assessed); [d]motor complications; [e]upper-limb bradykinesia score across both sides of the body (items 3.4, 3.5, and 3.6); [f]postural and kinetic tremor of the left and right hands (items 3.15 and 3.16)

Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS; Goetz et al., 2008). Because the study was conducted online, we only assessed the items of Part III (motor examination) of the MDS-UPDRS for speech, facial expression, upper-limb bradykinesia (i.e., slowness of movement), and tremor (items 3.4 – 3.6, 3.15, 3.16), and lip/jaw rest tremor. Therefore, the scores of each of the four subscales are reported separately (see Table 4.1). Since only a part of the motor examination of the MDS-UPDRS could be assessed, the Hoehn and Yahr stage could not be determined.

Materials

Depression and apathy were assessed online with the Beck Depression Inventory-II (BDI-II; Beck et al., 1996) and the Starkstein Apathy Scale (SAS; Starkstein et al., 1992). Self-report measures were used to assess apathy and depression, as caregiver reports have been questioned as a superior alternative (Schiehser et al., 2013; Valentino et al., 2018). The IQCODE-SR, BDI-II, SAS, MDS-UPDRS subscale IB and II, a demographics questionnaire, and a CR questionnaire were completed online via the Qualtrics XM Platform (Qualtrics, Provo, UT). The behavioural tasks to assess action language production (i.e., picture naming and verbal fluency) and motor ability (i.e., keyboard tapping task) were completed online via the Gorilla Experiment Builder (Anwyl-Irvine et al., 2020), whilst the experimenter was present via a video conference call on Microsoft Teams (Microsoft Corporation).

Cognitive Reserve

To obtain a comprehensive measure of CR, CR was quantified through years of education after the age of 16 (early-life CR), occupational attainment scores (mid-life CR) using the five-class National Statistics Socio-economic Classification method from the UK Standard Occupational Classification system (NS-SEC; Office for National Statistics, 2020), and a general activity questionnaire (late-life/current CR). The general activity questionnaire consisted of 21 questions about

social/leisure, cognitively stimulating, productive, and physical activities. The questions were adapted from previously published studies (Sörman et al., 2014; Wang et al., 2002). The frequency of participation was rated on a 5-point scale from never/rarely (0) to every day (4). For the analysis, we created a composite score by averaging the standard scores (i.e., z-scores) for early-life, midlife, and late-life CR (following the method by Soldan et al., 2013). There were 7 questions about social/leisure activities (max. score of 28), 4 questions on cognitively stimulating activities (max. score of 16), and 5 questions on productive activities and physical activities (max. score of 20 per sub-scale). This resulted in a single CR score per participant for the analysis. The CR scores for the general activity questionnaire and the NS-SEC score can be found in Table 4.2.

Table 4.2. *Cognitive Reserve Scores per Group*

	PD		**Controls**	
	Mean (*SD*)	Range	Mean (*SD*)	Range
NS-SEC	4.39 (1.15)	1 – 5	4.73 (0.69)	2 – 5
Social/Leisure	9.14 (2.92)	4 – 16	9.92 (3.18)	4 – 17
Cognitively stimulating	8.17 (2.69)	0 – 13	9.03 (3.03)	1 – 14
Productive	11.19 (2.71)	6 – 18	11.76 (2.45)	7 – 16
Physical	7.31 (3.40)	0 – 14	7.84 (3.51)	0 – 14
CR Composite Score (*z-score*)	-0.16 (0.71)	-2.12 – 1.19	0.16 (0.69)	-1.38 – 2.35

Picture Naming

Pictures with high picture-name agreement across individuals (object naming: 98.5%; action naming: 92.2%) were obtained from the Center for Research in Language International Picture-Naming Project (Szekely et al., 2004). The final set contained 50 action pictures and 50 object pictures, which were matched for age

of acquisition ($t(98) = 0.96$, $p = .337$), word frequency ($t(98) = 0.80$, $p = .427$), action ratings ($t(98) = -0.69$, $p = .493$), and familiarity ($t(79) = 0.15$, $p = .883$). To assess the relationship between upper-limb motor ability and upper-limb action word ratings, upper-limb action ratings of the picture names were obtained using the Lancaster Sensorimotor Norms (Lynott et al., 2020). Words in this database had a rating between 0 (upper limb not associated with performing that action) and 5 (upper limb highly associated with performing that action). For this study, the action ratings for object stimuli ranged from 0.619 to 4.55 ($M = 2.68$, $SD = 0.94$, $Mdn = 2.63$). Of the 50 object stimuli, 11 stimuli fell within an action rating of 0 to 2, and 20 stimuli fell within an action rating of 3 to 5. The action ratings for action pictures ranged from 0.05 to 4.81 ($M = 2.52$, $SD = 1.4$, $Mdn = 2.61$). Of the 50 action stimuli, 19 stimuli fell within an action rating of 0 to 2, and 22 stimuli fell within an action rating of 3 to 5. For the analysis, the items *"catching"* and *"telescope"* were removed due to low accuracy across both participant groups, likely due to the high visual complexity of the pictures. For example, the item *"catching"* resulted in answers, such as *"jumping"* or *"reaching"*. The item *"telescope"* resulted in several non-answers.

Before starting the task, the participant tested their microphone and computer volume. Next, the participant read the instructions on the computer screen and could ask the experimenter any questions. The participant was instructed to sit at arms-length from the computer screen and to name the pictures as quickly and accurately as possible. The task started with four practice trials, for which the participant received verbal feedback from the experimenter. After the practice trials, the actual experiment started. All trials started with a 500ms fixation cross, followed by a blank screen of 1000ms, after which the picture was presented for 4000ms. Differences in microphones used by the participants and the lags in audio recordings caused timing variability between participants and trials. Therefore, a trigger sound was added to indicate the onset of a picture. This trigger sound enabled the experimenter to compute the verbal reaction time more accurately.

Stimuli were never repeated to avoid practice effects and the trials were being presented in a pseudo-randomised order. Picture names starting with the same letter never followed each other to avoid phonetic priming by the previous word. Reaction times were calculated using CheckVocal (Protopapas, 2007).

Verbal Fluency

In addition to the picture-naming tasks, semantic and action fluency tasks were conducted. For semantic fluency, the participant was asked to name as many items belonging to the category "household items". This category was chosen to elicit the generation of names of objects involving upper-limb actions as opposed to a more commonly used category, such as "animals". The action fluency task was prompted by asking the participant to name as many "things people can do" following Piatt et al. (1999). For each of the verbal fluency tasks, the participant had 60 seconds to generate aloud as many words as possible. The responses were recorded and later transcribed by two transcribers.

Motor Ability

Bradykinesia is a core symptom of Parkinson's disease (Kalia & Lang, 2015). To obtain a quantitative measure of upper-limb bradykinesia, the participant performed a keyboard-tapping task. The task consisted of two parts, namely distal and proximal keyboard tapping. For distal keyboard tapping, the participant had to press down the left arrow key (when assessing the left hand) or the right arrow key (when assessing the right hand) with the middle finger whilst repeatedly pressing down the lower arrow key as many times as possible for 30 seconds (Akram et al., 2022). For proximal keyboard tapping, the participant had to alternately tap the "s" and ";" keys with either the left or the right index finger for 30 seconds (Noyce et al., 2014). For both distal and proximal keyboard tapping, the participant had a 5-second practice round. The participant started with either the left or right hand, after which the task was repeated with the other hand, and this order was

counterbalanced. In total, there were 4 rounds of 30 seconds (left distal, right distal, left proximal, and right proximal). For each round, a total score was obtained by summing up the number of keyboard taps. A single composite score, reflecting upper-limb motor ability, was obtained by creating standard scores (z-scores) for each round and averaging across these scores.

Procedure

The participant's eligibility was first assessed via email, after which the participant received a link to Qualtrics XM Platform to complete several questionnaires. These questionnaires included a demographics questionnaire, the BDI-II, SAS, IQCODE-SR, NS-SEC questionnaire, and the general activity questionnaire. The participants with PD additionally completed a disease information questionnaire and the MDS-UPDRS part IB and II. Within the same week of filling in the online questionnaires, the participant completed the behavioural tasks via the Gorilla Experiment builder. During the behavioural tasks, the researcher was continuously present via a conference call, to ensure the participant understood and correctly performed the tasks. During the video call, participants with PD were assessed the MDS-UPDRS part IA, III, and IV before the behavioural part of the study. The participant started with either the motor ability or with the language production tasks, in a counterbalanced order. To avoid priming effects, the language production tasks always started with verbal fluency, after which picture naming was assessed. At the end of the experiment, the participant was debriefed and thanked for their participation.

Statistical Analysis

Data pre-processing and data analysis were performed in R (RStudio Team, 2020). For data pre-processing, we used the package *tidyverse* (Wickham & Bryan, 2019). To analyse the picture-naming reaction times and accuracy, we used a generalised linear mixed-effects model (GLMM), using the *lme4* package (Bates et al., 2015).

Because the reaction time data was skewed, we selected the gamma distribution as the appropriate family for modelling the response variable (Lo & Andrews, 2015). A GLMM suitable for binomial data was used to analyse the accuracy data (1 for correct or 0 for incorrect; Gilmour et al., 1985). Because the distribution of the accuracy data was highly skewed, the model was run with a complementary log-log (cloglog) link function (Agresti, 2013).

For all GLMMs, random effects for Item (i.e., variance caused by between-item variability) and Subject (i.e., variance caused by between-subject variability) were included (Baayen et al., 2008). The Akaike Information Criterion (AIC) was used to justify the inclusion of both random effects (Akaike, 1998), with a lower AIC value indicating a better fit. To assess goodness of fit for all GLMMs, the conditional and marginal R-squared (R^2) were obtained using the function "r.squaredGLMM" of the package *MuMIn* (Barton, 2022). For the GLMM, we also tested goodness of fit by testing for overdispersion using "testDispersion" in the *DHARMa* package (Hartig, 2022). The predictive power of the GLMMs with binomial distribution were assessed through concordance and Somer's *D*, using the "somers2" of the *Hmisc* package (Harrell, 2023).

To analyse the verbal fluency data, we used multiple linear regressions with outcome variables 1) the number of correctly produced words and 2) the average upper-limb action rating of the correctly produced words. To obtain a value for the second outcome variable, we used the Lancaster Sensorimotor Database (Lynott et al., 2020) to obtain upper-limb action ratings for each of the correctly produced words. For the "number of correctly produced words", we employed a Generalized Linear Model (GLM), which is well-suited for count data (Nelder & Wedderburn, 1972). To address overdispersion, we opted for the Tweedie distribution, which is well-suited for handling overdispersed count data (Dunn & Smyth, 2005). The Tweedie GLMs were specified, using the *statmod* and *tweedie* package (Dunn, 2022; Smyth et al., 2023), with a variance power parameter of 1.5 and a log link function (link power = 0). For "the average upper-limb action rating of the correctly produced

words", we employed multiple linear regression analyses.

Furthermore, the models for all outcome variables included Task Type with two levels (picture naming: object and action naming; verbal fluency: semantic and action fluency) as a covariate to account for differences in task type. In all models, the categorical variable Group was coded using treatment contrasts, such that the first contrast reflected the control group and the second contrast reflected the Parkinson's group. The categorical variable Task Type was also coded using treatment contrasts where the first contrast reflected object naming, and the second contrast reflected action naming. For the exploratory analyses, we investigated the additive effects of apathy and depression for each naming reaction time and verbal fluency performance using the "anova" function from the package *stats*.

Model Predictors per Hypothesis

To test hypothesis 1, the main predictors for both reaction time and accuracy were the two-way interaction between Group with two levels (PD and healthy controls) and Action Rating (continuous variable; i.e., upper-limb action ratings of the picture names). For the verbal fluency outcome variables, the predictor variable was Group with two levels (PD and control group).

To test hypothesis 2, the predictors for both reaction time and accuracy data were the three-way interaction between Group with two levels (PD and control group), Action Rating, and Motor Ability composite score (continuous; obtained through the keyboard tapping task). For the verbal fluency outcome variables, the predictor variables were a two-way interaction between Group with two levels (PD and control group) and Motor Ability composite score.

To test hypothesis 3, the predictors for both reaction time and accuracy data were Task Type with two levels (object naming and action naming), and the three-way interaction between Group with two levels (PD and control group), Action Rating, and the standardised CR composite score. For the verbal fluency outcome variables, the main predictors were the interaction between Group and the standardise CR

composite score (continuous predictor). The skewness of the CR composite variable was -0.38, indicating that the distribution was not skewed.

Missing Data and Outliers

For picture-naming reaction time, no missing data was found after excluding all incorrect trials. For accuracy, 0.7% of the data was missing. Regarding verbal fluency, for the outcome variable "number of correctly produced words", 0.7% of the data was missing. For the outcome variable "average upper-limb action rating", 2.7% of the data was missing. Removing outliers for the model with the average upper-limb action rating was necessary to meet the assumptions of a multiple linear regression.

As per the preregistration, observations of the outcome variable were identified as outliers if they had a Cook's distance of more than 3 times the mean. Models with and without outliers were compared using AIC to see which fitted the data better. For picture-naming reaction times, the models without outliers were analysed as these had lower AIC values than the models with outliers included. The following number of influential data points were observed for picture-naming reaction times: the model for hypothesis 1 had 390 influential data points (5.5% of the full data set), hypothesis 2 had 387 influential data points (5.4% of the data), and hypothesis 3 had 410 influential data points (5.7% of the data). These influential data points were removed as outliers. For picture-naming accuracy, removing outliers resulted in minimal variability in accuracy due to the high accuracy scores. Therefore, the picture-naming accuracy data was analysed with outliers.

Regarding verbal fluency, for the outcome variable "number of correctly produced words", the models without outliers were analysed as these had lower deviation values than the models with outliers. The following number of influential data points were observed and subsequently removed: hypothesis 1 had 10 influential data points (6.8% of the full data set), hypothesis 2 had 11 influential data points (7.5% of the data), and hypothesis 3 had 11 influential data points (7.5% of the data). For

the outcome variable "average upper-limb action rating", only the models without outliers met the assumptions for linearity, independence of predictor variables, homoscedasticity, and normality of residuals for multiple linear regression. The following number of influential data points were observed and subsequently removed: hypothesis 1 had 17 influential data points (11.8% of the data), hypothesis 2 had 16 influential data points (11.1% of the data), and hypothesis 3 had 17 influential data points (11.8% of the data).

As was preregistered, CR composite scores and motor ability scores were considered outliers if they had a value of +/- 3 *SD* above the mean of each group. Because these scores were important predictors in our analysis, any outliers were winsorised at +/-3 *SD* to allow for the scores to remain on the extreme side of the distribution without loss of data. There was no missing data for the CR composite scores or the motor ability scores. For all models, except for the exploratory analyses, *p*-values were corrected for multiple comparisons using the False Discovery Rate (FDR; Benjamini & Hochberg, 1995).

Deviations from the Preregistration

In the preregistration, we included one model per outcome variable to test all three hypotheses. To answer the hypotheses more effectively, we ran reduced models with only the predictor variables needed to test each of the three hypotheses. Furthermore, the outcome variable Reaction Time for the picture-naming task was not normally distributed. Because transforming the reaction time variable can conceal group differences, we did not transform the outcome variable (Lo & Andrews, 2015). Instead, we implemented a GLMM with a Gamma distribution to capture the reaction time distribution as this approach has been demonstrated to provide a more accurate representation of the data compared to a linear mixed-effects model with an inverse transformation of reaction time (Lo & Andrews, 2015). For the outcome variable "number of correctly produced words" in the verbal fluency data, we opted for a generalized linear model as these are more suitable for count data

than normal multiple linear regression (Nelder & Wedderburn, 1972).

Although we preregistered to only run the exploratory analyses in the Parkinson's group, the literature indicates that depression and apathy can also influence cognition (e.g., slowing of speech production) in individuals without PD (Montoya-Murillo et al., 2019; Sawa et al., 2012). Therefore, we explored the effects of apathy and depression on word-finding ability in both groups. There were no other deviations from the preregistered analyses.

4.4 Results

Descriptives

Reaction time was analysed for accurate items only. For action naming, the mean reaction time was 1395.8ms (SD = 507.8ms) for the PD group and 1345.8ms (SD = 448.2ms) for the control group. For object naming, the mean reaction time was 1123.1ms (SD = 318.7ms) for the PD group and 1113.8ms (SD = 342.9ms) for the control group. Both the PD and control group reached accuracy scores at ceiling. Mean accuracy for action naming was 97.5% (SD = 15.5%) for the PD group and 98.4% (SD = 12.7%) for the control group. For object naming, the mean accuracy was 99.3% (SD = 7.8%) for the PD group and 99.3% (SD = 8.4%) for the control group.

For the Verbal Fluency tasks, the PD group generated an average of 21.8 (SD = 5.1) words correctly during the action fluency task and an average of 25.1 (SD = 6.3) words during the semantic fluency task. The control group produced an average of 21.8 (SD = 5.1) words correctly during the action fluency task and an average of 25.2 (SD = 5.8) words during the semantic fluency task. Mean upper-limb action ratings for the action fluency task were 2.35 (SD = 0.60) for the PD and 2.35 (SD = 0.41) for the control group. For the semantic fluency task, the mean upper-limb action ratings were 2.78 (SD = 0.29) for the PD group and 2.76 (SD = 0.25) for the control group.

Hypothesis 1: Action-Word Production

Hypothesis 1 stated that individuals with PD show greater difficulty in producing words that describe upper-limb actions (e.g., "throwing") compared to words associated with actions involving less upper-limb movement, when compared to individuals without PD. All non-significant model outputs for Hypothesis 1 are reported in Appendix A.1.

For picture naming reaction time, the model with a "log" link function without outliers fit the data best (AIC = 88406.6). Therefore, we proceeded with the gamma log model without outliers and back-transformed the estimates in the model by exponentiating the coefficients. There was no overdispersion, autocorrelation (i.e., independent residuals), or dependency between predictors.

The analysis did not reveal a main effect of upper-limb Action Ratings on reaction time (β = -0.001, t = -0.033, adjusted p = .974), indicating that upper-limb action words are not more difficult to produce than words associated with actions involving less upper-limb movement when controlling for task type. In addition, there was no significant interaction between upper-limb Action Ratings and Group β = 0.007, t = 1.923, adjusted p = .091). This suggests that the relationship between actionality and reaction time did not significantly differ between the groups. Marginal and conditional R^2 were calculated as a measure of model fit. Fixed effects explained 22.1% of the variance in the data (marginal R^2 = .231), indicating a moderate contribution of the predictors to explaining reaction time. 40.0% of the variance was explained by the full model, including random effects (conditional R^2 = .400), suggesting that both fixed and random effects together provide a better fit to the data. ICC showed that 11.9% of the total variance in reaction time was accounted for by the item-level random effects, and 10.1% was accounted for by the subject-level random effects, indicating that a portion of the variance is due to these random factors.

For picture naming accuracy, the model converged without the need for optimisers. There was no overdispersion, autocorrelation (i.e., independent

residuals), or dependency between predictors. The analysis revealed that neither upper-limb Action Ratings (β = -0.066, z = -0.895, p = .371, adjusted p = .463), nor the interaction between upper-limb Action Ratings and Group (β = 0.023, z = 0.369, adjusted p = .712) were significant predictors of accuracy. Concordance and Somer's D were .95 and .89 respectively, indicating the model had good predictive power. Marginal R^2 was 0.021 and conditional R^2 was .171.

For verbal fluency "number of correctly produced words", there was no difference between the PD and control group (β = 0.002, t = 0.059, adjusted p = .953). That is, individuals with PD did not have more difficulty in generating words on the verbal fluency tasks than the control group. For the outcome variable "average upper-limb action rating", the overall model significantly predicted the upper-limb action ratings of the correctly produced words ($F(2, 124) = 31.84$, $p < .001$, R^2 = .34, R^2_{Adjusted} = .33). However, there was no difference between the PD and control group (β = 0.070, t = 1.472, adjusted p = .145). That is, both the PD and control groups generated words with similar lower upper-limb action ratings.

In summary, the analyses did not reveal significant differences in upper-limb action word-finding ability between individuals with and without PD.

Hypothesis 2: Motor Ability

Hypothesis 2 stated that in individuals with PD, there is a positive correlation between the ability to produce upper-limb action words and their upper-limb motor ability, measured by a keyboard tapping task. All non-significant models are reported in Appendix A.2. For picture naming, the reaction time model converged after application of the "bobyqa" optimiser (Bates et al., 2023). The AIC for the log model without outliers (AIC = 88948.0) was lower than the model with outliers (AIC = 99132.6). Since the model with a "log" link function converged, we proceeded with the gamma log model and back-transformed the estimates in the model by exponentiating the coefficients. There was no overdispersion, autocorrelation (i.e., independent residuals), or dependency between predictors.

The analysis revealed a main effect of motor ability on reaction time (β = -0.108, t = -2.755, adjusted p = .018), indicating that greater motor ability is associated with faster reaction times. The back-transformed estimate indicated a percentage change of -10.2% in reaction time per unit increase in motor ability (z-scale). Figure 4.1 shows the relationship between motor ability score and reaction times for the PD and control group. There was no significant interaction between Motor Ability and Group (β = 0.094, t = 1.721, adjusted p = .192), suggesting that the relationship between motor ability and reaction time did not significantly differ between the groups. Additionally, there was no significant three-way interaction between Group, Motor Ability, and Action Ratings (β = 0.004, t = 0.708, adjusted p = .616), indicating that the combined effect of these variables on reaction time was not significantly different between the groups. The model's formula and results are reported in Table 4.3.

Table 4.3. *Results of the Fixed Effects for Picture Naming Reaction Time and the Relationship with Motor Ability*

Model	RT ~Group * Action Rating * Motor Ability Score + Type + (1 | Subject) + (1 | Item)							
Effect	Estimate	*SE*	*z*-value	*p*-value	*CI* Low	*CI* High	Back-Transformed Estimate	Percentage Change
Intercept	6.954	0.042	166.669	< .001	6.873	7.036	1047.677	104667.4
Group	0.027	0.037	0.718	.473	-0.046	0.100	1.027	2.725
Action Rating	-0.001	0.018	-0.031	.975	-0.036	0.035	0.999	-0.057
Motor Ability Score	-0.108	0.039	-2.755	.006*	-0.184	-0.031	0.898	-10.208
Task Type	0.194	0.036	5.330	< .001*	0.122	0.265	1.214	21.364
Group * Action Rating	0.005	0.004	1.297	.194	-0.002	0.012	1.005	0.469
Group * Motor Ability Score	0.094	0.054	1.721	.085	-0.013	0.200	1.098	9.818
Action Rating * Motor Ability Score	0.001	0.004	0.358	.720	-0.006	0.009	1.001	0.137
Group * Action Rating * Motor Ability Score	0.004	0.005	0.709	.479	-0.007	0.014	1.004	0.376

Note. *SE* = standard error, *CI* = 95% Confidence Intervals. Action Rating reflects the upper-limb action ratings of the picture names. Motor Ability Score was obtained through a keyboard tapping task (i.e., number of taps). Task Type reflects the type of picture-naming task (i.e., object vs. action naming). Predictors remaining significant after FDR corrections are marked (*). The adjusted *p*-values can be found in the main text.

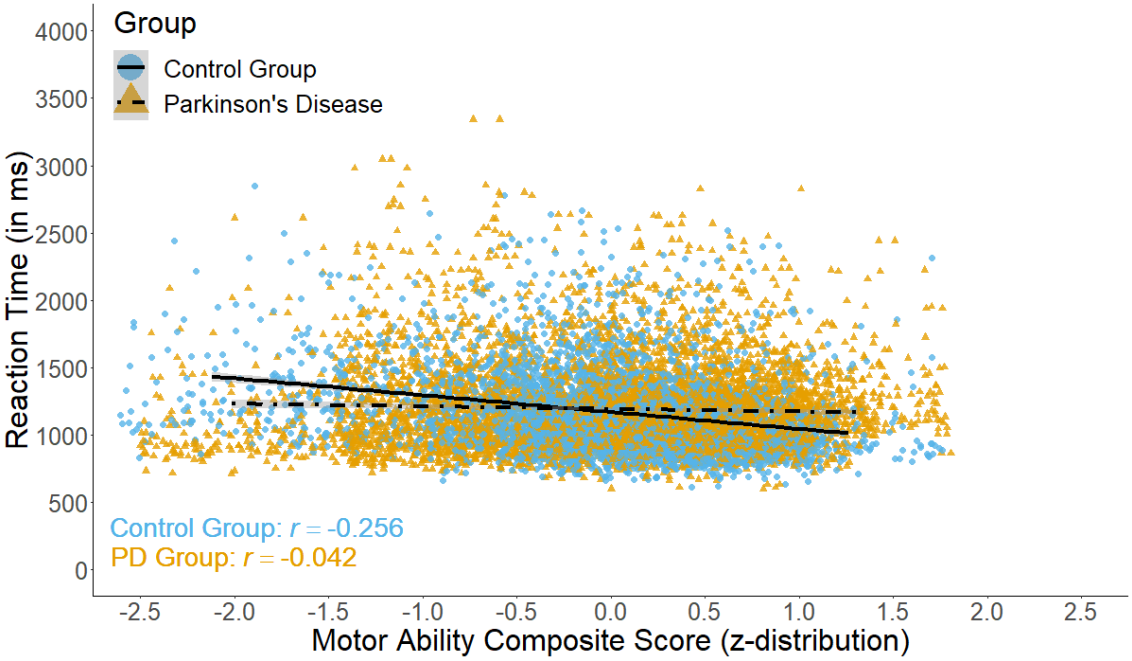

Figure 4.1. The linear relationship between picture-naming speed and motor ability in the groups with and without Parkinson's disease. The correlations between picture-naming speed and motor ability per group are also presented.

Marginal and conditional R^2 were calculated as a measure of model fit. Fixed effects explained 27.6% of the variance in the data (marginal $R^2 = .276$), indicating a moderate contribution of the predictors to explaining reaction time. 43.0% of the variance was explained by the full model, including random effects (conditional $R^2 = .430$), suggesting that both fixed and random effects together provide a better fit to the data. ICC showed that 12.0% of the total variance in reaction time was accounted for by the item-level random effects, and 9.0% was accounted for by the subject-level random effects, indicating that a portion of the variance is due to these random factors.

For picture naming accuracy, the model converged after applying the "nloptwrap" optimiser (Bates et al., 2015). There was no overdispersion, autocorrelation (i.e., independent residuals), or dependency between predictors. The analysis revealed no main effect of motor ability ($\beta = 0.172$, $z = 1.958$, adjusted $p = .151$). In addition, neither the two-way interaction between motor ability and group ($\beta =$

-0.097, z = -0.834, adjusted p = .520) nor the three-way interaction between group, motor ability, and action ratings (β = 0.103, z = 1.236, adjusted p = .390) were significant predictors of accuracy. Therefore, the relationship between accuracy and motor ability, either independently or in interaction with other variables, was not statistically significant. Concordance and Somer's D were .94 and .89 respectively, indicating the model had good predictive power. Marginal R^2 was 0.026 and conditional R^2 was .171.

For verbal fluency "number of correctly produced words", the model without outliers fitted the data better (deviance = 26.0) than the model with outliers (deviance = 35.3). Therefore, we proceeded with the model without outliers. The analysis revealed a main effect of motor ability (β = 0.195, t = 3.765, adjusted $p < .001$). The back-transformed estimate for motor ability indicates that for each unit increase in motor ability, the expected number of correctly produced words increases by approximately 13.9%. The two-way interaction between group and motor ability was also significant (β = -0.153, t = -2.228, adjusted p = .028). That is, the relationship between motor ability and verbal fluency performance differed between the PD and control groups (see Figure 4.2). Specifically, with greater motor ability, the expected number of correctly produced words decreases by approximately 10% in the PD group compared to the control group. The model's formula and results are reported in Table 4.4.

Table 4.4. *Results of the Generalised Linear Model for Verbal Fluency "Number of Correctly Produced Words" and the Relationship with Motor Ability*

Tweedie Model	Number of Correctly Produced Words ˜Group * Motor Ability Score + Task Type							
Effect	Estimate	*SE*	*t*-value	*p*-value	*CI* Low	*CI* High	Back-Transformed Estimate	Percentage Change
Intercept	3.102	0.040	78.301	< .001*	3.024	3.179	7.908	690.822
Group	0.133	0.048	2.781	.006*	0.040	0.227	1.093	9.299
Motor Ability Score	0.195	0.052	3.765	< .001*	0.094	0.297	1.139	13.908
Task Type	-0.135	0.035	-3.858	< .001*	-0.203	-0.066	0.914	-8.585
Group * Motor Ability Score	-0.153	0.069	-2.228	.028*	-0.287	-0.019	0.903	-9.683

Note. *SE* = standard error, *CI* = 95% Confidence Intervals. Motor Ability Score was obtained through a keyboard tapping task (i.e., number of taps). Task Type reflects the type of verbal-fluency task (i.e., semantic vs. action fluency). Predictors remaining significant after FDR corrections are marked (*). The adjusted *p*-values can be found in the main text.

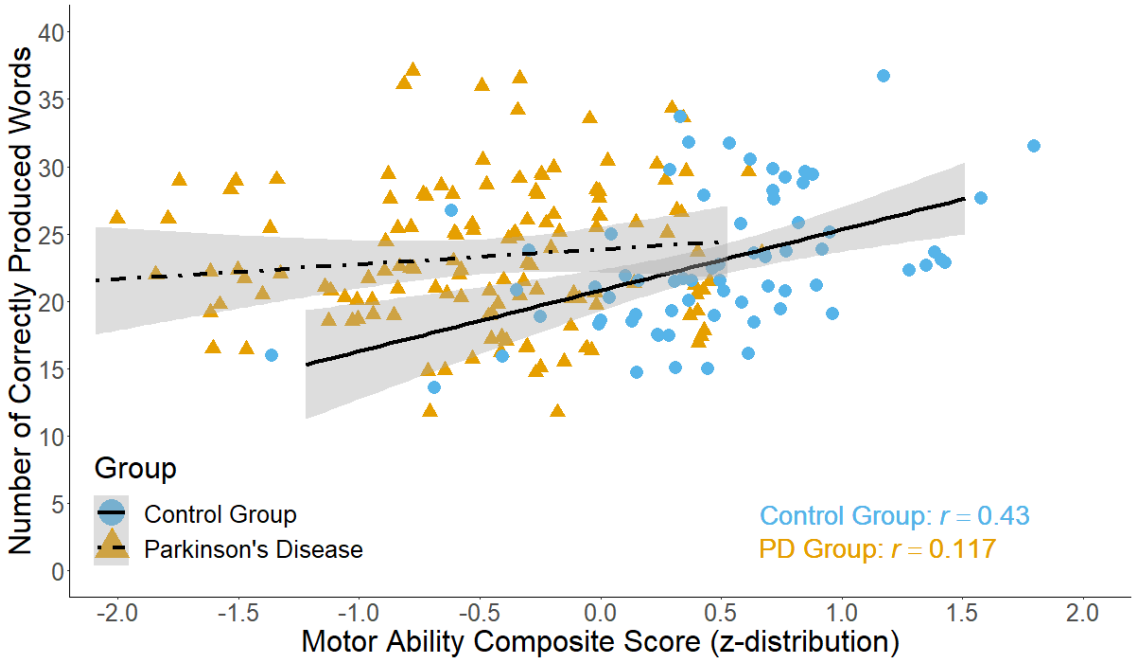

Figure 4.2. The linear relationship between the number of correctly produced words on the verbal fluency task and motor ability in the groups with and without Parkinson's disease. The correlations between the number of correctly produced words and motor ability per group are also presented.

For verbal fluency "average upper-limb action rating", the overall model significantly predicted the upper-limb action ratings of the correctly produced words ($F(4, 123) = 15.13$, $p < .001$, $R^2 = .33$, $R^2_{\text{Adjusted}} = .31$). However, neither motor ability (β = -0.008, t = -0.124, adjusted p = .902) nor the two-way interaction between group and motor ability (β = -0.046, t = -0.506, adjusted p = .767) were significant predictors.

In summary, the analyses revealed significant effects of motor ability on overall word-finding ability in both individuals with and without PD.

Hypothesis 3: Cognitive Reserve

Hypothesis 3 stated that an engaging lifestyle is positively associated with better performance in producing action words in individuals with and without PD. All non-significant models are reported in Appendix A.2. For picture naming, the reaction

time model converged after application of the "bobyqa" optimiser (Bates et al., 2023) and implementing a log-link function. The AIC for the log model without outliers (AIC = 88388.8) was lower than the log model with outliers (AIC = 99089.0). Therefore, we proceeded with the gamma log model without outliers and back-transformed the estimates in the model by exponentiating the coefficients. There was no overdispersion, autocorrelation (i.e., independent residuals), or dependency between predictors.

The analysis did not reveal a main effect of Cognitive Reserve on reaction time (β = -0.009, t = -0.218, adjusted p = .931). That is, Cognitive Reserve did not affect reaction time. In addition, there was no significant two-way interaction between Cognitive Reserve and Group β = 0.024, t = 0.402, adjusted p = .884). This suggests that the relationship between Cognitive Reserve and reaction time did not significantly differ between the groups. Finally, the analysis did not reveal a three-way interaction between Group, Action Ratings, and Cognitive Reserve (β = -0.011, t = -2.144, adjusted p = .070).

Marginal and conditional R^2 were calculated as a measure of model fit. Fixed effects explained 23.4% of the variance in the data (marginal R^2 = .234), indicating a moderate contribution of the predictors to explaining reaction time. 40.4% of the variance was explained by the full model, including random effects (conditional R^2 = .404), suggesting that both fixed and random effects together provide a better fit to the data. ICC showed that 11.9% of the total variance in reaction time was accounted for by the item-level random effects, and 10.1% was accounted for by the subject-level random effects, indicating that a portion of the variance is due to these random factors.

