Sensory Gating and EEG Oscillatory Markers in the Context of Cognitive Reserve in Healthy Ageing

Emma Staley

Institute of Inflammation and Ageing

University of Birmingham

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Abstract

The number of older adults (> 65 years) developing a neurological or neuropsychiatric disease will rise as the population aged over 80 years old grows. Ageing has diverse impacts on cognitive function, significantly affecting daily life in older adults. Cognitive Reserve (CR), the brain's ability to resist age-related changes, is thought to be built up over a person's lifetime through various intellectual, educational, and social activities. Measuring CR consistently proves challenging due to varied approaches and tools used throughout the literature.

Studies utilising electroencephalography (EEG) and magnetoencephalography (MEG) for non-invasive brain measurement demonstrate that high CR individuals exhibit increased connectivity and amplified event-related potentials (ERPs) or oscillatory amplitudes. However, establishing causal relationships between MEG or EEG measures and CR remains challenging due to methodological variations and participant heterogeneity.

We investigated inhibitory EEG measures using sensory gating (SG). A paired stimulus click paradigm was applied to measure the P50, N100 and P200. Our study found an age-related decline in neuropsychological function and CR but not in SG among healthy older adults (n = 27). Significant relationships were observed between P200 and verbal as well as visual long-term memory (both $p < .05$), and N100 with inhibitory memory ($p < .001$). No other neuropsychological measures correlated with SG.

Auditory Steady-State Responses (ASSR) are electrophysiological evoked oscillatory responses entrained to the frequency and phase of temporally modulated tones. These responses are often deficient in disorders of consciousness, such as schizophrenia. Three blocks of tones

were presented: 2.5 Hz and 40 Hz, 2.5 Hz and 80 Hz, and 2.5 Hz and 40 Hz. Results revealed associations between verbal fluency and lower ASSR power responses (n = 14, p = .039), independent of age or other neuropsychological assessments.

Alpha frequency is thought to represent inhibiting irrelevant sensory pathways, and the peak frequency can be calculated over a short period of EEG recording time (~4 minutes). Older participants had significantly lower peak alpha results than the younger participants (p = .023), and age significantly predicted the peak alpha frequency (PAF) (p = .017). The PAF was also significantly predicted by IQ (p = .017) and a digit span task (p = .039), but this was not seen when age was controlled for, implying that this relationship isn't robust. Similar predictors were found for SG measures as well as PAF.

Results from each chapter contribute to the overall understanding of the relationships between SG, neural measures, and CR in healthy older adults. Our chosen EEG responses all demonstrated associations with inhibition measures. These findings provide insights into the neural underpinnings of sensory processing and inhibitory functions, contributing to our understanding of their potential impact on overall cognitive functioning in the ageing population. Limitations of methodological chapters are discussed with recommendations for future research.

Emphasising clinical significance, the thesis suggests using an EEG setup with fewer electrodes and a passive listening task for faster, less burdensome assessments. This approach allows for a faster setup, reducing burden on patients. The findings suggest that measuring cognitive vulnerability, especially in older adults, is crucial in clinical settings, offering support before major healthcare events such as planned major surgery.

Declaration

I hereby declare that except where specific reference is made to the work of others, the contents of this dissertation are original and have not been submitted in whole or in part for consideration for any other degree or qualification in this, or any other University. This dissertation is the result of my own work and includes nothing which is the outcome of work done in collaboration, except where specifically indicated in the text. This dissertation contains less than 55,000 words not including appendices, bibliography, footnotes, tables, and equations and has less than 150 figures.

The original idea for the thesis (EEG and neuropsychological markers in predicting the outcome of postoperative delirium) was presented as a poster and as an abstract at the European Delirium Association conference in Utrecht November 2018. However, this thesis has changed dramatically since then due to Covid-19, so the work included has not been presented at conferences. The data utilised in my research in Chapter 7, was originally collected for a distinct purpose in the study conducted by Markiewicz, Segaert, & Mazaheri (2021), as published in the European Journal of Neuroscience.

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List of abbreviations

AD, Alzheimer's Disease;

ADLs, Activities of Daily Living;

AERPs, Auditory Event-Related Potential;

aMCI, Amnesic Mild Cognitive Impairment;

ASSR, Auditory Steady State Response;

AUROC, Area Under Receiver Operating Characteristic;

BIS, Bi-spectral Index EEG;

BP, Bereitschaftspotential;

CI, Cognitive Impairment;

CNS, Central Nervous System;

CPT, Conner's Continuous Performance Task;

CR, Cognitive Reserve;

CRH, Cognitive Reserve Hypothesis;

CRIq, Cognitive Reserve Index Questionnaire;

dlPFC, Dorsolateral Prefrontal Cortex;

EEG, Electroencephalography;

EF, Executive Functioning;

E/I, Excitation/Inhibition;

ERD, Event-Related Desynchronisation;

ERF, Event-Related Field;

ERP, Event-Related Potential;

FH, Family History;

FHA, Frontal Hypothesis of Ageing;

fMRI, Functional Magnetic Resonance Imaging;

GABA, Gamma-Aminobutyric Acid;

IAF, Individual Alpha Frequency;

IQ, Intelligence Quotient;

ISI, Inter-Stimulus Interval;

KBIT, Kaufman Brief Intelligence Test

LAN, Left Anterior Negativity;

LLC, Lagged-Linear Connectivity

MCI, Mild Cognitive Impairment;

MEG, Magnetoencephalography;

MMSE, Mini-Mental State Exam;

MoCA, Montreal Cognitive Assessment;

NMDA, N-methyl-D-aspartate;

NART, National Adult Reading Test;

PAF, Peak Alpha Frequency;

PD, Panic Disorder;

PET, Positron Emission Topography;

PFC, Prefrontal Cortex;

rsEEG, Resting State EEG

RT, Reaction Time;

S1 or S2; Stimulus 1, Stimulus 2;

SE, Spectral Entropy;

SG, Sensory Gating;

SSR, Steady State Response;

TMS, Transcranial Magnetic Stimulation;

WAIS, Wechsler Adult Intelligence Scale;

WASI, Wechsler Abbreviated Scale of Intelligence;

WM, Working Memory;

WRAT, Wide Range Achievement Test;

$\overline{x}$, Mean;

Chapter 1 Background of the Thesis

1.1 Introduction

Clinicians working with older adults and the medically ill frequently come across delirium, which is the most common neuropsychiatric syndrome in these cases (Maldonado, 2018). Delirium is depicted by disturbances in attention, awareness, and multiple cognitive functions, which develops acutely following a major bodily insult such as major surgery or infection (Lorenzl et al., 2012). Delirium is diagnosed as representing a change or deviation from the patient's usual cognitive functioning and cannot be attributed to any pre-existing neurocognitive disorder or other known causes (Maldonado, 2018). It is associated with worse outcomes for patients, such as longer length of hospital stay, increased risk of long-term cognitive decline, and mortality (Ely et al., 2004). Some patients are at higher risk of developing delirium than others and the risk factors are multi-faceted and highly complex (Inouye et al., 2014; Ormseth et al., 2023).

The intricate puzzle of delirium, particularly its selective manifestation in elderly patients following surgery, has motivated an in-depth exploration into the underlying predisposed vulnerability factors (Ely et al., 2007; Ormseth et al., 2023; Sauër et al., 2017). Every individual possesses cognitive reserve (CR) which is the brain's ability to maintain normal cognitive function and resist the effects of brain damage or pathology before showing signs of noticeable cognitive impairment (Steffener & Stern, 2012; Stern, 2014). It is thought

to be built up over a person's lifetime through various intellectual, educational, and social activities (R. S. Wilson et al., 2019). Previous research has suggested that older adults with lower CR were more likely to develop postoperative delirium, with a higher severity (Tow et al., 2016). This thesis aimed to delve into a comprehensive investigation focused on unravelling the intricate interplay between pre-operative cognitive profiles, neural oscillations, and the potential susceptibility to post-operative delirium. Due to the COVID-19 pandemic, which imposed substantial limitations on research methodologies, the thesis research question has changed substantially.

It is important to highlight that due to the constraints imposed by the pandemic, our investigation has been constrained to healthy elderly participants, providing practical and valuable insights within this distinct context. What we aimed to do was create a standardised protocol that could be done at patients' pre-operative appointments to see if they would be at risk of developing postoperative delirium. This is why it was important to consider electroencephalographic (EEG) mechanisms that could be done with the patient in a passive state; these patients are very ill and are not usually capable of or willing to do a long extensive EEG active engagement task. We wanted to make the pre-operative cognitive and EEG assessment stages as simple as possible for these patients, so we used a simplified EEG system of only six channels (see 5.4.5 for details). Through our choices of EEG mechanisms (expanded upon in 1.3), the patients were able to relax and watch their show/film of choice while passively listening to the noises presented to them through noise-cancelling headphones. The cognitive assessment incorporated short tests that examined different cognitive aspects in detail (see 5.4.3). This provided more valuable information than standard measures of CR (see 2.4.7).

The original process of this PhD was to use this protocol in healthy older participants and for them to function as a control group against the patient group that would be collected from the hospital. However, due to the covid outbreak, recruitment had to be stopped and only a few patients were collected with incomplete data. For the healthy participants to act as a control group for the patients, there was a requirement for them to be over the age of 70 years, as those were the same restrictions for our patients. The idea was that older patients were more likely to develop delirium so they should be monitored more closely (Ormseth et al., 2023). Even though this research focuses on ageing healthy participants, the aim of the PhD is not the investigation of the ageing process. Rather, our research endeavours to explore the intricate relationship between specific properties of EEG and performance on neuropsychological tests. By delving into this correlation, we aim to elucidate how EEG patterns can be used to objectively quantify the cognitive changes observed in individuals experiencing delirium.

If there is a strong significant correlation between EEG mechanisms and neuropsychological scores, then only the EEG part of the experiment needs to be carried out. EEG is far more objective than neuropsychological scores and is less anxiety provoking for the patient as they will not be aware of how well they are performing (Dorenkamp & Vik, 2018). Objective EEG tests have advantages over traditional neuropsychological tests, as EEG provides a direct and quantitative measure of brain activity, allowing for a more precise assessment of cognitive functions (Biasiucci et al., 2019; Teplan, 2002). EEG's real-time monitoring capability captures dynamic changes in neural activity, offering insights into the temporal aspects of cognitive processing (Møller et al., 2020). Furthermore, EEG is non-invasive and does not rely on subjective self-reporting, reducing the potential for biases

associated with traditional neuropsychological assessments (Møller et al., 2020; Teplan, 2002). The objectivity of EEG results enhances the reliability and reproducibility of findings, contributing to the overall validity of the study.

To see if this would be possible, the chosen cognitive and EEG mechanisms are discussed below, with explanations of why we chose to investigate them and how they would further our understanding of pre-operative susceptibility to developing delirium.

1.2 Pre-operative Cognitive Assessment

Thorough pre-operative cognitive profiling of participants was central to our investigative approach. Employing a battery of carefully curated neuropsychological assessments, we wanted to investigate specific cognitive domains encompassing memory, attention, executive functions, and language, as these tend to be compromised during delirium (Androsova et al., 2015). We didn't want to use composite cognitive scoring measures such as the Mini Mental Stat Examination (MMSE), as this had been done already (Veliz-Reissmüller et al., 2007), and it is not very informative of a full cognitive profile. Standardised measures of CR, namely the Cognitive Reserve Index Questionnaire (CRIq), also do not incorporate tests of neuropsychological functioning, only lifestyle factors. We were interested in patients' pre-operative cognitive profile and how this related to their EEG responses. Therefore, we aimed to measure a full cognitive profile with as minimum a burden for the patients as possible.

1.3 Preoperative EEG Assessment

The following EEG responses were chosen on the basis that the patients can be passive during the measurements, as this reduces cognitive burden, particularly when they have completed cognitive assessments prior. Additional reasons include that delirium is a disorder of consciousness and altered mental status (Charlton & Kavanau, 2002; Jacobson, 1997), therefore, we selected responses that are also highly investigated in neuropsychiatric disorders of consciousness, e.g. schizophrenia, due to the overlapping symptomatology (discussed in 6.1.2).

1.3.1 Sensory Gating: P50, N100, P200

Our investigation extends to sensory gating (SG), a phenomenon integral to the brain's ability to filter out extraneous sensory stimuli (C. H. Cheng et al., 2018). While our research is constrained to control participants, the relevance of SG becomes apparent in disorders like schizophrenia and Alzheimer's Disease (AD), which are also characterized by overlapping symptomatology with delirium (e.g. hallucinations, disorientation, and memory dysfunction (Oliver, 2016)). The assessment of SG within our control cohort adds a dimension to our exploration, shedding light on shared vulnerabilities and mechanisms that might underpin delirium.

1.3.2 The Auditory Steady-State Response

Within the scope of our research framework, the Auditory Steady-State Response (ASSR) has been widely explored in the context of neuropsychiatric disorders such as schizophrenia (O'Donnell et al., 2013) and disorders of consciousness (Plourde & Boylan, 1991), both sharing symptomatic parallels with delirium (e.g. hallucinations, Charlton & Kavanau, 2002; consciousness disturbance, Boustani et al., 2014). Despite the restriction of our research to control participants, the application of ASSR can potentially discern underlying neurophysiological mechanisms contributing to predisposed vulnerability to delirium. This approach allows us to explore the subtleties of neurophysiological indicators, providing a foundation for identifying potential markers associated with the predisposition to delirium.

1.3.3 Peak Alpha Frequency

The final component of our multifaceted approach revolves around the examination of alpha activity, namely peak alpha frequency (PAF). These neural oscillations, noted for their age-related alterations (Polich, 1997) and their association with frailty (Hight et al., 2018), and post-surgical pain (Millard et a al, 2022), collectively capture risk factors for the manifestation of delirium (Kalimisetty et al., 2017). As such our analysis of alpha wave patterns within our control participants aims to unearth potential neurophysiological markers indicative of predisposed vulnerability to post-operative delirium (Chapter 7).

1.4 Conclusion

The pursuit of understanding predisposed vulnerability to delirium within the complex landscape of the COVID-19 pandemic emphasises the flexibility of scientific inquiry even amid challenging circumstances. While our research endeavours have been constrained to control participants, the multifaceted investigation into pre-operative cognitive profiles, auditory neural responses via ASSR, SG mechanisms, and PAF, collectively provide a roadmap for untangling factors contributing to postoperative delirium susceptibility. These initial findings show how flexible scientific research can be, and they give us a starting point for creating specific ways to help reduce the effects of delirium in a vulnerable group of people. This is important even in research restricted by a worldwide pandemic.

1.5 Outline of the Thesis

The overarching aim of the thesis is to investigate the role of sensory processing and neural functioning in relation to neuropsychological abilities in healthy older adults, to test the feasibility of such a protocol in pre-operative hospital assessment appointments.

Chapter 2 is an introduction into the mechanisms involved in CR, and how this is mediated by ageing and what can happen to someone's physiology as the age, is they have a low or high CR. Here, I discuss different mechanisms which may make some adults more vulnerable than others in the context of CR.

Chapter 3 concerns the methodology and the background behind EEG. I describe the science behind how EEG works, the strengths and limitations, and why it is an appropriate method in this setting.

In Chapter 4, we were interested in what the previous research had stated on this topic and, mainly, what EEG setup was used, how they measured the patients' cognitive abilities, and what their results were.

Chapter 5 was set up to evaluate the ERPs P50, N100, and P200 and relate these to measures of neuropsychological functioning. These paradigms are well-documented in the literature and are the best ways to measure SG in older adults.

We wanted to investigate more measures of inhibition and SG to strengthen our conclusions, so we included the ASSR within the experiment. The results of the ASSR were also related to cognitive tests in older adults in Chapter 6.

In Chapter 7, we examined the peak alpha frequency in both young and old participants to see if there was a significant difference between their peak alpha frequencies and cognitive reserve built up over the lifespan.

The general discussion in Chapter 8 includes a summary of previous research, our findings, the limitations of our study, conclusions, and ideas for future research.

Chapter 2 General Introduction

2.1 The Ageing Brain

The number of older adults (> 65 years) developing a neurological or neuropsychiatric disease will rise as the population aged over 80 years old grows (Béjot & Yaffe, 2019). As of 2021, 32% of adults over 85 years old suffer from a form of dementia or cognitive decline (Alzheimer's Association Report, 2020). This burdens the healthcare system, family members, and caregivers (Alzheimer's Association Report, 2020).

Ageing has multiple impacts on our brains, with significant consequences on daily life functioning for older adults (Murman, 2015; Peters, 2006). Within brain ageing, there are varying amounts of dysfunctional severity in crucial cognitive networks, mainly within the medial temporal lobe (Jagust, 2013; West, 1996). Brain shrinking also occurs during ageing, predominantly in the frontal regions of the brain, such as the prefrontal cortex (PFC) (Bishop et al., 2010; Peters, 2006). With this, memory decline can also materialise with ageing. Brain activation during memory tasks requires more areas of the brain to interact due to specific areas no longer being easily accessible (Bishop et al., 2010; Jagust, 2013). Environmental factors, genetics and neural functioning all have an essential role in ageing (Anderton, 2002).

Those with higher levels of education and active brains are more likely to have more cognitive reserve than others (Griffa et al., 2021). Cognitive reserve (CR) refers to the brain's

ability to maintain normal cognitive function and resist the effects of brain damage or age-related changes (Steffener & Stern, 2012; Stern, 2014). This concept suggests that individuals with higher CR can tolerate a greater degree of brain pathology before experiencing noticeable cognitive decline or impairment (Stern, 2012). It is thought to be built up over a person's lifetime through various intellectual, educational, and social activities (R. S. Wilson et al., 2019). Engaging in mentally stimulating tasks, such as learning new skills, pursuing education, engaging in complex cognitive activities, and maintaining a socially active and intellectually rich lifestyle, is believed to contribute to the development of CR (Thow et al., 2018).

Individuals with a higher CR are better able to adapt to brain changes or damage; even if their brains show signs of pathology or injury, they may still be able to function at a relatively higher cognitive level compared to individuals with lower CR (Barulli & Stern, 2013). Those who live a healthy lifestyle are likely to be more protected against cognitive decline (Bishop et al., 2010). Higher CR in psychopathological and psychiatric contexts is linked to a delayed onset and diminished symptom severity, helping to reduce impacts among individuals with schizophrenia (Herrero et al., 2020). It also plays a role in the trajectory and outlook for those with bipolar disorder (X. Lin et al., 2020), and moderates the impact of major depressive disorder on neurocognitive test results (Venezia et al., 2018). Therefore, some may be more at risk of neurological and neuropsychiatric disease than others during old age (Mungas et al., 2010).

As the central nervous system (CNS) ages, there is significant age-related brain shrinkage, ventricles and sulci enlargement, and synaptic loss (Raz et al., 2005; Raz et al.,

2007; Tsvetanov, 2012). Research suggests that brain volume decreases at approximately 5% every ten years after 40 years old (Peters, 2006; Svennerholm et al., 1997), and this decline accelerates over the age of 70 (Scahill et al., 2003). Reduction of grey matter in the brain is commonly stated to result from neuronal cell death (Raz et al., 2007) and this brain volume reduction can create extra impacts on an ageing brain (Peters, 2006). The PFC, temporal lobe and hippocampus are notably reduced in grey matter volume due to age (Boyke et al., 2008; Morrison & Baxter, 2012). These authors suggest that grey matter volume in the PFC is most affected, and grey matter volume in the occipital lobe is the least affected by ageing (Peters, 2006). This conclusion aligns with the cognitive fluctuations noted in ageing populations, such as reduced working memory, problem solving and attentional deficits, although some research has also postulated that ageing has the most significant impact on grey matter reduction in the hippocampus (Anderton, 2002; Barnes, 2003). This heterogeneity in volume reduction highlights inconsistencies within the ageing brain, which may make some older adults more vulnerable than others to mild cognitive impairment (MCI) and Alzheimer's Disease (AD) (Mungas et al., 2010).

Additionally, it has been shown that neuronal loss, vascular changes, and glial and dendritic dysfunctions are highly correlated with an age-associated decline in cognitive performance (Raz et al., 2007). Multiple studies have consistently observed age-related degeneration in several cognitive domains, including perception, long-term memory, working memory (WM), language, attention, and speed processing (Smits et al., 2015).

There is consensus in research that older adults are heterogeneous regarding their cognitive abilities. The heterogeneity in the literature on cognitive abilities in older adults provides valuable insights and implications for understanding ageing, cognitive decline, and potential interventions. The variability in cognitive ageing across older adults highlights the significance of individual differences (Whalley et al., 2004). Not all older adults experience the same degree of cognitive decline, and some may even exhibit improvements in certain cognitive domains (Thow et al., 2018). This stresses the need to consider a range of factors such as genetics, lifestyle, education, and health status when studying cognitive abilities in older populations (Pettigrew & Soldan, 2019).

Heterogeneous outcomes in ageing further emphasise the role of CR. Some older adults may possess higher CR due to factors like education, engaging in mentally stimulating activities, and maintaining social connections (Fittipaldi et al., 2023). This reserve can act as a buffer against cognitive decline and may explain why some individuals perform better than expected on cognitive tasks (Zarantonello et al., 2020). The variation in cognitive decline patterns across different cognitive domains (e.g., memory, attention, executive functions) highlights the importance of studying these abilities separately (Zarantonello et al., 2020). Some domains may decline earlier or more rapidly than others, indicating that interventions and assessments should be tailored to specific cognitive functions (Opdebeeck et al., 2014).