For picture naming accuracy, the model converged after application of the "bobyqa" optimiser (Bates et al., 2023). There was no overdispersion, autocorrelation (i.e., independent residuals), or dependency between predictors. The model's formula and results are reported in Table 4.5.

The analysis revealed a main effect of Cognitive Reserve (β = 0.216, z = 2.347,

adjusted $p = .043$). That is, accuracy was higher with higher cognitive reserve. The back-transformed value indicated a significant minimal percentage change of 10.4% in accuracy per unit increase in Cognitive Reserve (z-scale). In addition, the two-way interaction between Group and Cognitive Reserve was significant (β = -0.362, z = -2.814, adjusted $p = .015$). That is, the effect of Cognitive Reserve on picture-naming accuracy differs between the control and PD groups. The back-transformed value indicated a significant minimal percentage change of -14.0% in accuracy per unit increase in Cognitive Reserve, in individuals with PD compared to the control group. That is, higher Cognitive Reserve seems to have a more detrimental effect on accuracy for individuals with PD compared to the control group. The three-way interaction between Group, Cognitive Reserve, and Action Ratings was not significant ($\beta = 0.048$, $z = 0.513$, adjusted $p = .764$). Concordance and Somer's D were .94 and .89 respectively, indicating the model had good predictive power. Marginal R^2 was 0.030 and conditional R^2 was .171.

Table 4.5. *Results of the Fixed Effects for Picture Naming Accuracy and the Relationship with Cognitive Reserve*

Model	Acc ~Group * Action Rating * Cognitive Reserve + Type + (1 | Subject) + (1 | Item)							
Effect	Estimate	*SE*	*z*-value	*p*-value	*CI* Low	*CI* High	Back-Transformed Estimate	Percentage Change
Intercept	2.180	0.169	12.929	< .001	1.858	2.510	1	NA
Group	-0.094	0.084	-1.125	.261	-0.259	0.070	0.597	-40.245
Action Rating	-0.068	0.074	-0.928	.354	-0.213	0.076	0.607	0.959
Cognitive Reserve Score	0.216	0.092	2.347	.019*	0.036	0.396	0.711	10.380
Task Type	-0.388	0.136	-2.859	.004	-0.654	-0.122	0.493	-21.826
Group * Action Rating	0.026	0.062	0.414	.679	-0.096	0.147	0.642	14.899
Group * Cognitive Reserve Score	-0.362	0.129	-2.814	.005*	-0.614	-0.110	0.502	-13.985
Action Rating * Cognitive Reserve Score	-0.016	0.068	-0.233	.816	-0.150	0.118	0.626	12.459
Group * Action Rating * Cognitive Reserve Score	0.048	0.094	0.513	.608	-0.136	0.232	0.650	2.353

Note. *SE* = standard error, *CI* = 95% Confidence Intervals. Action Rating reflects the upper-limb action ratings of the picture names. Cognitive Reserve Score was obtained through a task. Task Type reflects the type of picture-naming task (i.e., object vs. action naming). Predictors remaining significant after FDR corrections are marked (*). The adjusted *p*-values can be found in the main text.

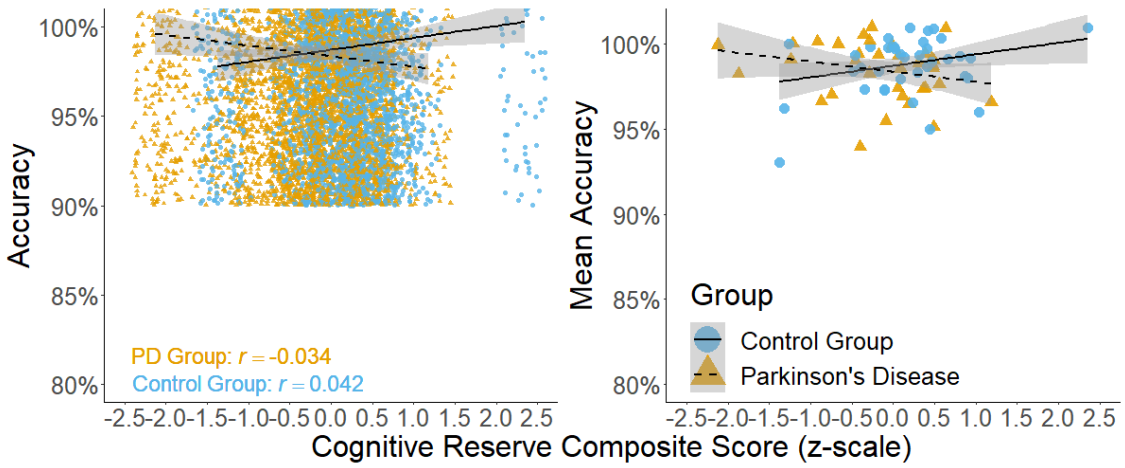

Figure 4.3. The linear relationship between picture-naming accuracy and the composite score for Cognitive Reserve in the groups with and without Parkinson's disease. The left plot shows the individual data points. The right plot shows the mean accuracy score per participant. The correlations between picture-naming accuracy and Cognitive Reserve per group are also presented.

For verbal fluency "number of correctly produced words", the model without outliers fitted the data better (deviance = 26.1) than the model with outliers (deviance = 37.6). Therefore, we proceeded with the model without outliers. There was no main effect for Cognitive Reserve (β = 0.038, t = 0.930, adjusted p = .443). That is, Cognitive Reserve did not affect the number of words that were correctly generated by both participant groups. The two-way interaction between Group and Cognitive Reserve was also non-significant (β = -0.116, t = -2.148, adjusted p = .056). That is, the relationship between Cognitive Reserve and verbal fluency performance did not differ between the PD and control groups. For verbal fluency "average upper-limb action rating", the overall model significantly predicted the upper-limb action ratings of the correctly produced words ($F(4, 122) = 14.74$, $p < .001$, $R^2 = .33$, $R^2_{\text{Adjusted}} = .30$). However, neither Cognitive Reserve (β = 0.061, t = 1.126, adjusted p = .328) nor the two-way interaction between Group and Cognitive Reserve (β = 0.014, t = 0.189, adjusted p = .851) were significant predictors.

In summary, the analyses only revealed significant effects of Cognitive Reserve

on overall word-finding ability in both individuals with and without PD. Specifically, the results indicate that higher levels of CR seem to have a more negative effect on picture-naming accuracy in individuals with PD compared to controls.

Exploratory Analyses

Apathy and Depression

Apathy and depression have both been linked to cognitive impairments in PD, including verbal fluency and picture-naming (Cohen et al., 2015; D'Iorio et al., 2018; Dujardin et al., 2009; Fernandez et al., 2009; Ng et al., 2015). We conducted an exploratory analysis to investigate the effects of depression and apathy on language. In the PD group, the mean apathy was 11.1 (SD = 5.1, range = 3 - 22) and 9.8 (SD = 5.5, range = 1 - 26) for depression scores. The control group had a mean apathy score of 9.0 (SD = 4.3, range = 1 - 18) and a mean depression score of 7.1 (SD = 6.6, range = 0 - 30). In the PD group, the correlation between reaction time and apathy scores was r = -.06 and r = .16 between reaction time and depression scores. In the control group, the correlation between reaction time and apathy and depression scores was r = .20 and r = .07, respectively. The correlation between apathy and the number of correctly produced words on the verbal fluency task was r = .11 for the PD group and r = -.31 for the control group. The correlation between depression and the number of correctly produced words on the verbal fluency task was r = -.22 for the PD group and r = -.11 for the control group.

For each of the models for picture-naming reaction time and verbal fluency "number of correctly produced words", we explored the additive effects of apathy, depression, and the inclusion of both (see Appendix A.4). For hypothesis 1, the inclusion of apathy scores, depression scores, or both did not significantly improve the fit of the models for picture naming. Adding depression scores to the verbal fluency model significantly improved the model fit compared to the model without depression scores ($\chi^2(1) = 1.042, p = 0.017$; see Table A.14). No additive effects

for apathy scores, depression scores, or both were found for the picture naming and verbal fluency models of hypotheses 2 and 3.

Levodopa Equivalent Daily Dosage

Several studies have demonstrated that action-language impairments can be masked when individuals with PD are ON medication (Boulenger et al., 2008; Herrera, Cuetos, et al., 2012; Péran et al., 2013). Therefore, we ran exploratory analyses to investigate the additive effect of Levodopa Equivalent Daily Dosage on the different outcome variables. Table 4.1 provides information on Levodopa Equivalent Daily Dosage. Please, refer to the Supplementary Materials for the results of the Levodopa Equivalent Daily Dosage exploratory analyses (Appendix A.4). Exploratory analyses showed only an additive effect of Levodopa Equivalent Daily Dosage on the models for verbal fluency performance for hypothesis 1 ($\chi^2(1) = 0.763, p = .049$, see Tables A.17 and A.18) and for hypothesis 2 ($\chi^2(1) = 1.176, p = .019$, see Tables A.22 and A.23).

4.5 Discussion

The current study aimed to investigate PD-related impairments in the production of action language, specifically focusing on upper-limb action language and motor skills, and the influence of CR on task performance. Action word-finding ability was investigated through picture naming, and semantic and action fluency. We quantified CR through a comprehensive questionnaire on lifestyle and life experiences (e.g., occupational attainment and education), and motor ability through a keyboard-tapping task. Our first hypothesis was not supported: individuals with PD did not have more difficulty producing words that describe upper-limb physical actions than age-matched individuals without PD when controlling for task type. Our second hypothesis was a positive relationship between the ability to produce upper-limb action words and upper-limb motor ability in

individuals with PD. Although we only hypothesised to find such a relationship in individuals with PD, the study demonstrated such a relationship in individuals with as well as without PD. As a secondary aim, we hypothesised that CR (i.e., an engaging lifestyle) would be positively related to the ability to produce action words. The current study only revealed such a relationship between CR and picture-naming accuracy, independent of the upper-limb actionality of the words.

The Production of Upper-Limb Action Words with High vs. Low Motor Content

We did not find a distinct impairment in action word-finding in individuals with PD compared to a matched control group for either picture naming or verbal fluency. These findings are not in line with previous studies that demonstrated a clear distinction in action language between individuals with PD and without PD (Auclair-Ouellet et al., 2021; Birba et al., 2017; Johari et al., 2019; Salmazo-Silva et al., 2017). Most previous studies investigated the difference between nouns and verbs to detect PD-related impairments in action language (Bertella et al., 2002; Herrera, Rodríguez-Ferreiro, et al., 2012; Salmazo-Silva et al., 2017), while other studies focused on the action content of words, that is, whether words involved manual actions or whether objects were manipulable or not (Auclair-Ouellet et al., 2017; Bocanegra et al., 2017; Cotelli et al., 2007; Johari et al., 2019). Such studies showed that individuals with PD have difficulties when words, both nouns and verbs, are related to manual actions, in contrast to our findings. Whilst some researchers categorised the words into low vs. high motion categories, our study used the Lancaster Sensorimotor Database (Lynott et al., 2020) to assign upper-limb action ratings to the words. Action-word difficulties may be very subtle in individuals with PD and using a continuous scale could have masked such subtle difficulties compared to when using distinct categories. Future studies should investigate whether there is a difference in categorising words into high- and low-action categories compared to continuous action ratings in individuals with PD.

The Relationship Between Word Finding and Motor Ability

Motor ability predicted picture-naming reaction times and the number of generated words, irrespective of the words' action ratings, both in individuals with and without PD. This suggests the potential of a shared neuronal circuit for both single-word production and upper-limb motor ability. That is, the relationship between motor ability and word-finding ability might reflect some domain-general mechanism, with a role of the basal ganglia in inhibition and selection during word-finding (Copland et al., 2021). Furthermore, our study suggested that the relationship between motor ability and word-finding ability may be stronger in the healthy control group compared to the PD group. That is, the relationship between motor ability and naming speed and between motor ability and verbal fluency may diminish in individuals with PD. Future studies powered to detect small effects may confirm this relationship.

One possible explanation for the relationship between word-finding and motor ability in both healthy individuals and individuals with PD is that the basal ganglia could have a domain-general role in word-finding ability (Camerino et al., 2022). The basal ganglia have connections to the anterior cingulate cortex (ACC), which is part of the frontostriatal pathway (i.e., between frontal cortices and caudate nucleus), and is associated with both cognitive and motor control (Haber, 2016). The ACC is activated during various cognitive tasks, contributing to cognitive flexibility, adaptability, and performance monitoring, such as whether errors occur, conflict monitoring, or when there are competing response alternatives (Botvinick et al., 2004; Duncan, 2010; Duncan & Owen, 2000; MacDonald et al., 2000).

The ACC is also involved during word production, such as in picture naming and verbal fluency tasks, and finger tapping (Grill et al., 2021; Indefrey & Levelt, 2004; Piai et al., 2013). Piai and colleagues (2013) demonstrated that the ACC underlies performance monitoring during word production tasks. Hence, the ACC's role in performance monitoring may explain the relationship between word-finding and motor abilities in our study. Future studies should incorporate measures of

domain-general functions, such as performance monitoring, to explore whether such functions link word-finding and motor abilities. Other corticostriatal circuits from the basal ganglia to frontal cortices may also be engaged depending on the type of task, or the same circuits may be engaged during various cognitive functions, depending on task demands (see Copland et al., 2021, for a review). Hence, the same corticostriatal circuits may be involved to achieve faster naming and keyboard-tapping speeds.

Actionality does Not Affect Word-Finding Ability in Parkinson's

The frontostriatal pathway has been proposed to involve combining linguistic and motor information (Birba et al., 2017; Ullman, 2008; Ullman, 2004). A disruption of this pathway due to a dopaminergic deficit may lead to a specific action-language deficit in individuals with PD (Birba et al., 2017; Zgaljardic et al., 2003). The current study did not find any effect of action ratings on word-finding ability. That is, words describing greater upper-limb physical action were not more difficult in PD compared to matched controls without PD. This finding is in line with Aiello et al. (2022), who did not find a distinctive noun-verb dissociation in individuals with PD compared to healthy controls, nor did they find an effect of action ratings on picture naming performance in PD. Hence, the amount of physical action a word describes might not be related to the word-finding or action-word difficulties in Parkinson's.

However, several alternative reasons could explain the lack of association between action ratings and word-finding ability. All participants with PD were on dopamine medication, which could have decreased the impact of brain pathology on word finding in this group (Auclair-Ouellet et al., 2017). Although our exploratory analysis did not show a predictive effect of LEDD on word-finding ability in PD (see Appendix A), the type of PD medication may be important to consider in such analyses. Furthermore, frontostriatal dysfunction in PD might induce neuroplasticity whereby, for example, Broca's area becomes important to restore action-word-specific impairments (Péran et al., 2009). Hence, both dopamine

medication and pathology-induced neuroplasticity might diminish the relationship between actionality and word-finding ability in Parkinson's.

In addition, this study specifically focused on upper-limb motor ability of both the left and right sides of the body. However, studies showed that the left and right basal ganglia might serve different functions during language production (Crosson et al., 2003). Word-finding difficulties in PD might also depend on the side of the basal ganglia most affected at the onset of the disease (Tomer et al., 1993). The current study did not consider the side of PD-related motor symptoms, which may mask action-specific language impairments further. Future studies should investigate whether the same patterns can be found when looking at lower-limb motor ability and whether such patterns are specific to the side of the body most affected by PD.

Effects of Cognitive Reserve On Word-Finding Ability

As a secondary aim, we investigated whether lifestyle choices and lifetime experiences, such as education and engagement in leisure activities, mitigate the negative influences of Parkinson's on the production of action words. Lifestyle choices and lifetime experiences could build up CR. In the case of neurodegenerative diseases, such as Parkinson's, CR can enable individuals to compensate for cognitive difficulties caused by disease-related brain pathology (Stern et al., 2020). However, as the disease progresses and the brain deteriorates further, CR resources may no longer suffice to compensate for the cognitive difficulties caused by the disease. Our findings indicate that high CR may help individuals with PD to accurately name words. However, a negative effect of CR was only found in picture-naming accuracy and not in any of the other word-finding tasks. Due to ceiling-level performance in both groups, reflecting little variance in accuracy, the practical implications of this finding are minimal. Future studies aiming to replicate this study should include a PD group with a wider range of CR scores and adopt a picture-naming task that is more challenging.

Our findings are not in line with previous studies demonstrating an association

between CR and cognitive function, including executive functioning and psychomotor speech, in individuals with PD (Guzzetti et al., 2019; Hindle et al., 2016; Koerts et al., 2013). Currently, there is no consensus on how to measure CR and researchers use different proxies, such as education, IQ, or lifestyle choices (Oosterhuis et al., 2022). Differences in how CR is quantified might account for the discrepancy between the results of this study and previous studies. However, whilst Koerts and colleagues (2013) used education and premorbid intelligence as a proxy of CR, Hindle et al. (2016) and Guzzetti et al. (2019) used education, occupational attainment, and activities, similar to the current study. Alternatively, CR might not benefit all cognitive domains, such as word-finding ability, equally (Lavrencic et al., 2018; Oosterhuis et al., 2023). Indeed, while studies revealed a relationship between CR and executive functioning, for example, they did not always demonstrate an effect of CR naming or verbal fluency (Guzzetti et al., 2019; Hindle et al., 2016). Hence, the beneficial effects of CR might depend on 1) how CR is measured, and 2) the cognitive domain under investigation.

Finally, CR might not be a useful resource for older adults and individuals with PD. In individuals with PD, CR might be drawn upon during the prodromal phase (i.e., the period before the clinical manifestations of Parkinson's; Postuma et al., 2012) but other cognitive resources, such as working memory, might be drawn upon when the disease further progresses (for a discussion, see Oosterhuis et al., 2022). This is in line with a recent study that revealed a benefit of CR in maintaining word-finding abilities for middle-aged but not for older adults (Oosterhuis et al., 2023). The results of this study suggest that both older adults and individuals with PD relied on resources other than CR to maintain their word-finding abilities. One such potential resource is vocabulary (Cansino et al., 2020). In contrast, CR might be most beneficial during the late stages of the disease instead of the prodromal phase (Guzzetti et al., 2019). Due to the online nature of the current study, we could not determine the disease stage. However, all participants were high functioning, suggesting they were in the early stages of the disease. Also, visual inspection showed

that the CR scores differed between groups. Increasing task demands may result in the need for an additional resource such as CR. Hence, future studies should explore the effects of CR (and other cognitive resources) on cognition during the different stages of the disease, including the prodromal stage, and during various task difficulties.

Limitations

It is important to note that the study was conducted online and differences in browsers, operation systems, and the use of keyboards and microphones could have resulted in variance within and between participants. This influenced the picture-naming and motor ability task, as the verbal fluency task was conducted via a conference call with the researcher recording and timing the task. By increasing the stimulus presentation to 6 seconds for the picture-naming task, we made sure that all participants had at least 4 seconds to name the picture as the recording did not always last the full 6 seconds. In the data analysis, we then capped the reaction times at 4 seconds to adhere to the maximum time limit. For this study, we used the Gorilla Experiment Builder (Anwyl-Irvine et al., 2020), which offers the highest precision of reaction times of keyboard presses compared to other experiment platforms (Anwyl-Irvine et al., 2021). Moreover, we used the same method as Oosterhuis et al. (2023) to reduce the timing variability in picture-naming speed whilst also instructing the participants to sit at arm's length from their computer screen (see Oosterhuis et al., 2023, for the method). Moreover, we accounted for within- and between-subject differences in the analysis of naming speed and accuracy. Hence, the variance due to the online nature of the study has been reduced as much as possible and should not have significantly influenced the results.

Furthermore, we could not assess the complete MDS-UPDRS scale as only the upper body was visible during the conference call and certain tasks were not deemed safe without the experimenter being present to support the participant. Hence, we could not determine the disease stage nor assess overall motor ability. All

participants in the current study were high functioning without Mild Cognitive Impairment or dementia, hence, it is highly unlikely that participants were in the later stages of the disease. Furthermore, to quantify upper-limb motor ability more reliably, we used a keyboard-tapping task. This task has been validated in PD (Akram et al., 2022; Noyce et al., 2014) and, thus, should provide more reliable estimates of upper-limb motor ability than the MDS-UPDRS in this study.

Conclusion

In conclusion, the current study found no distinct impairment in the production of upper-limb action words in individuals with PD compared to a matched control group, nor were action ratings related to word-finding ability. In addition, CR did not predict word-finding in either group. However, the current study revealed that motor ability predicted naming speed and the number of generated words, suggesting a potential shared neuronal circuit involved in both word production and motor ability. The relationship between motor and word-finding ability may diminish in individuals with PD, and further research is needed to confirm this. Overall, our findings enhance the understanding of the relationship between word-finding and motor abilities in PD, contributing to existing knowledge of action word-finding difficulties in individuals with PD.

Chapter 5

Brain Segregation and Integration Relate to Word-Finding Abilities in Older and Younger Adults

Linking Statement:

The previous chapters discussed the neurobiology and lifestyle contributions to age- and PD-related cognitive decline, specifically in word-finding abilities. Brain function is one of the neurobiological aspects influenced by ageing. Age-related changes in brain function can impact cognitive abilities, such as word-finding. This chapter investigates the use of functional brain networks utilising graph theory to investigate whether age-related changes in resting-state EEG brain networks are linked to word-finding abilities. This chapter used advanced EEG data analysis to extract graph theoretical measures that reflect the functional organisation of EEG brain networks in healthy younger and older adults. Because of COVID-19, we could not collect the data ourselves. Instead, we conducted a secondary data analysis using data from the Leipzig Study for Mind-Body-Emotion Interactions dataset (LEMON; Babayan et al., 2019).

Author Note:

The study hypotheses, design, and statistical analyses were preregistered on the

Open Science Framework (https://osf.io/u6p42).

This paper is being prepared for submission in "Neurobiology of Language" and was produced in collaboration with Dr. Neil Bailey, Dr. Kate Slade, Dr. Patrick May, and Dr. Helen Nuttall as co-authors.

5.1 Abstract

Previous research has shown that word-finding difficulties in older age are associated with functional and structural brain changes. However, the use of functional brain networks, measured through electroencephalography, to predict word-finding in older and younger adults has not yet been investigated. This study utilised resting-state electroencephalography data (61 channels) from the Leipzig Study for Mind-Body-Emotion Interactions dataset (Babayan et al., 2019) to investigate the relationship between functional brain networks and word-finding ability in healthy younger and older adults. Graph theory-based measures in the delta, theta, alpha, and beta bands were computed to assess brain segregation and integration of 53 older (aged 59-77) and 53 younger right-handed adults (aged 20-35). Word-finding ability was quantified as the number of orally produced words during a semantic and letter fluency task. Multiple linear regression revealed that, in older adults, greater functional connectedness in the delta band was associated with lower semantic fluency. Irrespective of age, greater modularity in the alpha band was related to lower semantic fluency. A greater small-world index in the delta band was related to better semantic fluency, irrespective of age. Increased brain integration in the delta band corresponded to greater semantic fluency in older adults. Hence, word-finding ability seems to be related to brain segregation and integration specific to the frequency band, possibly indicating alterations in cognitive control or compensatory shifts to less functionally specific frequency bands. The article further provides a discussion on neural dedifferentiation, hyper-synchronisation, study limitations, and directions for future research.

Keywords: functional brain networks; graph theory; word-finding ability; healthy cognitive ageing; brain segregation; brain integration.

5.2 Introduction

In older age, people experience problems with lexical access, typically commencing around the age of 40 or 50 years (Kavé & Knafo-Noam, 2015). These problems manifest as word-finding difficulties (Burke & Mackay, 1997; Kavé & Knafo-Noam, 2015; Marini & Andreetta, 2016; Mortensen et al., 2006), and are one of the most prominent problems associated with cognitive ageing (Burke & Shafto, 2004). Previous studies have linked word-finding difficulties to both functional and structural brain changes in older adults (Meinzer et al., 2009; Stamatakis et al., 2011; Wierenga et al., 2008). Functional brain networks, both task-related and at rest, reflect the neurophysiological organisation of the brain (Bullmore & Sporns, 2009) and change with age due to deterioration of brain structure. Such changes could explain age-related decreases in cognitive performance, such as deterioration of memory (Bullmore & Sporns, 2009; Gaál et al., 2010; Zangrossi et al., 2021). However, the link between age-related changes in functional brain networks and the association with word-finding difficulties has not yet been investigated. The current study aimed to establish whether such a link exists in healthy older adults. We expect that such an investigation may inform future development of neurocognitive biomarkers associated with communicative ability.

The identification of functional brain networks via electroencephalography (EEG) offers a promising tool for investigating the effects of physiological ageing and identifying biomarkers for age-related pathology, including dementia (Valizadeh et al., 2019; Vecchio et al., 2020). Using graph theory, functional brain networks and measures of functional connectivity can be derived, such as the strength of synchronisation between neuronal populations (for methodology, see Bullmore & Sporns, 2009). Such measures indicate the brain's efficiency or strength of information transfer between different brain regions (Bullmore & Sporns, 2009; Fries, 2005). Functional brain networks can be characterised in terms of segregation and integration, which underlie cognition (Sporns, 2013; Sporns et al., 2004). Functional

segregation reflects neuronal communication between neighbouring brain regions, with more segregation reflecting a pattern where brain regions are more strongly connected with neighbouring nodes than more distant nodes, and less segregation reflecting the opposite pattern. Functional integration refers to the connections between modules, enabling the network to integrate information that is distributed over multiple brain regions (Sporns, 2013). A balance between segregation and integration leads to a small-world network, allowing for global efficacy of information transfer between brain regions (Achard & Bullmore, 2007; Bassett & Bullmore, 2006; Bullmore & Sporns, 2009; Watts & Strogatz, 1998). Studies using resting-state EEG show that the small-world index decreases with age (Gaál et al., 2010; Moezzi et al., 2019; Petti et al., 2016; Vecchio et al., 2014; Vecchio et al., 2020), due to decreases in functional segregation with age (Damoiseaux, 2017).

Age-related changes in functional brain networks have also been linked to decreases in cognitive performance, for example, in executive functioning and memory (Andrews-Hanna et al., 2007; Fleck et al., 2016). Moreover, higher segregation in older adults might relate to better memory ability (Chan et al., 2014; Zangrossi et al., 2021). Andrews-Hanna et al. (2007) argued that ageing is accompanied by the disruption of functional networks underlying higher-order cognitive functions. Since age-related declines in word-finding abilities have been previously linked to changes in brain structure and function (Meinzer et al., 2009; Stamatakis et al., 2011; Wierenga et al., 2008), it is possible that changes in functional brain networks also relate to word-finding difficulties in older age.

A relationship between age-related changes in functional brain networks and word-finding difficulties could be explained by the neural dedifferentiation hypothesis, which posits that brain regions and networks become less functionally specific to cognitive processes with age (Li et al., 2001). Moreover, age-related decreases in neurotransmitters, such as dopamine, reduce the efficiency of information transfer between brain regions (Koen & Rugg, 2019; Li & Lindenberger, 1999; Li & Rieckmann, 2014). This then causes neural dedifferentiation and

consequently increases interindividual differences in cognitive performance (De Felice & Holland, 2018; Hultsch et al., 2002; Koen & Rugg, 2019). It is therefore proposed that, neural efficiency and, hence, cognitive processes are optimal in younger adults (McIntosh et al., 2014). Goh (2011) hypothesised that both the differences in behaviour between younger and older adults and the age-related neural dedifferentiation are directly related to age-related changes in functional connectivity. Hence, age-related changes in functional brain networks seem to be associated with changes in cognitive performance.

Finally, age-related changes in functional brain networks have been found to be specific to EEG frequency band (e.g., Gaál et al., 2010; Micheloyannis et al., 2007; Smit et al., 2012; Vecchio et al., 2014) and different cognitive functions have been linked to certain EEG frequency bands (for an overview, see Başar et al., 2001). Delta activity is involved in inhibiting irrelevant responses and is important for internal concentration (Harmony, 2013; Mousavi et al., 2020). Greater delta power in younger adults and greater connectivity in the delta band in older adults have been linked to higher semantic fluency performance (Fleck et al., 2016; Mousavi et al., 2020). Hence, functional connectivity in the delta band might be important in supporting verbal fluency performance in older adults. Moreover, theta oscillations may play an important role in cognitive control, semantic-related processing, working memory, behavioural monitoring, and letter fluency (Cavanagh & Frank, 2014; Mousavi et al., 2020; Wang, 2010). Alpha band activity has been proposed to reflect attention, working memory, and inhibition (Başar et al., 1999; Jensen & Mazaheri, 2010; Klimesch et al., 2007; Stam, 2000). Lastly, beta band activity may play a role in working memory, decision-making, and lexical-semantic retrieval processes (Gola et al., 2013; Siegel et al., 2009; Weiss & Mueller, 2012).

To our knowledge, this is the first study investigating the relationship between functional brain networks and age-related changes in word-finding ability using EEG. We used data from the Leipzig Study for Mind-Body-Emotion Interactions (LEMON; Babayan et al., 2019) to investigate this relationship. First, we

hypothesised that the decline in word-finding ability with age is linked to a decrease in the connectedness of functional brain networks. Specifically, we predicted a main effect of delta-band brain segregation on semantic fluency in older adults. Second, we hypothesised that the age-related decreases in brain segregation (which are reflective of neural dedifferentiation) are positively related to word-finding ability. That is, we predicted a positive main effect of segregation and small-world index on verbal fluency. Lastly, because individual variability in cognitive performance increases with age, with minimal variation between younger adults, and because of optimal neural efficiency in younger adults, we hypothesised that the relationship between word-finding ability and the connectedness of functional brain networks is absent in younger adults. Thus, we predicted that brain segregation does not predict verbal fluency in younger adults. The hypotheses, predictions, and experimental design were preregistered on the Open Science Framework website at https://osf.io/u6p42.

5.3 Methods

Participants

Data were obtained from the LEMON dataset (Babayan et al., 2019), which contains resting-state EEG recordings and psychological assessments of 153 younger adults, aged 20-35 years, and 74 older adults, aged 59-77 years (mean age and *SD*s are unavailable in the LEMON database to protect participants' anonymity). All participants in the dataset were German speakers. We selected data for the older adult group based on the following criteria: the availability of EEG resting state and verbal fluency data; the participants being right-handed, not suffering from depression (i.e., Hamilton Depression Rating Scale score lower than 14), not having an alcohol or substance use disorder (i.e., Alcohol Use Disorder Identification Test, AUDIT, score < 8 and a negative result on the drug screening test). Based on these criteria, we included the data of 53 older adults (25 females) in the current study. Data from the younger adults were filtered based on the same criteria and,

subsequently, a subset of 53 younger adults (21 females) were randomly selected to match the sample size of the older adult group (see Table 5.1). The sample size was based on an a priori power analysis using data simulation (Brysbaert & Stevens, 2018; DeBruine & Barr, 2021). More detailed information on the a priori power analysis can be found in Appendix B.1. Further information on the LEMON dataset can be found in Babayan et al. (2019).

Table 5.1. *Sample Characteristics and Comparisons between Age Groups*

	Younger adults (N=53)	Older adults (N=53)	t-test
Sex	21 females; 32 males	25 females; 28 males	$t(104)$ = -0.78, p = .438
Hamilton Depression Rating Scale	M = 2.70 (SD = 2.44)	M = 2.28 (SD = 2.67)	$t(104)$ = -0.80, p = .427
AUDIT	M = 3.30 (SD = 1.73)	M = 2.75 (SD = 1.79)	$t(104)$ = -1.60, p = .112

Materials

To quantify word-finding ability, we used the scores of the verbal fluency tasks (i.e., the Regensburger Wortflüssigkeitstest), which were available in the dataset. Within two minutes, participants had to generate as many German words as possible starting with the letter "s" (i.e. letter fluency) or words belonging to the category "animals" (i.e., semantic fluency). For the current study, we used the number of correctly produced words of both tasks that were generated within the first minute, which is the time limit commonly used in standard versions of the task (Shao et al., 2014).

EEG Recordings and Pre-processing

Resting-state EEG was recorded for 16 minutes, with alternating 60-second blocks of eyes-closed and eyes-open conditions. Only the eyes-closed condition was analysed in the current study. The set-up consisted of 61 channels arranged according to the 10-10 international system, with one additional electrode recording the vertical electrooculogram to monitor eye movements (see Babayan et al., 2019, for more information on the EEG recording setup). Data were pre-processed using MATLAB R2018a (MathWorks) and Fieldtrip (Oostenveld et al., 2010). The pre-processing pipeline 'Reduction of Electroencephalographic Artifacts' (RELAX), which makes use of both Fieldtrip and EEGLAB, a MATLAB toolbox (Delorme & Makeig, 2004), was used to clean the continuous EEG data with the RELAX_wICA_ICLabel setting since the effect of the default multi-channel Wiener Filter cleaning approach has not been tested for use prior to analysis of EEG connectivity (Bailey, Biabani, et al., 2023; Bailey, Hill, et al., 2023).

Before cleaning the data with RELAX, the raw EEG data were downsampled from 2500 Hz to 1000 Hz. A 1-45 Hz Butterworth bandpass filter was applied. The RELAX pipeline identifies noisy channels via the PREP pipeline algorithm (Bigdely-Shamlo et al., 2015). Data from these channels were subsequently removed. Data from the remaining noisy channels were further removed using the default settings from RELAX. The mean proportion of the EEG data removed due to noisy channels was 0.047 and data from 59 channels ($SD = 3$), on average, were left after this removal. The cleaned data were re-referenced to the robust average reference before running the Independent Component Analysis (ICA) with the FastICA algorithm (Hyvarinen, 1999) and reducing artifacts identified by ICLabel (Pion-Tonachini et al., 2019) using Wavelet Enhanced ICA (Castellanos & Makarov, 2006). After data cleaning, excluded channels were interpolated using spherical spline (Delorme & Makeig, 2004).