Inconsistencies in the literature reflect differing reported levels of neural plasticity among older adults (Barulli & Stern, 2013). Some individuals have capabilities similar to those of much younger adults (Markiewicz et al., 2021), whereas others show noticeable decline

(Fein et al., 2007). The conventional opinion of cognitive ageing is that older adults will often suffer from attention deficits, distractibility, inability to follow a conversation and memory loss (Biss et al., 2013). However, some cognitive domains, predominantly semantic memory or knowledge, are relatively well preserved in old age (> 65 years old) (Park et al., 2002). Cognition that most consistently declines with age includes processing speed, WM, and episodic memory (Cheng et al., 2015; Milham et al., 2002; Murman, 2015; Park et al., 2002). Understanding the neural mechanisms behind this plasticity could inform interventions to enhance cognitive functioning.

The heterogeneity may be partly attributed to variations in health conditions and lifestyle factors. Chronic diseases (Pawelec et al., 2014), physical activity (Kramer et al., 2006), nutrition (Vauzour et al., 2017), and sleep quality (Gildner et al., 2014) can influence cognitive ageing. Accounting for these variables is crucial for accurate interpretations of cognitive outcomes. The use of different assessment tools, research designs, and participant characteristics across studies can also contribute to heterogeneous findings (Harrison et al., 2015). A critical examination of methodologies can provide insights into how variations in results may be attributed to methodological discrepancies.

The variability in cognitive trajectories emphasises the need for personalised and targeted interventions. A one-size-fits-all approach may not be effective. Tailoring interventions based on individual characteristics and needs can potentially yield more positive outcomes (Griffa et al., 2021). The diversity of outcomes highlights the importance of early detection and monitoring of cognitive changes (Sirály et al., 2015; Valdes et al., 2016). Regular

cognitive assessments can help identify individuals who might be at risk for decline and enable timely interventions (Valdes et al., 2016).

The heterogeneity in the literature on cognitive abilities in older adults highlights the complexity of cognitive ageing. It encourages researchers and clinicians to adopt a refined approach that considers individual differences, CR, domain-specific changes, health factors, and methodological considerations. By embracing this complexity, we can gain a deeper understanding of cognitive ageing and develop more effective strategies to promote cognitive health in older adults.

2.2 Frontal Hypothesis of Ageing

The Frontal Hypothesis of Ageing (FHA) (West, 1996) postulates an age-related decline in cognitive functions requiring inhibitory or attentional regulation. This hypothesis posits that there is a more significant decrease in volume, white matter density and synaptic density in ageing in the PFC than in other brain areas (Andrews-Hanna et al., 2007; Hedden & Gabrieli, 2004). Neuroimaging studies have indicated that the changes in brain structure and function in ageing happen first in the frontal lobes (Raz et al., 2005). Subsequently, other cognitive processes that are anatomically located close to the frontal lobes are more vulnerable to the effects of ageing than cognitive domains related to other brain areas (Phillips & Henry, 2008). Inhibition is a critical component that reduces with age, and it is thought to be also located in the PFC (Munakata et al., 2011).

Attentional networks are also affected by ageing (Guerreiro et al., 2010). Older adults are more at risk of being easily distracted. They have decreased attention (Sebastian et al., 2013), require increased time for an appropriate response (Anguera & Gazzaley, 2012), show increased forgetting (Ludowig et al., 2010; Waldhauser et al., 2012), difficulty in understanding speech when background speech or noise is present (Scurry et al., 2021), and struggle with ignoring visually distracting information while reading (Bell & Buchner, 2007). They are more likely to encounter more interference from task-irrelevant stimuli (Nielson et al., 2002) when learning a new task and less fluency when doing a verbal fluency task (Pekkala, 2012). Irrelevant information also persists in WM tasks which compete with information relevant to the task at hand (Gamboz et al., 2009).

Deficits in inhibitory processes facilitate both motor control and sensory gating (SG) (Wan et al., 2017). Increased difficulty in managing more than one situation using sensory and motor areas is common in healthy ageing (Anguera & Gazzaley, 2012). Sensory gating is a cognitive process that filters and regulates incoming sensory information to prevent sensory overload and enhance the brain's ability to focus on relevant stimuli (C. H. Cheng et al., 2018). It involves mechanisms that enable the brain to distinguish between significant stimuli and background noise (Smucny et al., 2013). Key cognitive mechanisms associated with SG include inhibitory gating, and underlying cortical processes (L. A. Jones et al., 2016a). A way of investigating SG is using paired-stimulus paradigms; this involves presenting two closely spaced sensory stimuli in rapid succession (Dalecki et al., 2011). The brain's response to the second stimulus is often reduced if the first stimulus is deemed non-salient or irrelevant (Croft

et al., 2001). This phenomenon reflects the brain's ability to prioritise and allocate resources to salient stimuli while filtering out redundant or less important information (Meier, 2014).

Sensory gating is often achieved through inhibition, where inhibitory neurons in the brain prevent excessive neural firing in response to repetitive or redundant stimuli (Cromwell et al., 2008; Grunwald et al., 2003). This inhibition prevents the brain from becoming overwhelmed by unimportant sensory input, allowing it to focus on pertinent information (C. H. Cheng et al., 2015; Cromwell et al., 2008). An example of SG in the context of attention can be illustrated through the Attention Network Test (ANT) (Balter et al., 2019; Wan et al., 2008). This test evaluates three distinct attentional networks: alerting, orienting, and executive control (Balter et al., 2019; Wan et al., 2008). Sensory gating mechanisms are engaged when the brain filters out irrelevant stimuli, allowing the individual to focus on the relevant cues that drive their attention and response (L. A. Jones et al., 2016a; Light et al., 2010). This process ensures that the brain allocates its cognitive resources efficiently, enhancing attentional performance (Rosburg, 2001; Zumer et al., 2014). This aligns with the bottom-up process, where the brain's initial assessment of sensory input guides attentional allocation (C. H. Cheng et al., 2018). This enables the brain to filter out irrelevant stimuli, enhance attentional focus, and optimize cognitive resource allocation (C. H. Cheng et al., 2018; Zumer et al., 2014).

Despite this decline in the efficiency of inhibitory processes with cognitive ageing, not all inhibitory functions are impaired. Specifically, older adults are impaired in inhibition processes that involve controlled or top-down (TD) mechanisms (e.g. Go/No-Go tasks when compared with young adults; (Vallesi et al., 2009) but not necessarily in processes that can be

considered more automatic or unintentional (e.g. SG paradigms (Cheng et al., 2018)). Older adults may not be impaired, but SG abilities decrease with normal ageing (Golob et al., 2007); but it's still ambiguous whether this impacts CR in older adults and vice versa.

2.3 Cognitive Reserve Hypothesis

The Cognitive Reserve Hypothesis (CRH) proposes individual differences and variations in the brain's ability to adapt and use its cognitive networks to allow individuals to cope with brain insult, injury or change better than others (Steffener & Stern, 2012). Cognitive reserve is defined as individual differences in cognitive performance (Stern, 2013). It is thought that those who perform better on these tasks will be more resilient and less vulnerable than those who do not (Stern, 2012). Furthermore, CR provides individuals with a higher level of neural proficiency and increased neural capability. The brain is more able to compensate by recruiting extra brain areas when necessary (Tucker & Stern, 2011).

Cognitive reserve is commonly measured by using the intelligence quotient (IQ) (Gazes et al., 2021a) or level of education (Thow et al., 2018). It can also be estimated using social intelligence (Salas et al., 2021), job difficulty (Richards & Sacker, 2003), and even personality (Colombo et al., 2020). The literature is inconsistent regarding just including education as a marker of CR (Wilson et al., 2019).

Many domains within CR are interrelated, and this can make it challenging to discern valid causal relationships. For instance, more intelligent individuals with higher IQs will be

more likely to go on to further education, leading to increased IQ and more demanding jobs (Ceci, 1991; Richardson & Norgate, 2015). Researchers have also found that life events can contribute to CR in later life (Richards & Sacker, 2003). Childhood education, early adulthood education and job status in adulthood all contributed to cognitive performance at age 57 (Richards & Sacker, 2003). Therefore, while early childhood factors are central in the build-up of lifetime CR, it continues to be affected by different occurrences throughout the lifespan (Richards & Sacker, 2003).

Behavioural and cognitive assessments can both measure CR, and more recently, it has been measured by examining neural activity networks, using functional magnetic resonance imaging (fMRI) (Bartrés-Faz et al., 2009) and electroencephalography (EEG) (Balart-Sánchez et al., 2021). Changes in functional brain activity can result in changes in cognitive performance (Stam et al., 2006). As studied by behavioural, cognitive, or neural processes, CR can help preserve functioning by mediating the relationship between age, neural activity and cognitive performance (Gazes et al., 2021a; Tucker & Stern, 2011).

Those with higher CR are more likely to have improved clinical outcomes for any level of neural pathology (Steffener & Stern, 2012; Tucker & Stern, 2011). Many believe that CR helps older individuals counteract the ageing brain pathology by using remaining brain areas to cope with cognitive demands (Mortimer et al., 2003).

2.4 Role of Cognitive Reserve

2.4.1 Resilience

Cognitive reserve plays a significant role in ageing populations by promoting resilience against age-related cognitive decline and protecting individuals from the detrimental effects of brain pathology (Stern & Barulli, 2019; Tow et al., 2016). The main role of CR in ageing populations can be to delay cognitive decline in individuals (Stern et al., 2019). Cognitive reserve enables individuals to maintain cognitive function despite the presence of age-related brain changes, such as neurodegeneration or cerebrovascular disease (Amodio et al., 2017). Higher CR is associated with a delay in the onset of cognitive decline, allowing individuals to maintain their cognitive abilities for a longer period (Stern et al., 2019).

2.4.2 Compensation

Another role of CR is to compensate for changes in the brain; it involves the recruitment of alternative cognitive networks or compensatory strategies to mitigate the impact of brain pathology (Martínez et al., 2018). When age-related changes or pathology affect specific brain regions or neural networks, individuals with higher CR can engage alternative brain networks to compensate for the affected functions (Martínez et al., 2018; Steffener & Stern, 2012). This compensation helps maintain cognitive abilities even in the face of brain changes, which may occur with natural ageing or due to environmental insults (Montemurro et al., 2021).

2.4.3 Cognitive Flexibility

An additional aspect is enhanced cognitive flexibility. Cognitive reserve is linked to better cognitive flexibility, which refers to the ability to adapt and switch between different cognitive processes or strategies (Oosterman et al., 2021; Stern, 2014). This flexibility allows individuals to cope with cognitive challenges and find alternative solutions when faced with cognitive difficulties (Steffener & Stern, 2012). In ageing populations, cognitive flexibility can support adaptive cognitive strategies to compensate for age-related cognitive changes (Bhat, 2015). When facing challenges related to memory or processing speed due to ageing, being able to switch between tasks can help older adults find alternative ways to complete their daily demands (Hakuna et al., 2015). Age-related changes can impact cognitive processing, so being able to approach problems from different angles can lead to more effective solutions (Quinzi et al., 2020). For example, CR can help older adults to use techniques like chunking, visualisation, or association to enhance memory recall, compensating for potential age-related memory decline (Johnco et al., 2013). Cognitive flexibility also contributes to brain plasticity, the brain's ability to reorganise and form new connections (Barulli & Stern, 2013). This contributes to cognitive resilience, helping individuals adapt to and recover from cognitive challenges (Amodio et al., 2017; Stern et al., 2019).

2.4.4 Reduce Risk of MCI and/or Alzheimer's Disease

Higher CR has been linked to a reduced risk of developing MCI and/or AD (Montemurro et al., 2021; Stern, 2012). It acts as a buffer, allowing individuals to maintain

their original (or slightly reduced) cognitive abilities, considered above the threshold for clinical impairment, even in the presence of significant brain pathology (Soldan et al., 2018; Thow et al., 2018).

Within the realm of MCI, individuals often rely on neural compensation as a manifestation of CR (Clément & Belleville, 2012). This mechanism involves the recruitment of supplementary neural networks to counteract cognitive decline (Clément & Belleville, 2012). Functional neuroimaging studies have elucidated increased activation in regions beyond the initially affected areas (Clément & Belleville, 2012; Steffener et al., 2011). For example, research using functional near-infrared spectroscopy showed that during a stroop test, non-amnestic MCI individuals showed significantly higher activation in the right PFC compared to healthy controls (Yoon et al., 2019). This was postulated by the researchers to be due to compensatory activation in the MCI group. Thereby, experiencing memory deficits may exhibit heightened activity in alternative memory-associated brain regions, compensating for the compromised function (Johnson et al., 2006).

Some patients experiencing MCI may progress further to develop AD, but some do not (E. J. Golob et al., 2001; Mazaheri et al., 2018). As AD progresses, the brain initially engages in neural compensation, similarly to MCI which entails the activation of additional brain regions to mitigate cognitive deficits (Sheng et al., 2021). However, as neurodegeneration ensues, a phenomenon known as neural dedifferentiation emerges (Koen & Rugg, 2018). This involves the broadening of neural networks responsible for specific functions, leading to a reduced specialisation of brain regions (Koen & Rugg, 2018). Neuroimaging studies reveal

altered activation patterns, indicating the brain's attempt to maintain cognitive performance through diverse routes, albeit less efficiently (Cassady et al., 2021). The advancing stages of AD prompt functional reorganisation as part of the compensatory response. This involves the redistribution of cognitive functions across brain areas that remain relatively intact (Hill et al., 2011). Functional neuroimaging investigations highlight the recruitment of non-traditional brain regions for specific tasks (D. C. Park & Reuter-Lorenz, 2009). This resilience highlights the role of CR in allowing the brain to flexibly reallocate functions and mitigate cognitive deficits, particularly in domains like memory and language (Stern et al., 2019).

In the late stages of AD, when extensive neural damage occurs, CR-driven adaptation becomes vital. Although neural resources are severely compromised, CR may sustain adaptive abilities through the utilisation of intact brain regions (Stern, 2012). Neuroimaging and neuropsychological studies show that individuals with higher CR exhibit relatively preserved cognitive functions even in the face of substantial neuronal loss (Lee et al., 2022). Research by Lee et al. (2022) discovered using a CR marker (made up of actual cognitive performance and estimated performance, calculated by AD neuropathology and demographics), that over time, a higher CR marker corresponded to lower disease conversion rate among prodromal AD and cognitively unimpaired individuals. Furthermore, a higher CR marker relates to accelerated cognitive decline within those with a severe disease progression, while being linked to a lessened decline in cognitively unimpaired individuals. The proposed CR marker included years of education and adjusted the influence of pathological burden on cognitive performance within the AD spectrum. These outcomes stress that CR likely influences clinical progression differently dependent on the individual’s disease status.

The intricate compensatory processes in MCI and AD emphasise the fundamental role of CR in the brain's adaptive capacity. Neural compensation, cognitive strategy adaptation, and functional reorganisation act as the brain's responses to early-stage cognitive decline (Gazes et al., 2021b). These mechanisms, influenced by CR, aim to maintain cognitive performance despite neuronal compromise (Barulli & Stern, 2013; López et al., 2014). In AD's progressive stages, the phenomena of neural dedifferentiation and late-stage adaptation reveal the brain's flexibility and resilience, facilitated by CR (Cassady et al., 2021; Koen & Rugg, 2018).

Overall, CR in ageing populations acts as a protective factor, allowing individuals to maintain cognitive function and adapt to age-related changes and brain pathology (Varela-López et al., 2022). It enhances cognitive resilience, delays cognitive decline, and reduces the risk of cognitive impairment and dementia. Nurturing CR through lifelong learning, cognitive stimulation, and engaging in intellectually challenging activities can promote healthy ageing and cognitive well-being (Thow et al., 2018).

2.4.5 Genetic Factors in Cognitive Reserve

Cognitive reserve is influenced by a combination of genetic and environmental factors. While genetics can contribute to the development and functioning of the brain, including cognitive abilities, CR is not solely determined by genetics and is strongly influenced by environmental and lifestyle factors (Yegla & Foster, 2022).

Genetic factors play a role in cognitive abilities and can contribute to individual differences in CR (Pietzuch et al., 2019). Certain genes are associated with cognitive function,

neuroplasticity, and resilience against cognitive decline. For example, the APOE ε4 allele is a genetic risk factor for late-onset Alzheimer's disease and may affect CR (Christie et al., 2012; Pietzuch et al., 2019). However, the influence of genetics on CR is complex and likely involves interactions with environmental factors.

Environmental factors, such as education, occupation, cognitive engagement, and social activities, are known to contribute significantly to CR (Song et al., 2022). These factors provide intellectual stimulation, promote learning, and help build cognitive skills and neural networks (Klingberg et al., 2022). Environmental experiences throughout life shape CR and can have a substantial impact on cognitive abilities, even in individuals with genetic predispositions (D. Ward, 2015). Engaging in intellectually stimulating activities and continued learning throughout life contribute to CR (Flexman, 2021). Lifelong learning helps build cognitive skills, increases brain connectivity, and enhances neural plasticity (Ersoezlue et al., 2023). Activities such as reading, solving puzzles, playing musical instruments, or learning new languages can strengthen CR (Ersoezlue et al., 2023). Other lifestyle factors, including physical exercise, a healthy diet, social engagement, and the management of chronic diseases, can influence CR (Lavrencic et al., 2016; Sanchez-Lopez et al., 2018; Vauzour et al., 2017). These factors promote brain health, improve vascular health, and reduce the risk of cognitive decline and neurodegenerative diseases (Delgado-Gallén et al., 2021).

2.4.6 Studying Neural Mechanisms of Cognitive Reserve in Ageing

Cognitive reserve comprises cognitive processes' efficiency, capacity and flexibility when faced with a task or challenge. It explains the subject's adaptiveness of their brain processes (Šneidere et al., 2020). The biomarkers of CR per sé are still unclear, but several studies have postulated that neural differences between individuals could explain this (Gazes et al., 2021a; Speer & Soldan, 2015). Neural Reserve Theory states that there is variability in the way in which brain networks function together during a task in an efficient manner (Stern, 2009), this is also explained earlier (see 2.4). Neural compensation suggests that other brain networks can activate and compensate for the damage when there is a brain pathology or atrophy (Stern, 2009). Research investigating these networks found that higher CR individuals demonstrated reduced connectivity in the dorsal attention network (DAN), and increased activation within frontal regions in the left fronto-parietal control network (FPCN) (Varela-López et al., 2022). Both the reduced DAN and increased FPCN network activity were highly correlated with increased executive function (EF), memory and language. The author's suggested that this showed a protective role of CR, as it increased neural capacity and efficiency.

Healthy older adults with high CR have strong performance on neuropsychological tests and reduced brain activity compared to those with a lower CR (Fleck et al., 2017; López et al., 2014). However, the opposite has also been found in high CR individuals with AD and MCI; they show higher network activation than those with lower CR (Steffener et al., 2011). Those with high levels of CR can also act as a protection and are thought to delay the onset of

cognitive symptoms in AD (Steffener & Stern, 2012). Therefore, CR could provide a process where neural efficiency can aid neural compensation during age-related cognitive decline (Barulli & Stern, 2013).

Two proposed neural mechanisms describe CR: neural reserve and neural compensation (Stern, 2006). Neural reserve is thought to encompass the cognitive networks developed throughout the lifespan due to genetics and environmental experiences (Barulli & Stern, 2013). It could also be argued that someone with higher neural reserve also has more efficient cognitive networks; this includes less energy used to complete a task or 'smarter' use of brain networks (Steffener & Stern, 2012). Therefore, neural reserve incorporates and explains many of the variabilities between healthy ageing individuals in CR (Speer & Soldan, 2015; Steffener & Stern, 2012). Other models also posit that higher intelligence can give individuals higher neural efficiency (Neubauer & Fink, 2009).

This neural efficiency can be tested using event-related potentials (ERPs) in EEG, as they can detect very subtle and preclinical neural abnormalities that may not be seen with conventional neuropsychological measurements (Yang et al., 2011). These ERPs can identify these cognitive deficits by measuring early brain responses to sensory stimuli (e.g. P50 suppression, N100, P200 (Lijffijt et al., 2009)), which reflect sensory input while other ERPs measure higher-order cognitive functions (e.g. P300, P600 (Olichney et al., 2008)) which reflect decision making and semantic input (Olichney et al., 2011).

As previously discussed, cognitive and physiological ageing is associated with a decline across cognitive domains. The inhibition abilities of cortical and subcortical neurons, which

are affected by ageing, play an essential role in the higher-order cognitive functions (Gazzaley et al., 2005). The brain's ability to prevent over flooding of sensory input through SG is crucial because it protects the executive brain areas from irrelevant sensory stimuli, which is shown to decline in ageing using select ERPs (Cheng et al., 2015). These ERPs in SG have been linked to various neuropsychological abilities involved in CR, such as intelligence (Jones et al., 2016b), EF (Thomas et al., 2010), and psychiatric history (Clementz et al., 1997; Neylan et al., 1999).