Functional Brain Networks

After cleaning the data, we applied a lowpass filter of 30 Hz and segmented the continuous data into 12-second epochs with 50% overlap (for more information on optimal epoch length for the debiased weighted Phase Lag Index (dwPLI), see Fraschini et al., 2016; Miljevic et al., 2022). Segments of the data were visually inspected to check data quality. The average proportion of data removed due to bad epochs was 0.205 ($SD = 0.193$). The average number of remaining epochs was 98. Next, we obtained the cross-spectral densities of the alpha, beta, theta, and delta bands using a Fourier transformation using the multitaper method based on Hanning tapers (see Figure 5.1A).

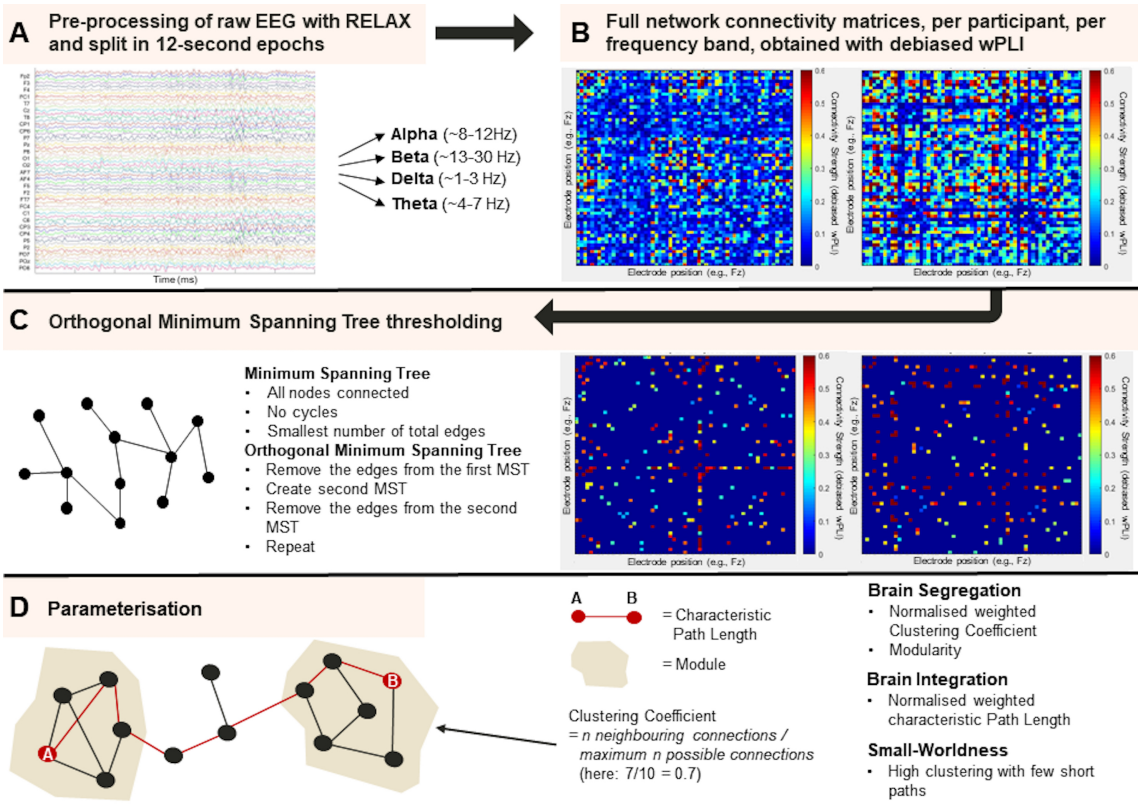

Figure 5.1. Processing Pipeline of the Resting-State Eyes-Closed EEG Data

Studies have consistently shown that neurophysiological rhythms slow with ageing and that including conventional frequency bands can introduce a bias against

older adults, also when conducting connectivity analyses (Chiang et al., 2011; Scally et al., 2018). Therefore, the alpha, beta, theta, and delta spectral boundaries were determined using the individual alpha peak frequency (IAPF). IAPF was calculated with eyes-closed resting-state EEG data using the restingIAF toolbox in Matlab (see Corcoran et al., 2018, for more information on how the IAPF was computed). The mean IAPF of older adults was 9.4 Hz (SD = 0.9 Hz) and 10.1 Hz (SD = *0.9 Hz*) for younger adults. The alpha band was determined as IAPF -4 Hz to IAPF +2 Hz, theta as IAPF –6 Hz to IAPF -4 Hz, and delta as IAPF -8 Hz to IAPF -6 Hz (Babiloni et al., 2020; Klimesch, 1999). The beta band was determined as IAPF +2 Hz up to and including 30 Hz (Babiloni et al., 2020; Henelius et al., 2011).

To detect brain networks, the dwPLI was used to calculate the functional connectivity between all 61 channels, for each frequency per participant. Please, refer to Appendix B.2 for the details on how dwPLI was computed. For the subsequent graph statistical processing steps and graph theoretical indices, we obtained the absolute values of the dwPLI to get an indication of the strength of connectivity between pairs of electrodes. The network construction resulted in a 61-by-61 weighted matrix for each frequency band and per participant (see Figure 5.1B).

We applied a data-driven method, namely the Orthogonalized Minimum Spanning Tree (OMST) algorithm to threshold the connectivity matrices (Dimitriadis et al., 2017). A minimum spanning tree is a graph with a minimum number of total edges, without cycles (i.e., the graph does not contain any loops), and where all nodes are connected (see Figure 5.1C). The OMST algorithm computes the minimum spanning tree (MST) over multiple iterations. These iterations are necessary as using a single MST might result in a graph that is too sparse for computing robust connectivity measures. For a more detailed explanation as to how the network graphs were thresholded using the OMST algorithm, please refer to Appendix B.2.

Graph Theoretical Network Analysis

After thresholding, we applied graph theoretical analysis of the brain networks using Fieldtrip (Oostenveld et al., 2010) and the Brain Connectivity Toolbox (Rubinov & Sporns, 2010) in MATLAB (see Figure 5.1D). In the current study, the EEG sensors represent the nodes and the dwPLI values represent the weighted edges of the graph. Because we used weighted matrices, graphs for each frequency band were first normalised before computing the measures of brain segregation and integration, resulting in normalised weighted measures. All thresholded graphs were normalised by rescaling all weight magnitudes ranging between 0 and 1 (Bullmore & Sporns, 2009).

To quantify brain segregation (i.e., the clustering of functional networks into separate communities/groups), we calculated the weighted variant of the clustering coefficient (Onnela et al., 2005; Rubinov & Sporns, 2010) as well as of modularity (Newman, 2006; Rubinov & Sporns, 2010). Please, refer to Appendix B.2 for the mathematical equations and descriptions of all connectivity measures. The clustering coefficient and modularity offer alternative statistics of brain segregation. Higher values of either statistic reflect greater local efficiency of information transfer in the brain (Bullmore & Sporns, 2009). That is, brain regions or communities are more specialised and have stronger connections within themselves (i.e., intra-community connections), facilitating efficient communication within those localised communities.

The degree of brain integration is quantified through the weighted version of the characteristic path length, which is the shortest path length between two nodes averaged across all node pairs (Rubinov & Sporns, 2010; Watts & Strogatz, 1998). Lower characteristic path length indicates greater global efficiency of information transfer in the brain. The clustering coefficient and modularity (brain segregation) and characteristic path length (brain integration) values were calculated for each participant for each frequency band separately. To examine the balance between brain segregation and integration, we computed the small-world index of each graph

(Humphries & Gurney, 2008). Small-world indices with values higher than 1 indicate that the network is a small world (see Appendix B.2).

Statistical Analysis

After obtaining the functional connectivity measures described above, the final data pre-processing and analysis were conducted in R (R Core Team, 2020). Following the preregistration, verbal fluency scores +/- 3 *SD*s would be considered outliers, however, no outliers were detected in the verbal fluency data. Missing values for all connectivity measures for OMST-thresholded networks can be found in Table 5.2. Full networks did not have any missing values. Even though the missing values in the OMST-thresholded graphs reduced the number of data points, the data will still provide important insights into the relationship between word-finding ability and age-related changes in functional brain networks. After the initial model fit, leverage points were identified as 2(number of predictors + 1)/number of observations, and subsequently removed to obtain the model's best-fit.

Table 5.2. *Missing Values for Each of the Connectivity Measures of the OMST-Thresholded Networks per Frequency Band*

Age Group	Band	dwPLI	Modularity	Clustering Coefficient	Characteristic Path Length	Small-World Index
Younger	Alpha	0	0	5	0	8
	Beta	0	0	10	0	11
	Delta	0	0	7	0	8
	Theta	0	0	8	0	12
Older	Alpha	0	0	8	0	11
	Beta	0	0	8	0	11
	Delta	0	0	14	0	15
	Theta	0	0	19	0	22

Note. dwPLI = debiased weighted phase lag index. Each age group has a maximum sample size of $N = 53$.

To investigate whether age-related changes in brain segregation and integration are related to word-finding ability, we performed multiple linear regression analyses for each frequency band and each verbal fluency measure (i.e., letter and category fluency) separately. Because the networks were thresholded using a model-driven algorithm (i.e., OMST) and weighting was employed, we did not apply multiple corrections (which meets the criteria for optimal validity within a connectivity study, see the checklist by Miljevic et al., 2022). The outcome variables were the number of correctly produced words for the letter and category fluency tasks. To investigate the effect of age-related changes in brain segregation on verbal fluency, we included the interaction between clustering coefficient and age, and the interaction between modularity and age as predictors. To investigate the connectedness of the functional brain networks, we ran multiple linear regression analyses with the interaction between age and the small-world index as predictors of verbal fluency performance.

For brain integration, the predictor was the interaction between characteristic path length and age. All models included sex as a covariate because studies have shown that brain networks can differ between males and females (Foo et al., 2021). Both age and sex were contrast coded using "treatment contrasts" whereby younger adults were set as the reference level. All numerical predictors (i.e., the functional connectivity measures) were scaled for model interpretation. Assumptions of linearity, homoscedasticity, and normality of residuals were all met. Model diagnostics revealed the presence of leverage points for most models (i.e., values above 2(number predictors + 1) / number of observations), which were subsequently removed (Cook, 1977). Only the results after the removal of leverage points are reported in the results section.

This study was preregistered on the Open Science Framework (https://osf.io/u6p42). The quality of the connectivity analysis was checked against the checklist by Miljevic and colleagues (2022) and obtained a score of 5.5, which reflects high study quality.

Deviations from the Preregistration

As preregistered, functional connectivity measures with values +/- 3 *SD*s from the mean were originally also considered as outliers. However, due to the sparsity of some functional brain networks, there were missing values in both age groups for the clustering coefficient and small-world index. To avoid reducing the dataset even further by removing outliers for the functional connectivity measures, we analysed the data with the detected outliers. Regarding brain segregation measures, the preregistration only mentioned the clustering coefficient as a brain segregation measure for hypotheses 1 and 2. However, since brain segregation is reflected by both clustering coefficient and modularity (Rubinov & Sporns, 2010), we included both the interaction between clustering coefficient and age, as well as the interaction between age and modularity in the statistical models. Such models would represent brain segregation better than solely including the clustering coefficient.

5.4 Results

Behavioural Data

Before analysing the functional brain networks, a behavioural difference in verbal fluency performance between younger and older adults was confirmed. For semantic fluency, older adults obtained a mean score of 22 correctly produced words (SD = 5.5; range = 12-37 words) and younger adults obtained a mean score of 25 correctly produced words (SD = 5.1; range = 15-39 words), and this difference between age groups was significant ($t(418.68 = -5.80$, $p < .001$). For letter fluency, older adults obtained a mean score of 13 correctly produced words (SD = 3.1; range = 5-19 words) and younger adults obtained a mean score of 15 correctly produced words (SD = 3.5; range = 7-23 words), and this difference between age groups was also significant ($t(416.4) = -6.72$, $p < .001$).

Graph Analysis

To investigate the age-related changes in functional brain networks, the brain segregation and integration measures were computed for the alpha, beta, delta, and theta bands. Mean and standard deviations for the graph theoretical measures of the OMST-weighted graphs can be found in Table 5.3.

Table 5.3. *Mean and Standard Deviation of the OMST-Thresholded Graph Theoretical Indices per Age Group*

	Younger adults				Older adults			
	Alpha	Beta	Delta	Theta	Alpha	Beta	Delta	Theta
dwPLI	0.53 (0.12)	0.42 (0.14)	0.53 (0.08)	0.50 (0.08)	0.55 (0.11)	0.43 (0.15)	0.52 (0.07)	0.44 (0.11)
Clustering Coefficient	0.10 (0.05)	0.08 (0.04)	0.08 (0.03)	0.06 (0.03)	0.09 (0.04)	0.09 (0.04)	0.06 (0.03)	0.06 (0.03)
Modularity	0.48 (0.07)	0.52 (0.07)	0.49 (0.08)	0.50 (0.07)	0.48 (0.09)	0.51 (0.07)	0.47 (0.06)	0.48 (0.08)
Characteristic Path Length	6.33 (2.09)	9.51 (5.48)	6.18 (1.60)	6.96 (2.10)	6.13 (1.78)	9.45 (4.99)	6.28 (1.35)	8.30 (2.95)
Small-World Index	1.11 (0.67)	1.23 (0.71)	0.97 (0.56)	0.81 (0.51)	0.83 (0.58)	1.39 (0.79)	0.93 (0.49)	0.92 (0.55)

Functional Connectivity Strength

First, we hypothesised that age-related decreases in functional connectivity, as measured through dwPLI, would be positively related to age-related word-finding difficulties. Multiple linear regression analysis was used to investigate whether age and dwPLI would predict letter and semantic fluency. The predictors in the delta band explained 13.4% of the variance in semantic fluency scores ($R^2 = .10$, $F(4,95) = 3.66$, $p = .025$). Age and the interaction between age and dwPLI were significant

predictors of semantic fluency scores (β = -2.45, p = .020 and β = -3.85, p = .004, respectively). That is, age-related increases in dwPLI were related to lower semantic fluency scores (see Figure 5.2). Semantic fluency was not related to an age-related change in dwPLI in any of the other frequency bands, nor was letter fluency related to age-related changes in dwPLI in any of the four frequency bands.

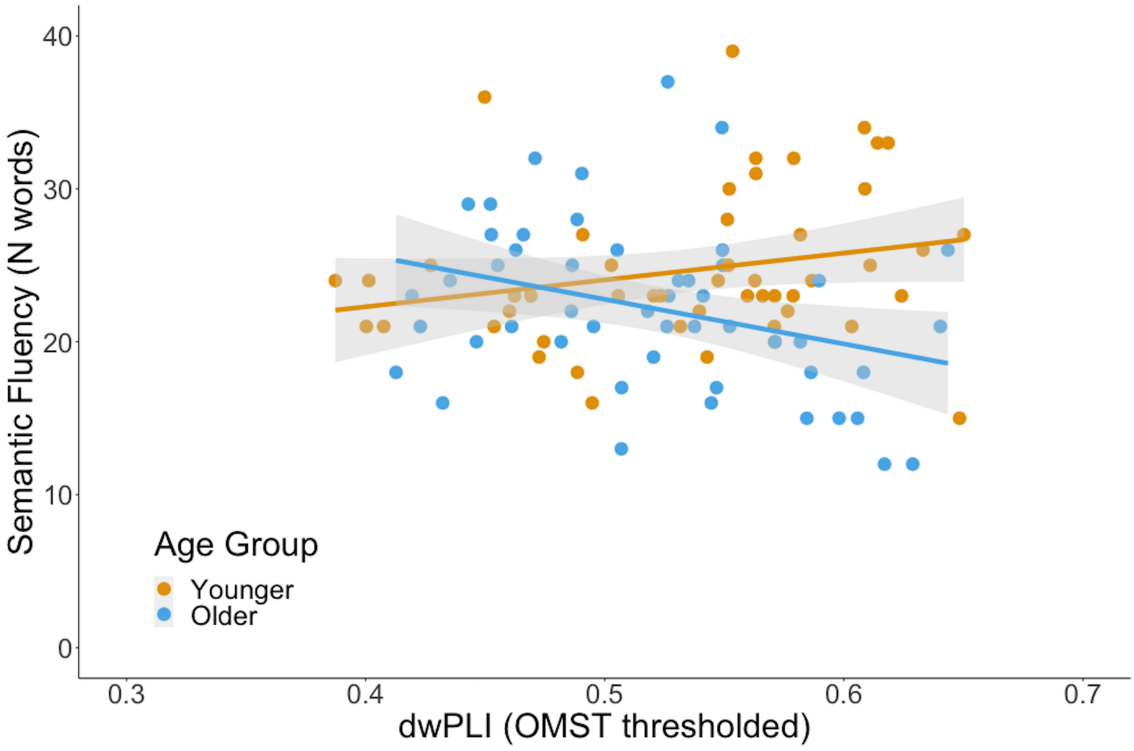

Figure 5.2. The interaction between age and dwPLI as a significant predictor of semantic fluency in the delta band.

Brain Segregation

Our second hypothesis was whether age-related decreases in brain segregation, reflecting neural dedifferentiation, are related to reduced word-finding ability. We predicted that age-related changes in brain segregation, as measured through modularity, clustering coefficient, and small world index, would be related to verbal fluency performance. Multiple regression analysis was used to investigate the effect

of modularity and clustering coefficient on semantic and letter fluency separately. The predictors in the alpha band explained 14.4% of the variance in semantic fluency scores (R^2 = .08, F(6,80) = 2.25, p = .047). In the alpha band, both modularity and age independently predicted semantic fluency (β = -2.23, p = .049 and β = -2.83, p = .022, respectively). That is, higher modularity scores predicted lower semantic fluency scores, independent of age (see Figure 5.3). None of the models for letter and semantic fluency indicated that age-related changes in clustering coefficient or modularity predicted letter and semantic fluency scores.

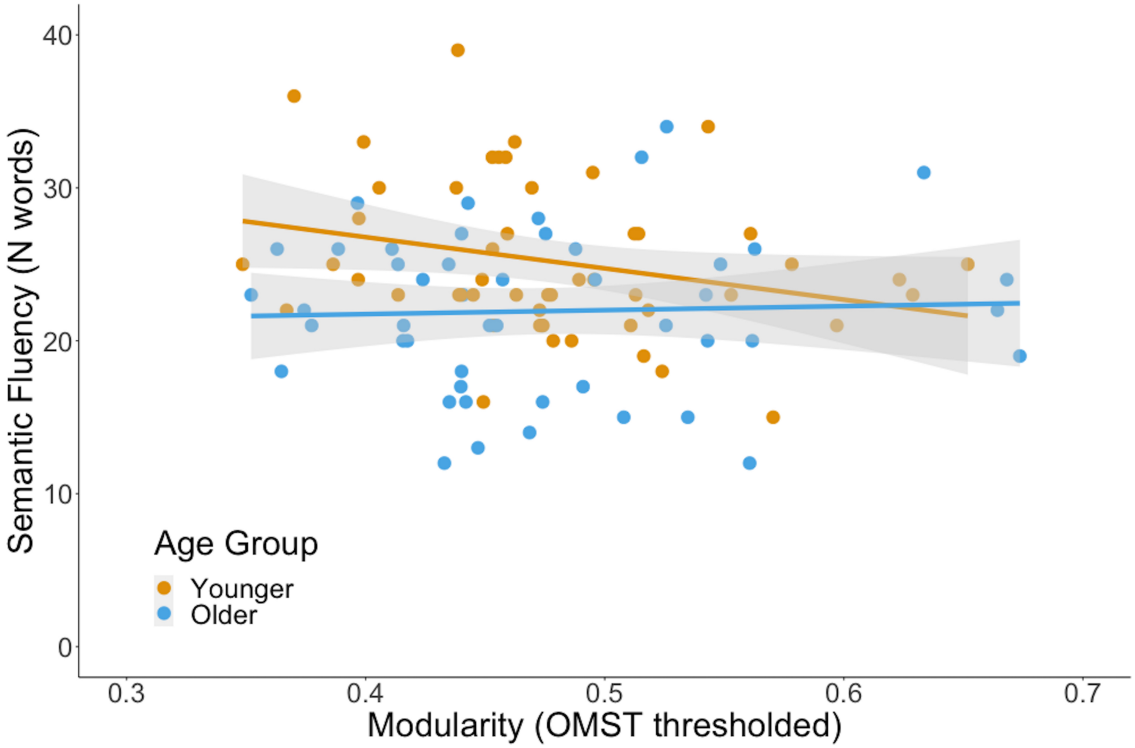

Figure 5.3. Modularity as a significant predictor, irrespective of age, of semantic fluency in the alpha band.

Because the small-world index suggest a balance between brain integration and segregation, we also ran multiple linear regressions to investigate the effect of age-related changes in the small-world index on verbal fluency performance. In the delta band, the predictors explained 16.6% of the variance in semantic fluency scores (R^2 = .12, F(4,76) = 3.78, p = .007). Both age and the small-world index significantly

predicted semantic fluency scores (β = -4.08, $p < .001$, and β = 2.69, $p = .041$, respectively). That is, a greater small-world index predicted higher semantic fluency scores, irrespective of age (see Figure 5.4). None of the models for letter and semantic fluency indicated that age-related changes in the small-world index predicted letter and semantic fluency scores.

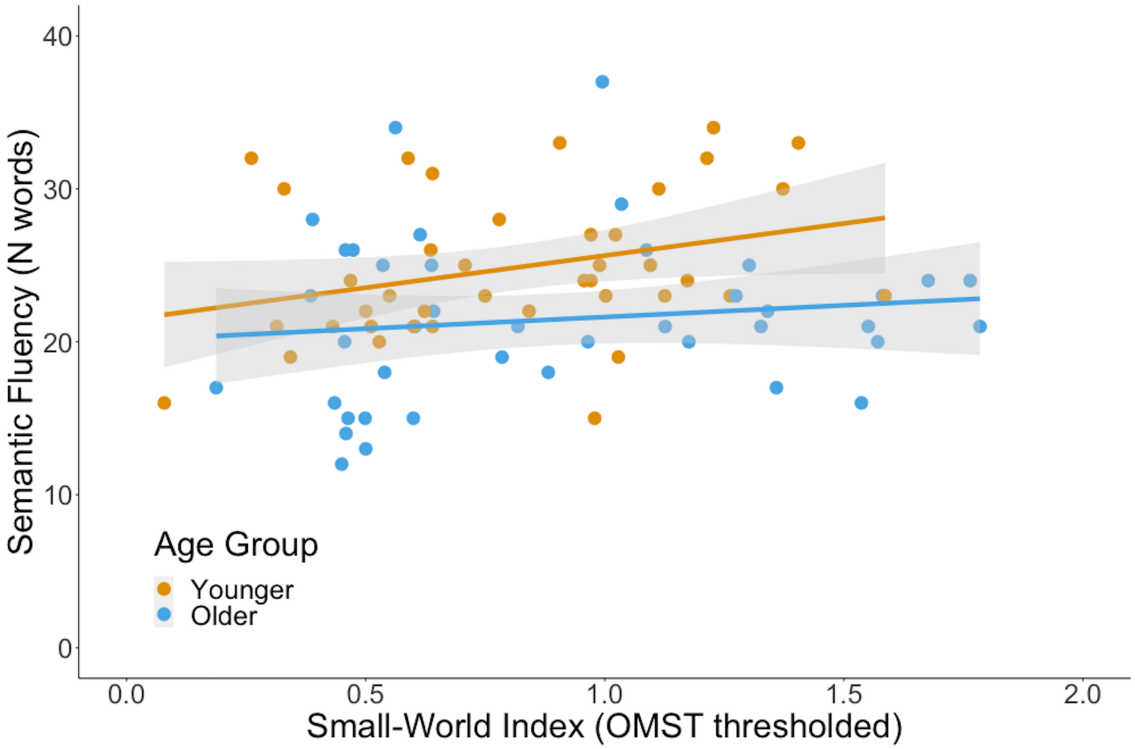

Figure 5.4. The small-world index as a significant predictor, independently of age, of semantic fluency in the delta band.

Exploratory Analysis of Brain Integration

Although we did not have a-priori hypotheses about the relationship between age-related changes in brain integration and verbal fluency performance, previous studies linked age-related changes in brain integration measures, such as path length, to changes in cognitive performance (e.g., Stanley et al., 2015). Therefore, we conducted an exploratory analysis (i.e., not preregistered with a-priori hypotheses)

using multiple linear regression to investigate the effect of age-related changes in brain integration on verbal fluency performance. In the delta band, the predictors explained 13.2% of the variance in semantic fluency scores (R^2 = .09, $F(4,94)$ = 3.57, $p < .001$). Age and the interaction between age and characteristic path length predicted semantic fluency scores (β = -1.24, p = .027 and β = 3.64, p = .028, respectively). That is, older adults with higher characteristic path length achieved higher semantic fluency scores (see Figure 5.5). Characteristic path length did not predict semantic fluency in the other frequency bands, nor did it predict letter fluency in any of the frequency bands.

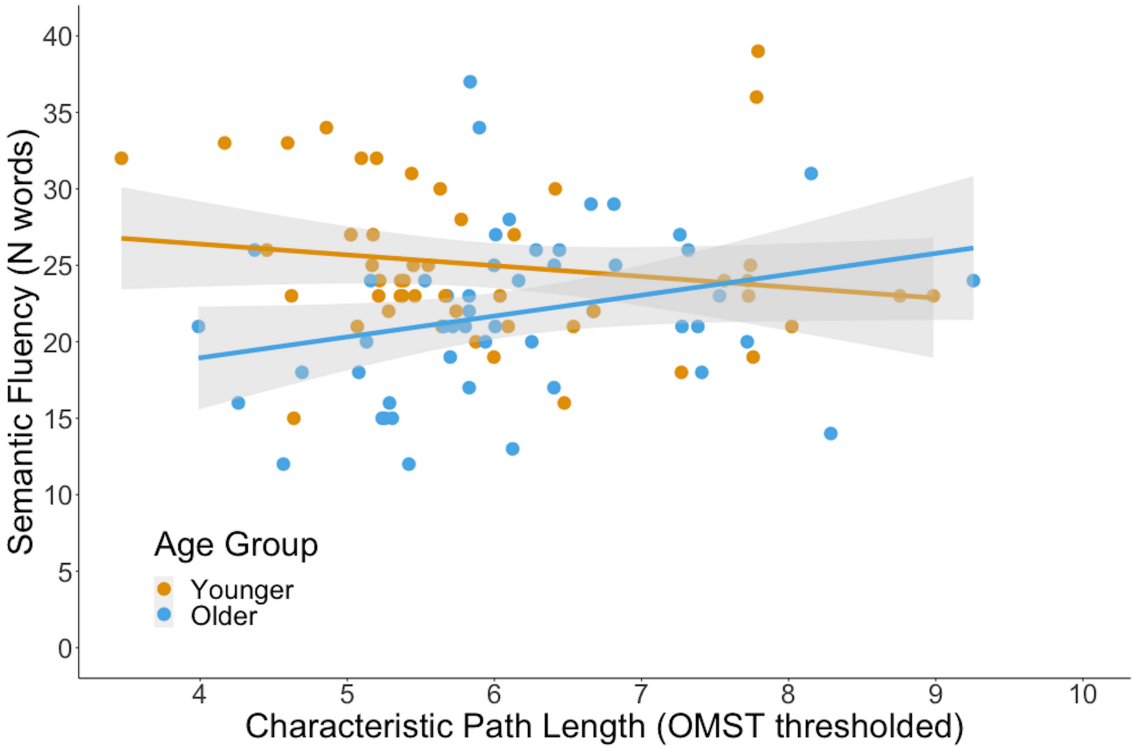

Figure 5.5. The interaction between age and characteristic path length as a significant predictor of semantic fluency in the delta band.

5.5 Discussion

Using resting-state EEG data, the current study aimed to investigate the relationship between word-finding difficulties in older age and age-related changes in functional brain networks. We hypothesised that age-related decreases in word-finding ability are related to decreases in the connectedness of functional brain networks in older compared to younger adults. We found that, in older adults, greater functional connectedness in the delta band, as measured through dwPLI, was related to lower semantic fluency scores. Several other findings were not in line with our hypotheses. A greater small-world index in the delta band was related to higher semantic fluency performance in both younger and older adults. Greater modularity in the alpha band was related to higher semantic fluency scores, but this was irrespective of age. In an exploratory analysis of brain integration, we found a positive relationship between characteristic path length and semantic fluency in the delta band, only in older adults.

Age-Related Changes in Functional Connectedness and Word-Finding Ability

Our finding that greater functional connectedness related to lower semantic fluency in older adults is in line with previous studies demonstrating age-related changes in the connectedness of functional brain networks (Gaál et al., 2010; Sala-Llonch et al., 2014; Zangrossi et al., 2021), but not with their link with decreases in cognitive performance (Andrews-Hanna et al., 2007; Chow et al., 2022; Fleck et al., 2016). That is, previous studies found that increased connectedness in older adults was related to better cognitive performance. Greater functional connectedness has been hypothesised to indicate greater efficacy of information transfer between different brain areas (Fries, 2005). In this case, increased dwPLI, reflecting overall brain connectedness, would lead to an increase in the brain's efficiency of information transfer between different brain areas, that is, reduce the slowing of information

transfer. Because verbal fluency is a timed task, age-related slowing of information transfer between brain areas in older adults could mean that older adults need more time to access words from their memory. If higher dwPLI values (i.e., greater connectedness) reflect greater efficiency of information transfer between brain areas, one would expect that greater functional connectedness would be related to better word-finding ability. However, we found that greater connectedness in the current study was related to worse word-finding ability.

One possible explanation is that increased dwPLI in older adults represents a pattern of hyper-synchronisation or overload, reflecting noisy communication between different brain regions, and subsequently leading to poorer cognitive performance (Jones et al., 2016; López-Sanz et al., 2017). Our findings for word-finding ability are in line with the studies by Jones et al. (2016) and López-Sanz et al. (2017), who demonstrated that increased resting-state connectivity was related to worse language performance. Moreover, studies in Parkinson's disease demonstrated that greater functional connectedness, as measured with (dw)PLI in the delta and theta frequency band predicted whether someone had Mild Cognitive Impairment (MCI) or not (Cai et al., 2021; Chaturvedi et al., 2019). Hence, increased delta dwPLI could be explored as a potential marker of pre-onset dementia.

Research has also indicated that individuals with Huntington's disease exhibit greater delta-band connectivity, which could indicate either pathological or compensatory changes in brain function (Davis et al., 2022). That is, brain activity may be synchronising to a less functional frequency range (here, delta), perhaps as a pathology-related compensatory process, or perhaps reflecting the brain's inability to inhibit this (potentially less functional) rhythm. Increased delta connectivity may reflect entrainment to a basic resonance property of pyramidal neurons to sustain frequency preference, in contrast to more functional connectivity within task-related oscillatory frequencies (for a discussion on neuronal resonance, see Hutcheon & Yarom, 2000). Resonance plays a crucial role in enabling synchronised activity and oscillatory patterns, and a disruption in the temporal coordination of neuronal

activity may lead to cognitive impairments (Lehrer & Eddie, 2013; Uhlhaas & Singer, 2006). In conditions like Alzheimer's disease, even before disease onset, brain pathology may cause hyperactivity and/or inhibition of neurons, disrupting the neuronal excitation/inhibition (E/I) balance and affecting whole-brain network configurations (Alexandersen et al., 2022; Stam et al., 2023; van Nifterick et al., 2022). Our findings may suggest a similar disruption of the E/I balance in older adults experiencing word-finding difficulties. In this case, neurons exhibit resonance to lower frequencies, specifically the delta range, due to hyper-excitation and/or inhibition of more functional higher frequency ranges, such as beta frequencies.

As an alternative explanation, lower-frequency oscillations, such as delta oscillations, might be the result of compensatory processes to maintain high cognitive performance. With regard to ageing, studies have shown that greater delta band power in younger adults (Mousavi et al., 2020) and greater delta band coherence (i.e., a measure of connectivity) in frontal brain areas in older adults (Fleck et al., 2016) was related to higher semantic fluency scores. In the current study, however, whilst greater delta band connectivity was related to higher semantic fluency scores in younger adults, this was not the case in older adults. In older adults, increased delta connectivity may reflect failed compensatory processes, in line with the idea that the brain is less able to inhibit this lower-frequency oscillatory rhythm. Since our study took a whole-brain approach, we could not determine whether these connectivity effects were region-specific, and other oscillatory patterns may be found when looking at, for example, delta connectivity in frontal brain areas. In younger adults, greater overall connectedness in the delta band might reflect an individual's ability to inhibit irrelevant responses and maintain internal concentration (Harmony, 2013; Mousavi et al., 2020), which may reverse with age reflecting pathology-related compensatory processes.

Brain Segregation and Word-Finding Ability Across the Lifespan

Greater modularity in the alpha band predicted lower semantic fluency performance, irrespective of age. Greater brain modularity has been hypothesised to enable greater brain plasticity, because it increases the brain's efficiency and flexibility to adapt to, for example, age-related anatomical brain changes (Gallen & D'Esposito, 2019). Hence, we would expect that greater modularity would improve word-finding abilities. However, greater modularity was related to lower semantic fluency scores in both younger and older adults, contradicting the suggestion that greater modularity reflects greater brain plasticity and better cognitive functioning. Another explanation is that, to perform verbal fluency tasks, brain integration might be more important than segregation and it is possible that greater brain segregation could be related to lower integration. It has been suggested that greater brain integration is necessary for higher-level cognitive functions, such as language (Bagarinao et al., 2019; Bullmore & Sporns, 2012). However, this seems unlikely as there is a positive relationship between modularity (segregation) and characteristic path length (integration) in the alpha band (see Appendix B.3 for the analysis). Alternatively, resting-state modularity might perhaps positively relate to some cognitive functions, such as visuospatial working memory, but not others (e.g., numerical working memory Alavash et al., 2015), or perhaps modularity needs to reach a certain threshold after which it becomes detrimental to cognitive functioning.

Alternatively, one theory proposes that modular brain networks are necessary for quick and simple tasks, whilst complex tasks that require more time benefit more from a lower modular structure (Deem, 2013). For example, greater modularity was negatively related to performance on a complex task, which involved the ability to control attention, whilst modularity was positively related to performance on a simple task (i.e., not involving the control of attention Yue et al., 2017). Verbal fluency tasks are considered complex tasks as they involve a multitude of cognitive

functions to support lexical access (Shao et al., 2014). Hence, in line with the theory by Deem (2013), greater modularity could negatively predict verbal fluency performance. Moreover, our study did not reveal a negative relationship between modularity and letter fluency. The cognitive functions and brain regions underlying letter and semantic fluency are slightly different (Gordon et al., 2018; Shao et al., 2014; Vonk et al., 2019), which could explain the discrepancy between the two tasks in our study.

We also predicted that brain segregation, specifically in the delta band, would play an important role in predicting semantic fluency scores in older adults (Fleck et al., 2016; Mousavi et al., 2020). Fleck and colleagues (2016) argued that maintaining delta band brain segregation in older age is necessary to maintain cognitive performance and decreases will lead to cognitive decline. The current study demonstrated that alpha but not delta brain segregation, as measured through modularity, was related to cognitive performance, and this relationship was irrespective of age. Alpha band activity has been proposed to reflect attention, working memory, and switching abilities (Başar et al., 1999; Stam, 2000). It has been proposed that resting-state alpha band activity is an important indicator of an individual's readiness for subsequent task performance, potentially through the inhibition of irrelevant pre-task information (Jann et al., 2010; Klimesch et al., 2007). Hence, the current study might indicate that semantic fluency benefits more from a non-modular structure in the alpha band. Less-modular brain networks at rest may allow for a fast reorganisation of the brain network and the direction of attention to the task at hand. Alternatively, the finding in alpha but not delta frequency band modularity might reflect a compensatory mechanism whereby brain activity synchronises within a less functionally specific frequency band (Davis et al., 2022).

Neural dedifferentiation for word-finding abilities We hypothesised that brain segregation decreases with age, reflective of neural dedifferentiation. Age-related decreases in brain segregation have been proposed to reflect neural dedifferentiation

in older adults (Goh, 2011; Zuo et al., 2017), which means that brain regions and networks become less functionally specific to cognitive processes (Li et al., 2001). Previous studies have supported this idea and showed that greater brain segregation in older adults was related to better memory ability (Chan et al., 2014; Zangrossi et al., 2021). The current study demonstrated an inverse relationship between modularity and word-finding ability, irrespective of age. This is interesting given the expectation that greater modularity would reflect more functional specificity to cognitive functions and, consequently, benefit cognitive functioning. It is possible that modularity does not represent age-related neural dedifferentiation for semantic fluency. Moreover, modularity was computed using resting-state brain networks and not during the semantic fluency task. It is possible that resting-state modularity cannot capture neural dedifferentiation underlying age-related word-finding difficulties.

The Small-World Index and Word-Finding Abilities

The small-world index is a measure of the organisation of functional brain networks. The current study showed that a greater small-world index in the delta band was related to better semantic fluency performance, irrespective of age. Several studies have linked greater cognitive performance in middle-aged and older adults to a higher small-world index (Douw et al., 2011; Vecchio et al., 2016) and it has been hypothesised that a greater small-world index reflects a more efficient brain (Achard & Bullmore, 2007). A previous study in people with chronic fatigue syndrome demonstrated that the delta band small-world index was negatively related to cognitive dysfunction, which included problems with attention, remembering, and word-finding (Zinn et al., 2017). Our findings add to the literature and indicate that brain networks with small-world topologies could underlie semantic fluency performance in both younger and older adults. Hence, an optimal balance between local and global connectedness might be important for maintaining word-finding ability across the lifespan, irrespective of any age-related decreases.

Greater Brain Integration is Related to Better Word-Finding in Older Adults

In an exploratory analysis, we investigated the relationship between brain integration and age-related word-finding difficulties. In older adults, a longer characteristic path length in the delta band was associated with higher semantic fluency scores. Shorter characteristic path length would reflect greater global network efficiency because fewer nodes need to be traversed to transfer information from one brain area to another (Bullmore & Sporns, 2009). In contrast, we found that greater characteristic path length related to better semantic fluency in older age. Several studies showed that brain integration decreases with age (Bagarinao et al., 2019; McIntosh et al., 2014; Sullivan et al., 2019), including characteristic path length (Vecchio et al., 2014). Hence, greater characteristic path length (i.e., increased integration) might be necessary to maintain word-finding abilities in older age.

Limitations and Future Directions

The current study has several limitations. First, the OMST algorithm resulted in too sparse a network in some participants to compute the clustering coefficient and the small-world index. On the one hand, the study was still able to demonstrate the relationship between word-finding and clustering coefficient but, on the other hand, no interaction effects were observed. The latter could be the result of the reduced sample size due to missing values for the clustering coefficient. However, the choice of thresholding is an important one as the incorrect thresholding method can lead to biases and make it difficult to compare across studies. For example, arbitrary thresholding affects the reliability of a study, and bias can appear when one chooses a threshold based on what threshold leads to significant results (Miljevic et al., 2022). In contrast, data-driven thresholding is more objective as the user has no influence on what threshold is chosen. Therefore, we decided to implement the OMST algorithm as it is a data-driven threshold method created to reduce the sparsity of networks,

whilst maximising global efficiency (Dimitriadis et al., 2017). Moreover, a recent study indicated that with increasing age, the individual variability in functional brain networks increases (Ma et al., 2021). It is possible that data-driven methods are better suited when comparing functional brain networks, to account for networks that are highly variable between individuals (Bansal et al., 2018). To shed light on functional brain connectivity in ageing, more research is needed using the OMST algorithm for thresholding the brain connectivity graphs so that these studies can be compared.

Another debate in the field of functional brain connectivity obtained through EEG recordings is whether one should project the signals into sensor (i.e., electrodes) or source space (i.e., brain regions underlying the observed electrical activity). Many studies argue for projecting signals into source space as doing so is suggested to resolve problems such as volume conduction and field spread (see Schoffelen & Gross, 2009). However, source-space analyses have their own limitations. For example, there are multiple methods for identifying the underlying sources and the estimation of parameters needed for source localisation is very complex and relies on a number of assumptions (Mahjoory et al., 2017; Miljevic et al., 2022). In addition, a recent study showed that sensor space might be more suitable for conducting functional brain connectivity analyses as brain network indices, such as the characteristic path length, can change after projecting brain activity into source space (Koutlis et al., 2021). Moreover, the current study aimed to conduct whole-brain network analyses and we did not have a-priori hypotheses about the underlying brain regions. Whole-brain network analyses are important to understand the effect of age on how functional networks combine the information processed by the brain (Geerligs et al., 2015). To reduce the influence of volume conduction and field spread. the debiased weighted Phase Lag Index was used to compute the connectivity between the EEG sensors (Lai et al., 2018; Vinck et al., 2011). Hence, the issues created by volume conduction were addressed without the need to conduct source localisation in the current study. Nevertheless, future studies could build on the results of the current study by

investigating the sources underlying the functional brain connectivity patterns we have observed.

Finally, it is important to note that the current study identified brain networks from resting-state data, hence, these networks were not obtained during the verbal fluency tasks. Functional brain networks underlying verbal fluency tasks may yield different patterns from resting-state data, and age-related changes might be reflected differently in task-dependent functional connectivity. However, resting-state EEG analyses have been argued to be informative (Rosazza & Minati, 2011; van Diessen et al., 2015) and such analyses can be useful in providing insights into cognition, and the diagnosis, development, and treatment of neurodegenerative diseases (Ishii et al., 2017; O'Neill et al., 2018).

The current study also identified some gaps and recommendations for future research. First, we demonstrated that increased functional connectedness in the delta band was related to age-related word-finding difficulties. Future studies should explore this relationship among healthy older adults, adults at risk of dementia, and adults in the beginning stages of dementia. Investigate whether such a measure, in conjunction with neuropsychological assessments, could contribute to the early detection of cognitive impairment and dementia. Second, interventions could be developed that aim to increase delta band functional connectedness as this could increase neuroplasticity and, consequently, improve cognitive outcomes in older adults. Third, considering our contrasting finding that increased modularity was related to poorer word-finding ability irrespective of age, future studies could investigate when the extent of brain segregation becomes detrimental to word-finding ability. Additionally, examining potential differences in this effect between younger and older adults would be valuable. Finally, because modularity has been proposed to be important in predicting neuroplasticity outcomes following intervention, such as cognitive training (Gallen & D'Esposito, 2019), it is important to investigate the interactive effect between modularity, complexity of cognitive functioning, and intervention outcomes. Such research is essential not only in ageing populations but

also in those with neurodegenerative diseases.

Conclusion

The current study investigated the link between functional brain connectivity and word-finding abilities in younger and older adults. We found that changes in functional brain connectivity, such as in overall connectedness and characteristic path length, related to worse performance on semantic fluency, but only in older adults. Modularity and the small-world index also predicted semantic fluency performance, but this was irrespective of age. Moreover, changes in functional brain connectivity were specific to the frequency band, possibly reflecting changes in cognitive control and the ability to inhibit irrelevant responses or a compensatory shift to less functionally specific frequency bands. This is the first study demonstrating that age-related word-finding difficulties can be linked to changes in functional brain connectivity.

Chapter 6

The Role of Neuronal Phase Coherence Underlying Action-Word Comprehension in Healthy Ageing

Linking Statement:

The previous chapters discussed the neurobiology and lifestyle contributions to age- and PD-related word-finding abilities, utilising word production tasks. Instead, this chapter focused on word comprehension using a lexical decision task. Chapters 3 and 4 already discussed the difference between object- and action-word finding in healthy ageing and Parkinson's disease. Building on those previous chapters, this chapter specifically focused on the comprehension of words describing physical action (i.e., high-action words) in healthy ageing. Through an EEG time-frequency analysis using inter-trial phase coherence, this chapter investigated the neuronal phase coherence underlying action language and whether the link between action and language stays relatively preserved or weakens with age. Finally, this chapter will briefly discuss the effect of hearing status on neuronal phase coherence underlying action word-finding.

Author Note:

The study hypotheses, design, and statistical analyses were preregistered on the

Open Science Framework (https://osf.io/5qjkh). Octave code for the lexical decision task, MATLAB and R code for data pre-processing and analysis, pre-processed EEG files, the full participant dataset, and supplementary materials will be made openly available on the Open Science Framework website after publication.

This paper was produced in collaboration with Dr. Neil Bailey, Dr. Kate Slade, Dr. Patrick May, and Dr. Helen Nuttall as co-authors.

6.1 Abstract

The impact of age on action-word processing and whether the actionality of a word facilitates word retrieval in older adults remains unclear. This study investigated age-related differences in neuronal phase coherence during action-word processing and its relationship to action-word comprehension. Forty-four older (aged 60-81) and 44 younger adults (aged 18-29) completed a timed, written lexical decision task while undergoing electroencephalography (32 channels). The task included three conditions: high-action words describing upper- and lower-limb physical actions, low-action words representing abstract concepts or non-upper- or lower-limb actions, and pseudowords. The high- and low-action conditions included both nouns and verbs. All participants were right-handed, native-British English speaking, without any language, speech, neurological, or psychiatric disorders. Neuronal phase coherence was assessed during the lexical decision task through time-frequency inter-trial phase coherence (ITPC) over the frontocentral brain region. ANCOVA analysis and pairwise comparisons revealed greater mu and beta band ITPC for high-action words in older compared to younger adults. Multiple linear regression revealed that higher ITPC was related to faster processing of high-action words in both age groups. In the mu band, the relationship between ITPC and high-action word processing was stronger in older than in younger adults. These findings suggest age-related alterations in neuronal phase coherence during action-word processing and a strengthened link between action and language with age. This chapter will discuss the findings in the context of age-related neuroplasticity as well as the implications for future research.

Keywords: action language; healthy ageing; inter-trial phase coherence; lexical decision; electroencephalography.

6.2 Introduction

Ageing is accompanied by cognitive decline, and as part of this, older adults commonly experience word-finding difficulties (Burke & Shafto, 2004; Salthouse, 2009). One important lexical factor that influences word-finding is whether the word is a noun or verb, with nouns being processed faster than verbs (e.g., Cordier et al., 2013; Kauschke & Stenneken, 2008). The noun-verb distinction could be understood through the concept that words denoting physical actions, also known as action words, are grounded in the sensorimotor areas of the brain (Hauk et al., 2004). The difference in processing speed between nouns and verbs may be attributed to the neuronal processes underlying these word categories, specifically the additional activation of sensorimotor regions for verbs compared to nouns (e.g., Hauk et al., 2004). During language processing, sensorimotor systems support semantic knowledge, involving a wide range of brain regions and circuits (Pulvermüller, 2013), including the premotor cortex (Willems et al., 2011). It is currently unclear whether the sensorimotor system supports word-finding of words that describe physical actions (i.e., action words) in older adults.

Grounded cognition theory suggests that our cognitive processes are influenced by the interactions between our bodies and the world around us, based on perception as well as action (Jirak et al., 2010). More specifically, during the processing of action words, the word's meaning becomes linked to previous experiences related to that action word through one's world knowledge (Barsalou, 2008). Consequently, when we retrieve that action word from our memory, this coupling leads to the activation of brain regions associated with physically performing that action. This activation is also called motor simulation and facilitates access to the word's action-related features. The grounded cognition theory predicts that age-related sensory and motor declines would impede the simulation of perceptual and sensorimotor systems (Vallet, 2015). However, in the perceptual domain, both younger and older adults seem to be relying on sensory-dependent knowledge, such as a word's auditory

and visual features (Vallet, 2015; Vallet et al., 2013). Hence, younger as well as older adults seem to rely on the simulation of perceptual systems through visual and auditory imagery. Whether older adults rely on sensorimotor systems during action word perception similar to younger adults, remains unexplored.

Ageing studies that have explored the relationship between age and action language processing have produced conflicting findings (Bidet-Ildei et al., 2020; Reifegerste et al., 2021). Bidet-Ildei et al. (2020) proposed that the association between action and language weakens with age due to decreased activation of the brain regions underlying the action representations of the words. In their study, younger adults exhibited faster response times when a picture represented a previously heard action word, compared to when it did not match the previously heard action word, while older adults did not display this difference. The authors argued that older adults may have difficulties simulating the actions during action-word processing, potentially leading to decreased grounding of action words in the brain regions underlying the action representations of the words.

From another perspective, Reifegerste et al. (2021) concluded that the connection between words and motor or physical actions remains relatively intact with age. Their study utilised a lexical decision task with words describing varying levels of motor-relatedness, namely how much a word describes human bodily movements. The researchers found an effect of age on verbs with low motor relatedness, whereas the age effect on verbs with high motor relatedness was non-significant. That is, words with low motor content elicited slower and less accurate responses in older than younger adults, whilst this age difference was not found for words with high motor content. The researchers suggested that the neuronal networks and brain regions underlying words with high motor content remain relatively unaffected by age and that these neuronal networks may even support word-finding of words with high motor relatedness but not low motor relatedness in older age. Hence, the activation of the brain regions underlying the action representations of the words might facilitate word-finding in older adults.

Language processing involves the coordination of neuronal activity across various brain regions (Fries, 2005). Action words elicit activity in the frontocentral brain regions, while object words elicit activity in the temporo-occipital brain regions (Moseley et al., 2013). Moreover, frontocentral brain regions involved in motor functions, such as the primary motor and premotor cortex, might be additionally recruited to facilitate word-finding, for example, by simulating the action of the word described (Akinina et al., 2019). Age-related deterioration of these brain regions, potentially due to neural dedifferentiation, could diminish the link between sensorimotor systems and cognition (Baltes & Lindenberger, 1997; Costello & Bloesch, 2017). Event-related potential (ERP) studies have shown that action words elicit more positive potentials, such as in the P200 and N400 components, in frontocentral brain regions than non-action or object words (Zhao et al., 2017), even after controlling for grammatical class (Barber et al., 2010; Cervetto et al., 2021; Khader et al., 2003). Hence, it appears that the brain processes action and object words differently. Moreover, the N400 decreases in magnitude and the latency becomes longer with age (Friedman, 2011). However, it is currently unclear whether age-related changes in the N400 amplitude and action word processing are linked as well.

At the oscillatory level, different groups of neurons are involved in accessing verbs compared to nouns (Khader et al., 2003; Preissl et al., 1996). The 'neuronal communication through neuronal coherence' hypothesis states that groups of neurons communicate with each other by synchronising their oscillatory phase, which underlies cognitive functioning (Fries, 2005). Oscillatory phase coherence can be measured using Inter-Trial Phase Coherence (ITPC), which reflects the consistency of oscillatory phase across multiple trials of an EEG signal (Makeig et al., 2004). ITPC is thought to reflect neuronal population-level activity and could provide insights into the underlying neuronal activity of cognitive processes (Cohen, 2014). Regarding action language, ITPC has already been successfully applied in machine learning algorithms to classify action-related verbs and concrete nouns,

measured from the mu and beta bands in frontal and temporal brain regions (Jensen et al., 2019). Hence, word-finding seems to involve oscillatory phase coherence, with different processes underlying action and object words.

The relationship between ITPC and age has not received much attention yet. Theta band ITPC appears to increase from childhood into adulthood and decrease again in older adults, potentially reflecting increases and decreases in cognitive control or working memory-related attention processes (Ho et al., 2012; Papenberg et al., 2013). Increased ITPC in theta and alpha bands in younger adults compared to children and in stroke patients may reflect increased brain plasticity or reorganisation, driven by brain maturation and compensatory mechanisms in response to brain injury (Gyulai et al., 2021; Yordanova & Kolev, 2009). However, the relationship between age-related differences in ITPC and action language has not been investigated previously. Examining this relationship will provide insights into the neuronal processes underlying action word comprehension, which may be utilised to indicate healthy neuronal processing and detect the development of pathological neuronal activity.

Taken together, the influence of age on action-word processing and the extent to which the action features facilitate word retrieval in older adults is unclear. Investigating age-related changes in ITPC can provide valuable insights into the brain's sensorimotor mechanisms underlying age-related difficulties in accessing action words. Therefore, the aims of this study were two-fold: i) to replicate the N400 amplitude difference between high- and low-action words, and ii) to investigate age-related differences in ITPC underlying action word-finding as the influence of age on neuronal population-level activity associated with action words remains unclear. First, we hypothesised that neuronal population-level activity in the frontocentral brain region would correlate with processing action but not non-action words in both older and younger adults. Second, we hypothesised that ageing could lead to decreased neuronal synchronisation in older adults, related to action word-finding difficulties in older adults. Third, we hypothesised that neuronal population-level

activity in frontocentral brain regions underlying action words remains relatively preserved with age, related to preserved action word-finding abilities in older adults. The hypotheses, predictions, and experimental design were preregistered on the Open Science Framework website at https://osf.io/5qjkh.

6.3 Methods

Participants

A total of 89 participants took part in the study (44 older adults, 30 females, Mage = 67.2 SDage = 5.7; 45 younger adults, 31 females, Mage = 20.7, SDage = 2.6). All participants were right-handed, native speakers of British English. The sample size was based on a-priori power analysis using G*Power for a mixed ANCOVA with two covariates (Faul et al., 2007). A previous study investigating ITPC during cognitive performance reported large effect sizes (Papenberg et al., 2013). However, most previous literature on the relationship between ageing and ITPC or action language did not report any effect sizes. In addition, due to time and monetary resources, it was unfeasible to detect small effects. Therefore, the study was powered to detect a medium to large effect size (Cohen's f = .325). The power calculation resulted in a minimum sample size of 77 to reach a statistical sensitivity of 80% with an alpha level of .05. To account for data loss due to noise in the EEG data, we aimed to recruit up to 90 participants (45 older and 45 younger adults).

All participants had self-reported normal or corrected-to-normal vision (e.g., glasses). In addition, participants had no history of language or speech disorders (e.g., dyslexia or stuttering), no neurological disorders, such as stroke, epilepsy, current psychiatric disorders (e.g., bipolar disorder), nor current alcohol or substance use disorder (i.e., an alcohol or drug addiction). Both alcohol and drug use can affect the EEG signal (Parvaz et al., 2011; Porjesz et al., 2005). Therefore, alcohol and substance use disorders were assessed through the standardised Alcohol Use Disorders Identification Test (AUDIT Babor et al., 1992) and the Drugs Abuse

Screening Test (DAST-10 Skinner, 1982). Participants had a score of 16 or less on the AUDIT and 2 or lower on the DAST-10. Moreover, participants were screened for depression using the Beck Depression Inventory-II (BDI-II Beck et al., 1996), and all had a score of 18 or lower. Finally, all participants had normal cognitive functioning (i.e., a score of 24 or higher), as was assessed with the Mini-Mental-State Examination (MMSE Folstein et al., 1975). The study was approved by the Research Ethics Committee of the Faculty of Science and Technology of Lancaster University.

Experimental Task and Procedure

Participants provided digital consent and completed the AUDIT, DAST-10, and BDI-II online via the Qualtrics XM Platform (Qualtrics, Provo, UT) before coming to the lab. In the lab, participants signed a consent form and completed the MMSE. Next, pure tone audiometry was used to assess hearing status across octave frequencies .25-8 kHz in accordance with British Society of Audiology procedures (British Society of Audiology, 2018). Next, the EEG was set up and eyes-closed resting-state EEG was recorded for 3 minutes to obtain the Individual Alpha Peak Frequency (IAPF). Studies have consistently shown that neurophysiological rhythms slow with ageing and that including conventional frequency bands can introduce a bias against older adults (Chiang et al., 2011; Scally et al., 2018). Therefore, the EEG spectral boundaries were determined using the IAPF. Following the resting state recording, the participant completed a lexical decision task while continuous EEG was recorded. The task was presented on a Linux computer, using GNU Octave (Eaton et al., 2020) and Psychtoolbox-3 (Brainard, 1997; Kleiner et al., 2007) to present the stimuli. To reduce temporal jitter and uncertainty (e.g., that in monitor display rates), for which ITPC is sensitive, we used a computer monitor with a 144Hz refresh rate (Cohen, 2014; van Diepen & Mazaheri, 2018).

The procedure of the lexical decision task was as follows (see also Figure **??**): First, the participant saw a blank screen with a random interval between 1000 and

1500ms, after which a fixation cross was presented, randomly varying between 500 and 750ms, followed by another blank screen of 200ms. Next, a word was presented for a maximum of 2000ms (i.e., timeout) or until the participant responded by pressing a button on a button response box. The experiment consisted of 400 trials, split into three conditions (200 pseudowords, 100 high-action words, and 100 low-action words). The high-action words described hand/arm- and foot/leg-related physical action whilst the low-action words described non-upper- and lower-limb actions and abstract concepts (e.g., *"luck"*). Four different experimental lists were created, with pseudorandomised word order, counterbalanced across participants and age groups. Each condition was presented a maximum of two times consecutively, to control for priming effects. Each list had eight blocks, with self-paced breaks between blocks, and each condition was proportionally distributed across blocks. Three attention checks were implemented within each block, during which the participant had to indicate whether a picture matched a previously seen word, by pressing a key ("y" for yes and "n" for no). The attention checks also ensured participants processed the words beyond simple word recognition. Finally, each block started with a 1-minute open-eyes resting state condition during which participants were instructed to fixate on a fixation cross. Participants were presented with 5 practice trials, with a fixation cross of a fixed duration of 750ms, before starting with the real experiment.

For the high- and low-action conditions, real words were selected using the *LexOPS* package (Taylor et al., 2020) in R. The two conditions were matched for number of characters, number of syllables, word frequency, bigram frequency (all using SUBTLEX-UK; van Heuven et al., 2014), orthographic neighbourhood size (Coltheart et al., 2022), familiarity, age of acquisition (both using Glasgow Norms; Scott et al., 2019), and English Lexicon Project accuracy (Balota et al., 2007). Both conditions consisted of both nouns (high-action: $N = 65$; low-action: $N = 74$) and verbs (high-action: $N = 35$; low-action: $N = 26$) and were matched for grammatical class. Words did not match for imageability or concreteness (Glasgow Norms;

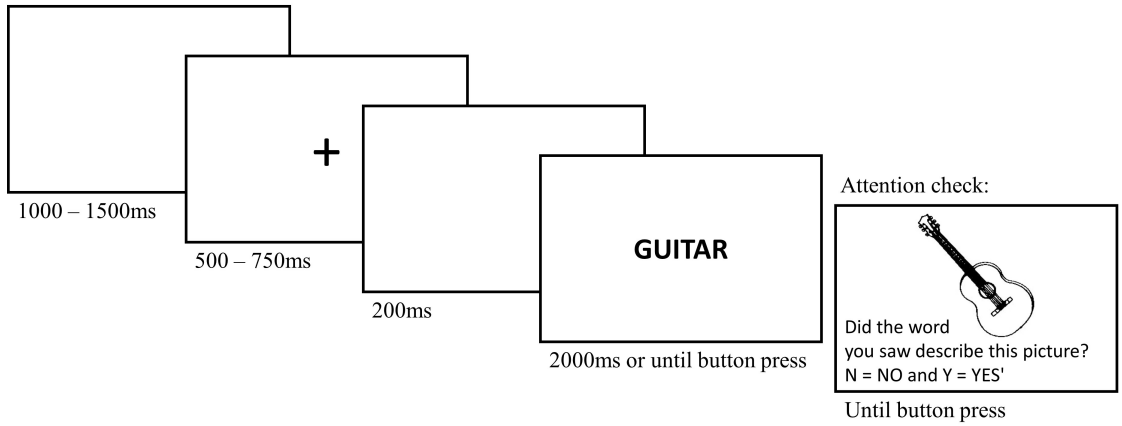

Figure 6.1. Procedure of the lexical decision tasks. The interval for the first blank screen and the fixation cross was at random. The real or pseudoword was presented for a maximum 2000ms or until the participant pressed a button on the button box. The attention checks only appeared three times per block.

Scott et al., 2019) because upper- and lower-limb-related high-action words are generally more concrete than low-action words (Banks & Connell, 2022). In addition, imageability ratings can be explained by other lexical factors (e.g., frequency) and sensorimotor information (e.g., relatedness to hand/arm actions; Dymarska et al., 2023), which were factors accounted for in this study. Pseudowords were created using the pseudoword generator software *Wuggy* (Keuleers & Brysbaert, 2010), which matches the subsyllabic structure of the real words. The Wuggy algorithm created 5 possible pseudowords for each real word, matching for letter length, transition frequencies, and 2/3 of syllables of the pseudoword were matched to the syllables of the real word. We manually selected one pseudoword for each real word, avoiding the inclusion of any pseudo homophones (i.e., non-existing words that sound like a real word).

EEG Recording and Pre-Processing

Electroencephalography data were recorded using the 32-channel BioSemi ActiveTwo system (Biosemi, Amsterdam). The Ag-AgCl electrodes were positioned according

to the international 10-20 system and the electrode placement was consistent across all participants to maintain data standardisation. Data were acquired at a 2048Hz sampling rate, digitised with a 24-bit A/D converter, and a DC high-pass and a 417Hz low-pass filter. BioSemi utilises a reference-free approach using a common mode sense (CMS) active electrode and a driven right leg (DRL) circuit. Electrode impedances were kept below 20kΩ.

Data were pre-processed using MATLAB R2022b (MathWorks) and Fieldtrip (Oostenveld et al., 2010). To clean the continuous downsampled EEG data, we used the pre-processing pipeline 'Reduction of Electroencephalographic Artifacts' (RELAX; Bailey, Biabani, et al., 2023; Bailey, Hill, et al., 2023), utilising Fieldtrip and EEGLAB (Delorme & Makeig, 2004). A notch filter (50Hz) to remove line noise and a 0.25-80Hz Butterworth bandpass filter were applied, after which the data were downsampled to 1000Hz. Noisy channels and EEG periods that exhibited exceptionally high or low values, indicating extreme outliers, were identified and removed via the PREP pipeline algorithm (Bigdely-Shamlo et al., 2015). The mean proportion of the EEG data removed due to noisy channels was 0.12 (SD= 0.06), leaving an average of 28 channels (SD= 2). The mean proportion of extreme EEG periods removed was 0.17 (SD = 0.14). Next, the data were re-referenced to the robust average reference before detecting any remaining artifacts through Independent Component Analysis (ICA) with the FastICA algorithm (Hyvarinen, 1999) and reducing artifacts identified by ICLabel (Pion-Tonachini et al., 2019) using Wavelet Enhanced ICA (Castellanos & Makarov, 2006). After data cleaning, excluded channels were interpolated using spherical spline (Delorme & Makeig, 2004).

The cleaned EEG data were segmented into high-action and low-action trials with a baseline correction of -200ms to 0ms pre-stimulus onset. Only epochs for correct trials for real words were included in the analysis. On average, the number of epochs for each of the two conditions (high- vs. low-action words) was as follows for the younger adult group: high-action *M(SD)* = 74.8(16.0); low-action *M(SD)*=

73.6(17.5); and for the older adult group: high-action *M(SD)* = 76.0(16.3); low-action *M(SD)*= 72.9(19.2). There were no group differences in the number of epochs for the high-action ($t(85) = 0.23$, $p = .814$, nor for the low-action condition ($t(85)$ = -0.10, $p = .918$).

EEG Time-Frequency Analysis

After cleaning the data, time-frequency analyses were performed on the real words of correct trials per condition (i.e., high vs. low action) and per frequency band. Using conventional frequency bands can cause a bias against older adults due to age-related oscillatory slowing (Babiloni et al., 2020; Chiang et al., 2011; Scally et al., 2018). To control for individual and age-related differences in oscillations, we defined the spectral boundaries using the IAPF obtained during a 3-minute eyes-closed resting-state condition at the beginning of the experiment: delta as IAPF -8 to -6 Hz, theta as IAPF -6 to -4 Hz, alpha as IAPF -4 to +2 Hz, and beta as IAPF +2 to 30 Hz (Babiloni et al., 2020; Henelius et al., 2011; Klimesch, 1999). Mean IAPF for the older adults was 10.1 Hz ($SD = 0.9$ Hz) and 9.4 Hz ($SD = 1.0$ Hz) for the younger adults.

Fieldtrip was used to compute the Fourier spectra for each frequency band (with 0.01Hz intervals) using Morlet wavelet convolution (2 – 7 cycles), using Hanning window tapering. Within a fixed window of time of 250ms to 500ms, with a step size of 0.01 seconds, Inter-Trial Phase Coherence (ITPC) and power were computed for the frontocentral region (electrodes C3, C4, Cz, FC1, FC2) and, for the exploratory analysis, over the temporo-occipital region (electrodes PO7, O1, Pz, O2, PO8). ITPC measures the synchrony between phases (i.e., the consistency between phases) that are time-locked to specific events or stimuli (Delorme & Makeig, 2004). The phase consistency obtained through ITPC has been suggested to reflect the synchronisation of neuronal activity across neuronal populations (Cohen, 2014). Lastly, for the same time window, we computed power per frequency band for the frontocentral region, after which time-frequency power was baseline normalised (-

300 to -50ms), standardised in decibels (dB) using log-transformation, and averaged across trials.

Statistical Analysis

The average ERPs time-locked to the stimuli over the frontocentral brain region were computed per participant and condition using the Fieldtrip Toolbox. Next, the grand average ERP was computed per condition, collapsing the two age groups. Using the Statistics and Machine Learning Toolbox in Matlab, a paired t-test was conducted to replicate the N400 amplitude difference between the High Action and Low Action conditions within the N400 time window (250-500ms; Kutas & Federmeier, 2000).

The behavioural and ITPC data were analysed in R (RStudio Team, 2020) using a 2x2 mixed analysis of covariance (ANCOVA) with fixed, main, and interaction effects. The outcome variable was the peak ITPC for high-action words minus peak ITPC for low-action words (continuous variable), with the predictors Age Group (younger vs. older) and Frequency Band (mu vs. beta), which were both sum-contrasted. Only correct trials were included in the computation of peak ITPC. To account for differences in the number of epochs, peak ITPC was transformed using Rayleigh's Z: peak ITPC $Z = n$*ITPC^2, where n was the number of epochs.

Because hearing loss affects a wide network of brain regions underlying language processing, including frontal brain regions (Peelle et al., 2011), hearing status was included as a covariate. Moreover, because alcohol use can affect neuronal processes (Porjesz et al., 2005), the AUDIT score was also included as a covariate to account for potentially confounding effects. Finally, log-ratio power for both frequency bands was calculated between the high-action and low-action conditions and was added as a covariate to control for potential power-induced ITPC differences between the two conditions (Bonnefond & Jensen, 2012; van Diepen & Mazaheri, 2018). All covariates were centred and scaled. For significant two-way interactions, simple main effect analyses were conducted using the *emmeans* package (Lenth, 2021),

including simple pairwise comparisons with Bonferroni adjustment to correct for multiple comparisons (Abdi, 2007). Effect sizes for the pairwise comparisons were computed using the "eff_size" function of the *emmeans* package.