2.4.7 Difficulties of Studying Cognitive Reserve

Measuring CR consistently in the literature presents a difficult challenge, primarily due to the absence of a standardised approach and the variability in measurement tools employed in the literature (Harrison et al., 2015). One such tool, the Cognitive Reserve Index questionnaire (CRIq), is not consistently utilised, further contributing to the complexity of measuring CR (Balart-Sánchez et al., 2021; Harrison et al., 2015). The dilemma is whether CR should be quantified exclusively through neuropsychological tasks, as demonstrated in this study, or if specific validated life experience instruments such as the CRIq should be solely used for CR.

For instance, the CRIq, designed to gauge CR, encompasses a range of factors such as educational attainment, occupation, and leisure activities (Nucci et al., 2012). These factors are important in determining one's level of CR, however, there is the danger that the CRIq may oversimplify the multi-faceted nature of CR, by ignoring complex cognitive abilities, and

relying solely on self-reported information which is subject to self-report bias (Del Boca & Noll, 2000). This makes the CRIq highly subjective which can reduce its reliability and consistency between administrators (Kartschmit et al., 2019). Some studies therefore opt to focus solely on neuropsychological tasks (e.g. language, memory, attention) (Alonso et al., 2019; Speer & Soldan, 2015), while others consider specific cognitive components like IQ and EF (Arakaki et al., 2022).

While the CRIq serves as a standardised tool, its inconsistent utilisation in the literature reflects the ongoing debate on how best to measure CR (Kartschmit et al., 2019; Nucci et al., 2012). The lack of consensus regarding the inclusion of IQ, EF, or other cognitive factors, and social factors compounds the challenge of achieving consistent measurements, and therefore consistent results (Kartschmit et al., 2019). This dilemma emphasises the need for further research and dialogue to establish a standardised approach that comprehensively captures the essence of CR while accounting for its multifaceted nature (Harrison et al., 2015; Opdebeeck et al., 2014; Pietzuch et al., 2019).

The current literature can be inconsistent on what measures best correlate with which neural activity for measures of CR. Therefore, the literature will be explored regarding neural measures including EEG and MEG brain signatures that have been correlated with CR measurements in the past (see Chapter 4). MRI will not be included, as this does not fulfil the aim of the thesis of being carried out at preoperative appointments quickly in hospitals. To further understand what is happening in the EEG and different neural signatures related to CR,

the subsequent chapter will explore the mechanisms behind EEG in detail to further understanding of these mechanisms.

Chapter 3 Neural Underpinnings of EEG

Following on from the previous chapter discussing theories of ageing, there are various neural mechanisms involved that are thought to mediate the relationship between cognition and healthy ageing. The following chapter will focus on the background of electroencephalography (EEG), its mechanisms, and how it can be utilised best to investigate cognitive reserve (CR) within ageing.

Abstract

EEG and magnetencephalography (MEG) are the most suitable and appropriate techniques to use for non-invasive brain measurement to investigate the brain's electrophysiological mechanisms. EEG has extremely high temporal resolution but also falls short when it comes to spatial resolution. EEG measures the large synchronous population-level neural activity in humans, so trying to narrow measurements down to only capture small-scale neuronal activity is near impossible. EEG is thought to be generated from the cortical pyramidal neurons perpendicular to the brain's surface. EEG can detect only a portion of all the varieties of electrical activity going on in the brain, and does so regardless of the presence of other physiologic electrical activity (such as cardiac, ocular, and other muscular activity) and environmental noise (such as computer screens and other electric equipment, power lines). This can create challenges when using EEG to measure participants and patients, which makes making causal conclusions between neural mechanisms and indicators of CR.

3.1 What is EEG?

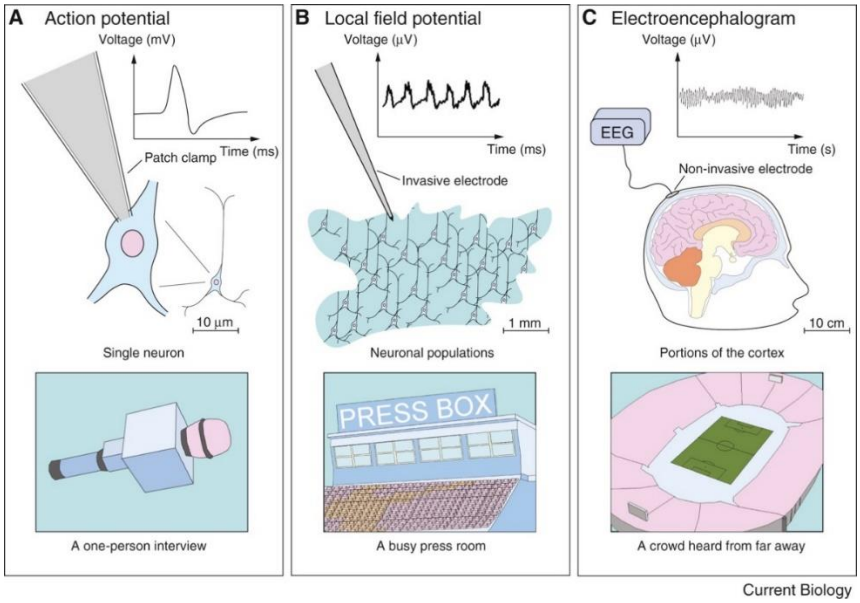
EEG offers many opportunities in how it can measure activity in the brain. Biasiucci et al. (2019) provide an informative and accessible analogy of the three main ways in which EEG can be used to measure varied sizes of neuronal populations. These are the method of single cell electrophysiology, which measures the activity of individual neurons, local-field potentials (LFP) and EEG which measures neuronal activity across cortices. Biasiucci et al. (2019) offer the diagram below (see Figure 3.1) with an explanation that EEG can measure the activity of single neurons, small populations of neurons and portions of the cortex.

EEG is thought to be primarily generated by cortical pyramidal neurons in the cerebral cortex that are oriented perpendicularly to the brain's surface (St. Louis et al., 2016). EEG captures the collective electrical potentials resulting from synchronous firing of excitatory and inhibitory postsynaptic potentials across large groups of neurons (St. Louis et al., 2016). However, conventional EEG, whether recorded from the scalp or cortical surface, cannot detect rapid changes in local-field potentials associated with neuronal action potentials (St. Louis et al., 2016).

From a biophysical standpoint, our understanding of the origins of LFP and EEG is relatively well-established (Buzsáki et al., 2012). According to the "standard model" of EEG, LFP and EEG represent extracellular currents resulting from the summation of dendritic postsynaptic potentials, occurring across thousands to millions of parallel-aligned pyramidal cells (Nunez & Srinivasan, 2006). While postsynaptic potentials contribute significantly, other

neural processes such as calcium and sodium spikes, glial cells, active and passive currents, and mono/quadripolar sources also contribute to LFP to varying degrees (M. X. Cohen, 2017). The relationship between LFP and EEG remains improperly understood, partly due to the distinct spatial scales of activity reflected in EEG and the complexity of their interrelationship (Mazzoni et al., 2010).

Figure 3.1 Methods of measuring electrical activity in the brain.



Note. From: (Biasiucci et al., 2019) "(A) The patch-clamp technique is used to record action potentials from individual neurons (single-unit recordings). Action potentials are short-duration (1 ms), high-amplitude (∼100 mV) pulses. (B) Electrode microarrays can be inserted in brain tissue to record the activity of populations of neurons. Depending on filter settings, one can isolate multi-unit activity (action potentials) or lower-frequency local field potentials (LFPs); the latter of which have spectral characteristics similar to scalp-recorded EEG. (C) In electroencephalography (EEG), macroscopic electrodes placed on the surface of the scalp measure the electrical activity of larger portions of the brain."

The anatomical structure of individual pyramidal neurons, with their organised columnar arrangement, plays a crucial role in EEG measurements (Casanova, 2010). When an excitatory postsynaptic potential occurs at the apex of a dendrite, it generates an intracellular local positive voltage and an extracellular negative current, which are the primary potentials detected by EEG (Oren & Paulsen, 2010). To be measurable at the scalp surface, neuronal populations must exhibit simultaneous activity (Biasiucci et al., 2019).

However, unclear statements such as "EEG reflects the integration of postsynaptic potentials across neural populations" do not offer researchers with a clear understanding regarding the spatial, spectral, and temporal features observed within EEG data (M. X. Cohen, 2017). These features, including frequency band-limited power modulations, functional connectivity, cross-frequency coupling, and event-related potential (ERP) components, reflect the dynamic interactions within neural microcircuits that underlie cognitive processes (M. X. Cohen, 2017). While the "standard model" explains the mechanisms of EEG, it does not elucidate the meaningful interpretation of EEG signals (M. X. Cohen, 2017; Nunez & Srinivasan, 2006).

The existing literature exploring the connection between EEG and neural microcircuit dynamics is still limited, leaving several crucial questions unanswered, especially the origins of EEG features. For instance, studies have shown a nonlinear relationship between spatial integration (measured through spike-count correlation) and EEG power (Snyder et al., 2015). Higher spike-count correlations were associated with both high and low EEG amplitudes, while low spike-count correlations occurred during time periods with intermediate EEG amplitudes

(Snyder et al., 2015). Hence, EEG and LFP offer distinct insights into brain function, and the relationship between spatial integration and EEG activity varies in intricate ways across different frequency bands (M. X. Cohen, 2017).

3.2 Neural Oscillations

Neural oscillations represent a prominent feature in EEG data, and extensive research spanning decades has consistently linked specific patterns of oscillations to perceptual (Romei et al., 2010), cognitive (Freunberger et al., 2011), motor (Ishii et al., 2018), and emotional processes (Jirakittayakorn & Wongsawat, 2017). Oscillations are detected throughout the nervous system and at multiple spatial and temporal scales (Varela et al., 2001), and they seem to be universal across species (Buzsáki et al., 2013). This therefore suggests that oscillations have important neural functions that have been preserved over the course of evolution (Buzsáki et al., 2013). Consequently, investigating neural oscillations provides valuable insights into the temporal precision and limitations of the neural computations underlying perception, cognition, and action (Cohen, 2017).

However, the term "neural oscillations" encompasses a broad and diverse range of phenomena. These oscillations arise from different biophysical mechanisms, incorporating intrinsic properties such as ion channels, neurite lengths, and wiring, as well as extrinsic properties like input strength and noise levels (X. J. Wang, 2010). Neural oscillations generated by distinct microcircuits and within different cognitive contexts may hold varying computational significance and cognitive implications (Cohen, 2017).

3.2.1 Oscillatory Examples

One specific EEG feature worth highlighting is alpha oscillations, which have been extensively studied since their discovery by Hans Berger in 1929 (Kropotov, 2009). It is suggested that alpha oscillations play a role in coordinating temporal fluctuations in neural network inhibition (Klimesch et al., 2007). Modelling and empirical studies have proposed several mechanisms to explain the generation of alpha oscillations, including thalamocortical loops, rhythmic firing of pyramidal cells, local interneurons, and interactions of synaptic inputs with different time constants (S. R. Jones et al., 2000). However, the lack of consensus on a single cellular mechanism indicates the involvement of multiple distinct mechanisms. Additionally, alpha oscillations can vary in their amplitude, time course, and peak frequency, depending on factors such as cognitive tasks, cortical regions, and cortical layers (Haegens et al., 2014). This variability suggests the existence of numerous independent sites in the brain for alpha oscillation generation and supports the conclusion that there are many independent alpha production sites in the brain (Romei et al., 2010). While these diverse roles highlight the importance of neural oscillations in brain function, they also pose challenges in formulating unified theories and drawing straightforward inferences from EEG to neural microcircuit structure (Cohen, 2017).

Another example relates to gamma oscillations, which occur within the frequency range of 30-80 Hz and have been associated with active sensory processing. Computational models have been proposed to explain gamma oscillations by accounting for gamma-band spike-timing correlations and LFP fluctuations (Pulizzi et al., 2016). However, empirical evidence linking

these cellular mechanisms to the larger-scale gamma oscillations measured by EEG remains limited.

These examples highlight the ongoing efforts to link EEG features to underlying neural circuit dynamics and computations. Although progress has been made through the convergence of macroscopic investigations involving EEG data, cognitive neuroscience theories, microscopic studies of neurobiology, and computational approaches, challenges persist. The significant uncertainty and ambiguity associated with even widely studied EEG features emphasise the substantial explanatory gap between detailed investigations of individual or small populations of neurons and the patterns observed through non-invasive human electrophysiology (M. X. Cohen, 2017).

3.3 Event-Related Potentials

Event-related potentials are one of the first-studied approaches of EEG/MEG research; simple to compute and with good temporal resolution, they have a decades-long history in the study of brain activity during specific cognitive and motor functions (Beppi et al., 2021). An ERP is an alteration in electric potential over time related to a specific event, which reflects changes in the firing patterns of neural cells and is obtained by averaging EEG data over several trials (S. Luck, 2005). The ERP response is ‘time-locked’ to a reference event, such as a sensory stimulus or an internal process (S. Luck, 2005). The polarity and onset of the positive or negative deflections in the ERP waveform indicate underlying cognitive processes (S. Luck, 2005).

Event-related activity occurring at the same or a similar phase relative to the reference event (endogenous or exogenous) at each trial is said to be evoked activity (S. Luck, 2005). It is different from induced activity, which is not phase-locked, yet still time-locked to the trial event (M. X. Cohen, 2018). Phase-locking and non-phase-locking responses are analysed differently (S. Luck, 2005). Evoked responses have a latency of 50–150 ms after stimulus-onset and are averaged over several trials before undergoing time or spectral analysis (Kalcher & Pfurtscheller, 1995). Conversely, as induced signals have variable onset (150–400 ms) induced signals are analysed on a trial-by-trial basis, and the obtained attributes, such as power, are then averaged across trials (David et al., 2006). Furthermore, evoked and induced signals have different neural underpinnings and assumed functional roles (Tanaka & Miyakoshi, 2019; Zubarev et al., 2019). Evoked signals are proposed to mirror the bottom-up processing of incoming sensory information (Beppi et al., 2021). Non-phase-locked activity seems to capture high-level control and top-down adjustments through short- and long-range cortical projections (C.-C. Chen et al., 2012).

ERPs, event-related synchronisation (ERS) and event-related desynchronisation (ERD), are neural phenomena associated with the onset of an endogenous (internal) event or an external (sensory) stimulus (Beppi et al., 2021). However, while ERPs constitute focal time-locked and phase-locked neural responses, power or ERD/ERS changes can be time-locked activity regardless of whether it is evoked or induced (M. X. Cohen, 2014). Oscillatory patterns are mostly not phase-locked in an enclosed frequency (Diers et al., 2020). Moreover, while the ERPs reflect neural activity in response to a given stimulus, ERS/ERD dynamics stem from changes in the interaction between neural cells affecting the frequency attributes of the signal

(Beppi et al., 2021). ERPs reflect the post-synaptic activity of pyramidal neurons (M. X. Cohen, 2017), whereas (de)synchronisation patterns related to a reference event are caused by alterations to multiple properties of neural function, including physical aspects of the cell membrane, ion influx and chemical transmission (A.-K. R. Bauer et al., 2020).

ERPs remain among the most extensively used methods for investigating the neurophysiological foundations of cognitive and motor functions. Various ERP components are delineated based on distinctive morphological features of the averaged response and the characteristics of the triggering event (Beppi et al., 2021). ERPs can be used to study preattention paradigms, such as the reaction to a sensory stimulus within the initial 100 milliseconds after the stimulus (Wan et al., 2008). This early response is typically measured by a small positive (P) voltage deflection and in quick succession, a negative (N) component, known as “P50”, “N100”, and “P200” responses (Rentzsch et al., 2008). ERP responses occurring after this timeframe, suggest individual-specific higher-order cognitive processes (Gutiérrez-Zamora Velasco et al., 2021). Multiple small negative deflections characterise the typical ERP response to such unexpected events, preceding the P300, which index early sensory processing (Gutiérrez-Zamora Velasco et al., 2021).

Crucially, the structure of ERPs differs based on the specific channel, as various cortical regions exhibit distinct responses to the event under consideration (Beppi et al., 2021). Within auditory perception, ERPs exhibit sensitivity to stimulus attributes like frequency, intensity, and duration as demonstrated by the auditory steady state response (ASSR) (Beppi et al., 2021; Y. Wang et al., 2018). Wang et al. (2018) found that the ASSR signals were the

strongest in the auditory cortex, and decreased sequentially in the hippocampus, amygdala, and prefrontal cortex in the brains of rats. These ERP components can accurately predict behavioural measures such as reaction time to sensory events, even at the single-trial level (Antonova et al., 2016).

Overall, ERPs offer valuable insights into the temporal dynamics of cognitive and motor processes, and their analysis provides a window into the underlying neural activity associated with specific events and cognitive functions (Woodman, 2010).

3.3.1 Evoked Responses to Steady-State Stimuli

The ASSR is a type of ERP that assesses the strength and synchrony of auditory pathways in response to temporally modulated acoustic stimuli (Brenner et al., 2009; O'Donnell et al., 2013). ASSR ERPs are stimulated by temporally modulated acoustic stimuli; these stimuli can include sequences of clicks with fixed inter-click intervals or amplitude modulated (AM) tones (O'Donnell et al., 2013). Following stimulus onset, the EEG or MEG rapidly replicates the frequency and level of the AM tone, indicating neural synchronisation in the auditory system (Brenner et al., 2009). Irregularities in the amplitude or phase of the ASSR at increased gamma-band frequencies (>30 Hz) may indicate deficits in neural synchronisation within the auditory system (Bohórquez & Özdamar, 2008).

The generation of the ASSR primarily involves activity within the auditory pathway (Farahani et al., 2021). Modulation frequencies up to 50 Hz are believed to originate from the auditory cortex, as supported by EEG (Y. Wang et al., 2018), MEG (Kuriki et al., 2013) and

animal studies (Vohs, Andrew Chambers, et al., 2010). Higher modulation frequencies (>80 Hz) are thought to arise from brainstem areas (Y.-H. Lin et al., 2009). The specific region of the auditory cortex that is stimulated depends on the type of auditory stimulus used (Farahani et al., 2021). The most common auditory stimuli used to evoke the ASSR are AM tones and successions or trains of clicks (Picton et al., 2003). AM tones are produced by temporally modulating a tone (or a sinusoidal wave), causing a deviation of the amplitude of the tone over time (Kallenberg, 2006). The frequency of the tone is referred to as the carrier frequency and the frequency of the modulation envelope (the waveform detected when the carrier, upper sideband and lower sideband are joined in a single impedance and observed as time versus amplitude, (Joris et al., 2003) is called the modulation frequency (O'Donnell et al., 2013; Joris et al., 2003). Alternatively, the click train stimuli, consists of clicks which are brief but broad-spectrum sound stimuli (Joris et al., 2003). Thus, the click stimulus has several harmonics, while the modulation frequency of AM tones has only one peak at the stimulus frequency (Joris et al., 2003).

The tonotopic organisation of the auditory cortex influences the area of the cortex that responds to the carrier frequency or frequency content of the stimuli, with clicks stimulating a larger cortical area compared to AM tones (O'Donnell et al., 2013). This difference is reflected in the amplitude of the ASSR responses, with clicks generating higher amplitude responses than AM tones (Joris et al., 2003; O'Donnell et al., 2013). The generation mechanisms of ASSRs vary depending on the frequency, but they likely involve a combination of the superposition of individual evoked potentials to each click or cycle of modulation, as well as intrinsic oscillatory processes within the auditory pathways (O'Donnell et al., 2013).

The ASSR has been used to investigate auditory processing, hearing screening (Picton et al., 2003), and monitoring arousal during anaesthesia (Brenner et al., 2009). It has also been proposed as a potential biomarker for psychiatric conditions like schizophrenia (Thuné et al., 2016) and developmental disorders (Seymour et al., 2020). Studies using the dipole model (M. Spencer, 2012; Mulert et al., 2011), LORETA model (Reyes et al., 2005), and independent component analysis (Farahani et al., 2017) have identified the primary auditory cortex as the source of the ASSR in humans, although potent ASSR signals have also been observed in central and/or midline frontal areas (Griskova-Bulanova et al., 2011). Rodent studies have provided additional evidence for the auditory cortex as the origin region of the ASSR based on direct electrode recordings from multiple brain areas (Y. Wang et al., 2018).

While deficits within the ASSR prove to be sensitive to schizophrenia, it is not specific to only schizophrenia (Rass et al., 2010). This might be attributed to a deficit in cortical N-methyl-D-aspartate (NMDA) transmission, impacting the modulation of ASSR (Sivarao et al., 2016). Notably, impaired cortical NMDA transmission is also not exclusive to schizophrenia but is observed in other disorders (Lau & Zukin, 2007). Sivarao et al. (2016) contend that the 40 Hz ASSR serves as a significant marker for cortical NMDA function rather than merely indicating a sensory deficit.

Similar deficiencies in ASSR have been documented in patients with bipolar disorder, mirroring those seen in individuals with schizophrenia. These deficiencies encompass decreased EEG signal power at stimulation frequencies of 20, 30, 40, and 50 Hz, along with diminished EEG phase synchronisation at 20, 40, and 50 Hz (O'Donnell et al., 2004). Many

researchers posit that these ASSR impairments in schizophrenia and bipolar disorder may signify malfunctioning Gamma-aminobutyric acid (GABA) neurotransmission within the auditory cortex and its circuits (Benes & Berretta, 2001). The GABA circuits and neurotransmission play a role in modulating the generation and synchronisation of beta and gamma range oscillations (Maharajh et al., 2007). Consequently, GABA dysfunction in bipolar disorder could disrupt the ASSR at frequencies of 20, 30, 40, and 50 Hz (Sivarao et al., 2016).