To investigate the relationship between age-related changes in ITPC and action-word finding ability (hypotheses 2 and 3), we conducted a multiple linear regression analysis. The outcome variable was reaction time, which was log-transformed to obtain normality. The predictors were the interaction between peak ITPC Z (scaled), Age Group, and Frequency Band. The covariates hearing status, AUDIT, and log ratio power were scaled as in the ANCOVA. Interactions were further explored by investigating the coefficients, plotting the predicted means, and pairwise comparisons using the *emmeans* package in R.

Deviations from Preregistration

Because ITPC values are influenced by epoch count, we preregistered that only EEG data with at least 60 epochs per condition would be included in the analysis. However, because this would lead to a high rate of data loss, we made this criterion less stringent and included data with at least 40 epochs per condition available. According to Cohen (2014), ITPC values become relatively stable after as few as 20 epochs but the ITPC values only become significant around 40-45 epochs. Making the epoch criterion less stringent helped in maintaining most of the EEG data. To further reduce the loss of data, we imputed missing IAPF values by taking the mean per age group. In the preregistration, we mentioned that we would exclude data of participants with missing IAPF values, but this would mean that we had to exclude 9 participants, reducing the power of our study.

Our second and third hypotheses explored the relationship between age-related changes in ITPC underlying action-word finding and its relationship with action-word finding abilities. Although the hypotheses were preregistered, the statistical analysis to investigate the relationship between action-word finding and age-related changes in ITPC had not been preregistered. To investigate this relationship, a

multiple linear regression model was conducted with the predictor variables being similar to the ones in the ANCOVA, including the same covariates. Multiple comparisons will be accounted for by a Bonferroni correction.

6.4 Results

Descriptives

Data from 41 older adults (27 females) and 45 younger adults (31 females) were included in the analysis. One older adult was excluded due to a missing text file with the lexical decision data, and one younger and two older adults were excluded due to noisy EEG data, leaving a total sample size of 86. The means and standard deviations for accuracy and reaction times (only correct trials) for the lexical decision task can be found in Table 6.1. Hearing status was calculated by averaging hearing thresholds over 250Hz, 500Hz, 1000Hz, 2000Hz, and 4000Hz, over both ears (see Figure **??**; British Society of Audiology, 2018). Older adults had a mean hearing threshold of 20.4dB (SD = 7.6dB, range 4.5dB – 40dB) and younger adults had a mean hearing threshold of 5.2dB (SD = 3.3dB, range -1dB – 14dB). Mean AUDIT scores were 3.9 for older adults (SD = 2.8, range 0 – 10) and 4.0 for younger adults (SD = 3.4, range 0 – 11).

Table 6.1. *Mean Accuracy and Reaction Times (RT) Scores (SD between brackets) on the Lexical Decision Task per Age Group and Condition*

Age Group	Condition	Accuracy	RT
Older	High Action	1.00 (0.11)	710.32 (169.22)
	Low Action	0.99 (0.12)	721.11 (184.35)
	Pseudowords	1.00 (0.21)	845.46 (243.70)
Younger	High Action	0.99 (0.16)	631.51 (186.70)
	Low Action	0.98 (0.17)	639.23 (192.33)
	Pseudowords	0.98 (0.25)	745.09 (224.82)

Note. The reaction times were only computed for correct trials

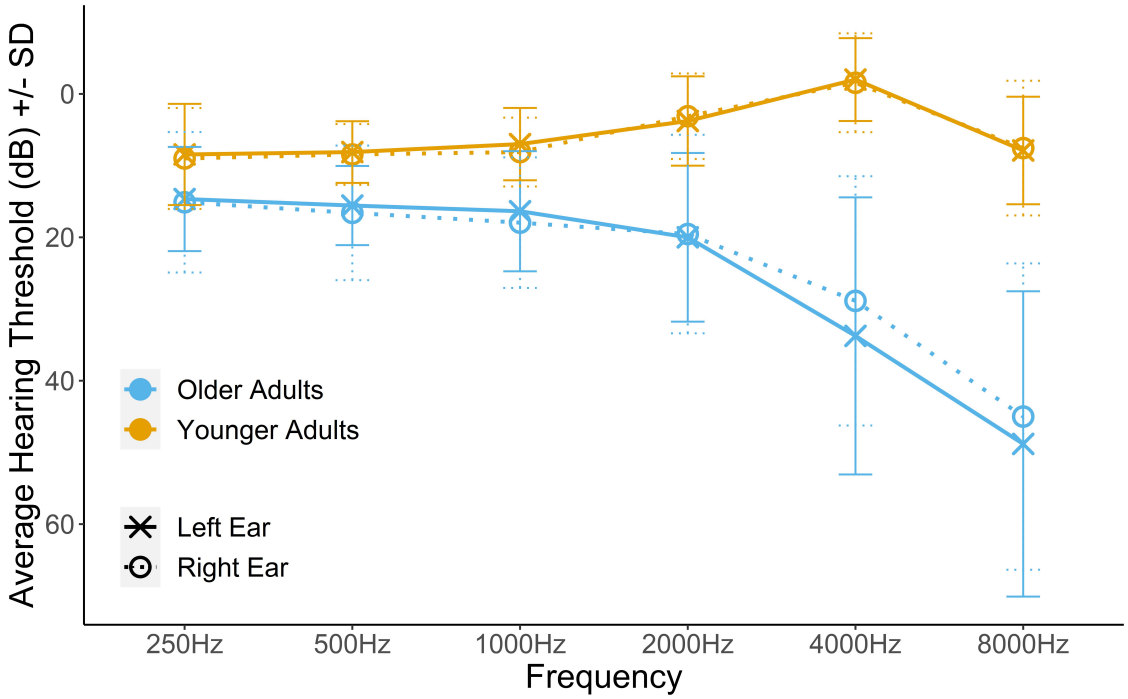

Figure 6.2. Audiogram of the average hearing thresholds (in dB) per frequency level, ear, and age group. The covariate for hearing status was created by averaging over 250 - 4000 Hz. The error bars represent +/- 1SD from the mean.

The ITPC index was computed by subtracting the peak ITPC for low-action words from the peak ITPC for high-action words. That is, negative values reflect a higher peak ITPC for low-action than high-action words, whilst positive values reflect a higher peak ITPC for high-action compared to low-action words (see Figure **??**). Table 6.2 presents the peak ITPC values, average power, and normalised power per age group, frequency band, and condition.

No N400 Difference Between Conditions

The first aim of this study was to replicate the N400 amplitude difference between the High Action and Low Action conditions (see Figure 6.4). A paired t-test did not reveal a statistically significant difference between the High Action and Low Action condition ($t(86)$ = -0.02, p = .987).

Table 6.2. *Peak ITPC and Power of the Frontocentral Region of the Mu and Beta Frequency Band Per Age Group and Task Condition*

		Older		**Younger**	
		High-Action	*Low-Action*	*High-Action*	*Low-Action*
Mu	Peak ITPC	0.71 (0.16)	0.70 (0.16)	0.62 (0.14)	0.62 (0.16)
	Peak ITPC Z	38.66 (17.44)	35.55 (16.71)	30.57 (13.34)	30.07 (14.64)
	Average Power	7.46 (4.01)	7.56 (4.01)	9.40 (6.71)	9.40 (6.80)
	Normalised Power (dB)	1.16 (1.18)	1.22 (1.19)	1.63 (0.94)	1.61 (0.93)
Beta	Peak ITPC	0.53 (0.14)	0.53 (0.13)	0.50 (0.15)	0.01 (0.15)
	Peak ITPC Z	22.29 (13.08)	21.30 (12.33)	19.62 (10.82)	19.54 (12.26)
	Average Power	2.72 (1.65)	2.77 (1.70)	2.49 (1.93)	2.50 (1.94)
	Normalised Power (dB)	-0.23 (0.65)	-0.18 (0.60)	0.75 (0.38)	0.77 (0.41)

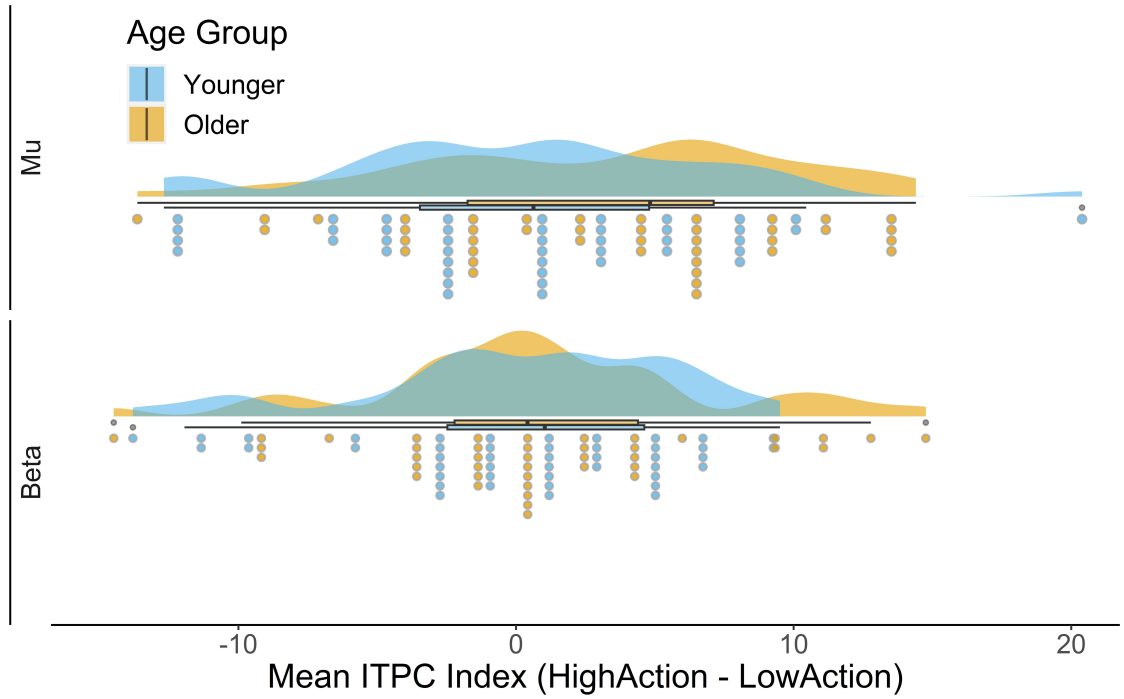

Figure 6.3. The mean ITPC index per Age Group and Frequency Band. The ITPC index was calculated as the difference between peak ITPC Z of the High Action and Low Action condition. Positive values indicate that the peak ITPC Z for the High Action condition was higher than that of the Low Action Condition.

Results of the ANCOVA

An ANCOVA was conducted to examine the effects of Age Group (younger vs. older) and Frequency Band (mu vs. beta) on the ITPC index, whilst controlling for hearing status, AUDIT scores, and log-ratio power (refer to Table C.1 for the full results table). Results revealed significant main effects for Age Group ($F(1, 85) = 1250.15$, adjusted $p < .001$, Cohen's $f = 0.14$) and Frequency Band ($F(1, 85) = 547.44$, adjusted $p < .001$, Cohen's $f = 0.09$). That is, the ITPC index differed between younger and older adults, and between the mu and beta frequency bands Finally, the interaction between Age Group and Frequency Band was significant ($F(1, 85) = 432.28$, adjusted $p < .001$, Cohen's $f = 0.08$; see Figure 6.5). That is, the relationship between Age Group and ITPC index varied depending on Frequency

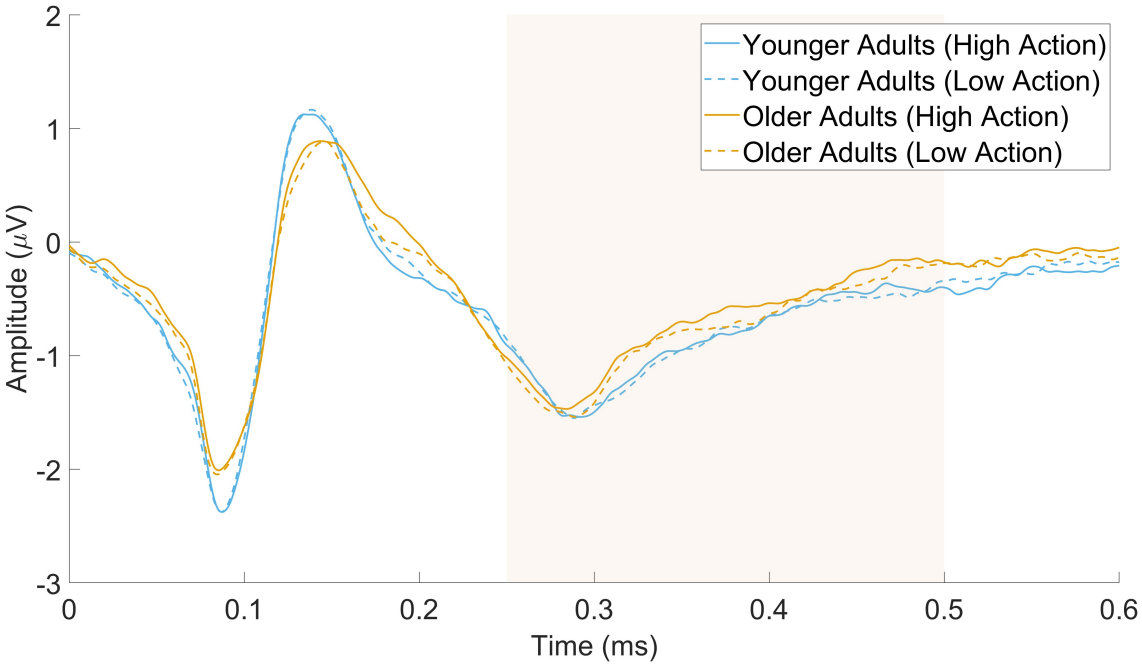

Figure 6.4. The ERPs 0ms to 600ms post-stimulus onset per age group and per condition. The highlighted area indicates the time window that was used to compute the N400.

Band.

The significant two-way interaction was further investigated using pairwise comparisons. For the mu frequency band, there was a significant difference in estimated marginal means (i.e., covariate-adjusted means) between younger adults (M = 0.228, SE = 0.057) and older adults (M = 3.240, SE = 0.059; $t(85)$ = -32.19, adjusted $p < .001$). The effect size was Cohen's d = -0.48 (95% CI [-0.51, -0.45]). That is, older adults showed a significantly higher ITPC index in the mu band than younger adults. In the beta frequency band, there also was a difference in estimated marginal means for younger adults (M = 0.110, SE = 0.057) compared to older adults (M = 1.086, SE = 0.060; $t(85)$ = -10.28, adjusted $p < .001$). The effect size for the comparison between younger and older adults in the beta frequency band was Cohen's d = -0.16 (95% CI [-0.19, -0.13]). That is, older adults had a significantly higher ITPC index in the beta band than younger adults.

Hearing status was a significant covariate for the ITPC index ($F(1, 85)$ = 21.06,

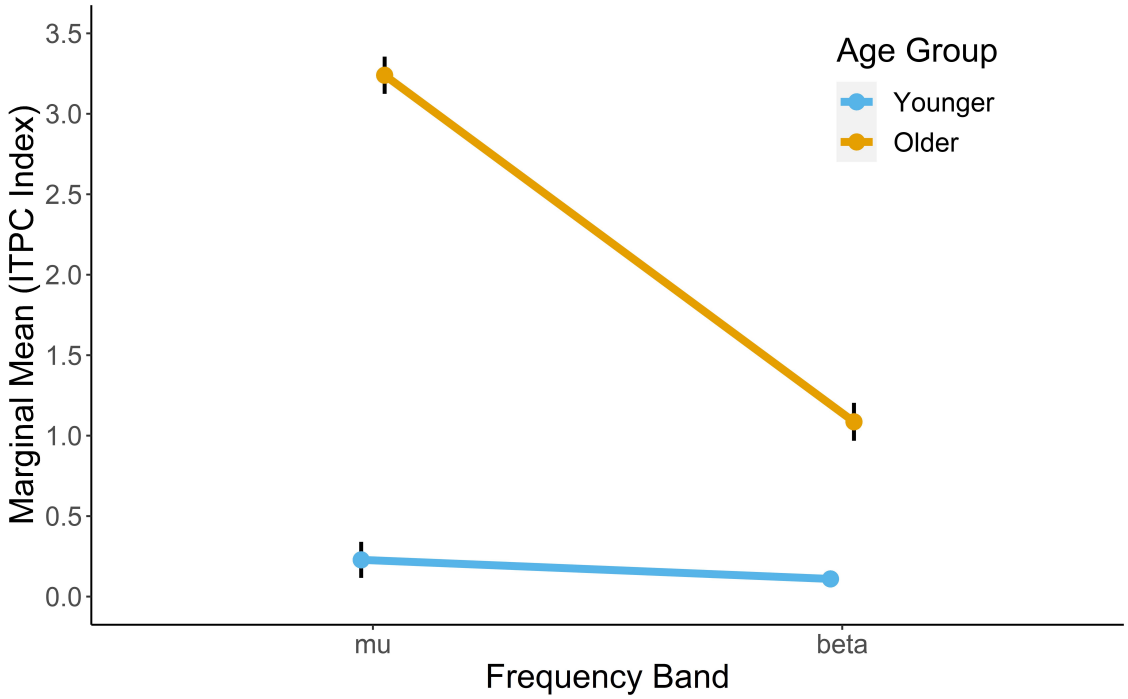

Figure 6.5. The interaction effect between Age Group and Frequency Band. The ITPC index was calculated as the difference between the ITPC of the High Action and Low Action conditions. Positive values indicate that the peak ITPC for the High Action condition was higher than that of the Low Action Condition. The bars represent the 95% Confidence Intervals.

adjusted $p < .001$, Cohen's $f = 0.02$), indicating an effect of hearing status on the ITPC index (see Figure 6.6). Log-ratio power and AUDIT score were also significant covariates for the ITPC index ($F(1, 85) = 42.90$, adjusted $p < .001$, Cohen's $f = 0.03$ and $F(1, 85) = 244.88$, adjusted $p < .001$, Cohen's $f = 0.06$, respectively).

Relationship Between Phase Coherence and Action-Word Finding

Multiple linear regression was performed to test the hypothesis that ageing leads to desynchronisation of neuronal population-level activity (i.e., lower peak ITPC values) associated with action language. As an alternative hypothesis, we stated that neuronal population-level activity in frontocentral brain regions during action language comprehension remains relatively preserved with age and is related to

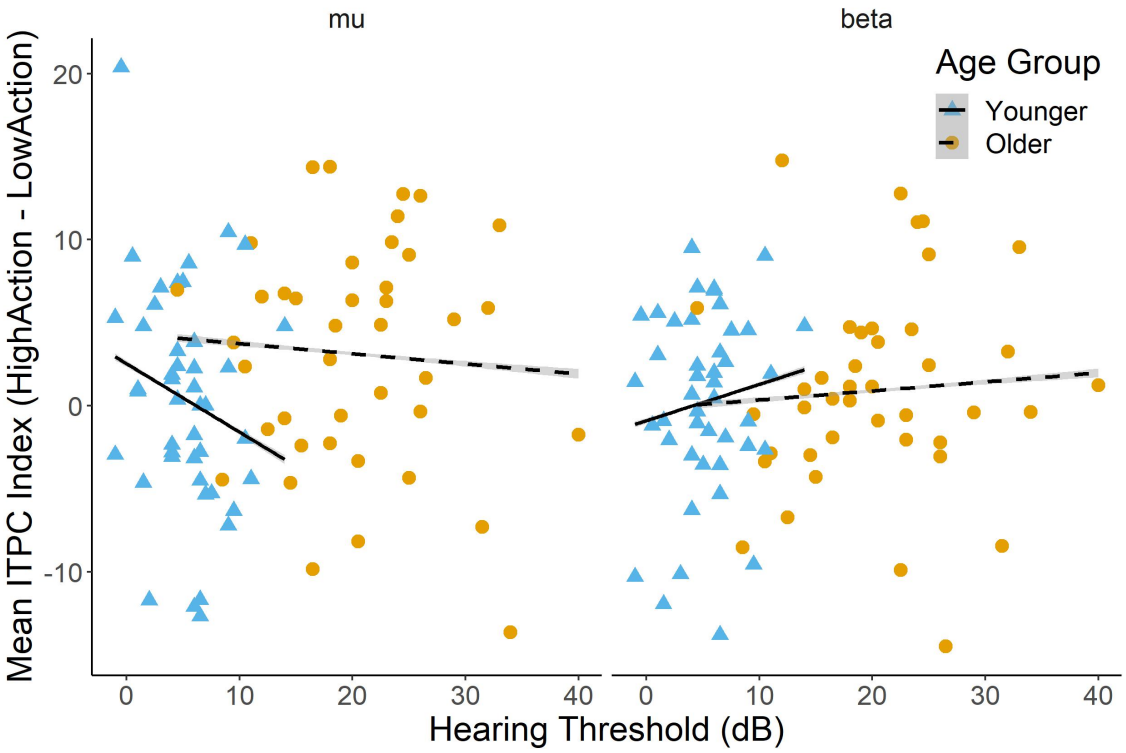

Figure 6.6. The relationship between hearing status and ITPC index per age group and for the mu and beta band separately. Positive values indicate that the ITPC for the High Action condition was higher than that of the Low Action Condition. Hearing thresholds at or below 20dB reflect normal hearing.

preserved action word-finding abilities in older age. The outcome variable was log-transformed reaction time, with peak ITPC *Z*, Frequency Band, and Age Group as predictors, whilst controlling for hearing status, AUDIT scores, and log-ratio power. A Bonferroni correction was applied to account for multiple comparisons. Please, refer to Table 6.1 and Table C.2 for the full results of the analysis.

The results of the linear regression analysis indicated that the predictors explained 15.1% of the variance (R^2=.15, $F(10, 15511)$= 275.4, $p < .001$). Age Group and peak ITPC were both significant predictors of action language comprehension (respectively, β = -0.026, $t(7755)$ = -23.48, adjusted $p < .001$, Cohen's f = 0.37 and β = -0.018, $t(7755)$ = -23.17, adjusted $p < .001$, Cohen's f = 0.13). That is, younger adults had faster reaction times than older adults and higher values of peak ITPC values were associated with faster reaction times. In

addition, hearing status was a significant predictor of the reaction time for action words (β = 0.007, $t(7755)$ = 6.30, adjusted p < .001, Cohen's f = 0.06). The analysis also revealed significant two-way interactions between peak ITPC and Age Group (β = 0.003, $t(7755)$ = 3.87, adjusted p = .001, Cohen's f = 0.02) and a three-way interaction between peak ITPC, Age Group, and Frequency Band (see Figure 6.7; β = 0.003, $t(7755)$ = 3.82, adjusted p = .001, Cohen's f = 0.03).

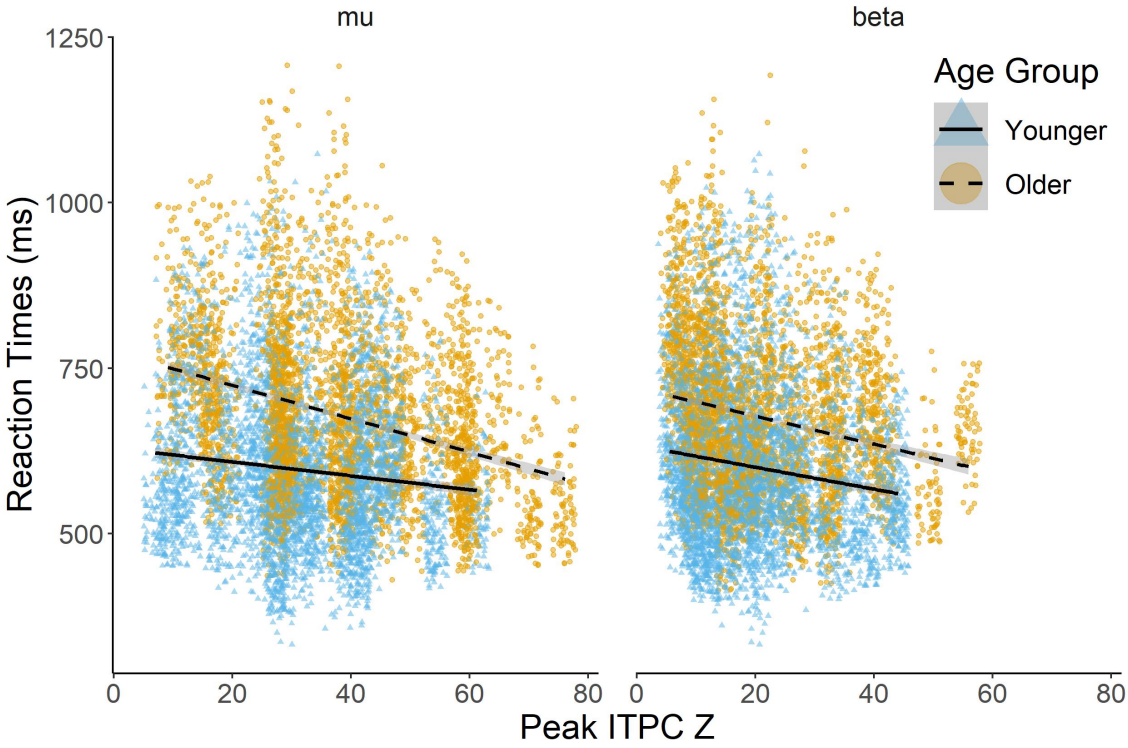

Figure 6.7. The relationship between peak ITPC Z and Reaction Times per age group and frequency band. Higher peak ITPC Z values represent stronger phase coherence.

The significant two-way interactions were further investigated using pairwise comparisons. For the mu frequency band, there was a significant difference in estimated marginal means (i.e., covariate-adjusted means) between younger adults (M = 2.78, SE = 0.002) and older adults (M = 2.83, SE = 0.002; $t(15511)$ = -22.14, adjusted p < .001). The effect size for the comparison between younger and older adults in the mu frequency band was Cohen's d = -0.75 (95% CI [-0.82,

-0.68]). There was also a significant difference in estimated marginal means in the beta band between younger adults (M = 2.77, SE = 0.002) and older adults (M = 2.81, SE = 0.002; $t(15511)$ = -1409, adjusted $p < .001$). The effect size for the comparison between younger and older adults in the beta frequency band was Cohen's d = -0.58 (95% CI [-0.65, -0.52]). Pearson's correlation showed a stronger association between mu peak ITPC and reaction times in older (r = -.33) than in younger adults (r = -.11), where higher mu peak ITPC was associated with faster reaction times (see Figure 6.7). These results indicate that the combined effect of age and peak ITPC on reaction times is similar in both frequency bands. Moreover, the relationship between mu peak ITPC and reaction times is stronger and has a stronger effect in older adults compared to younger adults.

Exploratory Analysis

As per preregistration, we explored the age-related changes in ITPC underlying action word-finding in the temporo-occipital region, to investigate whether the findings of the above ANCOVA analysis were specific to the frontocentral brain region. Mean peak ITPC over the temporo-occipital region for the High-Action condition, in the mu band, was 0.71 (SD = 0.16) for older and 0.74 (SD = 0.13) for younger adults. Mean peak ITPC for the High Action condition, in the beta band, was 0.58 (SD = 0.16) for older and 0.59 (SD = 0.15) for younger adults. For the Low Action condition, mean peak ITPC, in the mu band, was 0.72 (SD = 0.14) and 0.75 (SD = 0.12) for the older and younger adults, respectively. Mean peak ITPC for the Low-Action condition, in the beta band, was 0.59 (SD = 0.14) for older and 0.60 (SD = 0.15) for younger adults. Figure 6.8 shows the distribution of the mean ITPC index, which was calculated as the difference between peak ITPC Z of the High Action and Low Action condition. For the full descriptives of the EEG measures, please refer to Table C.3.

An ANCOVA was conducted to examine the effects of Age Group (younger vs. older) and Frequency Band (mu vs. beta) on the ITPC index, with log-ratio power,

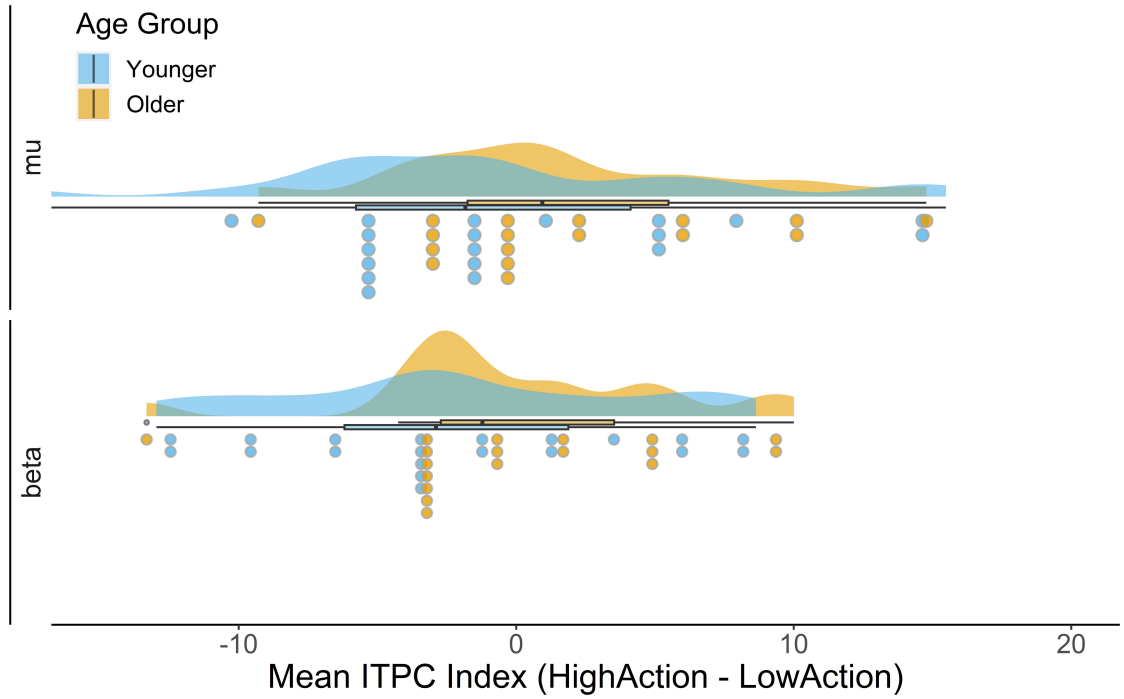

Figure 6.8. The mean ITPC index over the temporo-occipital region per Age Group and Frequency Band. The ITPC index was calculated as the difference between peak ITPC Z of the High Action and Low Action conditions. Positive values indicate that the peak ITPC Z for the High Action condition was higher than that of the Low Action Condition.

hearing status, and AUDIT score as covariates. Here, we will only report the findings of the effects of Age Group and Frequency Band on the ITPC index (refer to Table C.4 for the full results table). To obtain normality of residuals, the ITPC index was transformed by taking the square root. Results revealed significant main effects for Age Group ($F(1,\ 85) = 1036.92$, adjusted $p < .001$, Cohen's $f = 0.19$) and Frequency Band ($F(1,\ 85) = 413.00$, adjusted $p < .001$, Cohen's $f = 0.12$). That is, the ITPC index in the temporo-occipital region differed between younger and older adults, and between the mu and beta frequency bands. The interaction between Age Group and Frequency Band was not significant ($F(1,\ 85) = 6.76$, adjusted $p = .056$, Cohen's $f = 0.02$ see Figure 6.9). That is, the relationship between Age Group and ITPC index did not depend on Frequency Band

For the mu frequency band, pairwise comparisons did not show a significant

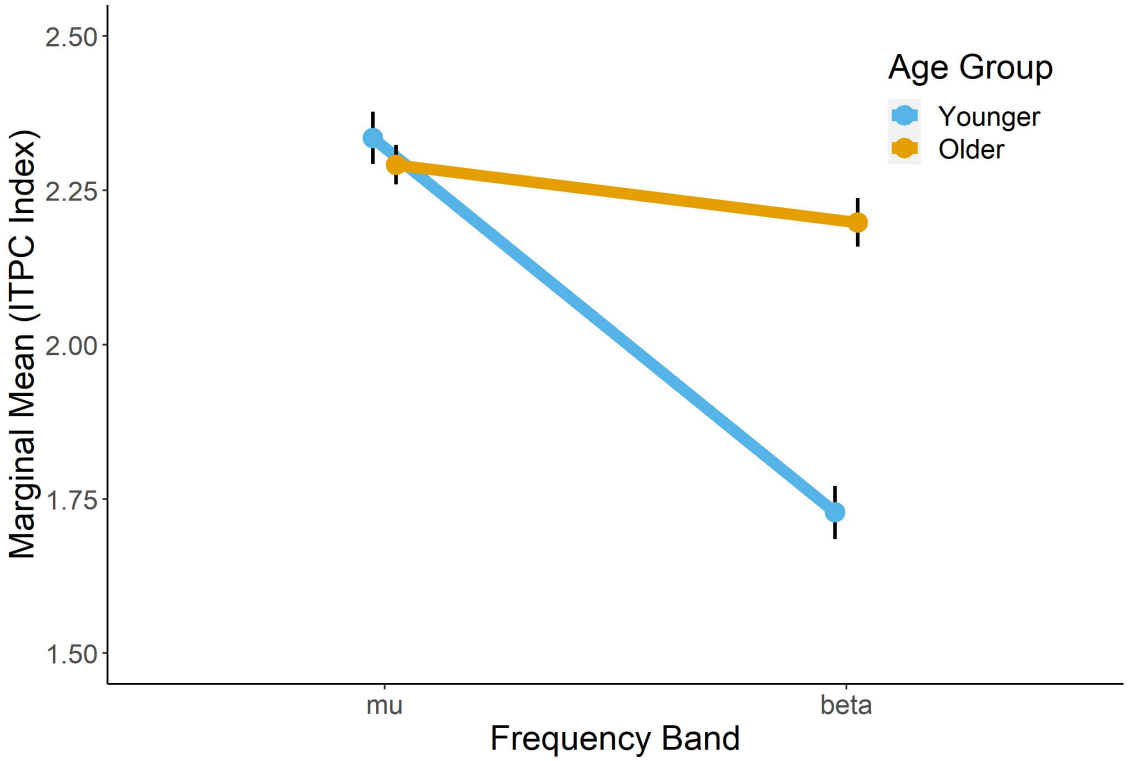

Figure 6.9. No significant interaction effect between Age Group and Frequency Band for the Temporo-Occipital Area. The ITPC index was calculated as the difference between the ITPC of the High Action and Low Action conditions. Positive values indicate that the ITPC for the High Action condition was higher than that of the Low Action Condition. The bars represent the 95% Confidence Intervals.

difference in estimated marginal means (i.e., covariate-adjusted means) between younger adults (M = 2.33, SE = 0.022) and older adults (M = 2.29, SE = 0.016; $t(85) = 1.41$, adjusted $p = .159$). In the beta frequency band, pairwise comparisons revealed a difference in estimated marginal mean for younger adults (M = 1.73, SE = 0.022) compared to older adults (M = 2.20, SE = 0.020; $t(85)$ = -13.50, adjusted $p < .001$). The effect size for the comparison between younger and older adults in the beta frequency band was Cohen's d = -0.54 (95% CI [-0.62, -0.46]). That is, older adults had a significantly higher ITPC index in the beta band than younger adults.