3.4 Importance

Understanding the dynamics of microcircuits that underlie EEG features is of paramount importance for researchers to leverage EEG as a tool for uncovering the neural mechanisms of human cognition (M. X. Cohen, 2017). This knowledge would facilitate the integration of findings from human EEG studies and nonhuman neurophysiology, which often remain separate due to differences in taking measurements (M. X. Cohen, 2017). Furthermore, EEG is currently being explored as a valuable biomarker for pathophysiological mechanisms, treatment prediction, and assessing treatment success (Crone et al., 2006; Niedermeyer, 2003). The National Institutes of Health Biomarkers Definitions Working Group defined a biomarker as “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention” (Atkinson Jr et al., 2001). Various biomarkers, including and oscillatory, and evoked, hold promise in this regard (Furman et al., 2018; J. Olichney et al., 2011; Schuelert et al., 2018).

Identifying the origins of the EEG signal would enhance the potential of EEG in diagnosing brain disorders and predicting treatment outcomes (e.g. automated EEG algorithms (Ditzel et al., 2022)) and predict treatment outcome success, as well as increasing the success of EEG brain–computer interfaces (M. X. Cohen, 2017). It would also contribute to the advancement of EEG brain-computer interfaces.

The aforementioned ERPs demonstrate their clinical and cognitive neuroscience value by highlighting biomarkers associated with different disorders. For instance, abnormalities in P50, N100, and P200 components have been observed in schizophrenia patients, indicating SG deficits (Shen et al., 2020). Delayed P300 responses have been reported in individuals with mild cognitive impairment and Alzheimer's disease (Elverman et al., 2021; Papaliagkas et al., 2011). The amplitude and latency of the central-parietal P300b ERP component are believed to be influenced by task-related cognitive demands and information processing speed, respectively (Gu et al., 2018). P300b amplitude is often thought of reflecting cognitive resource allocation (Polich, 2007), whereas P300b latency appears to be related to information processing speed (i.e., stimulus evaluation time). Additionally, intelligence has been associated with P300b characteristics and neural efficiency as measured by EEG alpha-band ERD (Neubauer & Fink, 2009), which is functionally related to the P300b (Peng et al., 2012), suggesting that the P300b would also be related to CR. Therefore, understanding ERPs can provide insights into cognitive resource allocation, stimulus evaluation time, and cognitive functioning.

The ERPs from the EEG signal can be interpreted using time-domain analyses, or by performing time-frequency signal decompositions. Spectral analyses rely on characteristics of oscillatory activity, encompassing the frequency (cycles per second), the phase denoted by the angle (in degrees or radians) where the sine wave intersects the 0 point, and the power (squared amplitude) signifying the quantity of energy within each frequency (M. X. Cohen, 2014). Time-frequency EEG/MEG signal attributes are more easily interpretable compared to the ERPs, as the underlying neurophysiological mechanisms are better understood (M. X. Cohen, 2014). Although a lower temporal accuracy is to be expected if a short-time Fourier transform is computed over a time window, the temporal resolution can be improved, at least for faster frequencies, by performing a wavelet analysis.

In the past two decades, the investigation of these signal attributes and their changes during specific tasks has gained attention due to their potential to uncover nuanced aspects of neural activity beyond traditional averaged measures like ERPs (Cohen, 2017). Phase-shifts, which occur at a faster pace compared to amplitude fluctuations, are particularly relevant for understanding the neural dynamics involved in specific cognitive processes (S. J. Luck et al., 2011). Stimuli can induce changes in the coordination of neural oscillations across brain areas, leading to alterations in EEG/MEG signal amplitude or power, such as ERD or ERS (Speer & Soldan, 2015). Importantly, these events are sensitive to the functional roles of specific brain areas, resulting in divergent synchronization patterns observed across different channels within the same timeframe (Beppi et al., 2021).

3.5 Limitations of EEG

There are several unfortunate realities of EEG that need to be addressed. EEG has emerged as a valuable tool in cognitive neuroscience due to its high temporal resolution and non-invasiveness. Nevertheless, it is imperative to critically assess the limitations of EEG to avoid unjustified conclusions and ensure accurate interpretation of findings.

One important limitation of EEG is its reduced spatial resolution. The electrical potentials recorded by EEG reflect the influence of multiple brain regions, making precise localisation of neural activity challenging. In contrast to imaging techniques such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) that provide detailed spatial information, EEG offers limited anatomical precision (St Louis, 2016). Consequently, accurately identifying the specific brain regions responsible for cognitive processes becomes challenging.

Closely related to spatial resolution, source localisation poses a complex problem in EEG (M. X. Cohen, 2017). The scalp-recorded signals represent a mixture of neural activity from multiple brain regions (M. X. Cohen, 2017). Estimating the origins of these signals, referred to as source localisation, is a challenging task as some neural activity is likely to stem from subcortical areas which are nearly impossible to measure with scalp EEG (St Louis, 2016). Various assumptions and models are employed to approximate the neural sources, but these approaches are not without limitations and uncertainties, potentially leading to inaccuracies in source localisation (Cohen, 2017).

Due to difficulties in source localisation, the cerebral activity of interest can be overshadowed by other electrical signals originating from the body or the surrounding environment (St. Louis et al., 2016). In order to be observed on the scalp surface, the minute EEG voltages generated by the brain must navigate various biological filters that not only diminish their amplitude but also spread the EEG activity across a wider area compared to its original source (St. Louis et al., 2016). These voltages must pass through the brain, cerebrospinal fluid (CSF), meninges, skull, and skin before reaching the recording site where they can be detected (St. Louis et al., 2016). Furthermore, other electrical activities generated by biological factors, such as scalp muscles, eye movements, tongue movements, and even the heart, produce substantial voltage potentials that often overpower and obscure the cerebral activity (Cohen, 2017). Likewise, temporary disruptions of the recording electrodes, known as "electrode pop ", artifacts, can further degrade the quality of the EEG or even mimic brain rhythms and seizures (M. X. Cohen, 2017; S. Luck, 2005). Ultimately, it is important to acknowledge that both biological and environmental electrical artifacts frequently impede the interpreter's ability to accurately identify normal rhythms as well as pathological patterns (M. X. Cohen, 2017). Nevertheless, artifacts have distinctive characteristics that can be discerned by well-trained and diligent observers (M. X. Cohen, 2017).

Interpreting EEG signals in terms of specific cognitive processes presents a further challenge. EEG measures the aggregated electrical activity of thousands of neurons, making it arduous to attribute specific cognitive functions to observed neural patterns (M. X. Cohen, 2014, 2017). While certain EEG components, such as ERPs, are associated with specific cognitive processes, the relationship between EEG signals and cognitive functions is complex

and only correlational (Polich, 1997). Caution should be used when establishing direct causal links between EEG measurements and cognitive processes.

Individual variability in brain structure and function can significantly impact EEG measurements. Factors such as age, sex, and individual differences in brain anatomy or electrode placement introduce variability in EEG recordings. This variability impedes the generalisation of findings across individuals or populations. Conclusions in cognitive neuroscience would need large-scale studies with homogeneous participants.

3.6 Conclusions

Although EEG offers valuable insights into the temporal dynamics of neural activity in cognitive processes, it is essential to acknowledge and address its inherent limitations. Challenges related to spatial resolution, source localisation, signal contamination, and the interpretation of neural activity impact the reliability and validity of EEG findings. By acknowledging these limitations and employing proper methodologies, statistical analyses, and complementary neuroimaging techniques, researchers can maximise the utility of EEG in investigating cognitive processes. Future advancements in EEG technology and analysis.

Chapter 4 Current literature

Abstract

Cognitive reserve (CR) is the brain's ability to maintain normal cognitive function and resist the effects of brain damage or age-related changes and provides individuals with a higher level of neural proficiency and increased neural capability. Electroencephalographic (EEG) oscillations and event-related potentials (ERP) can help us to demonstrate vulnerability in older adults for developing neuropsychiatric diseases and functional problems in daily living. A literature search was conducted to investigate existing findings linking EEG analyses and measure of CR. The initial search revealed 703 papers, of which, a total of 23 papers were included in analysis. Of the 23 included studies, 18 used EEG and five used MEG. Eleven of the 23 used ERPs, eight studies measured resting-state brain rhythms, three studies investigated neural connectivity and one study measured hemispheric asymmetry. The most common method to measure CR was by using the CR index questionnaire (CRIq) (n = 8). Results generally showed that high CR individuals demonstrated increased connectivity, and heightened ERP and/or oscillatory amplitudes. Establishing causal relationships between EEG measures and CR poses challenges due to varied methodologies, CR indices and heterogeneous participant populations. Limitations of the included studies are discussed, with thoughts for subsequent research.

4.1 Introduction

Neurophysiological dysfunctions seen using electroencephalography (EEG) paradigms such as event-related potentials (ERP) and oscillations can help us to predict vulnerability in older adults to developing neuropsychiatric diseases and functional problems in daily living (Elverman et al., 2021; Speer & Soldan, 2015). These findings have various clinical implications in predicting health outcomes in at-risk older adults. Therefore, the current literature will be reviewed for the existing knowledge and experimental paradigms.

Cognitive reserve (CR) has been estimated by researchers using various measures, such as years of education (Fleck et al., 2017), occupational attainment (Yang & Lin, 2020), verbal IQ (Speer & Soldan, 2015), or the Cognitive Reserve Index questionnaire (CRIq) (Quinzi et al., 2020). The neural basis of CR is more challenging to explain and relates to everyday functioning and cognitive abilities (Steffener & Stern, 2012).

To consolidate information on the relationship between CR and measured brain activity, an extensive literature search was conducted. This search specifically focused on studies that utilised EEG and magnetoencephalography (MEG) techniques. These studies aimed to explore and establish connections between the observed patterns of brain activity and the concept of CR. By synthesising these studies, the aim was to contribute to a more comprehensive understanding of how CR is reflected in the dynamic patterns of brain activity as measured through these advanced neuroimaging technologies.

4.1.1 Search Terms

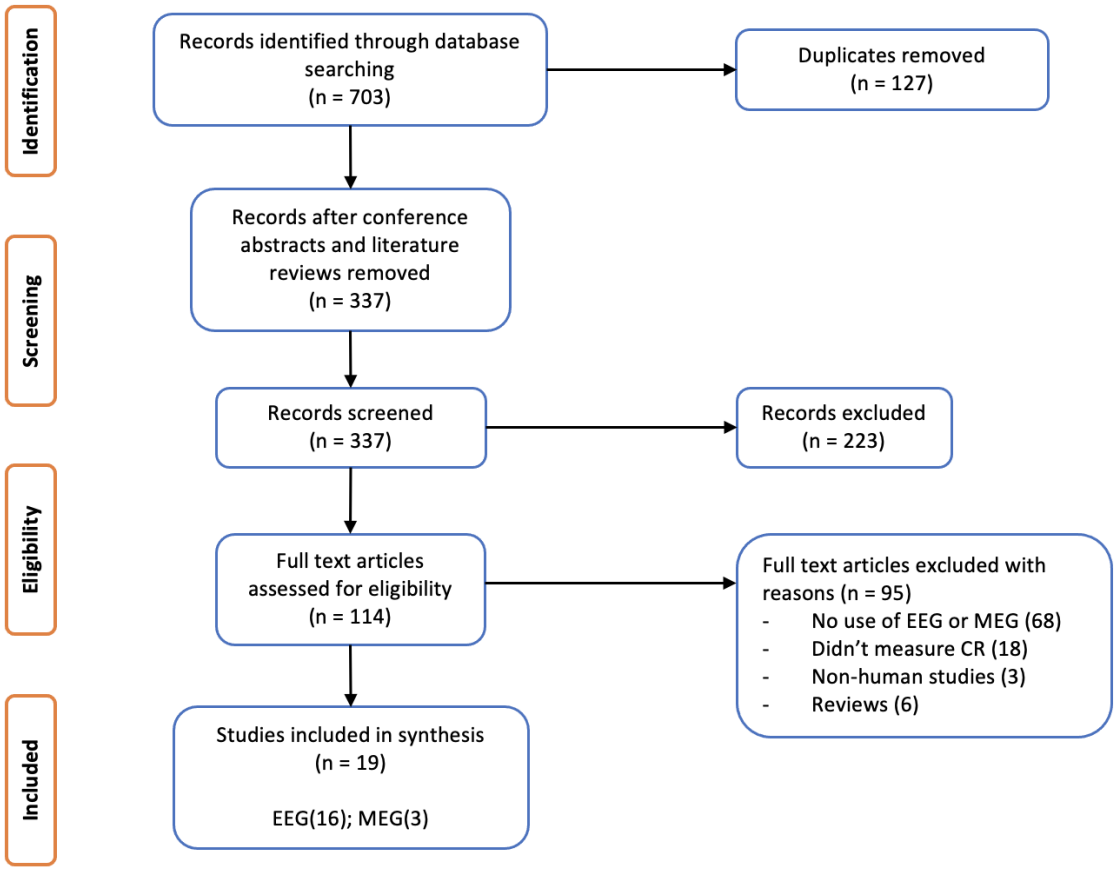
An electronic database search for relevant studies was carried out using Embase and PubMed and was made up to date as of 1st June 2022. The systematic review was executed according to Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines to review the literature of EEG and MEG findings in relation to CR. The search was aimed at the title, abstract and keywords also using MeSH and EMTREE terms: “EEG”, “MEG”, “cognitive reserve”, “neural reserve”, “brain reserve”, “neural efficiency”, “neural compensation”, “event-related potentials”, “ERPs”, and “evoked-related potentials”. These terms were inspired by the literature review terms from Balart-Sánchez et al. (2021). The publication date was set from 2010 to the present to act as an update on the Balart-Sánchez et al. (2021) review. Any papers that were included by Balart-Sánchez et al. (2021) before this date were also included, as they saw it to also be relevant.

The current author (ES) chose relevant articles through duplicate removal and inspecting titles and abstracts. Suitability was based on: (a) being an experimental study, (b) use of EEG or MEG, (c) human subjects, (d) use of a CR measurement, and (e) finally, they related the EEG/MEG to CR.

Reviews, case reports and conference abstracts were excluded. The current author (ES) completed data extraction. The complete process is shown in below.

Figure 4.1 below.

Figure 4.1 Flow chart of the literature review process, including study selection according to the PRISMA guidelines.



Note. Current author (ES) adapted terms and processes from Balart-Sánchez et al. (2021). CR, Cognitive Reserve; EEG, Electroencephalography; MEG, Magnetoencephalography.

The initial electronic database search showed 703 papers in total. There were 127 from PubMed and 576 from Embase. The 127 from PubMed were all duplicated from Embase, so these were removed. Some 239 conference abstracts, literature reviews and case reports were removed, which left 337. These abstracts were screened, and 114 were assessed as full texts. Some 95 of these were excluded as there were no EEG/MEG measures, no assessment of CR, they involved a non-human study, or some reviews were still left. The remaining studies included totalled 19 (below.

Figure 4.1.).

A total of 19 studies were found in the literature search, and Balart-Sánchez et al. (2021) had included two additional papers before the cut-off date of 2010 for this review, Bauer (2008) and Nunes et al. (2009), plus four more which were also deemed to be relevant for the topic of EEG in CR. These were also included in the analysis, totalling 23 studies which is seven more than what Balart-Sánchez et al. (2021) included in their review.

4.1.2 Results

Information from the 23 included studies is shown in Table 4.1. Of the 23 included studies, 18 used EEG and five used MEG. Eleven of the 23 used ERPs in their methodology; the most common ERP was the M/P300 (n = 8), during a GO/NO-GO task (Moussard et al.,

2016), Stroop colour-word interference task (L. O. Bauer, 2008), verbal task recognition task (Speer & Soldan, 2015), reaction time (RT) task (Sundgren et al., 2015), Sternberg-based task (Velasco et al., 2019), oddball paradigm (Khachatryan et al., 2021), or n-back task (Gu et al., 2018; Yang & Lin, 2020).

The second most popular ERPs were the P2 (n = 2) (Gajewski et al., 2020; Moussard et al., 2016) and the N2 (n = 2) (Gajewski et al., 2020; Moussard et al., 2016), followed by the P600a and LAN (n = 1) (Velasco et al., 2019). One study also examined event-related desynchronised (ERD) alpha activity during a stroop task (Arakaki et al., 2022). These studies mentioned have measured multiple ERPs in their research, exploring a wider range of EEG ERP mechanisms within their experiments in relation to CR.

Eight studies measured resting-state brain rhythms while participants were in a relaxed state with their eyes closed (Amodio et al., 2017; Babiloni et al., 2020; Buján et al., 2022; Fleck et al., 2017; López et al., 2016; Rosenich et al., 2022; Sanchez-Lopez et al., 2018), eyes open (Fleck et al., 2017) or pre and intra-operatively before and during anaesthesia using bispectral EEG (Alonso et al., 2019). Three studies investigated neural connectivity: (Fleck et al., 2019; López et al., 2014; Martínez et al., 2018) and one study measured hemispheric asymmetry (Nunes et al., 2009).

The most common resting-state brain rhythm measured was alpha (n = 7) (Amodio et al., 2017; Babiloni et al., 2020; Buján et al., 2022; Fleck et al., 2017; López et al., 2016; Rosenich et al., 2022; Sanchez-Lopez et al., 2018). The next most common was beta (n = 6) (Amodio et al., 2017; Babiloni et al., 2020; Buján et al., 2022; Fleck et al., 2017; López et al.,

2016; Rosenich et al., 2022), and the delta rhythm (n = 6) (Amodio et al., 2017; Buján et al., 2022; Fleck et al., 2017; López et al., 2016; Rosenich et al., 2022; Sanchez-Lopez et al., 2018). This was followed by theta (n = 5) (Amodio et al., 2017; Fleck et al., 2017; López et al., 2016; Rosenich et al., 2022; Sanchez-Lopez et al., 2018). The least popular was gamma (n = 2) (Babiloni et al., 2021; Rosenich et al., 2022). One reason for gamma being the least popular could be that alpha is the easiest to elicit during periods of relaxed wakefulness, and gamma waves are more prevalent during active cognitive processing rather than during a relaxed or resting state (Abhang et al., 2016).

The mode number of electrodes used in these studies was 64 (n = 8), with the second most common (excluding MEG) being 32 (n = 4) and then 129 (n = 2). The lowest number of electrodes was two (bispectral EEG) (Alonso et al., 2019). Larger numbers of electrodes allow for more analyses, such as connectivity analysis and isolating oscillatory dominant areas, and the ability to use ERPs (Cohen, 2017).

The most common method to measure CR was by using the CRIq (Nucci et al., 2012) (n = 8) (Amodio et al., 2017; Buján et al., 2022; Fleck et al., 2019; Gu et al., 2018; Khachatryan et al., 2021; Quinzi et al., 2020; Rosenich et al., 2022; Sanchez-Lopez et al., 2018), with the next most common being to make an index incorporating various factors such as education level (n = 6) (Babiloni et al., 2020; López et al., 2014, 2016; Martínez et al., 2018; Speer & Soldan, 2015; Yang & Lin, 2020), years of education (n = 5) (Fleck et al., 2017; Nunes et al., 2009; Speer & Soldan, 2015; Sundgren et al., 2015; Velasco et al., 2019), occupational attainment (n = 6) (López et al., 2014, 2016; Martínez et al., 2018; Speer & Soldan, 2015;

Velasco et al., 2019; Yang & Lin, 2020) and verbal IQ (n = 3) (Fleck et al., 2017; Speer & Soldan, 2015; Sundgren et al., 2015; Velasco et al., 2019). In contrast, others used standardised subtests from neuropsychological assessments (n = 3), such as the Wechsler Abbreviated Scale of Intelligence (WASI) (Alonso et al., 2019), the Wide Range Achievement Test (WRAT) (Alonso et al., 2019) and the Wechsler Adult Intelligence Scale (WAIS) (Arakaki et al., 2022).

Table 4.1 Results included studies of EEG, MEG, and CR

Author(s) (year)	*N*	Sample	EEG / MEG task	Channels (n)	ERPs / frequency band	Cognitive reserve measure	Results / Conclusions
Bauer (2008)	185	115 HIV-1 seropositive & 70 seronegative participants	ERP/Stroop colour-word interference task	32	Average P3 amplitude over anterior and posterior areas	VIQ from the KBIT	No correlation between VIQ and the average amplitude of P300 over either area. Presence of HIV/AIDS and a positive FH both resulted in a decrease in the average amplitude of anterior P300.
Nunes et al. (2009)	12	7 Ex-illiterate women >50 years, 5 controls	Auditory word recognition	MEG: 148	ERF hemispheric asymmetry	Years of education	The ex-illiterates exhibited more sources of activity in the right inferior frontal gyrus in the time window of 150–400 ms after stimulus onset, in comparison to controls.
Lopez et al. (2014)	21	Healthy adults	Memory task (modified Sternberg's Task)	MEG: 148	Theta, alpha, low beta, high beta	Education level, occupational attainment	An overall increase in connectivity in the low CI participants, compared to the high CR subjects

Author(s) (year)	*N*	Sample	EEG / MEG task	Channels (n)	ERPs / frequency band	Cognitive reserve measure	Results / Conclusions
Speer and Soldan (2015)	44	Healthy young and old adults	Delayed item recognition task	32	P3b amplitude and latency	NART, WAIS-IV Vocabulary, years of education	EEG data showed that as the task complexity increased, the amplitude of the parietal P3b component decreased, and its latency increased. This was negatively correlated with CR in both age groups.
Sundgren et al. (2015)	160	71 sclerosis patients, 89 matched controls	Reaction time task	23	P3 amplitude and latency	Years of education and vocabulary	High P3 amplitude and short RT were associated with better cognitive performance.
Lopez et al. (2016)	33	MCI patients (progressive/ stable)	rsEEG	MEG: 306	Spectral power in delta, theta, alpha, and beta frequency bands	Two CR proxies: education level and occupational attainment	Progressive MCI patients showed higher theta and lower beta power. Occipital theta power was a predictor for conversion to AD in a hierarchical linear regression model. CR proxies did not contribute to the prediction of conversion.

Author(s) (year)	*N*	Sample	EEG / MEG task	Channels (n)	ERPs / frequency band	Cognitive reserve measure	Results / Conclusions
Moussard et al. (2016)	34	17 musicians vs 17 non-musicians (59-80 yrs.)	Visual GO/NO-GO task	64	P2, N2, P3 amplitudes and latencies	Years of musical practice	The P2 did not show any association with the group condition. Musicians exhibited a larger N2-effect. Both groups exhibited a P3 effect that correlated with years of musical practice.
Fleck et al. (2017)	90	Healthy adults (45 – 64 yrs.)	rsEEG (eyes open and eyes closed)	129	Delta, theta, high alpha, low alpha, gamma	Verbal IQ and years of education	Greater coherence in participants with high CR, regardless of age
Amodio et al. (2017)	82	Cirrhosis patients	rsEEG	21	Delta, theta, alpha, beta relative power (%)	CRIq	Cognitive performance was related to CR whereas spectral EEG analyses were not influenced by CR.

Author(s) (year)	*N*	Sample	EEG / MEG task	Channels (n)	ERPs / frequency band	Cognitive reserve measure	Results / Conclusions
Gu et al. (2018)	85	(39 aMCI patients and 46 their matched controls)	N-back tasks	64	P300	CRIq	aMCI patients showed reduced accuracy, delayed mean RT, and decreased P300 amplitude at central-parietal and parietal electrodes. Higher CR increased neural efficiency.
Martinez et al. (2018)	20	Elder adults	Memory task (modified Sternberg's Task)	MEG: 148	Brain connectivity	Education level, occupational attainment	Individuals with high CR required functional networks with lower activity to successfully carry out the memory task.
Sanchez-Lopez et al. (2018)	97	Old healthy adults	rsEEG	19	Alpha, delta, theta	CRIq	rsEEG exhibited significantly slower activity involving the frontal, central, and temporal regions in the less active group
Alonso et al. (2019)	54	Preoperative patients	rsEEG (pre- and intra-operatively)	2 (BIS)	Bispectral index™ BIS score	WRAT and WASI	The EEG intra-individual variability calculated as the squared deviation from the mean BIS value, correlated negatively with the CR estimate.

Author(s) (year)	*N*	Sample	EEG / MEG task	Channels (n)	ERPs / frequency band	Cognitive reserve measure	Results / Conclusions
Fleck et al. (2019)	104	Healthy adults	rsEEG, GAMA, CANTAB	129	Connectivity analysis	CRIq	High CR participants exhibited greater eyes-closed long-range connectivity between the occipital lobe and other cortical regions in low alpha
Velasco et al. (2019)	40	Young adults (20-30 years)	Sternberg task	32	P300, P600a, LAN	Years of education, occupational attainment, verbal IQ, CR questionnaire	Subjects with both high and low CR showed bigger P300 amplitudes in low WM load tasks than high WM load tasks. Those with higher CR had greater modulation of LAN and P600a as WM demands increased. Greater levels of CR ameliorate neural efficiency and compensation.
Babiloni et al. (2020)	172	118 elderly amyloid negative & SMC, 54 amyloid positive	rsEEG	256	Power density in alpha, beta 1, beta 2, gamma bands	Education level	High CR participants had higher amplitude posterior alpha rhythms compared to low-moderate CR participants.
Gajewski et al. (2020)	246	Healthy adults	Stroop task	32	P2/N2	Sociodemographic data, IQ, personality, lifestyle, and quality of life	High performance was associated with higher level of education, usage of foreign languages and higher IQ (high CR)

Author(s) (year)	*N*	Sample	EEG / MEG task	Channels (n)	ERPs / frequency band	Cognitive reserve measure	Results / Conclusions
Quinzi et al. (2020)	42	Young and old adults	Visuo-motor simple and discriminative response tasks	64	PN, BP	CRIq	High CR group had faster reaction times and larger pN and BP
Yang & Lin (2020)	41	Healthy adults	N-back task	MEG: 148	M300	Education level, occupational attainment, leisure, and social activities	Low-CR subjects had higher P300 intensities than the high-CR subjects, especially in the left occipital region
Khachatryan et al. (2021)	20	Older adults	Oddball paradigm	64	P300	CRIq	Positive relationship between P300 latency and educational level. Older participants required more compensation, they used their CR.
Arakai et al. (2022)	41	Normal vs abnormal amyloid/tau ratio	Stroop task	64	ERD alpha, alpha SE	WAIS-III verbal IQ subtests	Abnormal tau subjects had more negative occipital alpha ERD, and higher frontal and occipital alpha SE in easier Stroop, indicating hyperactivity and demonstrated fewer frontal alpha SE changes with harder Stroop

Author(s) (year)	*N*	Sample	EEG / MEG task	Channels (n)	ERPs / frequency band	Cognitive reserve measure	Results / Conclusions
Bujan et al. (2022)	56	Healthy adults (18-82 years old)	3-minute rsEEG	64	Alpha, beta, delta	CRIq	Moderate negative correlations were found between the CR and occipital delta and high beta. Inter and intra-hemispheric LLC measures correlated with CR, showing a negative association with delta, and positive associations with low alpha, low beta, and high beta.
Rosenich et al. (2022)	10	Stroke patients	rsEEG	64	Delta, theta, alpha, beta, gamma	CRIq	CR can mediate the relationship between neural function, brain injury, stroke intensity and upper-limb motor recovery

Note. aMCI, Amnesic Mild Cognitive Impairment; BIS, Bi-spectral Index EEG; BP, Bereitschaftspotential; CI, Cognitive Impairment; CR, Cognitive Reserve; CRIq, Cognitive Reserve Index Questionnaire; ERD, Event-Related Desynchronisation; ERF, Event-Related Field; FH, Family History; KBIT, Kaufman Brief Intelligence Test; LAN, Left Anterior Negativity; LLC, Lagged-Linear Connectivity; NART, National Adult Reading Test; PN, Prefrontal negativity; rsEEG, Resting State EEG; RT, Reaction Time; SE, Spectral Entropy; VIQ, Verbal Intelligence Quotient; WAIS-IV, Wechsler Adult Intelligence Scale 4th Edition; WASI, Wechsler Abbreviated Scale of Intelligence; WM, Working Memory; WRAT, Wide Range Achievement Test.

4.1.2.1 Notable Studies

Velasco et al. (2019), Speer and Soldan (2015), and Gu et al. (2018) conducted studies that collectively reveal insights into the relationship between CR and sensory processing. These studies found that individuals with higher CR exhibited more prominent P300 amplitudes and greater neural efficiency. These findings suggest that individuals with higher CR may possess more effective inhibitory mechanisms that enable them to filter and process sensory information more efficiently. In the context of sensory gating, this implies that high CR individuals might excel at inhibiting irrelevant sensory input, allowing them to focus their cognitive resources more effectively on relevant stimuli (Gu et al., 2018; Speer & Soldan, 2015).

Quinzi et al. (2020) found that the P300 was delayed in the older subjects (both high and low CR), and the amplitude was more prominent in older high CR participants than the young participants. The authors explained this in terms of neural compensation, as greater activation enabled them to complete the task (Quinzi et al., 2020). Therefore, this is the other side of CR theory, which states that neural compensation and neural efficiency work together in high CR individuals (Stern, 2009). The greater amplitude could signify enhanced processing of relevant stimuli. This study highlights that the relationship between CR and sensory processing is multifaceted and may involve both inhibitory and compensatory mechanisms.

Yang and Lin (2020) found the same effect using MEG in subjects with differing levels of CR. Subjects with higher levels of CR had higher beta power in the parietal and occipital regions. In contrast, subjects with lower CR had larger M300 amplitudes, which was suggested to show inefficient use of neural activation (Yang & Lin, 2020). Additionally, Yang and Lin (2020) discovered that high CR individuals had greater neural efficiency, whereas low CR

individuals exhibited larger M300 amplitudes, suggesting differences in neural efficiency. High CR individuals showing increased neural efficiency could imply more effective inhibitory processes in sensory gating, allowing them to allocate cognitive resources optimally.

Fleck et al. (2019) examined resting-state EEG (rsEEG) of cortical connectivity in low vs high CR participants and young vs old. Older participants with high CR displayed greater "global organisation" than lower CR subjects regardless of age across the frequency bands, using years of education and verbal IQ as measures of CR (Fleck et al., 2019). High CR participants had stronger alpha connectivity between the occipital regions. These findings were also consistent with Sanchez-Lopez et al. (2018), who showed that those who performed better on subtests of the WAIS-IV had increased alpha but decreased delta and theta. Bujan et al. (2022) further confirmed this by showing lower delta activity in the occipital region and lower connectivity of high beta ranges (21-30 Hz) in the occipital and limbic areas. The authors stated that this could be used to index neuroprotective effects for cognition as we age (Buján et al., 2022).

Furthermore, Fleck et al. (2019), Sanchez-Lopez et al. (2018), and Bujan et al. (2022) delved into various aspects of neural connectivity and found differences between high and low CR individuals. Enhanced alpha connectivity in high CR participants and changes in delta and beta activity might reflect variations in inhibitory mechanisms. Alpha connectivity, particularly associated with attention and inhibitory control, suggests that high CR individuals may have more efficient attentional and inhibitory processes that aid in sensory gating (SG) (Foxe & Snyder, 2011).

In summary, these studies collectively show that CR can impact the brain's ability to filter and prioritise sensory information effectively through its potential influence on neural

efficiency and inhibitory processes. High CR individuals may excel at inhibiting irrelevant stimuli while enhancing the processing of relevant information, making their SG mechanisms more efficient.

4.2 Discussion

In summary, studies by Velasco et al. (2019), Speer and Soldan (2015), Gu et al. (2018), Quinzi et al. (2020), Yang and Lin (2020), Fleck et al. (2019), Sanchez-Lopez et al. (2018), and Bujan et al. (2022) collectively reveal a complex relationship between CR measures and SG responses. Overall, high CR individuals consistently show more prominent P300 amplitudes and greater neural efficiency, suggesting enhanced inhibitory mechanisms that facilitate efficient filtering of sensory information.

Quinzi et al. (2020) introduce a compensatory perspective, proposing that high CR individuals may employ both inhibitory and compensatory mechanisms in sensory processing. Yang and Lin (2020) reinforce these findings, demonstrating that high CR individuals exhibit greater neural efficiency and more effective inhibitory processes. Additionally, Fleck et al. (2019), Sanchez-Lopez et al. (2018), and Bujan et al. (2022) reveal enhanced alpha connectivity in high CR participants, indicative of efficient attentional and inhibitory processes.

4.2.1 Heterogeneous Results

Results in CR studies using EEG may exhibit heterogeneity due to several influential factors. Cognitive reserve is influenced by an array of individual variables, including education, occupational complexity, and lifestyle choices (Montemurro et al., 2021). Further

compounding this complexity is the use of different measures of CR across studies, such as years of education or social constructs, verbal IQ, or even years of musical practice (Montemurro et al., 2021). As these measures are fixed in unique life experiences, they vary significantly among individuals, contributing to deviating CR levels (Zijlmans et al., 2022). Because EEG measures are influenced by underlying neural activity, the interplay between CR and individual differences can produce not only varying results between studies but also within participants of the same study (Šneidere et al., 2020).

Methodological disparities represent another source of heterogeneity. Studies investigating CR through EEG may employ differing methodologies, encompassing variations in electrode placement, task paradigms, and data analysis techniques (Balart-Sánchez et al., 2021; Šneidere et al., 2020). Only 23 studies were discussed in this review, but there were already 10 different electrode experiment set-ups (including MEG), nearly each study had a different experimental task, and rarely measured similar participant samples. These differences can cause differences in recorded EEG signals and CR measures, thereby contributing to heterogeneity in study outcomes.

The characteristics of the study sample also play a significant role in result variability. Participant attributes, such as age, gender, cognitive abilities, and health status, can influence the relationship between CR and EEG measures (Buján et al., 2022; Fleck et al., 2017). The studies discussed used a variety of participants; there were healthy adults, older adults, stroke patients, HIV patients and illiterate adults. Differences in sample characteristics, including the presence of neurological disorders or the distribution of CR levels, can further lead to inconsistent findings (Balart-Sánchez et al., 2021), especially when there are neuropsychological measures (Velasco et al., 2019).

Task demands and cognitive domains represent an additional layer of complexity, as CR represents a multifaceted construct, including memory, attention, and executive functions (Pettigrew & Soldan, 2019). EEG studies often target specific cognitive tasks or domains, introducing variability in observed EEG measures (M. X. Cohen, 2017). For example, if one study uses executive function as a measure of CR and another uses memory, the results or relationships between a particular ERP/oscillatory marker are not likely to be comparable. Therefore, variations in task demands and cognitive domains examined across different studies can contribute to inconsistent findings.

The interaction between CR and brain pathology adds another layer of complexity. Cognitive reserve is thought to modulate the effects of brain pathology on cognitive functioning, with individuals possessing higher CR potentially exhibiting resilience to cognitive decline despite the presence of brain pathology (Quiroz et al., 2011; Stern et al., 2019). However, this is particularly difficult to quantify, and we don't yet fully understand the nature between CR and long-term prevention of neurocognitive decline/pathology (Opdebeeck et al., 2014; Yegla & Foster, 2022). This interaction can introduce heterogeneity in observed EEG patterns and their relationship with cognitive outcomes (Montemurro et al., 2021).

To address these sources of heterogeneity, future studies could consider standardising methodologies, increasing sample sizes, meticulously controlling for confounding variables, and adopting longitudinal designs. Additionally, exploring individual differences, combining multiple measures of CR, and investigating specific cognitive domains may enhance our understanding of the intricate nature of CR and its relationship with EEG measures.

4.2.2 Limitations of EEG in Cognitive Reserve

Using EEG to study CR in participants presents several limitations. One notable challenge is the interpretation of EEG data. Although EEG provides insight into brain electrical activity, it lacks specificity regarding underlying neural processes (M. X. Cohen, 2017). Interpreting EEG signals demands expertise and careful consideration, given that numerous factors can influence recorded brain activity. This complexity makes it difficult to pinpoint specific cognitive processes associated with CR. Furthermore, EEG has limited spatial resolution, hindering precise identification of the neural mechanisms contributing to CR (M. X. Cohen, 2017). It remains a challenge to discern whether observed EEG differences reflect neural compensation, neural efficiency, or other CR-related factors (Balart-Sánchez et al., 2021; Šneidere et al., 2020).

Establishing causal relationships between EEG measures and CR poses another challenge. It remains unclear whether specific EEG patterns actively contribute to CR or merely serve as markers of pre-existing cognitive abilities or brain health. While EEG offers indirect measures of neural activity linked to cognitive processes, it may not directly capture the underlying mechanisms associated with CR (M. X. Cohen, 2017). There is also little consensus on specific EEG markers reliably reflecting CR, even in this small-scale literature review. Various studies employ different EEG measures, such as alpha, theta, beta, delta power, or ERPs, and these can be resting state or participants completing tasks. The field lacks standardised and universally accepted markers for CR. In addition, while some studies report associations between EEG measures and CR, its ability to accurately predict cognitive outcomes, such as resistance to cognitive decline or susceptibility to cognitive impairment, is not well-established, due to a lack of longitudinal studies in this area.

4.3 Conclusions

In summary, the studies discussed showed interesting findings demonstrating that the EEG markers associated with CR can vary and can be shown with many different experimental design set-ups. EEG has shown to be related to processing, efficiency, and compensation within CR.

There are several reasons for heterogeneity in the results of studies associating CR with EEG responses. These include individual participant variables, methodological disparities, sample characteristics, and variations in task demands and cognitive domains. The interaction between CR and brain pathology further complicates the relationship, as it introduces additional variance in observed EEG patterns and their relationship with cognitive outcomes. The lack of standardised tests of CR in EEG studies also poses difficulty in being able to draw definitive conclusions from the literature.

The potential of inhibitory mechanisms and cognitive resource allocation in high CR individuals could be further explored through a more straightforward EEG setup, focusing on fewer electrodes to reduce participant burden while investigating the relationship between CR and SG in healthy older adults.

4.4 Future Directions

Individuals with higher CR may possess more efficient and flexible neural networks, thereby enabling superior allocation of cognitive resources and inhibition of irrelevant information (Moussard et al., 2016). This suggests that CR could facilitate the implementation of gating by inhibition, allowing individuals to complete important tasks while attenuating

distractions (Gu et al., 2018; Moussard et al., 2016). However, no studies were found in this literature search that investigated SG, ASSR and CR. Studies did investigate resting state alpha rhythms and CR (Amodio et al., 2017; Babiloni et al., 2020; Buján et al., 2022; Fleck et al., 2017; López et al., 2016; Rosenich et al., 2022; Sanchez-Lopez et al., 2018) in this literature review.

Sensory gating involves the brain's ability to filter sensory input, discerning salient stimuli from irrelevant noise (Lijffijt, Lane, Meier, Boutros, Burroughs, et al., 2009). As individuals with higher CR tend to exhibit better neural adaptation and compensation (Gu et al., 2018; Martínez et al., 2018; Velasco et al., 2019), they might also demonstrate improved SG abilities. This relationship implies that their brains are adept at allocating attention to pertinent stimuli while suppressing distractions, mirroring the principles of gating by inhibition (Cromwell et al., 2008; L. A. Jones et al., 2016a). Individuals with higher CR may inherently possess robust inhibitory control mechanisms (Arakaki et al., 2022; D. C. Park & Reuter-Lorenz, 2009), aligning with the idea that CR enhances the brain's efficiency in allocating cognitive resources (López et al., 2014; Velasco et al., 2019), which is a key principle of SG (Lijffijt, Lane, Meier, Boutros, Burroughs, et al., 2009).

To improve on the discussed research, EEG and MEG studies should find ways to make experiments and research less burdensome on participants, particularly those who are patients or vulnerable older adults. The least number of electrodes used was two (Alonso et al., 2019), which would’ve had a minimum burden on the patients, but this gave limited data regarding ERPs and oscillations. The second least amount of electrodes used was 19 (Sanchez-Lopez et al., 2018), which would have been quicker for the patients than a larger amount, e.g. 64 electrodes. We believe a more straightforward EEG setup is possible, making the experiment time shorter and much less burdensome for subjects/patients.

We want to use fewer electrodes while being able to explore the relationship between brain inhibitory capabilities and CR. Previous research discussed in Table 4.1 has not yet investigated the relationship between CR and SG abilities, only the alpha frequency band (also involved in inhibition), and we think this warrants investigating based on the fact that inhibition diminishes with age (Cheng et al., 2015; Reuter et al., 2019; West, 1996). We will choose a more straightforward setup with fewer electrodes to test the relationship between CR and SG in healthy older adults, as this has not been explored before. These investigations will be written about in the subsequent three chapters.

Chapter 5 P50, N100 and P200: Sensory Gating Components in a Healthy Ageing Population

Abstract

Preattentive processing abilities, including sensory gating (SG), are studied through P50, N100 and P200 auditory processing paradigms. This is measured by calculating peak amplitude changes in a dual-click conditioning-testing procedure, which can be used as neurophysiological markers of deficient SG. This study aimed to examine the influence of SG by using auditory event-related potentials (AERPs) on neuropsychological test scores as a measure of cognitive reserve (CR) in a healthy ageing population (n = 27). We used a paired stimulus click paradigm to measure the P50, N100 and P200. Amplitudes of stimulus 1 (S1) and stimulus 2 (S2) were recorded; the differences between the S1 and S2 ERP amplitudes were used as SG measures. The amplitudes of the dual-click responses and the neuropsychological test scores were analysed. The study reveals an age-related decline in neuropsychological function and CR but not in SG among healthy older adults. Significant relationships were found between the P200 and verbal and visual long-term memory measures. The N100 was significantly related to a measure of inhibitory memory. No other neuropsychological measures such as executive function, language or mood were related to SG. These findings suggest an age-related decline of neuropsychological function and CR, but not of SG in healthy older adults. This provides valuable insights into the complex interrelationships between SG components, cognitive functions, and their potential as diagnostic tools.