6.5 Discussion

It is currently unclear whether age affects action word-finding ability and whether action features facilitate word retrieval in older adults. Therefore, the current study aimed 1) to replicate the N400 amplitude difference between the high- and low-action words. However, no N400 amplitude difference was found. 2) We also aimed to investigate age-related differences in phase coherence (ITPC) underlying action-word comprehension. We hypothesised an association between neuronal population-level frontocentral brain activity and action words in younger and older adults, predicting a higher ITPC index in the mu but not the beta band during action-word comprehension. The results partially supported this, revealing a higher ITPC index in older compared to younger adults, but in both the mu and beta bands.

Given the uncertainty regarding the impact of age on neuronal population activity underlying action word-finding, we proposed two contrasting hypotheses regarding action word-finding performance. On the one hand, we hypothesised age-related phase desynchronisation underlying action words, predicting a decreased relationship between peak ITPC and action word-finding abilities in older compared to younger adults. On the other hand, we hypothesised preserved phase synchronisation, predicting a preserved relationship between peak ITPC and action-word finding in older and younger adults. Partially supporting the latter hypothesis, the results revealed a positive relationship between peak ITPC and action-word finding in both age groups in both frequency bands, but this relationship was stronger in older than in younger adults.

No Effect of Action Words on N400

Our study did not reveal an N400 amplitude difference between high- and low-action words. This is not in line with a previous study, which observed more positive N400 potentials for action compared to non-action words (Zhao et al., 2017). In the current study, we did not differentiate between grammatical classes but we

focused on the action content. The findings by Zhao and colleagues were also independent of grammatical class, although they utilised an auditory categorisation task (disyllabic words vs. white noise). However, differences in stimuli modality between the two studies (visual vs. auditory) might not explain the lack of an N400 amplitude difference between the high- and low-action words (Kutas & Federmeier, 2011). Alternatively, the lack of an N400 amplitude difference might be because the N400 was computed for only frontocentral electrodes in this study. Different semantic features (e.g., features associated with animals vs. tools) might result in different N400 topographic and amplitude patterns (Barber et al., 2010; Sitnikova et al., 2006). In the study by Zhao et al. (2017), general actionality of nouns and verbs was related to frontocentral brain regions, whilst other studies demonstrated frontocentral N400 for animals but a posterior N400 for manipulable objects (i.e., manipulable objects with high hand/arm actionality) and high-motion verbs (Kellenbach et al., 2003; Sitnikova et al., 2006). Hence, in the current study, a high- vs. low-action N400 amplitude difference may be present over the temporo-occipital instead of the frontocentral brain region.

Finally, the lack of an N400 amplitude difference compared to Zhao et al.'s study (2017) could be caused by differences in how the actionality of the words was determined. The current study utilised a normative database and focused on upper- and lower-limb actions whilst 20 participants rated the actionality of the words independent of body parts. Therefore, the non-action words in our study could still be related to non-limb-related actions and fully differentiating between action and non-action words could reveal the N400 potential differences as observed by Zhao et al. (2017). A normative database seems the preferred option as it provides more objective, normative scores for the action-relatedness of words and makes comparisons across studies feasible. However, future studies should investigate whether the action-relatedness of words is better captured using a normative database or using two distinct categorical groups (i.e., high-action vs. low-action). Although we did not demonstrate an N400 amplitude difference

between high- and low-action words, our results did demonstrate differences in phase coherence between the two conditions. Hence, phase coherence might be a more sensitive measure for the neuronal processes underlying action language. The next sections will discuss the age-related differences in phase coherence underlying action word processing.

Effects of age on the Neuronal Processes Underlying Action Language

Previous studies have offered different explanations of the link between age and action language. That is, the link between action and language may weaken in older age (Bidet-Ildei et al., 2020), or this link remains relatively preserved with age (Reifegerste et al., 2021). The current study revealed stronger frontocentral phase coherence underlying high-action words in the mu frequency band for older compared to younger adults. This finding may indicate that age might alter neuronal activity patterns. That is, neuronal population-level activity associated with action-word comprehension might change with age, which is in line with the notion of age-related differences in action-word processing proposed by Bidet-Ildei et al. (2020).

However, contradicting the idea by Bidet-Ildei et al. (2020) of a weakened age-related action-language link, this study demonstrated increased mu phase coherence for action versus object words in older compared to younger adults, suggesting a stronger link between action and language in older age. Indeed, we demonstrated a stronger relationship between peak ITPC and action-word finding in older compared to younger adults. This finding suggests that the neuronal networks and brain regions underlying action language might still be engaged and effective in older adults, similar to the observations of Reifegerste et al. (2021) and opposing the idea of a decreased link between action and language (Bidet-Ildei et al., 2020).

Phase Coherence as a Compensatory Mechanism

Increased mu phase coherence may also reflect a compensatory mechanism on the neuronal level, in line with phase coherence findings in stroke patients (Gyulai et al., 2021). Increased phase coherence in frontocentral brain regions was stronger during action-word comprehension in older than in younger adults, which may indicate a compensatory strengthening of the link between sensorimotor information and action-word finding in older adults. Akinina et al. (2019) previously proposed that frontocentral brain regions involved in actions might facilitate word-finding. The recruitment of these brain areas might be necessary to maintain action word-finding when faced with age-related brain deterioration, in line with the notion of brain plasticity or reorganisation. Previous studies have found increased phase coherence during a motor task after stroke, which was related to motor performance (Gyulai et al., 2021). Hence, age-related structural brain changes might induce the reorganisation of neuronal networks to maintain action word-finding, reflected by increased mu phase coherence in frontocentral brain regions. Future studies could implement a measure of brain deterioration to test whether age-related brain deterioration leads to increases in phase coherence as a mechanism of compensation.

Several theories of cognitive ageing have also proposed neuronal reorganisation following age-related brain deterioration (see Oosterhuis et al., 2022). One such theory proposes a posterior-to-anterior shift in ageing (PASA) to maintain cognitive functioning in older age (Davis et al., 2008). Greater ITPC index in the frontocentral brain region in older compared to younger adults might reflect a shift in phase coherence from posterior to anterior regions. To explore this idea further, we investigated whether younger and older adults would differ in ITPC index over posterior regions. Notably, younger and older adults did not differ in mu ITPC index over the posterior brain regions, indicating that the increased phase coherence in anterior brain regions is not necessarily the result of a neuronal shift. Instead, neuronal processes in anterior brain regions might reflect oscillatory synchronisation within the sensorimotor regions proposed by Akinina et al. (2019) to facilitate action-

word finding in older age. Hence, increased frontocentral mu phase coherence in older adults might be a form of neuroplasticity through the stronger involvement of sensorimotor brain regions to support action word-finding ability.

Older adults may potentially benefit more from stronger frontocentral phase coherence during action-word finding than younger adults, independent of the frequency band. Higher peak ITPC values in older adults were related to faster reaction times, indicating that phase coherence might be important for maintaining action-word finding ability in older age. If phase coherence in frontocentral brain regions is important for maintaining action-word finding, enhancing phase coherence in low-performing older adults through, e.g., non-invasive brain stimulation might increase action-word finding. Brain stimulation at specific frequencies (such as the mu peak frequency) may increase phase coherence at that specific frequency, however, not many studies have explored this option. One study found that median nerve stimulation at 12Hz increased ITPC over the somatosensory cortex also at 12Hz, indicating that oscillatory phase can be entrained to external stimulation at the same frequency (Houlgreave et al., 2022). Using brain stimulation, it may be possible to entrain the brain to healthy oscillatory rhythms and improve cognitive functioning in older adults with sub-optimal performance (Duchet et al., 2023; Grover et al., 2021). Future research could investigate the potential of brain stimulation over individual mu peak frequencies to improve action word-finding through increased phase coherence.

Age-Related Functional Specialisation

In addition, it has been proposed that lower-frequency phase coherence might reflect age-related functional specialisation of brain regions to increase information processing, due to the stabilisation of neuronal connections (Yordanova & Kolev, 2009; Yordanova & Kolev, 1996). Instead of a compensatory mechanism or a form of age-related brain plasticity, age-related differences in phase coherence in the current study could reflect greater functional specialisation of action-word processing in

older adults compared to younger adults. Moreover, it is possible that lower- but not higher-frequency phase coherence reflects functional specialisation. That is, mu but not beta phase coherence will reflect functional specialisation. However, the age-related difference in phase coherence between younger and older adults was present in both the mu and beta frequencies, although the difference was greater in mu compared to beta. Hence, both higher- and lower-frequency phase coherence might be reflective of age-related functional specialisation of action-word processing. Future studies should investigate whether such patterns are also observed in delta and theta frequencies.

Influence of Hearing Status

Hearing loss can affect a wide network of brain regions underlying language processing, including frontal brain regions (Peelle et al., 2011). Therefore, hearing status was added as a covariate in the current study. The results showed that hearing status affected phase coherence. More specifically, we revealed that lower hearing acuity was related to lower mu and beta band ITPC index in both age groups. Few studies have demonstrated that hearing loss across the lifespan is related to phase coherence. In children with hearing loss, ITPC decreased with increasing hearing loss (Nash-Kille & Sharma, 2014). In older adults, hearing loss was also associated with decreased phase coherence (Farahani et al., 2022). Hence, it is possible that changes in hearing acuity could affect the neuronal responses and synchronisation of cortical phases, and may affect cognitive functions that are (partially) dependent on phase coherence. However, the causal link between age-related hearing loss and neuronal changes is still under investigation (Slade et al., 2020).

This study adds that lower hearing acuity in both younger and older adults is related to differences in phase coherence patterns, specifically in frontocentral brain regions and the mu frequency band, underlying action, and object word-finding. Moreover, lower hearing acuity might be related to slower word-finding in older adults. Hence, phase coherence might be an important factor in hearing loss, or vice

versa, across the lifespan and may be related to word-finding difficulties in people with age-related hearing loss. However, our findings on the effects of hearing loss on phase synhronisation and subsequent cognitive decline may be limited. Previous research has shown that the relationship between hearing loss and cognition could be confounded by factors, such as poor health, age-related neurodegeneration, and even cardiovascular disease (Fischer et al., 2016; Slade et al., 2020; Xie et al., 2019). Despite these potentially confounding factors, hearing loss may increase the risk of dementia slightly (Ford et al., 2018). Therefore, incorporating a measure of hearing status is important when investigating the neuronal processes underlying age-related cognitive decline. Future studies should further investigate the links between phase coherence, hearing status, and subsequent impact on word-finding ability across the lifespan whilst considering potentially confounding factors.

Limitations

Evidence indicates that ITPC can be influenced by several factors other than the cognitive measure under investigation (van Diepen & Mazaheri, 2018). Such factors include stimulus expectation, whereby ITPC can increase before the onset of a predictable stimulus. In the current study, we generated temporal uncertainty by introducing random durations of the fixation cross and blank screen throughout the experiment. This way, the participant could not predict the timing of the stimulus unconsciously. Moreover, we only investigated ITPC values within a fixed time window of 250ms to 500ms, removing pre- and early-stimulus ITPC. Another factor that can greatly influence ITPC is differences in oscillatory power, which can lead to significant differences in ITPC between conditions (van Diepen & Mazaheri, 2018). To account for power differences, oscillatory power was included as a covariate in our analyses. ITPC can also be influenced by both temporal jitter and the number of trials (Cohen, 2014). Therefore, we used a computer screen with a very high refresh rate (144Hz) to reduce temporal jitter. We also only included EEG data with 40 or more epochs available per condition per participant and transformed the

peak ITPC using Rayleigh's Z (Cohen, 2014).

Furthermore, we chose to use the log ratio power between the mu and beta bands to account for individual differences in scalp thickness and electrode impedance (Moreno et al., 2013; Pineda & Oberman, 2006). Finally, mu rhythms can be contaminated by the occipital visual alpha rhythms (Hobson & Bishop, 2016, 2017). To address this issue, our region of interest was set to the frontocentral brain regions as alpha rhythms are more related to posterior brain regions while mu is generated by anterior sensorimotor regions (Fox et al., 2016; Hari et al., 1997). In addition, because mu and alpha signal peak at the same frequencies, we also investigated ITPC values computed from the beta band frequency (Fox et al., 2016). Because of the potential confounding effects of a multitude of other factors on ITPC and mu brain rhythms, it is important that future studies account for these influencing factors and run replication studies to confirm previous findings.

The age-related difference observed in the present study might not be driven by action-related language and other cognitive functions; for example, attentional processes might have played a role. Although this is a possibility, we found that frontocentral brain regions elicited stronger mu phase coherence during the high-action compared to the low-action condition in older adults, as reflected by a positive ITPC index. However, high-action words may also be more difficult to process than low-action words due to different cognitive processes involved, especially in older adults (Oosterhuis et al., 2023; Szekely et al., 2005). Increased cognitive effort might consequently require the recruitment of more cognitive resources such as attentional and working memory resources (Grady, 2012). Although we cannot exclude the possibility that the greater ITPC index in older adults reflected successful recruitment of additional cognitive resources, our findings provide evidence for the importance of mu phase coherence in frontocentral brain regions for fast action-word finding ability with increasing age. Future studies should explore the importance of frontocentral mu phase coherence for the successful recruitment of additional cognitive resources in older adults.

Conclusion

This study aimed to investigate age-related differences in ITPC underlying action word-finding. The results showed that older adults exhibited higher mu phase coherence than younger adults for action words compared to object words. Higher frontocentral mu and beta phase coherence predicted faster reaction times in both younger and older adults, but this relationship in the mu band appeared to be stronger in older adults with stronger correlations in older compared to younger adults. Furthermore, younger and older adults did not differ in mu ITPC index over the posterior brain region. Hence, healthy ageing might be associated with increased mu phase coherence in anterior brain regions to support complex cognitive functions, such as action word processing. Involvement of motor-related brain regions may also support action word-finding in older adults. Finally, because the covariate hearing acuity significantly predicted phase coherence in this study, hearing acuity might be an important factor in phase coherence underlying successful action word-finding ability. Hence, future studies investigating neuronal and/or language processes should ideally incorporate a measure of hearing status.

Chapter 7

General Discussion and Conclusions

7.1 General Thesis Overview

While some individuals manage to reach an advanced age (Beker et al., 2021), others may develop dementia, with over 50 million people living with dementia worldwide (Alzheimer's Disease International et al., 2020). It has become increasingly clear that research needs to consider individual ageing trajectories, as lifestyle choices and lifetime experiences throughout the lifespan can modify the risk for dementia (Livingston et al., 2020). Therefore, this thesis aimed to investigate the neurobiological and lifestyle contributions to healthy cognitive ageing. Because older adults recognise word-finding difficulties as one of the most prominent problems with ageing, this thesis specifically focused on word-finding ability. We explored both lifestyle choices and lifetime experiences as well as neural coherence patterns underlying word-finding ability across the lifespan.

With regard to lifestyle contributions to general cognitive ageing, Chapter 2 discussed two prominent cognitive ageing accounts, namely STAC-r (Reuter-Lorenz & Park, 2014) and CR (Stern et al., 2020), and evaluated which aspects of cognitive ageing are best explained by either STAC-r or CR. Both theories stress the importance of a healthy lifestyle to mitigate age-related decline. However, CR is unclear about what lifestyle factors and lifetime experiences should be used

to measure CR levels and whether CR can be accumulated across the lifespan. These literature gaps were further addressed in research Chapters 3 and 4, which investigated the effects of CR on word-finding ability in healthy younger, middle-aged, and older adults, and in individuals with PD. Furthermore, both STAC-r and CR recognise the influence of brain function to maintain cognitive performance in older age, for example, through increased brain activity or increased efficiency and flexibility of functional brain networks (Chapter 2). However, the interplay between brain function and word-finding ability, and how this interplay changes with age is currently unclear. Therefore, Chapters 5 and 6 investigated the relationship between brain function and word-finding ability in younger and older adults through EEG functional connectivity and time-frequency analyses.

Finally, many words describe either objects or actions, each engaging distinct neural mechanisms (Mätzig et al., 2009; Moseley & Pulvermüller, 2014; Vigliocco et al., 2011). Specifically, the brain's motor regions are activated during action word-finding (Akinina et al., 2019). It remains unclear whether individuals experience age-related difficulties in either object or action word-finding or both. Chapters 3 and 4 investigated the impact of lifestyle on word-finding, separately addressing object and action words, across the lifespan and in PD.

Furthermore, both verbs and nouns possess action-related features (Kellenbach et al., 2003), which can be quantified through actionality ratings, indicating to what extent a word is associated with human bodily actions. However, previous studies often implemented dichotomous categories, such as high- versus low-action words, without considering specific body parts involved in physical actions. As a result, it remains unclear whether age-related action word-finding difficulties depend on the body parts involved, whether a relationship between age and action word-finding difficulties depends on the actionality ratings of the words, and whether such a relationship is related to physical motor ability. Therefore, Chapters 4 and 6 further investigated the relationship between upper-limb actionality of words and word-finding ability in the context of healthy ageing and PD. Given the challenges

that individuals with PD face in terms of bodily movement, 4 also investigated the relationship between upper-limb motor abilities and word-finding difficulties of words that describe upper-limb movements in individuals with and without PD.

In the next sections, this discussion chapter will provide a summary of the main findings for each of the empirical chapters, after which we will discuss these main findings and their implications using the following themes: lifestyle contributions to word-finding ability across the lifespan, neurobiological contributions to word-finding ability across the lifespan, and action language and its relationship to ageing. Finally, the limitations and future directions of this thesis will be discussed.

7.2 Lifestyle Contributions to Word-Finding Ability Across the Lifespan

Summary of Main Findings

In Chapter 3, we examined the effects of CR on word-finding by investigating how CR affects age-related declines in word-finding ability, whilst also differentiating between object and action language. The study showed that age affected word-finding ability and middle-aged adults with higher CR scores achieved greater object and action naming accuracy. In older adults, we did not find a relationship between higher CR scores and better word-finding ability. Chapter 4 discussed word-finding ability in a population with a neurodegenerative disease, namely PD, and whether CR mediates action word-finding ability. We demonstrated that CR was not related to greater word-finding ability in older adults or in individuals with PD.

Cognitive Reserve in Healthy Ageing

The review Chapter 2 highlighted the abundance of research studies showing that positive lifestyle factors, such as education and engaging in a variety of activities, are crucial contributors to maintaining cognitive ability in older age. In Chapters 3 and

4, we included several lifestyle factors to create a comprehensive measure of CR. This included early-life CR through years of education, midlife CR through occupational attainment, and late-life/current CR through a general activities questionnaire, capturing leisure, cognitive, and physical activities. However, neither Chapter 3 nor Chapter 4 provided evidence of CR as a contributing factor for maintaining word-finding ability in older adults. In contrast, middle-aged adults did seem to benefit from greater CR scores during the word-finding ability tasks. Hence, CR may mediate word-finding difficulties in middle-aged but not in older adults.

One of the outstanding questions discussed in Chapter 2 was whether CR is a resource that can be built throughout the life span (Grotz et al., 2017), or whether CR can only be acquired before a certain age (Chan et al., 2018). The results of this thesis seem to be in favour of the latter idea that CR must be built before entering into older age. That is, engaging in a variety of different activities after the age of 60 might not contribute to greater CR that would facilitate word-finding ability. In middle-aged adults, current CR through engaging in activities was measured before the age of 60, whilst for older adults, current CR was measured after the age of 60. It is possible that if we had measured the engagement of activities throughout the lifespan in older adults, CR could have been a significant predictor of word-finding ability in older adults as well. However, methodological problems arise when asking older adults about the frequency of activities they participated in during early and mid-life as these activities can be forgotten or under-/overestimated.

Cognitive Reserve in Parkinson's Disease

CR has been hypothesised to decrease the impact of dementia-related diseases, such as PD, on cognition (Stern, 2009; Stern et al., 2020). Previous research has shown better cognition, including word-finding ability, in individuals with PD with high CR (e.g., Ciccarelli et al., 2018; Hindle et al., 2016). The study in Chapter 4 was the first to investigate the effects of CR on action word-finding ability in individuals with PD. The findings of this study, however, did not support the role of CR in

maintaining word-finding ability in individuals with PD. The participants in this study were all older adults and it is possible that engaging in activities later in life does not enable individuals with PD to compensate for their word-finding difficulties as was discussed in Section 7.2.

In addition, the impact of CR on cognition may differ between individuals with PD and healthy ageing, with CR positively influencing semantic fluency in healthy older adults but not in PD (Rouillard et al., 2017). Indeed, Hindle et al. (2016) and Guzzetti et al. (2019) revealed no effect of education, occupational attainment, or engagement in leisure activities on verbal fluency and language tasks in individuals with PD. However, these two studies had not included a healthy ageing group, so no conclusions could be made as to whether these findings are specific to PD or would also been observed in healthy older adults. Moreover, Chapters 3 and 4 together failed to show a relationship between CR and semantic fluency in both individuals with PD and healthy older adults. That is, this thesis did not reveal a different pattern of CR contributions between healthy older adults and individuals with PD. Hence, this thesis adds to the literature that a comprehensive measure of CR does not seem to predict word-finding ability in either individuals with PD or healthy older adults.

Implications

A shortcoming of CR theory is that it is currently unclear as to what lifestyle choices and lifetime experiences would help build CR and whether different proxies weigh equally (Borgeest et al., 2020; Oosterhuis et al., 2022). For example, education might be a stronger predictor than leisure activities for late-life cognition. In more general terms, there is currently no consensus as to what lifestyle choices are of importance in maintaining cognitive ability into older age. STAC-r argues for the inclusion of adverse factors when investigating the factors involved in cognitive ageing (Reuter-Lorenz & Park, 2014). Hence, a consensus is of paramount importance to disentangle what lifestyle choices counteract age-related cognitive decline and to what extent.

This thesis attempted to create a comprehensive measure of CR, covering early-life, midlife, and late-life lifestyle choices and lifetime experiences. Consequently, this thesis adds to the literature that a comprehensive measure, where the different CR proxies (e.g., years of education) are equally weighted in importance, does not predict word-finding ability in either older adults or individuals with PD. However, this comprehensive CR could predict cognitive performance in middle-aged adults. Future studies investigating the effect of CR, or lifestyle choices in general, on cognition should include a middle-aged group to confirm the findings of this thesis.

Moreover, the findings in Chapters 3 and 4 imply that positive lifestyle choices and lifetime experiences may be important before we are 60 years old. It is likely that brain deterioration, either due to normal ageing processes or in the case of neurodegenerative diseases, starts before the symptoms of cognitive decline. This would mean that healthy lifestyle choices and lifetime experiences should be implemented from a very young age. For example, engaging in physical activity during the teenage years might benefit cognition in older age more strongly than engaging in physical activity at an older age (Reas, Laughlin, Bergstrom, Kritz-Silverstein, & McEvoy, 2019; Reas, Laughlin, Bergstrom, Kritz-Silverstein, Richard, et al., 2019). However, relying on participants to recall their frequency of engagement in activities from over 40 years ago may not offer a suitable and objective measure.

Considering the way CR may be established prior the age of 60, it becomes imperative to mitigate dementia risk through positive lifestyle choices from a younger age. Therefore, this thesis holds significant implications for education and policies. Firstly, education should promote healthy lifestyle choices, including engaging in a diverse range of activities, to children, adolescents, and parents/caregivers. Secondly, policies to improve public health and decrease the rising numbers of dementia cases should be aimed at younger adults and stress the importance of early life choices for later life. Lastly, attending higher education seems to be an important factor in healthy cognitive ageing (see Oosterhuis et al., 2022). Therefore,

attending higher education could be made more accessible and should be promoted in both younger and middle-aged adults.

As STAC-r highlights, cognitive ageing is the result of complex interactions of different factors, including overall brain status (Reuter-Lorenz & Park, 2014). Therefore, neurobiological factors might be a stronger contributing factor to age-related word-finding difficulties. Hence, the next sections will discuss what the thesis adds to the current literature on the neurobiological contributions of age-related word-finding difficulties.

7.3 Neurobiological Contributions to Word-Finding Ability Across the Lifespan

Summary of Main Findings

We investigated the neurobiological contributions to word-finding by investigating a neurodegenerative disease, namely PD, and by focusing on neuronal phase coherence measured through EEG. Including a clinical population with a neurodegenerative disease, Chapter 4 revealed a positive relationship between upper-limb motor ability, assessed through a keyboard-tapping task, and word-finding in both individuals with and without PD. That is, participants with more keyboard tabs also achieved faster picture-naming speeds and were able to generate more words on the verbal fluency tasks.

Using EEG, Chapter 5 examined the relationship between resting-state functional brain networks, measured through phase coherence, and age-related word-finding difficulties. We showed that age-related increases in delta band functional connectedness were related to lower semantic fluency. Older adults with greater delta band functional brain integration (i.e., global network efficiency) achieved higher semantic fluency scores. Regarding functional brain segregation (i.e., local network efficiency), irrespective of age, higher alpha band modularity predicted lower

and greater delta band small-world index predicted higher semantic fluency scores. Hence, we found age-related changes in both the overall functional connectedness and global network efficiency, the latter being important for maintaining word-finding ability in older age.

Through time-frequency analyses, Chapter 6 investigated the relationship between age, phase coherence time-locked to high- and low-action words, and action word-finding ability. ITPC analyses revealed that older adults have greater frontocentral phase coherence in the mu and beta band underlying action words than younger adults. Greater frontocentral phase coherence was related to faster action-word processing in both younger and older adults. Exploratory analyses did not reveal an age group difference between mu band temporo-occipital phase coherence.

As discussed in the review in Chapter 2, STAC-r proposed that compensatory scaffolding, essentially a form of neuroplasticity, can happen through a range of different brain processes, such as increased engagement of frontoparietal brain regions, increased connectivity, and the recruitment of new brain regions. These brain processes are hypothesised to maintain the level of cognitive functioning and slow down the rate of cognitive decline. Here, we will discuss the potential of functional connectivity measured through phase coherence, time-locked phase coherence, and basal ganglia involvement as compensatory mechanisms of word-finding difficulties.

Neurobiological Changes as Compensatory Mechanism?

This thesis has demonstrated several links between phase coherence and word-finding ability in older adults. Chapter 2 briefly touched on several theories that propose age-related functional shifts in brain activity, such as more bilateral (i.e., HAROLD Cabeza, 2002) and frontal processing (i.e., PASA; Davis et al., 2008), to maintain cognition in older age. That is, age-related changes in functional brain processes would reflect compensatory changes. We discussed different mechanisms throughout this thesis, namely: changes in functional brain networks, increased frontocentral

phase coherence in older adults, and frequency band shifts. Below we will discuss whether the mechanisms reported in this thesis would be age-related compensatory contributions to word-finding ability. Following the PD study, we will discuss a theoretical role of the basal ganglia in word-finding in a separate section.

Chapter 6 revealed greater mu phase coherence underlying action word-finding in frontocentral regions compared to younger adults but no such age difference was found for mu phase coherence in the temporo-occipital regions. In this thesis, we discussed the possibility of a PASA-like shift in phase coherence. Originally, the PASA predicts that posterior brain activity decreases whilst anterior brain activity increases, and this posterior-to-anterior shift in brain activity enables older adults to maintain cognitive performance despite age-related brain deterioration (Davis et al., 2008). In this thesis, we only observed a partial posterior-to-anterior shift in coherence. That is, phase coherence might increase in frontocentral brain regions with age to support word-finding, whilst phase coherence in posterior brain regions remains relatively unchanged. Evidence for frontal phase coherence as a compensatory mechanism comes from the finding that greater mu phase coherence was related to faster word-finding, an effect which was more pronounced in older compared to younger adults (Chapter 6). However, the study did not compare the anterior and posterior phase coherence directly. Hence, future studies should further explore the possibility of a compensatory PASA in phase coherence underlying word-finding ability.

Chapter 5 found strengthened functional connectedness with age and a positive relationship between characteristic path length, reflective of long-ranged neuronal connections, and semantic fluency performance in older adults. Hence, brain integration may increase in older age and such integrated networks may benefit older adults during word-finding. In addition, we found that increased overall functional connectedness in the delta band was related to lower word-finding ability, but only in older adults. Increased whole-brain functional connectedness could potentially be a result of compensatory brain processes. However, increased

overall connectedness was related to decreased word-finding ability in this thesis. Since the study looked at whole-brain connectivity, we did not consider differences in functional connectedness dependent on brain region. Considering frontal and posterior functional connectedness separately might have revealed a beneficial compensatory increase in functional connectedness in the frontal brain region, which was previously shown in Fleck et al. (2016).

In contrast, increases in delta functional connectedness may be reflective of a maladaptive or failed compensatory process, leading to worse word-finding ability in individuals with greater delta functional connectedness. Examples of maladaptive processes discussed in this thesis were that of hyper synchronisation and a pathological shift to less functional brain rhythms (here, a shift to delta frequencies). Neuronal hypersynchronisation has been shown in pre-clinical Alzheimer's disease, affecting whole-brain network configurations (Alexandersen et al., 2022; Stam et al., 2023; van Nifterick et al., 2022). Hence, greater delta functional connectedness in Chapter 5 may potentially reflect pre-clinical Alzheimer's disease. However, increased age-related increases in phase coherence do not always have to be maladaptive, as was shown in Chapter 6, where we observed a potential beneficial compensatory role of the frontocentral brain region. Hence, distinguishing between brain regions when investigating functional connectedness could reveal more specific age-related compensatory processes in functional brain networks.

Finally, it is possible that changes in functional brain networks and increased frontocentral phase coherence reflect functional specialisation instead of either compensatory or pathological processes. Some of the findings discussed in Chapters 5 and 6 may be explained by functional specialisation of the language network due to the stabilisation of, especially low-frequency, neuronal connections or brain maturation (Yordanova & Kolev, 2009; Yordanova & Kolev, 1996). Vértes and Bullmore (2015) argued that high brain efficiency might depend on some long-ranged neuronal connections to integrate information across brain regions that are anatomically remote. Such efficient, integrated networks might result from brain

maturation from childhood to adolescence and further across the lifespan, leading to an increased small-world index (Boersma et al., 2011; Smit et al., 2012).

Contributions of the Basal Ganglia to Word-Finding

Whilst motor difficulties are core clinical symptoms in PD, word-finding difficulties have also been reported (Aarsland et al., 2021; Camerino et al., 2022; Postuma et al., 2015). It is important to note that we did not reveal a difference between the PD and control groups for any of the word-finding ability measures. However, we did reveal a positive relationship between upper-limb motor ability and word-finding ability in healthy older adults and individuals with PD. Moreover, this relationship seems to diminish in individuals with PD, which is potentially related to a dysfunction of the basal ganglia and its connections to the cortex. Below, we will discuss the role of the basal ganglia in word-finding. Since no subcortical neuroimaging was conducted in this study, the arguments discussed below should be approached with caution. Nonetheless, the ideas that we will outline can serve as hypotheses for future studies exploring the role of the basal ganglia in maintaining word-finding abilities throughout the lifespan.

In individuals with PD, dopamine loss leads to over-inhibition of the GPe (see Figure 1.3), potentially decreasing cognitive performance (McGregor & Nelson, 2019). However, the exact mechanism linking impaired GPe-cortical function to cognitive impairments in PD remains unknown. Dopamine medication may partially restore the functioning of the GPe as a complex hub (Dong et al., 2021), consequently restoring cognitive functioning in individuals with PD (Letanneux et al., 2021). This idea could explain the non-significant interaction between motor ability and group for predicting word-finding ability after correcting for multiple comparisons in Chapter 4. Hence, non-responsiveness to dopamine medication may exhibit weaker relationships between motor ability and word-finding ability.