5.1 Introduction

Daily cognitive and normal everyday functioning requires the capacity to effectively inhibit irrelevant stimuli, thoughts, and distractions (Boutros et al., 2008; Luís Pires et al., 2014). Inhibition is fundamental in coordinating various cognitive domains, including attention, memory, executive function (EF) and language (Freunberger et al., 2011). Shiffrin and Schneider (1977) initially suggested Automatic Attending Theory. According to this model, automatic processes typically occur without intention and conscious awareness (Shiffrin & Schneider, 1977). As a result, these processes are quick and can co-occur with other operations without impairment (Soshi et al., 2015). An automatic process is most notable because it can happen without conscious control (Wan et al., 2008).

Automatic inhibition happens without awareness and appears to be an involuntary response from the subject's central nervous system (CNS) (Banerjee et al., 2011). An example of this is sensory gating (SG) which occurs in several CNS networks, including the prefrontal cortex (PFC), temporoparietal region, striatum, amygdala, and the hippocampus (Grunwald et al., 2003). The CNS will inhibit or subdue responses to received irrelevant sensory input, which is thought to be an essential protective mechanism that will block the flooding of higher cortical centres with irrelevant information (Cromwell et al., 2008). Sensory gating can measure how well the CNS can do this (Miller et al., 2009).

Reduced inhibition abilities have been suggested to be a key element influencing age-related cognitive decline (Nielson et al., 2002; Pires et al., 2014). The ageing process can lead to inhibition dysfunction, diminishing the suppression and filtering of irrelevant stimuli and resistance to information interference (Fong et al., 2021; Hasher, 2015). Therefore, less

irrelevant stimuli are filtered and deleted, leading to more interference in higher-order cognitive functions (Cheng et al., 2018).

5.2 Inhibition Processes

Inhibitive information filtering is an essential cognitive process for humans that occurs early in information processing (Si et al., 2014). Perceiving changes in the surrounding environment outside our direct focus is vital for safety and survival (Jerger et al., 1992; Wan et al., 2008). Sensory gating occurs in several CNS networks, including the prefrontal cortex (PFC), temporoparietal region, striatum, amygdala, and the hippocampus (Grunwald et al., 2003). Quantifying preattention could reveal dysfunction in higher-order cognition, such as EF and working memory (WM) (Luck et al., 2011; Tsolaki et al., 2015). A healthy SG ability is thought to be a crucial indicator of a healthy CNS (Bak et al., 2017; Bak et al., 2011; Oranje et al., 2013).

5.2.1 EEG Measurements

The processing of sensory inputs can be analysed by using EEG to record auditory event-related potentials (AERPs) at the neuronal level (Schuelert et al., 2018). To measure AERPs, a large number of time-locked experimental trials are averaged, cancelling out randomly phase activity, and leaving behind responses phase and time-locked to the onset of the auditory stimulus (Näätänen et al., 2005). The AERPs elicited by the stimulus, reflect successive stages of information processing (Dalecki et al., 2011).

5.2.2 Sensory Gating Paradigms

Sensory gating functions as a critical filter for incoming sensory stimuli (Light et al., 2010). It operates by modulating or inhibiting responses to repeated or irrelevant stimuli, preventing sensory overload, allowing the brain to focus on salient information (Evans et al., 2007; Yamashita et al., 2005). This gating mechanism ensures that neural resources are allocated efficiently, contributing to the overall optimisation of cognitive processing (Bak et al., 2017; Meier, 2014).

Preattention, also known as preattentive processing, represents the initial stage of information processing that occurs before conscious awareness (Jerger et al., 1992; Wan et al., 2008). Preattention acts as a swift and efficient mechanism, allowing the brain to quickly group stimuli without the need for conscious effort (Wolfe & Utochkin, 2019). The link between preattention and sensory gating becomes evident in their shared goal of managing incoming sensory information (Boutros et al., 2008). Both preattention and sensory gating contribute to the ability to selectively focus on specific stimuli while ignoring others (Gmehlin et al., 2011; Wolfe & Utochkin, 2019).

To measure SG, two identical stimuli of auditory clicks (S1 and S2) are presented with a designated time gap (~500ms) between the pairs and a more extended period between 8-15 seconds between the pairs (Holstein et al., 2013). The generation of the first stimulus (S1) is thought to create a memory trace (likely in the hippocampal region) (Cromwell et al., 2008). Then when the second stimulus is given, it is compared to the memory trace and is actively inhibited as it contains no new information (Cromwell et al., 2008). Sensory gating is thought to be the result of neural excitation of a set of sensory neurons to the presentation of the S1 while simultaneously activating a second set of interneurons that inhibit any further excitatory

response (L. A. Jones et al., 2016). The normal suppression of P50 waves was believed to result from the neurons' need to regain their excitability following their discharge in response to the first stimulus (Mathiak et al., 2011; Santos et al., 2010).

5.2.2.1 P50 Suppression

The P50 is an unconscious sensory small-amplitude, positive ERP that occurs 50 ms after stimulus onset (Light et al., 2010). It is assessed by measuring responses to repeated pairs of clicks separated by about 500 ms. These pairs of clicks are typically presented with intervals of around 10 seconds between each pair (Takeuchi et al., 2017). Electrophysiologically, the cortical reaction to these stimuli is measured using ERPs (Rosburg, 2001). P50 suppression refers to the decrement of the P50 amplitude after the second stimulus (testing stimulus, S2) versus the P50 amplitude after the first stimulus (conditioning stimulus, S1) (Dalecki et al., 2015). The P50 has proven to be a very effective neurophysiological measure of SG (Micoulaud-Franchi et al., 2015).

Auditory SG can be assessed by examining the modulation of several evoked components including the P50, the N100 (negative ERP occurring 100 ms after stimulus onset) and the P200 (positive ERP occurring at 200 ms after stimulus onset), (Rentzsch et al., 2008). Boutros et al. (2008) postulated that these measures of SG (P50, N100, and P200) mean different periods in our sensory processing systems; the earlier the ERP, the more 'automated' it is by our CNS. The P50 is a "preattentive" gating process, N100 is "early attentive", and the P200 is "later attentive" (Boutros et al., 2008). Thus, the later the ERP, the more it participates in conscious attention.

5.2.2.2 N100 and P200 ERPs

The N100 and P200 SG ERPs are reported to be impaired or deficient in subjects with schizophrenia (Oranje et al., 2006), cocaine abuse (Fein et al., 1996), and bipolar I disorder (Cheng et al., 2016), and relate to diminished cognitive performance in these disorders. N100 and P200 SG may represent other cognitive or CNS functions than those of P50 gating (Gmehlin et al., 2011; Lijffijt et al., 2009).

The roles of the N100 and P200 may contrast with those suggested for P50 gating. Therefore, they could impact other features of cognition (Boutros et al., 2011). However, few studies have directly examined associations between cognitive performance and the N100 Field (Hsieh et al., 2004) and P200 Field (Lijffijt et al., 2009) gating. Increased performance on an implicit learning task led to improved N100 SG in healthy participants (Hsieh et al., 2004), and P200 SG was associated with scores on attentional tasks, indicating relationships between N100 and P200 gating in learning and attention (Hsieh et al., 2004; Lijffijt et al., 2009).

5.2.3 Sensory Gating Formula

Research such as Toyomaki et al. (2015) and Park et al., (2015) use the equation shown in Figure 1(a). Whereas other research (Smucny et al., 2013) prefer to use the second formula in Figure 1(b).

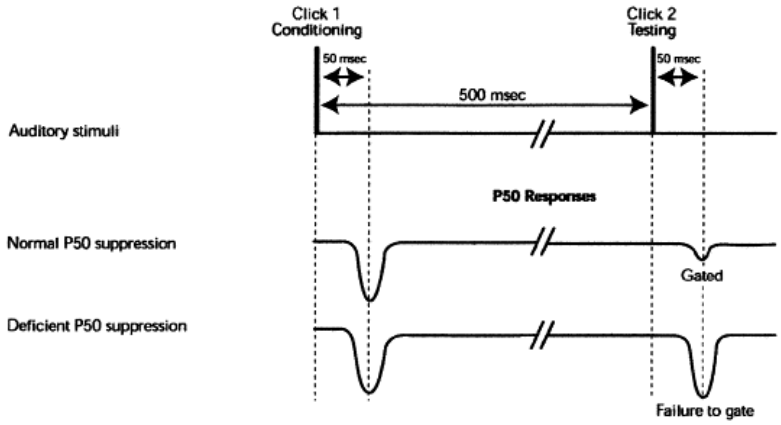
Figure 5.1 Different sensory gating ratio equations commonly used throughout the literature.

a.	b.
$\frac{\text{S2 amplitude}}{\text{S1 amplitude}} \times 100$	$\frac{\text{S1 amplitude}}{\text{S2 amplitude}} \times 100$

Note. a. S2 amplitude is divided by the S1 amplitude and multiplied by 100. b. S1 amplitude is divided by the S2 amplitude and multiplied by 100.

Equation a. means that a lower percentage indicates a higher difference between the two stimuli, indicative of 'healthy' SG. The higher the ratio, the smaller the differences and the worse the SG abilities. For Equation b. a higher result indicates a more considerable difference between the two measurements and more effective SG abilities. This is visualised in Figure 5.2 below.

Figure 5.2 Illustration of the P50 suppression paradigm, standard vs deficient.



Note. From: Light & Braff (2003), pp.50. "EEG is recorded in response to 120 auditory click pairs (89 dB, 1ms stimulus duration) separated by 500 msec. The P50 component of the ERP is measured in response to each of the clicks. P50 suppression (or 'gating') is the percentage of P50 amplitude reduction from the first to the second stimulus."

5.2.4 Neural Networks

The neural network underlying SG to external stimuli (i.e., auditory, visual or somatosensory) may include widely distributed neural networks, including the auditory neocortical regions as the main sites of the initial response to auditory stimulation, the frontal lobe, the parietal and cingulate cortices (Boutros & Peters, 2012). In addition, a significant role for the hippocampus has been documented (Boutros et al., 2008), and a substantial part for the thalamus has been proposed with some support from lesion studies (Staines et al., 2002). A considerable role for SG of emotional stimuli in the amygdala has been found (Cromwell & Woodward, 2007).

The involvement of key brain regions in SG to external stimuli, as previously discussed, is crucial for understanding how the brain processes and filters sensory information. While SG primarily deals with temporal processes, it's important to consider the wider spatial context because the brain's information processing is inherently interconnected and distributed across multiple regions.

The thalamus serves as a central hub for sensory processing (Boutros et al., 2011). It receives sensory input from various sensory organs and relays this information to different cortical regions for further processing (Cromwell et al., 2008). It's involved in the initial gating process, filtering out irrelevant or redundant sensory input (Boutros et al., 2011). Understanding its role is essential because it's the first point of entry for sensory information into the cortex.

The frontal cortex plays a significant role in higher-order cognitive functions, including attention, working memory, and executive control (Bak et al., 2011; Boutros et al., 2013). In

the context of SG, it helps prioritise and allocate attention to relevant sensory stimuli while suppressing distractions (Bak et al., 2011; Cromwell et al., 2008).

These regions are involved in spatial processing, sensory integration, and attention control. While they may not be primarily responsible for temporal gating, their engagement reflects the brain's comprehensive approach to sensory processing (Grunwald et al., 2003). These areas contribute to the spatial context by determining how the brain allocates attention and integrates sensory information across different modalities (Grunwald et al., 2003).

The spatial context is crucial because sensory processing is not a localised event but rather a distributed and integrated process involving multiple brain regions (Bak et al., 2011; Grunwald et al., 2003). Furthermore, studying SG provides insights into how the brain manages and filters sensory information across different cognitive and perceptual domains, contributing to a comprehensive understanding of sensory processing and its temporal dynamics (Cromwell et al., 2008).

5.2.4.1 EEG Channels

To effectively measure SG using EEG, researchers typically place electrodes on specific scalp regions where the responses are likely to be the largest. These electrode placements are strategically chosen to capture the ERPs associated with SG processes (C. H. Chen et al., 1997; Erwin et al., 1998; Lijffijt, Lane, Meier, Boutros, Burroughs, et al., 2009; Wan et al., 2008).

Frontal regions (such as Fz, F3, and F4) and central regions (including Cz, C3, and C4) are also commonly utilised (Erwin et al., 1998; Lijffijt, Lane, Meier, Boutros, Burroughs, et

al., 2009; Wan et al., 2008) as that is where the P50 is largest across the scalp (Green et al., 2015).

These areas provide insights into neural responses associated with SG, particularly the P50, N100 and P200 ERPs. Multisensory stimuli have been shown to evoke neural activity during preattentive sensory processing in the occipital electrodes (e.g., O1, O2, Oz) (Barutchu et al., 2013). Preattentive auditory processing have been associated with increased activity in parieto-occipital regions (P7, P8, O1, O2) (Barutchu et al., 2013).

5.2.4.2 Length of Intervals Between Sensory Gating Clicks

Scientists use different time gaps between clicks in the P50 auditory SG paradigm to explore specific aspects of sensory processing, attention, and neural responses. The interval between stimuli, known as the inter-stimulus interval (ISI), is a crucial factor that shapes the characteristics of the P50 response and the information it can provide (Pereira et al., 2014). The altering of ISIs allows investigation into the temporal dynamics of sensory processing (Pereira et al., 2014). Shorter ISIs, such as 500 milliseconds, are positioned closer in time and may capture rapid sensory adaptation, while longer ISIs, such as 8 seconds, provide insight into more sustained attention and gating processes (Ross et al., 2002). These varying intervals offer a window into how the brain responds to sensory stimuli over different timeframes.

In a study by Freedman and colleagues, they investigated P50 amplitudes in a conditioning-testing paradigm using various ISIs (75, 100, 150, 500, 1000, and 2000 ms). They found that the P50 response to the testing stimulus was smallest when the ISI was 75 ms (Freedman et al., 1983; Nagamoto et al., 1989, 1991). In contrast, McFarland et al. (1975) examined the impact of different stimulus rates (1, 2, 4, 8, and 16/s) and reported that P50 amplitudes were not influenced by the ISI (McFarland et al., 1975). In Onitsuka et al. (2000)'s

study, the P50 amplitude in the 0.5 s ISI conditions did not significantly differ from the P50 in the 1.5 s ISI conditions. However, the N100 amplitudes in the 0.5 s ISI conditions were significantly smaller compared to the N100 amplitudes in the 1.5 s ISI conditions (Onitsuka et al., 2000).

Furthermore, in clinical applications, different ISIs are used to evaluate SG abnormalities associated with specific conditions. For instance, in schizophrenia research, shorter ISIs may reveal deficits in early SG, while longer ISIs might indicate deficits in sustained attention or other higher-level cognitive processes (Davalos et al., 2003; Erwin et al., 1998; Nagamoto et al., 1991).

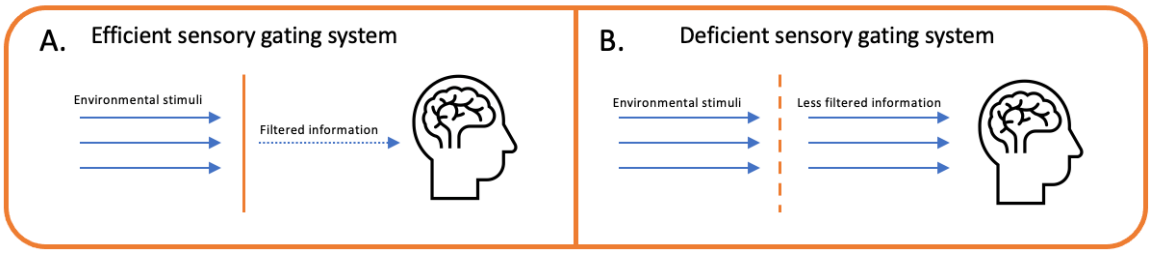
Additionally, individual differences in SG responses can influence the choice of ISIs (Edgar et al., 2003; Light et al., 2010). Some individuals may exhibit variations in SG at different ISIs, and researchers can account for these variations by employing a range of intervals. This approach allows for a more comprehensive understanding of gating processes and their variability across individuals.

5.2.5 Common Findings

When examining the P50, healthy controls usually show an effective suppression of 50%–70% being filtered out in response to the second stimulus after stimulus 1 (using equation b) (Light & Braff, 2000), whereas schizophrenic patients demonstrate significantly lower rates of suppression (Toyomaki et al., 2015; Yang et al., 2017), i.e., their brains are more flooded with sensory information. This measure has been used to identify and assess the core cognitive and attentional deficits present in schizophrenia patients.

Healthy subjects demonstrate a significant decrement from S1 to S2, whereas patients with schizophrenia do not demonstrate a significant decrement, and will often show poor P50 suppression (Rosburg, 2001), as seen in Figure 5.3. This inhibitory deficit of S2 has primarily been interpreted as an inability of schizophrenic patients to filter out sensory inputs properly (Moran et al., 2012; Perry et al., 1995; Wan et al., 2008), as shown in Figure 5.3. This may be due to impairments in preattentive sensory processing (Bak et al., 2017).

Figure 5.3 Visualisation of sensory stimuli flooding in efficient vs inefficient sensory gating systems



Note. In A., effective sensory gating can filter out irrelevant environmental stimuli; B., ineffective sensory gating means the individual is flooded with sensory stimulation, leading to inattention and poorer cognitive functioning (adapted from Braff & Light (2005)).

Reduced P50 suppression has been found among nonpsychotic family members of patients with schizophrenia, demonstrating that these deficits could reveal an intermediate phenotypic (gene * environment) marker (Light & Braff, 2000a, 2000b; Light et al., 2000). Patients with schizophrenia show deficits in SG, which may lead to a state of flooding of

sensory information, overloading higher brain functions, and ultimately may lead to the formation of psychoses (Oranje et al., 2013).

5.2.6 P50 in Neuropsychology

Previous studies have suggested that associations of the P50 with intelligence quotient (IQ) could apply to the cognitive functions employed in memory and attention tasks (Cusack et al., 2009). This is consistent with the proposed correlation between SG and IQ, which consists of measures in the different cognitive domains within the literature (Jones et al., 2016).

Clinicians use neuropsychological tests to measure intelligence and cognitive function to assess neuropsychological capabilities and cognitive reserve (CR) (Harvey, 2012). Gansler et al. (2017) found that neuropsychological tests have high correlations (r = .84) with IQ. Therefore, it makes sense that those neuropsychological capabilities may also impact SG if IQ does.

Several studies have investigated the relationship between P50 SG and cognitive dysfunction. Erwin et al. (1998) demonstrated that by grouping patients into "high- and low-P50 abnormality", the high-P50 abnormality group showed significantly more attention and other neuropsychological deficits than the low-P50 abnormality group. Thomas et al. (2010) found that the global cognition measure Mini-Mental State Exam (MMSE) correlated highly with the P50 ratio in AD patients. Therefore, overall cognitive abilities are likely to be related to SG.

5.2.6.1 Sustained Attention

Sustained attention is related to SG, as it can encourage neural fatigue in participants (Guo et al., 2016). Toyomaki et al. (2015) used the S2 amplitude as the dependent variable to reveal that longer reaction times (RT) during the Conner's Continuous Performance Task (CPT) were associated with an increase in S2 amplitude. Thus, longer RTs are related to a lack of SG, as there is not a large enough decrease in S2 amplitude compared to the S1 amplitude as they should be.

Thomas et al. (2010) found that the S2 amplitude correlated with digit span backward results, a task requiring sustained attention and inhibition in both controls and Alzheimer's Disease (AD) patients. There was a significant negative correlation between the S2/S1 ratio and attention scores; thus, the lower the ratio, the better the SG and better attentional measures.

5.2.6.2 Memory

In regards to memory, the P50 and SG ERPs (N100, P200) have shown consistently poorer SG in those with AD (Gmehlin et al., 2011; Thomas et al., 2010) or the beginnings of AD (Golob et al., 2007), which is commonly mild cognitive impairment (MCI). MCI is a medical disorder found in older adults with an episodic memory deficit which is more severe than in healthy ageing individuals, while other neuropsychological functions are preserved (Golob et al., 2001).

These ERPs have shown significant changes in individuals before the onset of behavioural symptoms and AD (Golob et al., 2009; Quiroz et al., 2011). Hsieh et al. (2004) reported impaired SG and memory function in healthy adults. In addition, MCI patients have a high risk of converting to AD (Michaud et al., 2017). Responses to particular ERPs using

auditory stimuli can comprise important discriminatory data that can determine which MCI patients may convert to AD (Cecchi et al., 2015) and amnestic MCI (aMCI) patients who are at a high risk of progressing to AD also have atypical ERPs (Olichney et al., 2008).

MCI patients who progress towards AD tend to demonstrate greater P50 amplitudes at reference measurements than non-converters (Golob et al., 2002; Golob et al., 2007). These higher P50 amplitudes in response to typical stimuli have shown a deficit in SG (Cheng et al., 2012; Golob et al., 2007). However, Thomas et al. (2010) concluded that long-term memory was not significantly associated with P50 suppression. The literature remains inconsistent on the subject of P50 and memory associations.

Therefore, SG ERPs have shown prospective effectiveness as biomarkers of syndrome advancement and after conversion to AD in patients with MCI (Cecchi et al., 2015; Moretti, 2015). Many recent studies have indicated that the P50 distinguishes early AD sufferers from age-matched controls and could effectively predict MCI development into AD (Golob et al., 2007; Mazaheri et al., 2018).