In addition, different tasks may engage different neuronal circuits from the basal ganglia to the frontal cortices may be engaged or, alternatively, the same circuits

may be engaged during various cognitive functions (see Copland et al., 2021, for a review). The same corticostriatal circuits may be involved to achieve faster naming and keyboard-tapping speeds, as was observed in Chapter 4. In individuals with PD, a dysfunction of such circuits could lead to impairments of cognitive functions, such as that of word-finding and motor abilities. As the severity of the disease increases, motor ability and word-finding may start engaging different corticostriatal loops or different brain regions, such as Broca's area, to maintain cognitive functioning (Auclair-Ouellet et al., 2017; Dagher et al., 2001; Ekman et al., 2012; Nagano-Saito et al., 2014; Péran et al., 2009; Sabatini et al., 2000). This idea would also support Copland and colleagues's (2021) proposal that specific corticostriatal loops are engaged based on task demands. Hence, in PD, dopaminergic deficits in the frontostriatal pathways may induce neuroplasticity, leading to the recruitment of alternative or additional neural circuits or brain areas, depending on the cognitive functions being assessed (in this thesis, motor ability vs. word finding).

Implications

This section discussed the potential role of compensatory and maladaptive neurobiological processes underlying word-finding ability in younger and older adults. This thesis showed a link between the small-world index and semantic fluency across the lifespan, demonstrating that the efficiency of networks is important for word-finding in both younger and older adults. The network configuration underlying the small-world index may, however, differ between the two age groups. Future studies should explore different patterns in functional brain network organisations.

We also discussed the potential of functional specialisation that could explain age-related changes in phase coherence. For example, increased frontocentral phase coherence may reflect an age-related functional specialisation of frontocentral regions in action word-finding. That is, brain maturation may result in groups of neurons in the frontocentral regions specialising to support action word-finding, whilst

the neuronal communication underlying action word-finding is more distributed in younger adults. An important but theoretical implication of this thesis is that ITPC may reflect the functional specialisation of brain processes with age. This argument should, however, be interpreted with caution as ITPC has not yet been specifically identified as a measure of functional specialisation, although increased ITPC was found in children as a function of brain maturation (Yordanova & Kolev, 2009). Future studies should further explore ITPC underlying a range of cognitive functions across the lifespan to investigate its potential role in functional specialisation. Furthermore, ITPC may be used as a measure of compensatory and pathological brain processes and future studies should investigate ITPC underlying a range of cognitive functions in both healthy ageing and neurodegenerative diseases.

In addition, the changes we observed in Chapters 5 and 6 were specific to the frequency band. Oscillatory activity underlies different cognitive functions, depending on the frequency of oscillations (Başar et al., 2001; Klimesch et al., 2007). For example, alpha band frequency is important for attentional control. This thesis implies that delta frequencies are important in explaining word-finding abilities across the lifespan but also in explaining age-related word-finding difficulties. Previous studies have identified delta functional connectedness as an important marker of MCI (Cai et al., 2021; Chaturvedi et al., 2019). If increased functional connectedness at the delta frequency range reflects a pathological process, then delta functional connectedness may serve as a neurobiological marker for pre-onset dementia.

Finally, this thesis implies theoretical functional changes in the basal ganglia following PD. Future research should explore the role of dopamine in the functioning of the GPe as a complex hub further, by including individuals with PD who are off dopamine medication or who are dopamine-resistant. In addition, deep brain stimulation can be used to investigate if the domain-general GPe can restore the connection between the GPe and cortex, and subsequently strengthen the relationship between motor ability and word-finding ability. Investigating the GPe's

involvement in action language and motor ability would help confirm its domain-general function during such tasks and clarify the effects of basal ganglia circuit dysfunction in PD. Currently, the findings of this thesis bring us a little step closer to developing new approaches to treatments by providing insight into different problems and characteristics of individuals with PD.

7.4 Action Language and Its Relationship to Ageing

Summary of Main Findings

A novel contribution of this thesis is that we made an explicit distinction between action and object language, as studies have shown that different neural networks and brain regions are involved in action and object language (Akinina et al., 2019; Mätzig et al., 2009; Moseley et al., 2013; Vigliocco et al., 2011). Moreover, action words might require more cognitive resources than object words (Szekely et al., 2005). This section will briefly discuss the findings of the thesis that were specific to action language, as well as the implications for cognitive ageing.

The behavioural study discussed in Chapter 3 revealed an age effect on both object and action naming accuracy, and faster object naming speeds in younger and middle-aged adults than older adults, but no age effect for action naming speed. The accuracy of object naming was higher than that of action naming, but this was across all age groups. Chapter 4 investigated action language further and investigated whether we can distinguish individuals with PD from healthy controls through upper-limb action word-finding ability. The study revealed no differences in action word-finding ability between individuals with PD and healthy controls. Finally, Chapter 6 investigated the effects of age on neuronal coherence underlying action word perception. We demonstrated that the N400 amplitude did not differ between high- and low-action conditions. Moreover, action words elicited greater

frontocentral mu phase coherence than object words, which was more pronounced in older than younger adults. The next section will discuss the relationship between age and action language, and the implications of our findings.

Implications: Preservation of Action Language in Older Age and Parkinson's Disease

One important question investigated in Chapter 6 was whether action word processing stays relatively preserved with age. Moreover, Chapters 3 and 4 revealed relatively preserved action word-finding in healthy older adults and in individuals with PD. Finally, this thesis showed that the neuronal processes underlying action language are still effective in older adults and may even increase with age. Together, these findings are indicative of maintained action word processing in older adults, compared to object word processing and younger adults.

Chapter 2 briefly touched on different cognitive ageing theories, which argue that age-related cognitive declines are the result of a decline in general cognitive resources (Hasher & Zacks, 1988; Salthouse, 1990, 1996). Action words have been argued to engage more cognitive resources (Szekely et al., 2005) and should be more difficult with age if the cognitive resources are limited in older adults. The increases in frontocentral phase coherence underlying action words in older compared to younger adults in Chapter 6 may reflect more neuronal effort as a function of limited cognitive resources. In contrast, increased phase coherence may reflect a compensatory shift or functional specialisation of neuronal populations as was discussed in Section 7.3. Hence, it is currently unclear whether increased phase coherence underlying action language reflects increased neuronal effort, functional specialisation, or a compensatory shift. Future studies should explore these options further.

This thesis does not support the idea that individuals with PD have specific difficulties with upper-limb action words. Therefore, the current findings advance the knowledge of action word-finding in individuals with PD through better

understanding and recognition of the problem. It is of paramount importance that new neuropsychological markers of PD are determined for a timely diagnosis (Delenclos et al., 2016) but action word difficulty may not serve as a sensitive clinical marker. Compensatory mechanisms in the basal ganglia and cortex may enable individuals with PD to maintain action word-finding. As the disease progresses, these compensatory processes may break down and result in action word-finding difficulties. Future studies should investigate these compensatory processes, such as the involvement of Broca's area, in individuals with PD across different disease stages.

7.5 Thesis Limitations and Challenges

One major limitation is that this thesis did not investigate the relationship between word-finding ability and neurobiological and lifestyle contributions. Since both scaffolding and CR are hypothesised to increase neural efficiency (Reuter-Lorenz & Park, 2014; Stern et al., 2020), lifestyle factors and lifetime experiences, such as years of education, could mediate the relationships we found between age, word-finding ability, and phase coherence (both functional connectivity and ITPC). Due to the impact of COVID-19-related restrictions, we were not able to investigate the link between lifestyle choices and functional brain processes underlying word-finding ability across the lifespan and in PD. The study discussed in Chapter 5 was a secondary data analysis and, hence, sufficient data on lifestyle factors, including education, was not available. For the study in Chapter 6, no data was collected to investigate the influence of lifestyle factors due to limited monetary and time resources but focused on the neurobiological contribution of phase coherence to word-finding abilities. This decision meant we could reduce the number of predictors in our models whilst achieving high statistical power.

Despite this methodological limitation, participants were screened for substance abuse, cognitive impairment, and depression as these factors can impact negatively

brain functioning (see Chapter 2). That is, participants were considered "healthy" within these areas. Moreover, we were able to investigate the lifestyle contributions to word-finding ability in a population affected by neurodegeneration. Unfortunately, we were not able to directly measure overall brain status in PD. Including direct measures of brain deterioration (e.g., grey matter volume) and functional connectivity measures will provide a more holistic view of the factors contributing to healthy cognitive ageing.

In addition, the studies included in this thesis were all cross-sectional. Many different neurobiological and lifestyle factors are involved in healthy cognitive ageing depending on the individual, stressing the importance of considering individual ageing trajectories (Oosterhuis et al., 2022; Oosterhuis et al., 2023). Longitudinal study designs are important when investigating individual ageing trajectories, however, such study designs are methodologically challenging due to time and monetary constraints, and high attrition rates. The increase in longitudinal studies, such as the English Longitudinal Study of Ageing (ELSA; Steptoe et al., 2013), the Irish LongituDinal Study on Ageing (TILDA; Kearney et al., 2011; Whelan & Savva, 2013), and the Survey of Health, Ageing and Retirement in Europe (SHARE; Börsch-Supan et al., 2013), provide an optimistic outlook for ageing and dementia-related studies. Moreover, the use of large public health and neuroimaging databases, such as OpenNeuro (Markiewicz et al., 2021, https://openneuro.org/) and UK Biobank (https://www.ukbiobank.ac.uk) enable the design of more complex research studies that are well-powered. Nonetheless, this thesis still provides valuable contributions to ageing research through clarification of the neurobiological and lifestyle contributions to age-related (action) word-finding difficulties.

7.6 Future Directions

Both Chapters 5 and 6 implemented EEG data to investigate the neurobiological factors involved in healthy cognitive ageing. However, combining different

neuroimaging and brain stimulation techniques, such as functional neuroimaging, EEG, and Transcranial Magnetic Stimulation will advance our understanding of the neurobiological processes related to ageing and age-related word-finding difficulties (Sui et al., 2014). Furthermore, a combination of these techniques, as well as including lifestyle and health factors, will enable the testing of the different components proposed by STAC-r (Reuter-Lorenz & Park, 2014). Computational models and machine learning enable further testing of the applications of STAC-r and other cognitive ageing models for different cognitive functions, including word-finding ability. Understanding the complex mechanisms underlying age-related word-finding difficulties and cognitive decline more generally can only happen when we have determined and clarified the neurobiological and lifestyle contributions. Ultimately, machine learning models should be able to map out cognitive ageing trajectories specific to the individual and predict whether someone will develop dementia or not, to start timely treatment and optimise care (Amini et al., 2021). Hence, future studies should investigate cognitive ageing using a combination of different neuroimaging techniques, as well as implement computational models to investigate the possibility of mapping cognitive ageing trajectories.

In this thesis, we demonstrated that the study discussed in Chapter 4 may offer some insights into the role of the basal ganglia in frontostriatal loops in word-finding abilities in healthy cognitive ageing and Parkinson's disease. In the shorter term, future research should further investigate the role of the basal ganglia and its subcomponents, such as the GPe and loops to frontal brain regions, in word-finding. If dopaminergic deficits indeed change the functions of the frontostriatal loops and infer the recruitment of more cortical regions (Copland et al., 2021; McGregor & Nelson, 2019), this could have major implications for the way cognitive deficits in individuals with PD are treated. Therefore, future studies could test the theoretical ideas discussed in 7.4, implementing a combination of different neuroimaging techniques and several clinical populations in which the basal ganglia have been affected. Moreover, future studies should aim to include a group of

individuals with PD who are resistant to dopamine medication to provide further insights into the functions of the frontostriatal loops when dopamine activity cannot be restored through medication.

Finally, all the studies discussed in this thesis were cross-sectional studies. However, longitudinal studies could provide objective measures of lifestyle choices throughout the lifespan and when investigating the interactions between lifestyle choices and overall brain status to determine cause-and-effect. This will help us determine what causes brain deterioration, subsequent word-finding difficulties, and whether functional brain changes are compensatory or maladaptive. Such research is of paramount importance to determine what lifestyle choices one should make to maintain cognition throughout life and whether we can reverse age-related cognitive decline through interventions, such as cognitive training and brain stimulation. Hence, future research should seek to replicate the findings in this thesis using longitudinal research designs.

7.7 Conclusion

This thesis demonstrated that lifestyle choices and neurobiological factors can provide us with an indication of someone's word-finding ability in older age. A combination of lifestyle choices seems to impact word-finding ability but in middle-aged and not in older adults. These findings could have important implications as to when lifestyle choices could contribute to compensatory mechanisms, like CR. Moreover, this thesis seems to be a link between motor and word-finding in both healthy adults and individuals with PD. This might reflect a general role of neural pathways between the basal ganglia and the cortex in word-finding and motor abilities. Functional connectivity measures are also linked to word-finding ability across the lifespan, with an important role of functional brain network efficiency. In addition, mu and beta phase coherence in frontocentral brain regions underlying action words was greater in older than in younger adults. These changes in functional

brain processes may reflect either compensatory or maladaptive processes with age. Finally, we demonstrated that action word-finding abilities seem preserved in older age and in individuals with PD, indicating that action word-finding may not be a sensitive marker for PD. Overall, this thesis demonstrated that different neurobiological and lifestyle factors contribute to word-finding abilities across the lifespan. In the future, machine learning algorithms could be developed at the individual level to predict when someone deviates from their healthy cognitive trajectory and potentially transitions into dementia.

Appendix A

Motor Ability Relates to Word Finding in Both Individuals With and Without Parkinson's Disease

(See next page)

A.1 All Models Hypothesis 1

Hypothesis 1 stated that individuals with PD show greater difficulty in producing words that describe upper-limb actions (e.g., "throwing") compared to words associated with actions involving less upper-limb movement when compared to individuals without PD.

Table A.1. *Results of the Fixed Effects for Picture Naming Reaction Time*

Model	RT ~Group * Action Rating + Type + (1 | Subject) + (1 | Item)							
Effect	Estimate	*SE*	*z*-value	*p*-value	*CI* Low	*CI* High	Back-Transformed Estimate	Percentage Change
Intercept	6.963	0.043	160.409	< .001	6.878	7.049	1057.271	105627.133
Group	0.018	0.041	0.434	.665	-0.062	0.097	1.018	1.771
Action Rating	0.000	0.018	-0.021	.983	-0.036	0.035	1.000	-0.038
Task Type	0.193	0.036	5.330	< .001*	0.122	0.265	1.213	21.347
Group * Action Rating	0.005	0.004	1.500	.134	-0.002	0.012	1.005	0.540

Note. *SE* = standard error, *CI* = 95% Confidence Intervals. Action Rating reflects the upper-limb action ratings of the picture names. Task Type reflects the type of picture-naming task (i.e., object vs. action naming).

Table A.2. *Results of the Fixed Effects for Picture Naming Accuracy*

Model	Acc ~Group * Action Rating + Type + (1 | Subject) + (1 | Item)							
Effect	Estimate	*SE*	*z*-value	*p*-value	*CI* Low	*CI* High	Back-Transformed Estimate	Percentage Change
Intercept	2.215	0.172	12.887	< .001	1.878	2.552	0.999	NA
Group	-0.097	0.088	-1.094	.274	-0.270	0.076	0.597	-40.326
Action Rating	-0.066	0.074	-0.895	.371	-0.210	0.078	0.608	1.126
Task Type	-0.386	0.136	-2.840	.005	-0.652	-0.119	0.493	-11.446
Group * Action Rating	0.023	0.061	0.369	.712	-0.098	0.143	0.640	14.701

Note. *SE* = standard error, *CI* = 95% Confidence Intervals. Action Rating reflects the upper-limb action ratings of the picture names. Task Type reflects the type of picture-naming task (i.e., object vs. action naming).

Table A.3. *Results of the Generalized Linear Model for Verbal Fluency "Number of Correctly Produced Words"*

Tweedie Model	Number of Correctly Produced Words ~Group + Task Type							
Effect	Estimate	*SE*	*t*-value	*p*-value	*CI* Low	*CI* High	Back-Transformed Estimate	Percentage Change
Intercept	3.194	0.029	109.400	< .001	3.137	3.251	8.408	740.768
Group	0.002	0.034	0.059	.953	-0.065	0.069	1.001	0.135
Task Type	-0.121	0.034	-3.573	.001	-0.188	-0.055	0.922	-7.772

Note. *SE* = standard error, *CI* = 95% Confidence Intervals. Task Type reflects the type of verbal-fluency task (i.e., semantic vs. action fluency).

Table A.4. *Results of the Multiple Linear Regression for Verbal Fluency "Average Upper-Limb Action Ratings"*

Model	Average Upper-Limb Action Ratings ~Group + Task Type					
Effect	Estimate	*SE*	*t*-value	*p*-value	*CI* Low	*CI* High
Intercept	2.744	0.040	69.112	$< .001$	2.666	2.823
Group	0.070	0.048	1.472	.143	-0.024	0.165
Task Type	-0.374	0.048	-7.767	$< .001$*	-0.469	-0.279

Note. *SE* = standard error, *CI* = 95% Confidence Intervals. Task Type reflects the type of verbal-fluency task (i.e., semantic vs. action fluency).

A.2 All Models Hypothesis 2

Hypothesis 2 stated a positive correlation between the ability to produce upper-limb action words and their upper-limb motor ability, measured by a keyboard tapping task, in individuals with PD.

Table A.5. *Results of the Fixed Effects for Picture Naming Reaction Time and the Relationship with Motor Ability*

Model	RT ~Group * Action Rating * Motor Ability Score + Type + (1 | Subject) + (1 | Item)							
Effect	Estimate	*SE*	*z*-value	*p*-value	*CI* Low	*CI* High	Back-Transformed Estimate	Percentage Change
Intercept	6.954	0.042	166.669	< .001	6.873	7.036	1047.677	104667.694
Group	0.027	0.037	0.718	.473	-0.046	0.100	1.027	2.725
Action Rating	-0.001	0.018	-0.031	.975	-0.036	0.035	0.999	-0.057
Motor Ability Score	-0.108	0.039	-2.755	.006	-0.184	-0.031	0.898	-10.208
Task Type	0.194	0.036	5.330	< .001	0.122	0.265	1.214	21.364
Group * Action Rating	0.005	0.004	1.297	.194	-0.002	0.012	1.005	0.469
Group * Motor Ability Score	0.094	0.054	1.721	.085	-0.013	0.200	1.098	9.818
Action Rating * Motor Ability Score	0.001	0.004	0.358	.720	-0.006	0.009	1.001	0.137
Group * Action Rating * Motor Ability Score	0.004	0.005	0.709	.479	-0.007	0.014	1.004	0.376

Note. *SE* = standard error, *CI* = 95% Confidence Intervals. Action Rating reflects the upper-limb action ratings of the picture names. Motor Ability Score was obtained through a keyboard tapping task (i.e., number of taps). Task Type reflects the type of picture-naming task (i.e., object vs. action naming). Predictors remaining significant after FDR corrections are marked (*). The adjusted *p*-values can be found in the main text.

Table A.6. *Results of the Fixed Effects for Picture Naming Accuracy and the Relationship with Motor Ability*

Model	Acc ~Group * Action Rating * Cognitive Reserve + Type + (1 | Subject) + (1 | Item)							
Effect	Estimate	*SE*	*z*-value	*p*-value	*CI* Low	*CI* High	Back-Transformed Estimate	Percentage Change
Intercept	2.236	0.174	12.883	< .001	1.896	2.576	1	NA
Group	-0.121	0.087	-1.386	.166	-0.293	0.050	0.588	-41.227
Action Rating	-0.079	0.076	-1.039	.299	-0.228	0.070	0.603	1.545
Motor Ability Score	0.172	0.088	1.958	.050	0	0.343	0.695	9.183
Task Type	-0.385	0.137	-2.811	.005	-0.653	-0.116	0.494	-20.120
Group * Action Rating	0.039	0.064	0.616	.538	-0.086	0.164	0.647	15.282
Group * Motor Ability Score	-0.100	0.119	-0.834	.404	-0.334	0.134	0.596	-5.100
Action Rating * Motor Ability Score	-0.041	0.062	-0.656	.512	-0.162	0.081	0.617	2.165
Group * Action Rating * Motor Ability Score	0.103	0.084	1.236	.216	-0.06	0.267	0.670	5.284

Note. *SE* = standard error, *CI* = 95% Confidence Intervals. Action Rating reflects the upper-limb action ratings of the picture names. Motor Ability Score was obtained through a keyboard tapping task (i.e., number of taps). Task Type reflects the type of picture-naming task (i.e., object vs. action naming).

Table A.7. *Results of the Generalised Linear Model for Verbal Fluency "Number of Correctly Produced Words" and the Relationship with Motor Ability*

Tweedie Model	Number of Correctly Produced Words ~Group * Motor Ability Score + Task Type							
Effect	Estimate	*SE*	*t*-value	*p*-value	*CI* Low	*CI* High	Back-Transformed Estimate	Percentage Change
Intercept	3.102	0.040	78.301	< .001	3.024	3.179	7.908	690.822
Group	0.133	0.048	2.781	.006	0.040	0.227	1.093	9.299
Motor Ability Score	0.195	0.052	3.765	< .001	0.094	0.297	1.139	13.908
Task Type	-0.135	0.035	-3.858	< .001	-0.203	-0.066	0.914	-8.585
Group * Motor Ability Score	-0.153	0.069	-2.228	.028	-0.287	-0.019	0.903	-9.683

Note. *SE* = standard error, *CI* = 95% Confidence Intervals. Motor Ability Score was obtained through a keyboard tapping task (i.e., number of taps). Task Type reflects the type of verbal-fluency task (i.e., semantic vs. action fluency). Predictors remaining significant after FDR corrections are marked (*). The adjusted *p*-values can be found in the main text.

Table A.8. *Results of the Multiple Linear Regression for Verbal Fluency "Average Upper-Limb Action Ratings" and the Relationship with Motor Ability*

Model	Average Upper-Limb Action Ratings ~Group * Motor Ability Score + Task Type					
Effect	Estimate	*SE*	*t*-value	*p*-value	*CI* Low	*CI* High
Intercept	2.745	0.052	52.879	< .001	2.643	2.848
Group	0.048	0.066	0.728	.468	-0.083	0.180
Motor Ability Score	-0.008	0.067	-0.124	.902	-0.140	0.124
Task Type	-0.388	0.051	-7.573	< .001	-0.489	-0.286
Group * Motor Ability Score	-0.046	0.090	-0.506	.614	-0.224	0.133

Note. *SE* = standard error, *CI* = 95% Confidence Intervals. Motor Ability Score was obtained through a keyboard tapping task (i.e., number of taps). Task Type reflects the type of verbal-fluency task (i.e., semantic vs. action fluency).

A.3 All Models Hypothesis 3

Hypothesis 3 stated that an engaging lifestyle (i.e., Cognitive Reserve), indicated by engaging in social and cognitively stimulating activities, physical activity, and higher education, is positively associated with better performance in producing action words in individuals with and without PD.

Table A.9. *Results of the Fixed Effects for Picture Naming Reaction Time and the Relationship with Cognitive Reserve*

Model	RT ~Group * Action Rating * Cognitive Reserve Score + Type + (1 | Subject) + (1 | Item)							
Effect	Estimate	*SE*	*z*-value	*p*-value	*CI* Low	*CI* High	Back-Transformed Estimate	Percentage Change
Intercept	6.969	0.044	158.935	< .001	6.883	7.055	1062.908	106190.824
Group	0.017	0.042	0.405	.686	-0.065	0.098	1.017	1.696
Action Rating	-0.001	0.018	-0.044	.965	-0.036	0.034	0.999	-0.079
Cognitive Reserve Score	-0.009	0.042	-0.218	.827	-0.091	0.073	0.991	-0.907
Task Type	0.193	0.036	5.373	< .001	0.123	0.264	1.213	21.321
Group * Action Rating	0.008	0.004	2.066	.039	0	0.015	1.008	0.757
Group * Cognitive Reserve Score	0.024	0.059	0.402	.688	-0.091	0.139	1.024	2.387
Action Rating * Cognitive Reserve Score	0.008	0.004	2.338	.019	0.001	0.016	1.009	0.852
Group * Action Rating * Cognitive Reserve Score	-0.011	0.005	-2.144	.032	-0.021	-0.001	0.989	-1.096

Note. *SE* = standard error, *CI* = 95% Confidence Intervals. Action Rating reflects the upper-limb action ratings of the picture names. Cognitive Reserve Score was obtained through a task (e.g., CR Composite Score). Task Type reflects the type of picture-naming task (i.e., object vs. action naming).

Table A.10. *Results of the Fixed Effects for Picture Naming Accuracy and the Relationship with Cognitive Reserve*

Model	Acc ~Group * Action Rating * Cognitive Reserve + Type + (1 | Subject) + (1 | Item)							
Effect	Estimate	*SE*	*z*-value	*p*-value	*CI* Low	*CI* High	Back-Transformed Estimate	Percentage Change
Intercept	2.180	0.169	12.929	< .001	1.850	2.510	1	NA
Group	-0.094	0.084	-1.125	.261	-0.259	0.070	0.597	-40.245
Action Rating	-0.068	0.074	-0.928	.354	-0.213	0.076	0.607	0.960
Cognitive Reserve Score	0.216	0.092	2.347	.019	0.036	0.396	0.711	10.380
Task Type	-0.388	0.136	-2.859	.004	-0.654	-0.122	0.493	-21.826
Group * Action Rating	0.026	0.062	0.414	.679	-0.096	0.147	0.642	14.899
Group * Cognitive Reserve Score	-0.362	0.129	-2.814	.005	-0.614	-0.110	0.502	-13.985
Action Rating * Cognitive Reserve Score	-0.016	0.068	-0.233	.816	-0.150	0.118	0.626	12.459
Group * Action Rating * Cognitive Reserve Score	0.048	0.094	0.513	.608	-0.136	0.232	0.650	2.353

Note. *SE* = standard error, *CI* = 95% Confidence Intervals. Action Rating reflects the upper-limb action ratings of the picture names. Cognitive Reserve Score was obtained through a task. Task Type reflects the type of picture-naming task (i.e., object vs. action naming). Predictors remaining significant after FDR corrections are marked (*). The adjusted *p*-values can be found in the main text.

Table A.11. *Results of the Generalised Linear Model for Verbal Fluency "Number of Correctly Produced Words" and the Relationship with Cognitive Reserve*

Tweedie Model	Number of Correctly Produced Words ~Group * Cognitive Reserve Score + Task Type							
Effect	Estimate	*SE*	*t*-value	*p*-value	*CI* Low	*CI* High	Back-Transformed Estimate	Percentage Change
Intercept	3.193	0.031	102.108	< .001	3.132	3.254	8.404	740.368
Group	0.002	0.036	0.052	.959	-0.069	0.073	1.001	0.126
Cognitive Reserve Score	0.038	0.041	0.930	.354	-0.041	0.117	1.026	2.574
Task Type	-0.136	0.035	-3.918	< .001	-0.204	-0.068	0.913	-8.657
Group * Cognitive Reserve Score	-0.116	0.054	-2.148	.034	-0.220	-0.011	0.926	-7.424

Note. *SE* = standard error, *CI* = 95% Confidence Intervals. Cognitive Reserve Score was obtained through a task (e.g., CR Composite Score). Task Type reflects the type of verbal-fluency task (i.e., semantic vs. action fluency).

Table A.12. *Results of the Multiple Linear Regression for Verbal Fluency "Average Upper-Limb Action Ratings" and the Relationship with Cognitive Reserve*

Model	Average Upper-Limb Action Ratings ~Group * Cognitive Reserve Score + Task Type					
Effect	Estimate	*SE*	*t*-value	*p*-value	*CI* Low	*CI* High
Intercept	2.720	0.042	65.212	< .001	2.638	2.803
Group	0.118	0.050	2.347	.021*	0.018	0.217
Cognitive Reserve Score	0.061	0.054	1.126	.262	-0.046	0.168
Task Type	-0.354	0.049	-7.156	< .001*	-0.451	-0.256
Group * Cognitive Reserve Score	0.014	0.073	0.189	.851	-0.131	0.159

Note. *SE* = standard error, *CI* = 95% Confidence Intervals. Cognitive Reserve Score was obtained through a task (e.g., CR Composite Score). Task Type reflects the type of verbal-fluency task (i.e., semantic vs. action fluency).

A.4 Exploratory Analyses

Hypothesis 1

Additive Effects of Apathy and Depression

Table A.13. *Hypothesis 1 - Comparisons between the Picture Naming Reaction Time Null Model and the Models with the Additive Effects of Apathy, Depression, and Both*

Model	df	χ^2	*p*-value	AIC	BIC	logLik	deviance
Incl. Apathy	1	0.548	.459	88408.0	88469.3	-44195.0	88390.0
Incl. Depression	1	2.393	.122	88406.2	88467.5	-44194.1	88388.2
Incl. Both	2	2.394	.302	88408.2	88476.3	-44194.1	88388.2

Note. df = degrees of freedom. AIC = Akaike Information Criterion, BIC = Bayesian Information Criterion, logLik = log-likelihood. Lower AIC, BIC, and deviance values indicate better model fit. Each of the models was compared to the null model without additive effects.

Table A.14. *Hypothesis 1 - Additive Effects of Depression on Verbal Fluency Performance*

Tweedie Model	Number of Correctly Produced Words ˜Group + LEDD + Task Type					
Effect	Estimate	*SE*	*t*-value	*p*-value	*CI* Low	*CI* High
(Intercept)	3.183	0.029	109.050	< .001	3.126	3.240
Group	0.024	0.035	0.676	.500	-0.044	0.091
Depression Score	-0.042	0.018	-2.374	.019*	-0.076	-0.007
Task Type	-0.122	0.033	-3.637	< .001*	-0.187	-0.056

Note. *SE* = standard error, *CI* = 95% Confidence Intervals. Task Type reflects the type of verbal-fluency task (i.e., semantic vs. action fluency). Depression Scores were standardised.

Table A.15. *Hypothesis 1 - Comparisons between the Verbal Fluency Null Model and the Models with the Additive Effects of Apathy, Depression, and Both*

Model	**Resid. Df**	**Resid. Dev.**	**Deviance**	**Df Diff.**	**Deviance Diff.**	χ^2	*p*-value
Incl. Apathy	133	25.563	0.116	1	0.116	0.116	.434
Incl. Depression	133	24.637	1.042	1	1.042	1.042	.017*
Incl. Both	132	24.597	1.083	2	1.083	1.083	.053

Note. Resid. Df. = Residual degrees of freedom, Resid. Dev. = Residual deviance, Deviance = Deviance, Df Diff. = Difference in degrees of freedom, Deviance Diff. = Difference in deviance. Each of the models was compared to the null model without additive effects.

Additive Effects of Levodopa Equivalent Daily Dose (LEDD)

Table A.16. *Hypothesis 2 - Comparisons between the Models for Picture Naming With and Without Levodopa Equivalent Daily Dosage*

Model	**npar**	**AIC**	**BIC**	**logLik**	**deviance**	χ^2	**Df**	*p*-value
Without LEDD	8	43591.7	43640.5	-21787.8	43575.7	NA	NA	NA
With LEDD	9	43592.9	43647.8	-21787.5	43574.9	0.7	1	.388

Note. npar = number of parameters, AIC = Akaike Information Criterion, BIC = Bayesian Information Criterion, logLik = log-likelihood, Df = Degrees of freedom, LEDD = Levodopa Equivalent Daily Dosage. LEDD Scores were standardised.

Table A.17. *Hypothesis 1 - Additive Effects of Levodopa Equivalent Daily Dosage on Verbal Fluency Performance*

Tweedie Model	Number of Correctly Produced Words ~Group + LEDD + Task Type					
Effect	Estimate	*SE*	*t*-value	*p*-value	*CI* Low	*CI* High
Intercept	3.180	0.035	91.112	< .001	3.111	3.248
LEDD	-0.051	0.026	-1.996	.050*	-0.102	0
Task Type	-0.091	0.050	-1.835	.071*	-0.188	0.006

Note. *SE* = standard error, *CI* = 95% Confidence Intervals, LEDD = Levodopa Equivalent Daily Dosage. Task Type reflects the type of verbal-fluency task (i.e., semantic vs. action fluency). LEDD Scores were standardised.

Table A.18. *Hypothesis 1 - Comparisons between the Models for Verbal Fluency With and Without Levodopa Equivalent Daily Dosage*

Model	Resid. Df	Resid. Dev	Df	Deviance	*p*-value
Without LEDD	65	13.532	NA	NA	NA
With LEDD	64	12.769	1	0.763	.049*

Note. Resid. Df = Residual degrees of freedom, Resid. Dev = Residual deviance, Df = Difference in degrees of freedom, Deviance = Difference in deviance. LEDD = Levodopa Equivalent Daily Dosage. LEDD Scores were standardised.

Hypothesis 2

Additive Effects of Apathy and Depression

Table A.19. *Hypothesis 2 - Comparisons between the Picture Naming Reaction Time Null Model and the Models with the Additive Effects of Apathy, Depression, and Both*

Model	df	χ^2	*p*-value	AIC	BIC	logLik	deviance
Incl. Apathy	1	.005	.942	88950.0	89038.6	-44462.0	88924.0
Incl. Depression	1	1.649	.199	88948.3	89036.9	-44461.2	88922.3
Incl. Both	2	2.075	.354	88949.9	89045.3	-44460.9	88921.9

Note. df = degrees of freedom. AIC = Akaike Information Criterion, BIC = Bayesian Information Criterion, logLik = log-likelihood. Lower AIC, BIC, and deviance values indicate better model fit. Each of the models was compared to the null model without additive effects.

Table A.20. *Hypothesis 2 - Comparisons between the Verbal Fluency Null Model and the Models with the Additive Effects of Apathy, Depression, and Both*

Model	**Resid. Df**	**Resid. Dev.**	**Deviance**	**Df Diff.**	**Deviance Diff.**	χ^2	*p*-value
Incl. Apathy	130	26.0	0.016	1	0.016	0.016	.777
Incl. Depression	130	25.7	0.318	1	0.318	0.318	.204
Incl. Both	129	25.6	0.349	2	0.349	0.349	.415

Note. Resid. Df. = Residual degrees of freedom, Resid. Dev. = Residual deviance, Deviance = Deviance, Df Diff. = Difference in degrees of freedom, Deviance Diff. = Difference in deviance. Each of the models was compared to the null model without additive effects.

Additive Effects of Levodopa Equivalent Daily Dose (LEDD)

Table A.21. *Hypothesis 2 - Comparisons between the Models for Picture Naming With and Without Levodopa Equivalent Daily Dosage*

Model	**npar**	**AIC**	**BIC**	**logLik**	**deviance**	χ^2	**Df**	*p*-value
Without LEDD	8	43591.7	43640.5	-21787.8	43575.7	NA	NA	NA
With LEDD	9	43592.9	43647.8	-21787.5	43574.9	0.700	1	.388

Note. npar = number of parameters, AIC = Akaike Information Criterion, BIC = Bayesian Information Criterion, logLik = log-likelihood, Df = Degrees of freedom, LEDD = Levodopa Equivalent Daily Dosage. LEDD Scores were standardised.

Table A.22. *Hypothesis 2 - Additive Effects of Levodopa Equivalent Daily Dosage on Verbal Fluency Performance*

Tweedie Model	Number of Correctly Produced Words ~Motor Ability + LEDD + Task Type					
Effect	Estimate	*SE*	*t*-value	*p*-value	*CI* Low	*CI* High
Intercept	3.238	0.042	77.03	< .001	3.156	3.320
Motor Ability	0.069	0.048	1.435	.156	-0.025	0.163
LEDD	-0.065	0.028	-2.361	.021*	-0.119	-0.011
Task Type	-0.118	0.052	-2.294	.025*	-0.219	-0.017

Note. *SE* = standard error, *CI* = 95% Confidence Intervals, LEDD = Levodopa Equivalent Daily Dosage. Task Type reflects the type of verbal-fluency task (i.e., semantic vs. action fluency). LEDD Scores were standardised.

Table A.23. *Hypothesis 2 - Comparisons between the Models for Verbal Fluency With and Without Levodopa Equivalent Daily Dosage*

Model	**Resid. Df**	**Resid. Dev**	**Df**	**Deviance**	***p*-value**
Without LEDD	64	15.072	NA	NA	NA
With LEDD	63	13.897	1	1.176	.019*

Note. Resid. Df = Residual degrees of freedom, Resid. Dev = Residual deviance, Df = Difference in degrees of freedom, Deviance = Difference in deviance, LEDD = Levodopa Equivalent Daily Dosage (standardised).

Hypothesis 3

Additive Effects of Apathy and Depression

Table A.24. *Hypothesis 3 - Comparisons between the Picture Naming Reaction Time Null Model and the Models with the Additive Effects of Apathy, Depression, and Both*

Model	**df**	χ^2	***p*-value**	**AIC**	**BIC**	**logLik**	**deviance**
Incl. Apathy	1	0.551	.458	88390.3	88478.9	-44182.1	88364.3
Incl. Depression	1	2.405	.121	88388.4	88477.0	-44181.2	88362.4
Incl. Both	2	2.406	.300	88390.4	88485.8	-44181.2	88362.4

Note. df = degrees of freedom. AIC = Akaike Information Criterion, BIC = Bayesian Information Criterion, logLik = log-likelihood. Lower AIC, BIC, and deviance values indicate better model fit. Each of the models was compared to the null model without additive effects.

Table A.25. *Hypothesis 3 - Comparisons between the Verbal Fluency Null Model and the Models with the Additive Effects of Apathy, Depression, and Both*

Model	**Resid. Df**	**Resid. Dev.**	**Deviance**	**Df Diff.**	**Deviance Diff.**	χ^2	*p*-value
Incl. Apathy	130	25.875	0.205	1	0.205	0.205	.307
Incl. Depression	130	25.698	0.382	1	0.382	0.382	.160
Incl. Both	129	25.673	0.407	2	0.407	0.407	.352

Note. Resid. Df. = Residual degrees of freedom, Resid. Dev. = Residual deviance, Deviance = Deviance, Df Diff. = Difference in degrees of freedom, Deviance Diff. = Difference in deviance. Each of the models was compared to the null model without additive effects.

Additive Effects of Levodopa Equivalent Daily Dose (LEDD)

Table A.26. *Hypothesis 3 - Comparisons between the Models for Picture Naming With and Without Levodopa Equivalent Daily Dosage*

Model	**npar**	**AIC**	**BIC**	**logLik**	**deviance**	χ^2	**Df**	*p*-value
Without LEDD	8	43436.9	43485.7	-21710.4	43420.9	NA	NA	NA
With LEDD	9	43438.2	43493.1	-21710.1	43420.2	0.600	1	.429

Note. npar = number of parameters, AIC = Akaike Information Criterion, BIC = Bayesian Information Criterion, logLik = log-likelihood, Df = Degrees of freedom, LEDD = Levodopa Equivalent Daily Dosage. LEDD Scores were standardised.

Table A.27. *Hypothesis 3 - Comparisons between the Models for Verbal Fluency With and Without Levodopa Equivalent Daily Dosage*

Model	**Resid. Df**	**Resid. Dev**	**Df**	**Deviance**	***p*-value**
Without LEDD	65	14.905	NA	NA	NA
With LEDD	64	14.872	1	0.032	.707

Note. Resid. Df = Residual degrees of freedom, Resid. Dev = Residual deviance, Df = Difference in degrees of freedom, Deviance = Difference in deviance, LEDD = Levodopa Equivalent Daily Dosage (standardised).

Appendix B

Brain Segregation and Integration Relate to Word-Finding Abilities in Older and Younger Adults

B.1 A-Priori Power Analysis for Sample Size

A-priori power analysis using data simulation was used to confirm power for the final sample size (Brysbaert & Stevens, 2018; DeBruine & Barr, 2021). Because this study uses secondary data analysis, the number of participants in this study was already known. Therefore, the sample size was held constant in the power analysis. For the analysis, we estimated means and standard deviations for verbal fluency based on existing literature (Aita et al., 2019; Bäckman & Nilsson, 1996; Gibson et al., 2019; Gonzalez-Burgos et al., 2019; Sokołowski et al., 2020) and EEG parameters (Feklicheva et al., 2021; Gaál et al., 2010; Utianski et al., 2016) that closely resembled our study design (DeBruine & Barr, 2021). For the power analyses, we simulated the data set with verbal fluency and functional connectivity values, which were randomly generated with a normal distribution centred around the mean, for 1000 runs using a script in RStudio (DeBruine & Barr, 2021). Multiple linear regression models were defined within a function and performed for each simulation run. We used R (R Core Team, 2020) to simulate the data and to run the statistical models.

Following the method outlined by DeBruine and Barr (2021), power was defined as mean (p-value ¡ alpha), where alpha was set at 0.05. We obtained average to high power (60-90%) for our models depending on the frequency band and the EEG measure, and hence, concluded that our sample size is sufficient for our analyses. For more information on the power analysis, please see the pre-registration.

B.2 Functional connectivity measures

Debiased weighted Phase Lag Index

Oscillatory phase (which is provided by the EEG data) can be visualised with a circular axis, where the x-axis is called the real axis and the y-axis the imaginary axis. Imaginary numbers on the imaginary axis are necessary when we cannot use the real number system (i.e., the numbers we use in our day-to-day life) to solve a mathematical problem, for example, when taking the square root of a negative number. Complex numbers are the sum of a real and an imaginary number and are necessary to obtain information, such as phase and power information from EEG data (Cohen, 2014). The dwPLI measures phase synchrony, whilst reducing the effect of volume conduction by ignoring 0 or π phase differences between electrodes, which reflect instantaneous synchronisation. These instantaneous synchronisations are physiologically implausible as markers of neural synchronisation through synaptic transmission (however, see Hajizadeh et al., 2022, for a biologically plausible mechanism of instantaneous synchronisation) and are more likely to reflect volume conduction of electrical potentials to both electrodes simultaneously (Vinck et al., 2011). As such, the dwPLI measures how much a signal of one channel leads or lags compared to the signal of another channel and is weighted by the magnitude of the imaginary component of the cross-spectrum (i.e., the cross-correlation between two time-series). The formula to compute the dwPLI is as follows (Vinck et al., 2011):

$$\hat{\Omega}_w(f) = \frac{\sum_{j=1}^{N} \sum_{k \neq j} Im\{X_j\} Im\{X_k\}}{\sum_{j=1}^{N} \sum_{k \neq j} |Im\{X_j\} Im\{X_k\}|},$$

where $\hat{\Omega}_w(f)$ is the dwPLI at frequency f and N is the total number of epochs. The numerator is the sum of the imaginary component of all pairwise products of the cross-spectra X between epoch j and epoch k, which is the computation of between-electrode connectivity, reflect the same time epoch, but epochs extracted from two different electrodes. The denominator is the sum of all pairwise products of the magnitude of the imaginary component between epoch j and epoch k. The computation of the dwPLI preserves the sign (i.e., whether the denominator is positive or negative).

Orthogonal Minimum Spanning Trees

We applied a data-driven method, namely the Orthogonalized Minimum Spanning Tree (OMST) algorithm to threshold the connectivity matrices (Dimitriadis et al., 2017). A minimum spanning tree is a graph with a minimum number of total edges, without cycles (i.e., the graph does not contain any loops), and where all nodes are connected. The OMST algorithm computes the minimum spanning tree (MST) over multiple iterations. These are necessary because it is possible that by using only a single MST, one ends up with a graph that is too sparse for computing robust connectivity measures. After each iteration, the edges (N-1) of the minimum spanning tree in that iteration are set to infinity so the algorithm ignores those connections in the subsequent iteration. Because the OMST algorithm computes multiple spanning trees to threshold the connectivity matrices for further analyses, it preserves as many connections as possible (i.e., reducing wiring cost, where adding connections comes at the expense of the performance or

efficiency of the network), whilst maintaining an optimal global efficiency of the network. The OMSTs are calculated from the inverse-weighted graph, which can be calculated from the connectivity matrix. In an inverse-weighted graph, the strongest connections represent the brain areas that are functionally closer or more strongly connected.

Weighted Clustering Coefficient

The weighted clustering coefficient (C^W), expresses how frequently, on average, a node is part of a local triangle of connections. That is, how often when a node is connected to one of its neighbours, these neighbours are also connected to each other. The formula of the weighted clustering coefficient is as follows (Onnela et al., 2005; Rubinov & Sporns, 2010):

$$C^W = \frac{1}{n} \sum_{i \in N} \frac{2t_i^w}{k_i(k_i - 1)},$$

where i is the node index, n is the total number of nodes in graph N, and k_i^w represents the summed weight of all edges that are connected to that node (i.e., weighted degree of node i). t^w is the geometric mean of the triangles' weight at node i. Finally, the clustering coefficient is calculated by averaging the clustering coefficient at all nodes.

Modularity

Modularity measures the prevalence of non-overlapping modules or sub-networks in a graph according to (Newman, 2006; Rubinov & Sporns, 2010):

$$Q^W = \frac{1}{l^W} \sum_{i,j \in N} \left(w_{ij} - \frac{k_i^W k_j^W}{l^W} \right) \delta_{m_i m_j},$$

where Q^W is the weighted modularity. L^W is the sum of all weights in graph N, and w_{ij} is the undirected weight of the edge between node i and j. k_i^w is the weighted degree of node i. m_i is the module containing node i and where the delta function $\delta_{m_i m_j}$ is 1 if $i = j$ and 0 otherwise. The maximum value of Q^W is 1, which means that the network is strongly divided into communities (i.e., significantly more intra-community connections compared to inter-community connections).

Characteristic Path Length

The formula is as follows (Rubinov & Sporns, 2010; Watts & Strogatz, 1998):

$$L^W = \frac{1}{n} \sum_{i \in N} \left(\frac{\sum_{j \in N, j \neq i} d_{ij}^W}{n-1} \right),$$

where L^W is the weighted characteristic path length. To calculate d_{ij}^W, the weights of the edges are converted to length by calculating the reciprocal of the weights (1/weight) in the matrix (i.e., taking the inverse of the weighted matrix) to reflect the distance between node i and j when there is a connection between i and j. Stronger connections represent stronger associations between node i and j and a shorter distance.

Small-World Index

To examine the balance between brain segregation and integration, we computed the small-world index of each graph. First, we created random networks by randomly swapping (100 times) the edge weights of the original networks, whilst preserving the weight, degree, and strength distribution (Rubinov & Sporns, 2010). Next, we calculated the clustering coefficient (C^W_{rand}) and characteristic path length (L^W_{rand}) of the random networks. The small-world index was obtained through the following formula (Humphries & Gurney, 2008):

$$S^W = \frac{C^W / C^W_{rand}}{L^W / L^W_{rand}},$$

where a value higher than 1 indicates that the network is a small world.

B.3 The Relationship between Characteristic Path Length and Modularity

Our study showed an inverse between alpha band modularity and semantic fluency scores, irrespective of age. In our discussion, we proposed that brain integration might be more important for semantic fluency performance than brain segregation and it is possible that greater brain segregation could be related to lower integration. Hence, we hypothesised an inverse relationship between brain integration (characteristic path length) and brain segregation (modularity) in the alpha band. That is, if brain integration is more important than segregation for semantic fluency, the relationship between greater modularity and lower semantic fluency scores could potentially be explained by a lower characteristic path length.

To investigate this idea, we conducted a multiple linear regression analysis

with the OMST-thresholded characteristic path length as the outcome variable and the OMST-thresholded modularity as the predictor. To keep in line with our previous models, we added Sex (2 levels) as a covariate. Leverage points were removed accordingly. We did not include Age as a predictor or covariate as the relationship between modularity and semantic fluency did not interact with age. After the initial model fit, leverage points were identified as 2(number of predictors + 1)/number of observations, and subsequently removed to obtain the model's best fit. The predictors explained 13.5% of the variance in semantic fluency scores (R^2 = .12, $F(2,96) = 7.50$, p = .001). Modularity was a significant predictor of the characteristic path length ($\beta = 0.60$, $\beta < .001$). Hence, in the alpha band, when brain segregation is higher, brain integration is also higher (see Figure B.1).

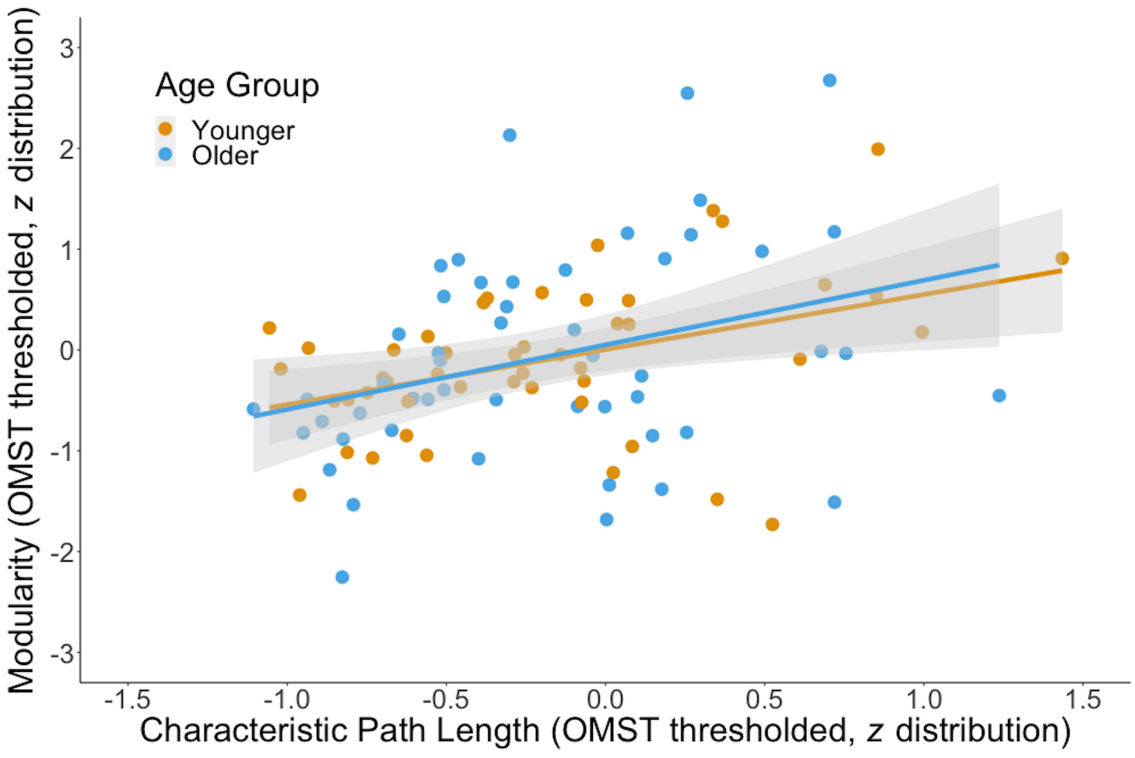

Figure B.1. The relationship between brain segregation (modularity) and brain integration (characteristic path length) in the alpha band.

Appendix C

The Role of Neuronal Phase Coherence Underlying Action-Word Comprehension in Healthy Ageing

Table C.1. *Full 2 X 2 with 3 Covariates ANCOVA Results Table with the ITPC Index as Outcome Variable over the Frontocentral Brain Region*

Predictor	Sum of Squares	F-statistic	p value	Adjusted p value
Age Group	48881.54	1250.15	$< .001$	$< .001$
Frequency Band	21405.06	547.44	$< .001$	$< .001$
Age Group * Frequency Band	16902.35	432.28	$< .001$	$< .001$
Covariates:				
Hearing Status	823.623	21.06	$< .001$	$< .001$
Log-ratio power	1645.705	42.09	$< .001$	$< .001$
AUDIT scores	9574.888	244.88	$< .001$	$< .001$

Note. The ITPC index was computed by subtracting peak ITPC Z for the High Action condition from the peak ITPC Z for the Low Action condition. AUDIT scores reflect alcohol use. Log-ratio power was the log-ratio of the power between the mu and beta bands and was included to account for the influence of power on ITPC. The adjusted p value is the p value corrected for multiple comparisons using Bonferroni.

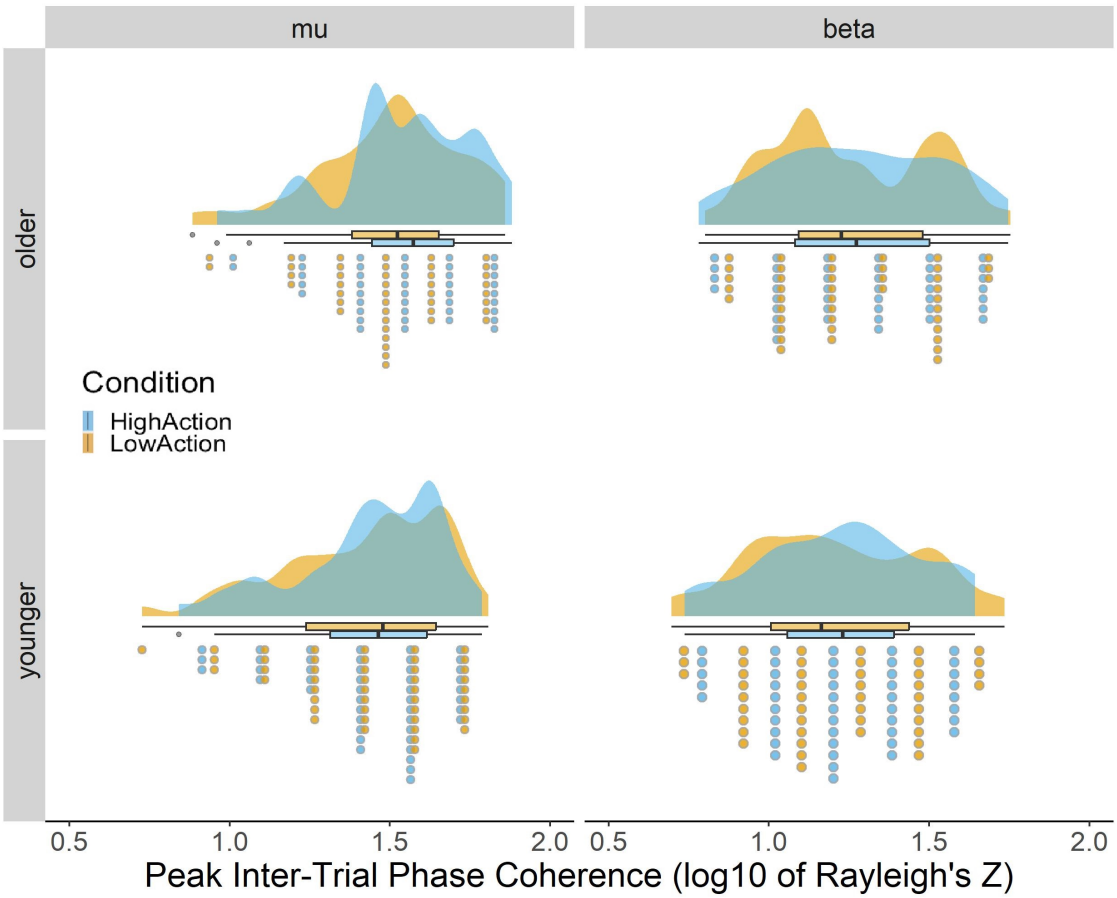

Figure C.1. Raincloud plots showing the distribution of the frontocentral Rayleigh's Z peak ITPC values per age group and for the mu and beta band separately.

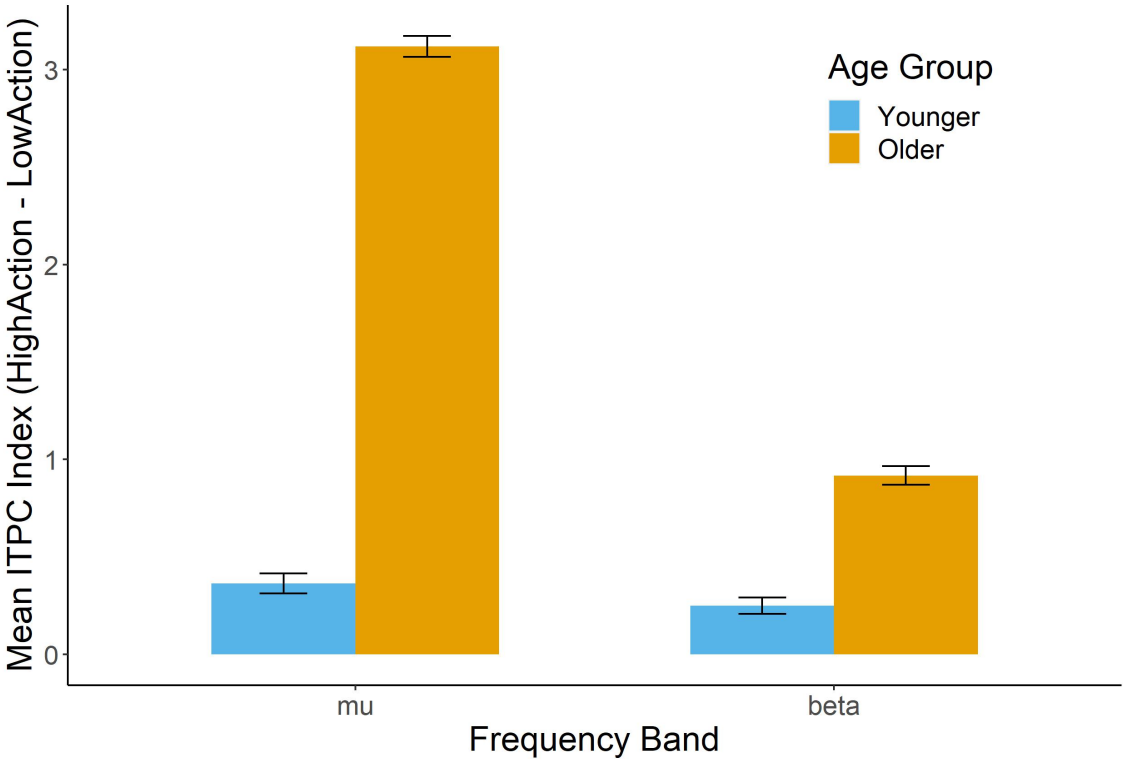

Figure C.2. The mean ITPC index per Age Group and Frequency Band. The ITPC index was calculated as the difference between peak ITPC Z of the High Action and Low Action condition. Positive values indicate that the peak ITPC Z for the High Action condition was higher than that of the Low Action Condition. The bars represent the standard error (*SE*).

Table C.2. *Multiple Linear Regression Results Table with the Reaction Times for Action Words as Outcome Variable over the Frontocentral Brain Region.*

	Estimate	*SE*	*t*-value	*p*-value	Adjusted *p*-value
Intercept	2.786	0.001	2054.813	$< .001$	$< .001$
Peak ITPC *Z*	-0.018	0.001	-23.172	$< .001$	$< .001$
Age Group	-0.026	0.001	-23.457	$< .001$	$< .001$
Frequency Band	0.008	0.001	10.834	$< .001$	$< .001$
Peak ITPC *Z* * Age Group	0.003	0.001	3.869	$< .001$	.001
Peak ITPC *Z* * Frequency Band	0.001	0.001	0.776	.438	1
Age Group * Frequency Band	-0.003	0.001	-4.464	$< .001$	$< .001$
Peak ITPC *Z* * Age Group * Frequency Band	0.003	0.001	3.824	$< .001$	.001
Covariates:					
Hearing Status	0.007	0.001	6.297	$< .001$	$< .001$
Log-ratio power	-0.1	0.011	-9.362	$< .001$	$< .001$
Audit Scores	-0.003	0.001	-5.141	$< .001$	$< .001$

Note. *SE* = standard error. AUDIT scores reflect alcohol use. Log-ratio power was the log-ratio of the power between the mu and beta bands and was included to account for the influence of power on ITPC. The adjusted p value is the p value corrected for multiple comparisons using Bonferroni.

Table C.3. *Peak ITPC and Power of the Temporo-Occipital Region of the Mu and Beta Frequency Band Per Age Group and Task Condition*

		Older		**Younger**	
		High-Action	*Low-Action*	*High-Action*	*Low-Action*
Mu	Peak ITPC	0.71 (0.16)	0.72 (0.14)	0.74 (0.13)	0.75 (0.12)
	Peak ITPC Z	39.67 (18.20)	39.62 (18.02)	41.81 (15.96)	40.94 (15.12)
	Average Power	18.75 (12.54)	18.69 (12.69)	16.31 (12.90)	16.41 (12.72)
	Normalised Power (dB)	0.95 (1.34)	0.93 (1.34)	1.19 (1.30)	1.22 (1.35)
Beta	Peak ITPC	0.58 (0.16)	0.59 (0.14)	0.59 (0.15)	0.60 (0.15)
	Peak ITPC Z	27.20 (16.14)	27.41 (15.33)	26.85 (13.89)	27.45 (14.42)
	Average Power	5.58 (3.49)	5.56 (3.49)	4.87 (3.17)	4.92 (3.19)
	Normalised Power (dB)	0.50 (0.66)	0.50 (0.66)	0.55 (0.64)	0.58 (0.62)

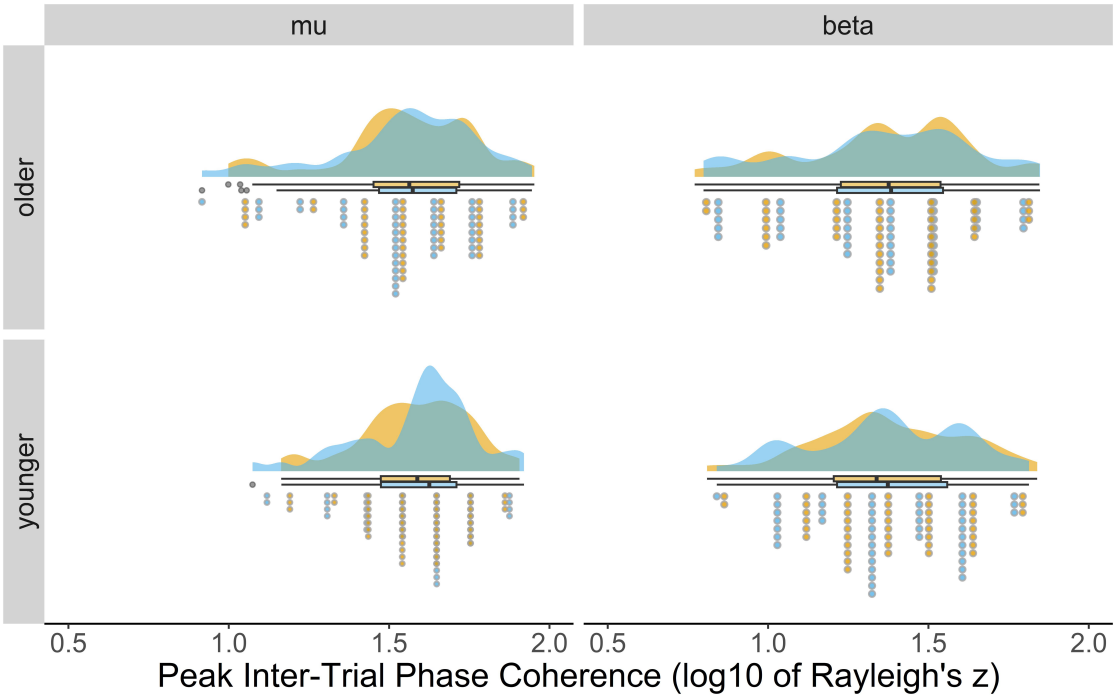

Figure C.3. Raincloud plots showing the distribution of the temporo-occipital Rayleigh's Z peak ITPC values per age group and for the mu and beta band separately.

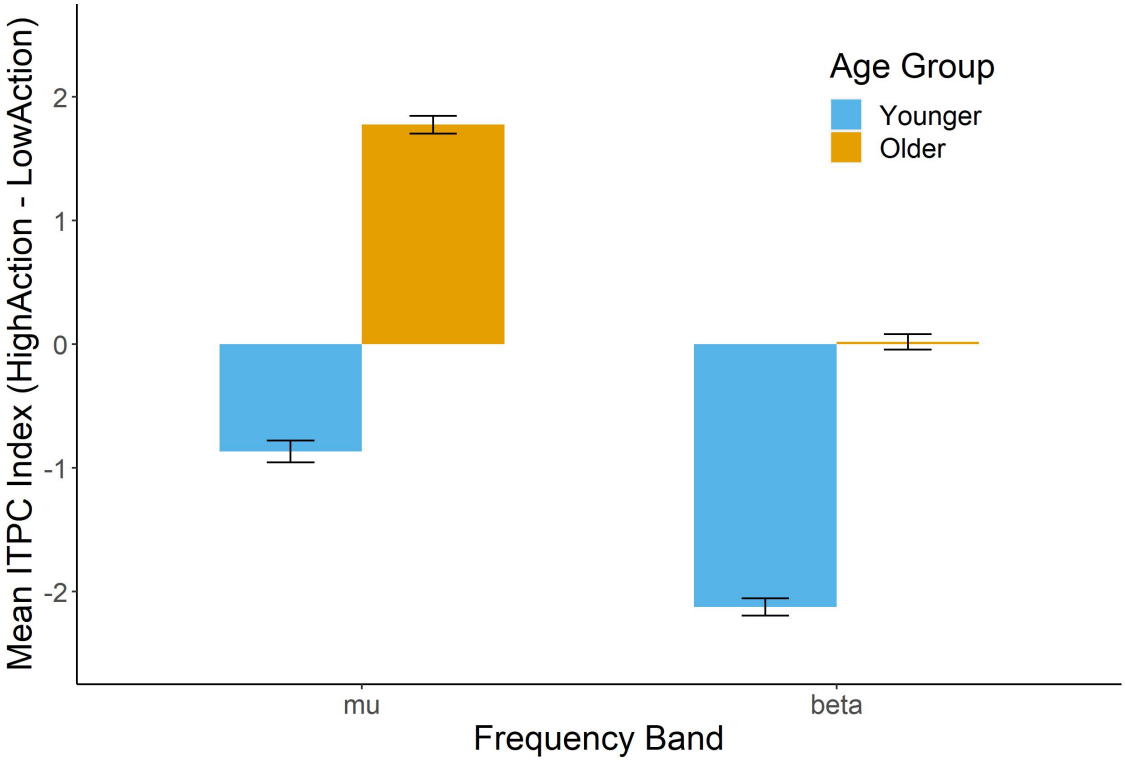

Figure C.4. The mean ITPC index over the temporo-occipital region per Age Group and Frequency Band. The ITPC index was calculated as the difference between peak ITPC Z of the High Action and Low Action condition. Positive values indicate that the peak ITPC Z for the High Action condition was higher than that of the Low Action Condition. The bars represent the standard error (SE).

Table C.4. *Full 2 X 2 with 3 Covariates ANCOVA Results Table with the ITPC Index as Outcome Variable over the Temporo-Occipital Brain Region*

Predictor	Sum of Squares	F-statistic	p value	Adjusted p value
Age Group	41191.71	1036.92	$< .001$	$< .001$
Frequency Band	16405.84	413.00	$< .001$	$< .001$
Age Group * Frequency Band	268.50	6.76	.009	.056
Covariates:				
Hearing Status	15701.84	395.26	$< .001$	$< .001$
Log-ratio power	20598.94	518.55	$< .001$	$< .001$
AUDIT scores	653.85	16.46	$< .001$	$< .001$

Note. The ITPC index was computed by subtracting peak ITPC Z for the High Action condition from the peak ITPC Z for the Low Action condition. AUDIT scores reflect alcohol use. Log-ratio power was the log-ratio of the power between the mu and beta bands and was included to account for the influence of power on ITPC. The adjusted p value is the p value corrected for multiple comparisons using Bonferroni.

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