5.2.6.3 Executive Functioning

Toyomaki et al. (2015) claimed that the P50 ratio could be correlated with EF deficits. A regression analysis using the P50 ratio as the dependent variable demonstrated that more Nelson perseverative errors (repetition of a response) during the Wisconsin Card Sorting Test (WCST) were associated with an increased P50 ratio, indicating an SG deficit. Findings suggest that an increased P50 ratio or S2 amplitude is related to cognitive deficits, as there is less controlled flooding of sensory information.

It has also been found that the S2 amplitude of the P50 was significantly negatively correlated with the Trail Making Test part B in healthy participants (Thomas et al., 2010). The smaller the size of the S2 amplitude, the better the SG and the better the EF.

5.2.6.4 Verbal Fluency

Verbal fluency, considered a frontal neuropsychological test, places demands on WM and inhibition, both skills attributed to the prefrontal cortex (Thomas et al., 2010). Thomas et al. (2020) found a robust correlation between SG and verbal fluency in individuals diagnosed with AD. This correlation suggests that the efficiency of SG, a process related to filtering irrelevant sensory information, is interconnected with verbal fluency performance in AD patients. Moreover, the researchers observed that deficits in auditory gating, which involves the ability to filter and process auditory stimuli, were associated with the global cognitive functioning of these individuals. This implies that disruptions in the neurocognitive processes related to SG may have broader implications for overall cognitive functioning in individuals with AD.

5.2.7 Anxiety

Anxiety is a strong feeling of nervousness that occurs in all individuals at varying degrees and is associated with detrimental health effects and hindering concentration (Stout et al., 2013). Numerous brain regions are associated with anxiety levels, such as the anterior limbic system, paralimbic system, hippocampus, and PFC (Meier, 2014).

These systems have activities related to SG. It encompasses cognitive, affective, physiological, and behavioural components associated with negative mood and emotion (Engel-Yeger & Dunn, 2011). Much research has found that stress and anxiety impact the P50

response (White et al., 2003) and that the P50 is negatively associated with benzodiazepine use which reduces anxiety (Ghisolfi et al., 2006).

5.2.8 Sensory Gating in Ageing Populations

Physiological ageing is associated with functional impairments affecting cognitive processes such as memory, EFs and attention (Terrasa et al., 2018). The type and severity of sensory and cognitive decline in older individuals vary due to differing neuronal vulnerability (Mattson & Magnus, 2006).

In terms of auditory processing, physiological and neuronal ageing first affects the peripheral auditory system, which causes difficulties when sounds have to be detected, localised, or distinguished (Gmehlin et al., 2011). These age-related declines in the acoustic system impact "inhibitory neurotransmission of subcortical and cortical neurons and may result in changes of response properties of neurons, temporal processing, and response reliability" (Caspary et al., 2008, p. 1781).

The reduction in early sensory processing with age has been linked to altered sensory cortices, including decreased inhibition in the primary somatosensory cortex (Cheng et al., 2015). During preattentive SG studies, older adults produce reduced ERP amplitudes when faced with an unusual stimulus compared to younger participants, which could mean a reduction in neural efficiency (Kisley et al., 2004).

The evidence of age-related effects on SG of these components, and which variables are involved, is still limited and unclear (Terrasa et al., 2018). Previous studies have reported significant age-related impairments in auditory gating (Zhu et al., 2017). In contrast, recent

studies failed to replicate this effect, where no age-related effects on SG were found in the P50 component (Gmehlin et al., 2011).

5.2.9 Conclusions

Some authors (Sánchez-Morla et al., 2013), have *not* observed a significant association between the P50 ratio and the neuropsychological tests they employed. Sanchez-Morla et al. (2013) found no association between the P50 ratio and cognitive functioning. Therefore, the literature on the association between the P50 and cognitive dysfunction remains inconsistent, and the association is yet to be proven.

However, despite the inconsistencies in the SG-cognition link, these ERPs have emerged as promising clinical biomarkers in neuropsychiatry (Gmehlin et al., 2011; Green et al., 2015; J. Olichney et al., 2011). When individuals engage in tasks that do not require conscious attention, preattentive sensory processing can be assessed effectively (Gmehlin et al., 2011). This preattentive processing is crucial for distinguishing between healthy older adults and individuals at risk of neuropsychiatric diseases (Schuelert et al., 2018). It is advantageous for this purpose because it does not impose a heavy cognitive task load on participants, as highlighted by Schuelert et al. (2018).

Comparatively, measuring ERPs, such as the P50 response, offers several practical advantages over other biomarker approaches, such as cerebrospinal fluid (CSF) analysis. ERPs are non-invasive, cost-effective, and more widely accessible. They have the capability to reveal irregularities in neural activity that may signify disease-related modifications within the brain. This potential has been recognised in various neurological conditions, including schizophrenia (Luck et al., 2011), AD patients (Green et al., 2015), and individuals with MCI (Olichney et al., 2011). Abnormal ERPs in these populations suggest that these measures hold promise as

diagnostic and monitoring tools in neuropsychiatric disorders. ERPs can expose irregularities in neural activity that reveal organic disease-related modifications in the brain (Quiroz et al., 2011; Seer et al., 2016). Abnormal ERPs have been documented in schizophrenia (Luck et al., 2011), AD patients (Green et al., 2015) and patients with MCI (Olichney et al., 2011).

In summary, while the connection between the P50 SG response and cognitive dysfunction remains inconsistent in the literature, SG measures offer a valuable possibility for exploring neuronal circuitry and distinguishing between healthy individuals and those with susceptibility for neuropsychiatric diseases. The non-invasive, cost-effective nature of ERPs, coupled with their ability to detect neural irregularities, making them promising clinical biomarker tools in neuropsychiatry, offering potential benefits for early diagnosis and monitoring of conditions like schizophrenia, AD, and MCI.

5.3 Hypotheses

The present study aimed to characterise the P50, N100 and P200 responses in a healthy older population using a paired-clicks paradigm, and relating this to measures of neuropsychological functioning to examine cognitive functioning. We wanted to test whether we could do this using an EEG system using as few channels as possible for time efficiency and ease, in order to be carried out on preoperative patients in hospital settings in a future study.

Therefore, our hypotheses were that we would find significant associations between the P50, N100, P200 with measures of neuropsychological functioning, particularly measures of executive functioning and inhibition.

Due to conflicting findings in the literature regarding neuropsychological scores and SG, there may be an underlying effect of age. Therefore, ageing will also be analysed in the findings due to age-related cognitive and sensory decline previously discussed in section 5.2.8.

5.4 Method

5.4.1 Participants

Complete participant demographics are outlined in Table 5.1. Participants were recruited from the "Thousand Elders" database at the University of Birmingham via email; subjects were compensated £20 for their participation of 2.5 hours of attendance at the University of Birmingham.

Table 5.1 Participant Demographics.

	Value
N	30
Gender (M/F)	14/16
Mean average Age (years)	76.2 (4.4)
Mean education (years)	15.2 (2.7)
Hearing Aid (Yes/No)	8/22
Urbanicity (1-3)	2.1 (.8)

Note. Values in brackets are standard deviations.

They were all given anonymous ID numbers for ethical reasons; none had any history of neurological or psychiatric disorders.

5.4.2 Design

The study was a within-subjects design; all participants completed the same

components. Participants completed the neuropsychological tests before the EEG experiment. The tests took approximately 50 minutes to complete, and the EEG section took between 80-90 minutes (including setup).

5.4.3 Neuropsychological Test Materials

Rather than only have one measure of CR, such as the Cognitive Reserve Index Questionnaire (CRIq), we decided to examine the complete neuropsychological profile of each participant, thereby measuring the many aspects of CR. The neuropsychological testing materials used are shown in Table 5.2 and are discussed in more detail below. All Neuropsychological test forms can be found in A.2.

5.4.3.1 Verbal Fluency

Participants were asked to name as many words as they could in 60 seconds, beginning with 'F', 'A', and followed by 'S'. They were asked not to give names of people, places, or numbers. Participants were asked to name as many animals as they could (beginning with any letter) in 60 seconds, then as many fruits as they could (starting with any letter) in 60 seconds. Their score is the total number of correct words given in the allotted time (Fine & Delis, 2011). The test form used can be seen in A.2.1

5.4.3.2 National Adult Reading Test (NART)

The NART involves participants reading aloud 50 words of increasing difficulty to the experimenter. Their pronunciation was marked and scored either 0 or 1, totalling 50. This can be used to predict a measure of the participants' IQ and their language abilities. The predicted

WAIS-IV Full-Scale IQ is calculated as: 127.7 – (0.86*NART Errors) (Nelson & Willison, 1982). The words used are shown in A.2.2

5.4.3.3 Colour Trails Test (CTT)

The Colour Trails Test (CTT) is a non-verbal alternative to the commonly used Trail Making Test (TMT), which was created to examine sustained attention in adults regardless of language. This measures EF, planning and task switching without using language (Maj et al., 1993). The CTT includes two forms, 1 and 2. Form 1 acts as a practise task, while Form 2 is the critical EF, as it requires alternating and switching between number and colour sequences A.2.3.

5.4.3.4 Brain Injury Rehabilitation Trust, Memory, and Information Processing Battery (BMIPB) Form 1

There are three parts (story, list, figure) to the memory section from the BMIPB (Brain Injury Rehabilitation Trust).

Story

Participants were read a short fictional story (131 words) and asked to remember as many details of the story as they could. The story was read aloud once, an immediate recall was taken, and they were then told they would be asked about the story again later. A delayed recall 40+/- 2 minutes later was recorded too. This measures immediate and delayed verbal recall. The story (immediate and delayed) is shown in A.2.4.

List Recall

The second verbal memory component is list learning. A list of 15 unrelated words was read aloud five times (A1-5); after each time, the participant had to say how many words they could remember from the list. Following the five times, a second list (B) was read aloud once, and recall was measured. Subjects were then asked to recall as many words as they could from the first list (A6) while inhibiting words from the second list. The word list used can be seen in A.2.5.

Figure

A complex figure drawing was placed in front of participants. They were asked to copy it as best as they could with no time limit; this measures their visuoperceptual functioning and planning abilities. Participants were not told that they would have to draw the figure again from memory. The figure and their copy were removed, and they were asked to reproduce the drawing at a 3-minute delay (immediate recall). A second recall was repeated at a 40-minute delay (delayed recall). The figure they were required to copy is in A.2.6.

5.4.3.5 WAIS-IV: Matrix Reasoning

This WAIS-IV sub-test measures perceptual reasoning using non-verbal abstract problem-solving tasks. The participants were asked to fill in pattern sequences and find which shape options fit in the correct boxes; raw scores are out of 26, and scale scores are computed using both raw scores and age (Wechsler, 2005). The matrix reasoning form is seen in A.2.7 with an example of a trial.

5.4.3.6 Hospital Anxiety and Depression Scale (HADS)

The HADS (Zigmond & Snaith, 1983) is a 14-item scale questionnaire which measures levels of anxiety and depression that a person may be experiencing. Anxiety and depression are both marked out of 21; a higher score denotes higher levels of anxiety and depression. The questionnaire used is in A.2.8.

5.4.3.7 Cognitive Failures Questionnaire (CFQ)

The CFQ measures self-reported dysfunction in domains including: perception, memory and motor abilities (Broadbent et al., 1982). There are 25 items, and subjects rated how often they occur in everyday life (from 0-4). These were then totalled; the higher the score, the more cognitive failures experienced by participants. This applied questionnaire is in A.2.9.

Table 5.2 Neuropsychological testing protocol

Test Name	Task	Time Taken (mins)	Skills tested
Verbal Fluency	Naming max. no. of words beginning with a certain letter or category in 60 secs	5	Flexibility and lucidity of language
NART	Premorbid intelligence through reading abilities	2 – 3	Reading abilities and knowledge of language
Colour Trails Test	Timed trail making in two different tests	3	Problem solving and executive functioning
BMIPB Form 1 Story	Recall story after it's read once immediately, and at 40-minute delay	48 (inc. 40-min delay)	Short-term and long-term verbal memory
BMIPB Form 1 List	Five 15-word list recall attempts followed by a second distractor list	10	Short-term and long-term verbal memory, discrimination between lists
BMIPB Figure 1	Copying the image, and recalling it twice immediately and 40-minute delay	45 (inc. 40-min delay)	Short-term and long-term visual memory
WAIS-IV: Matrix Reasoning	Solve patterns and finishing the sequences	10	Problem solving, pattern predicting, non-verbal reasoning
HADS	Mood questionnaire	3 – 4	Measures amounts of anxiety and depression
CFQ	25-item questionnaire measuring how often cognitive mistakes occur in daily life	3 – 4	Quantifies the occurrence of cognitive errors

Note. BMIPB, Brain Injury Rehabilitation Trust Memory and Information Processing Battery; CFQ, Cognitive Failures Questionnaire; HADS, Hospital Anxiety and Depression Scale; NART, National Adult Reading Test; WAIS-IV, Wechsler Adult Intelligence Scale, Fourth Edition.

5.4.4 Procedure

Participants first completed neuropsychological testing in a quiet room with plenty of daylight and were made to feel comfortable during the experiment. The neuropsychological testing was completed by every participant in the same order: NART, BMIPB Story, BMIPB List, BMIPB Figure, WAIS-IV Matrix Reasoning, Verbal Fluency, HADS and finally the CFQ. This took around one hour to complete. Participants were then offered a break and taken to our EEG lab where they were seated, where the EEG cap could be applied.

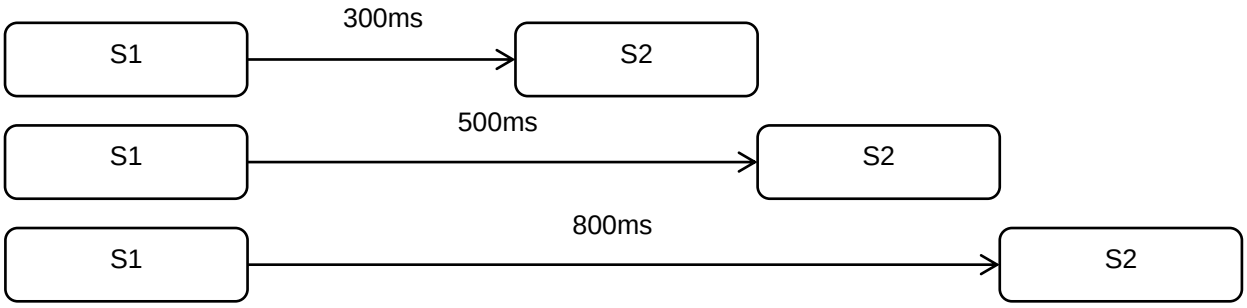
Once the EEG cap was fully applied, participants received a brief explanation of the task: they were told to ignore the sounds from the headphones during the experiment and just to relax and watch a film of their choice with subtitles.

They were then asked to sit in a sound-proof booth. Once comfortable, noise cancelling headphones were placed on the EEG cap; subjects were asked to be relaxed and not produce large motor movements. The headphone volume depended on participants' hearing levels. Participants heard sample sounds to ensure they could listen to the sounds, and we could adjust the volume for them. They were asked to tell us when they thought the sounds were 6/10 for loudness; volume levels ranged from 21 to 50 out of 100. A Windows 10 desktop computer produced the sound outside of the soundproof booth, and the headphone wires were fed through to the sound booth where the participants sat. The sound booth was dark, so they could focus on the screen without any distractions.

We measured SG within a more extensive experiment (discussed in a subsequent chapter). The whole experiment took ~60 minutes to complete and was comprised of four blocks; participants were offered breaks between the blocks. Within this experiment, subjects completed one block of approximately 15 minutes to measure SG. Clicks were randomly

presented with 300, 500 and 800ms interstimulus intervals (ISI) between clicks (see Figure 5.4). Participants listened to 41 pairs of clicks in this click trial block; the ISI pairs were randomly dispersed throughout the block, but the order was the same for every participant.

Figure 5.4 Illustration of the different interstimulus intervals between clicks.



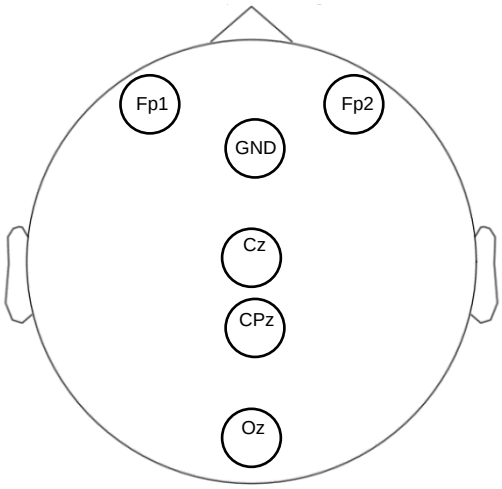
Note. Subjects' sensory gating can vary ~500ms. The three interstimulus intervals were all randomly dispersed in the same block, lasting 15 minutes.

A pure tone (1,500 Hz, 6-ms duration) was used as the click sound and presented during varying intervals.

5.4.5 EEG Acquisition

This setup provides good head coverage but is impractical for fast EEG acquisition in a clinical sample. We planned to record EEG using a total of six electrodes. Our lab (School of Psychology, University of Birmingham) validated this setup to record brain activity reliably, and it is ideal for the P50 signals (Nagamoto et al., 1991) we planned to investigate. This setup is indicated in Figure 5.5.

Figure 5.5 Illustration of the six-channel EEG setup.



Note. Fp1, frontoparietal area 1; Fp2; frontoparietal area 2; GND, ground reference; Cz, central area channel; CPz (active reference) central parietal channel; Oz, occipital area.

The EEG cap (WaveGuard^{TM} 10-20 system, ANT Neuro, 2016) with 32 Ag/AgCl electrodes was fitted to the participant, and the electrodes' impedance was adjusted to be below 20 kΩ during the recording. Data was sampled at 1,000 Hz. EEG data were collected from five scalp sites (Fp1, Fp2, GND, Cz, and Oz) referenced to the CPz electrode. The Oz served as reference, and the Fp1 and Fp2 electrodes recorded eye movements.

5.4.5.1.1 EEG Processing

The signals were digitised for an epoch of 400ms starting 200ms before the presentation of each auditory stimulus. Individual trials were rejected when the EEG voltage was greater than ± 35 μV, indicative of excessive muscle activity, eye movements, or other artefacts.

We measured the peak-to-peak amplitude from a preceding negative trough to the positive peak. This was done because the baseline before the second stimulus onset often

fluctuated based on the ERP from the first stimulus; the baseline-to-peak amplitude was not appropriate for assessment.

The six-channel EEG was recorded at 1,000 Hz. It was high-pass filtered from 0.5 and low-passed filtered at 80 Hz. The data were pre-processed using EEGLAB (Delorme & Makeig, 2004). Fieldtrip (Oostenveld et al., 2011) was used to lock EEG epochs to the onset of the auditory clicks and was manually inspected for non-physiological artefacts. Independent component analysis was then used for the removal of eye movement artefacts (Delorme & Makeig, 2004).

5.5 Results

This section discusses the results we collected from the participants. The neuropsychological results will be addressed first in relation to participants' EEG analyses.

5.5.1 Neuropsychological Results

We began with 30 participants, but only 28 could complete the total amount of assessments due to health reasons. We were worried about another participant being cognitively healthy, as they scored zero on long-term memory measures (BMIPB story and figure). This is abnormal, and they were excluded too, as they displayed severe episodic memory deficits, which were more severe than the other individuals. Their other neuropsychological functions were preserved. Due to MCI's potential impact on SG (see A.3), we removed this participant from our sample.

The participants' overall neuropsychological test scores were analysed, and the descriptive statistics are shown in Table 5.3 below. In total, 27 neuropsychological variables per participant were collected in the experiment.

Table 5.3 Generalised statistics of each neuropsychological component for control subjects.

Neuropsychological Variables	Mean	SD	Skewness	Kurtosis	Shapiro-Wilk
N = 27					
NART					
Raw Score (/50)	43.4	3.1	-0.76	-0.15	0.93
Pred. WAIS FSIQ	122.3	2.6	-0.82	-0.24	0.89**
WAIS: Matrix Reasoning					
Raw (/20)	18.4	4.8	-0.77	0.07	0.94
Scaled Score	14.4	2.8	-0.82	1.47	0.94
BMIPB Form 1					
List A1-5 Total	47.4	10.7	-0.04	-1.00	0.94
A6	10.3	2.7	-0.48	0.53	0.96
Story Immediate Recall	32.8	8.0	0.37	-0.30	0.97
Story Delayed Recall	30.0	9.9	-0.68	1.77	0.97
Story retained (Del/Imm) (%)	94.8	8.6	0.52	0.89	0.97
Figure Copy	78.5	1.9	-1.95	4.25	0.76***
Figure Immediate Recall	53.6	10.2	-0.24	-0.76	0.95
Figure Delayed Recall	53.0	9.5	-0.14	-0.74	0.97
Figure retained (Del/Copy) (%)	67.5	11.5	-0.29	-0.38	0.97
Verbal Fluency					
Letter Fluency (F, A, S)	17.9	4.6	-	-	-
Category Fluency (Animals, Fruits)	18.7	4.8	-	-	-
Total	93.9	17.9	0.85	0.39	0.93
Colour Trails Test					
Form 1 Raw (secs)	48.3	16.8	0.83	1.98	0.93
Form 1 Standard Score	102.1	13.3	-0.13	-0.81	0.96
Form 2 Raw (secs)	88.3	25.6	0.49	-0.46	0.95
Form 2 Standard Score	105.3	10.9	0.16	-0.74	0.97
CFQ					
Raw (/100)	41.6	11.1	0.05	0.87	0.97
HADS					
Anxiety	6.5	2.8	0.69	0.49	0.92*
Depression	3.6	2.9	1.06	1.42	0.91*

Note. *p < .05, **p < .01, ***p < .001.

Most of the results appear to have low variability and be normally distributed, with slight skewness and kurtosis in the data. We have a sample with a relatively high average age of 76.2 years (see Table 5.1) and high intelligence with a predicted IQ of 122.3.

5.5.1.1 Neuropsychology and Ageing

We undertook a Pearson's correlation analysis to investigate the relationships between age, years of education and neuropsychological performance, namely EF. According to the Frontal Hypothesis of Ageing (section 2.2) and Cognitive Reserve Hypothesis (section 2.3), EF abilities should decrease with age, and the more educated should perform better. The EF abilities selected for analysis included the BMIPB list A1 – 5, a measure of WM, and ability to learn, which are part of EF. The A6 is a measure of inhibitory memory because participants must suppress the learning of the new list (list B) (retroactive interference) and try to access the old list (list A). Verbal fluency is a measure of oral functioning and executive control, as they have to focus on the task with constraints (i.e., letter or category) and avoid repetition (Shao et al., 2014). The CTT was also chosen because it requires planning and involves colour-number switching, cognitive flexibility, and part of EF. These correlations are shown in Table 5.4.

Table 5.4 Ageing and education correlations with executive functions

	Age (years)	Education (years)
BMIPB A1-5	-.641**	.461*
A6	-.541**	.448*
Total Verbal Fluency	-.505**	.468*
Colour Trails Test 2 (SS)	-.037	.044

Note. Pearson's *R* values given; *$p < .05$, **$p < .01$. SS = standard score; A6 = inhibitory memory.

Table 5.4 shows that there are moderately significant negative correlations between BMIPB A1-5, A6 and verbal fluency with age ($p < .01$), but not between the colour trails test and age ($p = .854$). It's possible that the low standard deviation in age could have skewed the regression, and the participants were from the same area in Harborne, Birmingham so were

likely to be of the same demographic. After discounting participant 19, we were able to rule out the other participants having possibility of MCI.

Therefore, the older we age, the worse we can expect to do on the three previous tests of EF. It also shows significant positive correlations between BMIPB A1-5, A6 and verbal fluency with years of education ($p < .05$). This effect was not found for the colour trails test. The association shows that the more educated participants are, the better they perform on the EF functioning tests.

5.5.2 EEG Click Paradigm Analyses

5.5.2.1 Signal Processing

Data were analysed offline, bandpass filtered (10–50 Hz; 24 dB/octave roll-off) and averaged. Before averaging, epochs were rejected if they were contaminated by substantial movement artefacts such as eye blinks. Averages were calculated for each subject and each of S1 and S2 separately. Averages were computed over the whole recording session (41 tone pairs).

5.5.2.2 Peak Selection and Quantification

The heights of each peak of interest were calculated in MATLAB with a range of 50ms on either side of the point of interest (S1 or S2) to allow for individual variability; for example, the P50 at 300ms ISI would be calculated between 25-75ms, and 325-375ms. This also meant we did not produce a minus result for a positive peak. These peaks were chosen due to the interspersion of different ISIs throughout the experiment (see 5.4.5).

These peaks (given in μV) were extracted as continuous data, showing six ERP results per participant per component; we could then use these for statistical analyses.

5.5.2.3 EEG Descriptive Statistics

The overall descriptive statistics for each EEG component are shown in Table 5.5 below.

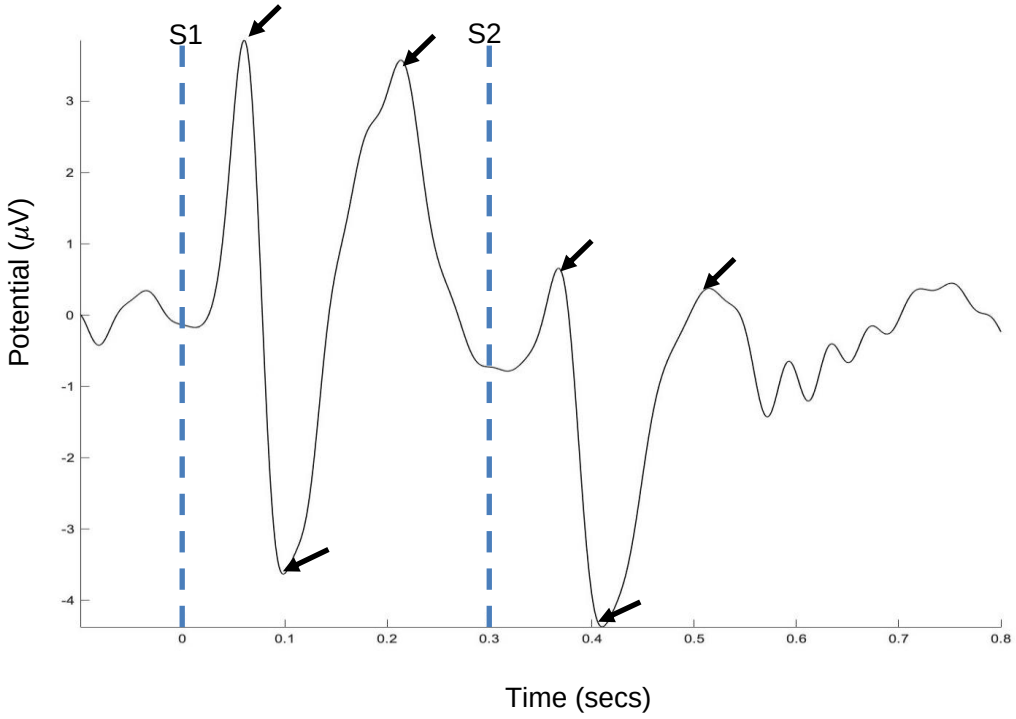
Table 5.5 EEG descriptive statistics for participants.

ERPs	Mean	SD	Skewness	Kurtosis	Shapiro-Wilk
		P50			
300ms ISI (μV)					
S1	3.27	2.66	1.29	1.87	0.896**
S2	0.09	1.82	0.39	-0.08	0.970
500ms ISI (μV)					
S1	3.02	2.12	0.25	-1.19	0.940
S2	1.19	1.85	0.81	-0.02	0.915*
800ms ISI (μV)					
S1	3.65	3.23	1.63	4.18	0.876**
S2	2.12	3.04	0.76	2.12	0.944
		N100			
300ms ISI (μV)					
S1	-3.22	2.69	-0.48	1.63	0.938
S2	-3.12	2.89	-1.91	5.57	0.846***
500ms ISI (μV)					
S1	-3.84	2.72	-1.23	2.34	0.902*
S2	-3.09	2.32	0.14	0.12	0.990
800ms ISI (μV)					
S1	-3.31	2.60	-0.82	0.65	0.918*
S2	-1.96	2.56	0.16	-0.48	0.974
		P200			
300ms ISI (μV)					
S1	3.10	2.45	0.62	-0.42	0.930
S2	0.38	1.44	0.57	0.55	0.962
500ms ISI (μV)					
S1	3.38	2.49	1.21	3.24	0.924*
S2	1.66	1.91	0.99	2.91	0.931
800ms ISI (μV)					
S1	3.43	2.88	0.35	0.55	0.980
S2	2.32	2.11	0.29	0.18	0.974

Note. (n = 27) *Indicate significance at the $p < .05$ level; ** $p < .01$; *** $p < .001$ level.

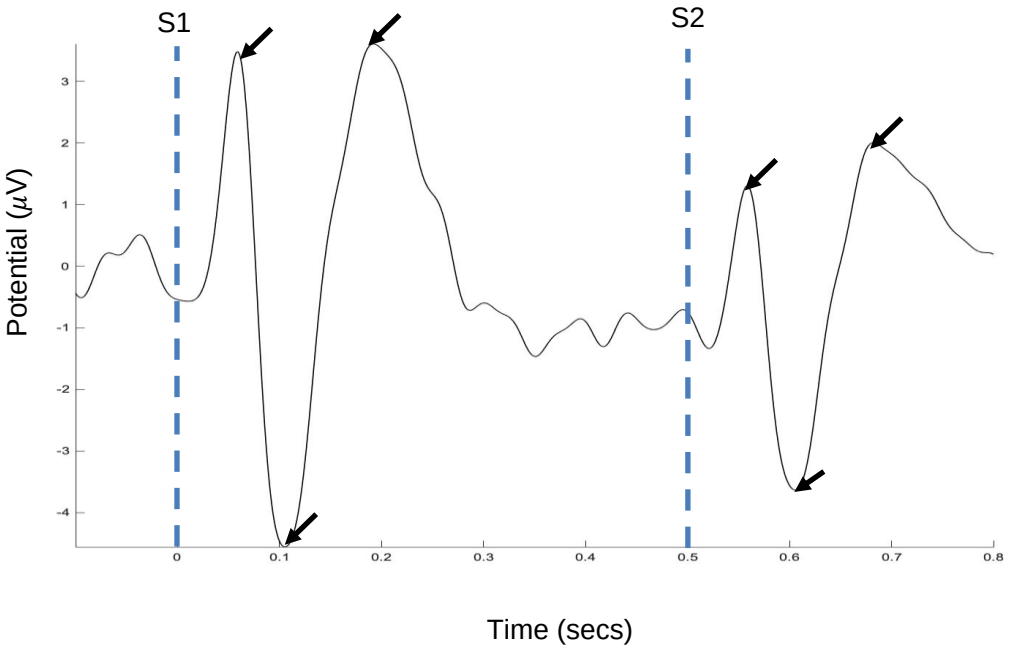
Graphs were constructed using the ERP grand average of the SG peaks across participants for each SG ISI (300ms, 500ms, 800ms) of the waveforms 100ms before the click, and 800ms after the click (-100ms – 800ms). These ERPs are shown in Figure 5.6, Figure 5.7, and Figure 5.8.

Figure 5.6 Grand average sensory gating across participants for the 300ms paradigm.



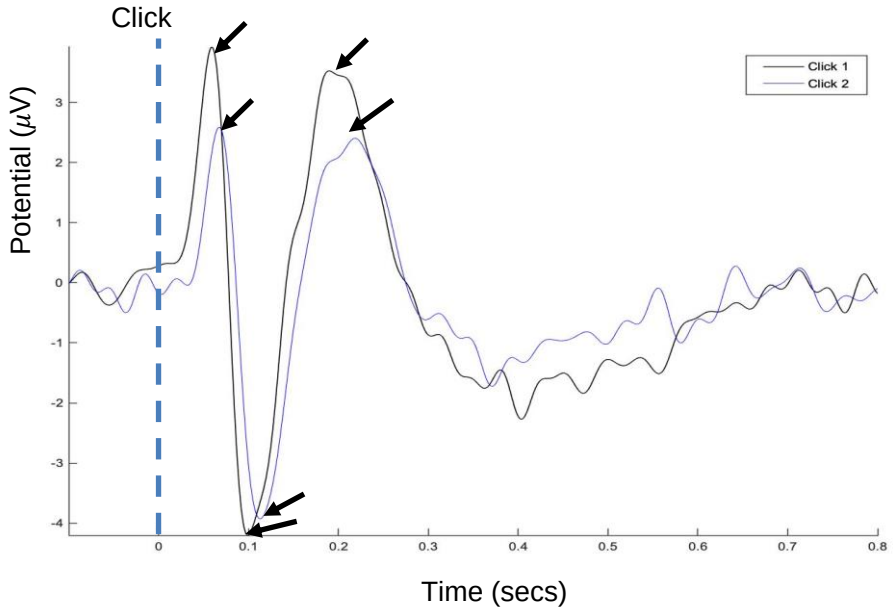
Note. Peaks of interest occur at 50ms (P50), 100ms (N100), 200ms (P200), 350ms (P50), 400ms (N100), 500ms (P200) (n = 27).

Figure 5.7 Grand average sensory gating across participants for the 500ms paradigm.



Note. Peaks of interest occur at 50ms (P50), 100ms (N100), 200ms (P200), 550ms (P50), 600ms (N100), 700ms (P200) (n = 27).

Figure 5.8 Grand average sensory gating across participants for the 800ms paradigm.



Note. Peaks of interest occur at 50ms (P50), 100ms (N100), 200ms (P200), 850ms (P50), 900ms (N100), and 1secs (P200). The S2 has been cut and placed on top of the S1; all peaks have been set to the clicks occurring at 0secs on the graph (n=27).

5.5.3 ANOVA analyses

A repeated measures ANOVA was calculated for each EEG component (P50, N100, P200) to find any significant differences between the potentials for the ISI, S1 and S2. Results of the follow-up t-tests are shown in Table 5.6.

5.5.3.1 P50 Suppression

There was a significant main effect of ISI on the ERP potentials (Sphericity Assumed: F (2, 52) = 4.717, p = .013). There was a significant main effect of click (S1 or S2) on ERP potential (Sphericity Assumed: F (1, 26) = 69.28, p < .001). There was also a significant main effect of interaction between the two factors (Sphericity Assumed: F (2, 52) = 4.484, p = .016).

Table 5.6, shows that values significantly differ across the ISIs, and the S2 P50 response is significantly lower than the S1 in all three ISIs. This indicates that effective SG occurs at ISIs of 300, 500 and 800ms across participants.

A second repeated measures ANOVA found significant differences between the S2 amplitudes (sphericity assumed: F (2, 52) = 6.382, p = .003). Follow-up t-tests found that S2 in the 800ms ISI had significantly higher amplitude (M = 2.12, SD = 3.04) than S2 in 300ms ISI (M = 0.09, SD = 1.82), showing higher P50 suppression in 300ms ISI (t (26) = -3.116, p = .004). S2 in the 500ms ISI had significantly higher amplitude (M = 1.19, SD = 1.85) than S2 in 300ms ISI (M = 0.09, SD = 1.82), showing higher P50 suppression in 300ms ISI (t (26) = -2.075, p = .048). There were no significant differences between S2 amplitudes in 500ms and 800ms. There were no significant differences between S1 amplitudes.

5.5.3.2 N100 Response

A repeated measures ANOVA on the N100 responses showed there was no significant main effect of ISI on the ERP potentials (Sphericity Assumed: F (2, 52) = 2.217, p = .119). There was a significant main effect of click (S1 or S2) on ERP potential (Sphericity Assumed: F (1, 26) = 6.924, p = .014). There was no significant main effect of interaction between the two factors (Sphericity Assumed: F (2, 52) = 1.935, p = .155).

Follow-up t-tests showed no significant differences between the S1 amplitudes (sphericity assumed: F (2, 52) = 1.546, p = .223) or S2 amplitudes (sphericity assumed: F (2, 52) = 2.326, p = .108).

5.5.3.3 P200 Response

There was a significant main effect of ISI on the ERP potentials in the P200 analyses (Sphericity Assumed: F (2, 52) = 4.806, p = .012). There was a significant main effect of click (S1 or S2) on ERP potential (Sphericity Assumed: F (1, 26) = 25.543, p < .001). There was a significant main effect of interaction between the two factors (Sphericity Assumed: F (2, 52) = 5.677, p = .006).

There were no significant differences between the S1 amplitudes (sphericity assumed: F (2, 52) = 0.446, p = .643). But there were significant differences between S2 amplitudes (sphericity assumed: F (2, 52) = 7.712, p = .001).

S2 in the 300ms ISI had significantly lower amplitude than S2 in 500ms ISI (t (26) = -2.75, p = .011), and 800ms ISI (t (26) = -3.381, p = .002). There were no significant differences between S2 amplitudes in 500ms and 800ms (p = .165).

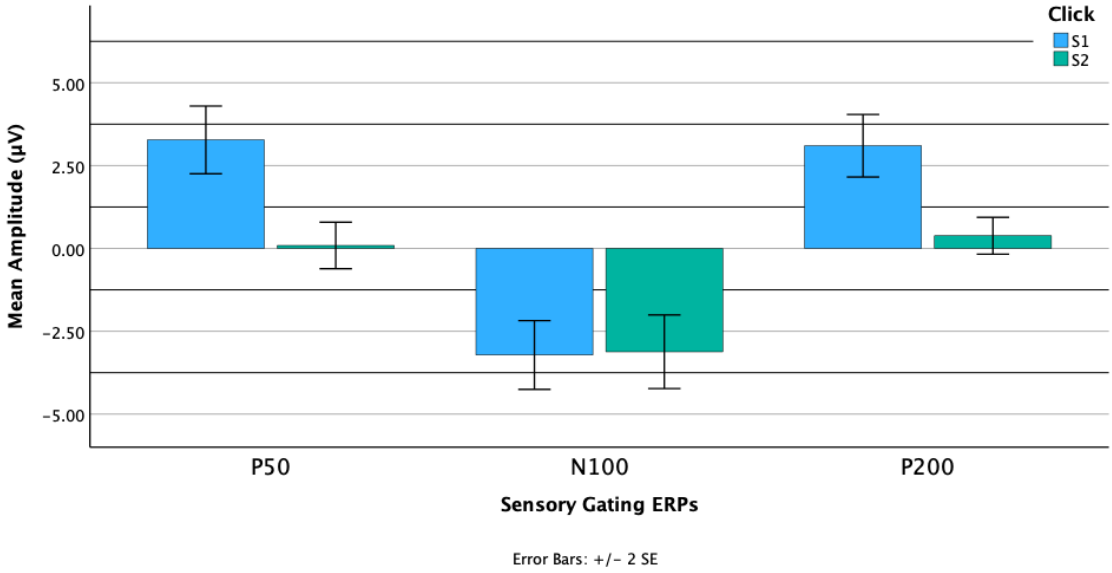
Table 5.6 T-tests of mean potentials for each click in the ISIs averaged across participants.

	S1	S2	*t*	*p*
ERPs		*P50*		
300ms ISI (**μ**V)	3.27 (2.66)	0.09 (1.82)	5.86	<.001
500ms ISI (**μ**V)	3.02 (2.12)	1.19 (1.85)	5.072	<.001
800ms ISI (**μ**V)	3.65 (3.23)	2.12 (3.04)	4.275	<.001
		N100		
300ms ISI (**μ**V)	-3.22 (2.7)	-3.12 (2.89)	-.214	.833
500ms ISI (**μ**V)	-3.84 (2.72)	-3.09 (2.32)	-1.524	.14
800ms ISI (**μ**V)	-3.31 (2.6)	-1.97 (2.56)	-3.15	.004

		P200		
300ms ISI (***μ***V)	3.1 (2.45)	0.38 (1.44)	6.067	<.001
500ms ISI (***μ***V)	3.38 (2.49)	1.66 (1.91)	4.415	<.001
800ms ISI (***μ***V)	3.43 (2.88)	2.32 (2.11)	2.109	.045

Note. Units are given in mean μV, with standard deviations in brackets (n = 27).

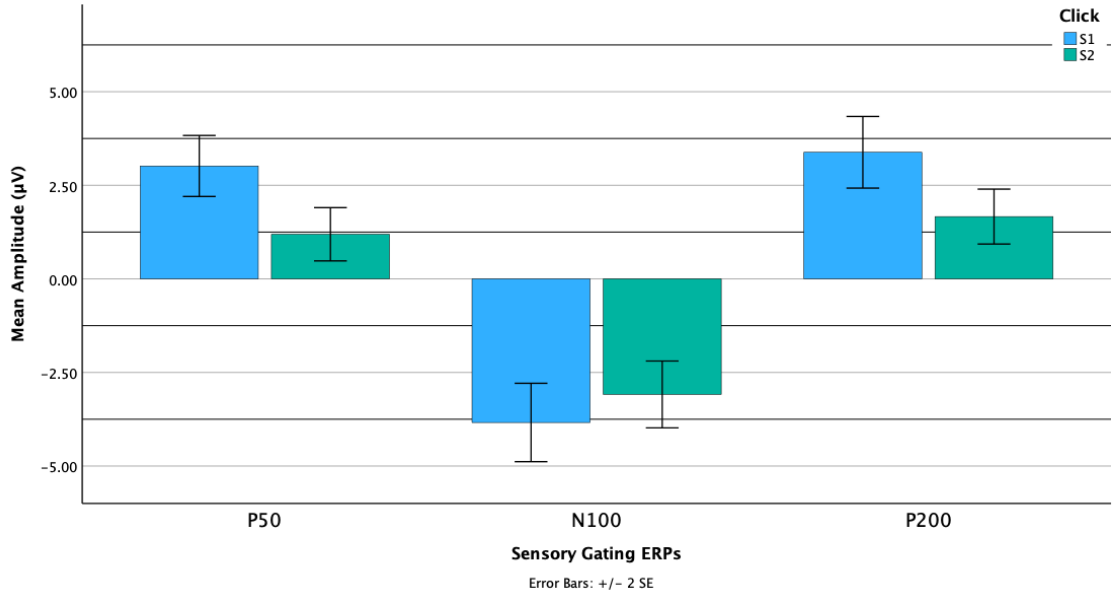
Figure 5.9 300 ms ISI of all three Sensory Gating ERPs: P50, N100, P200.



Note. (n = 27)

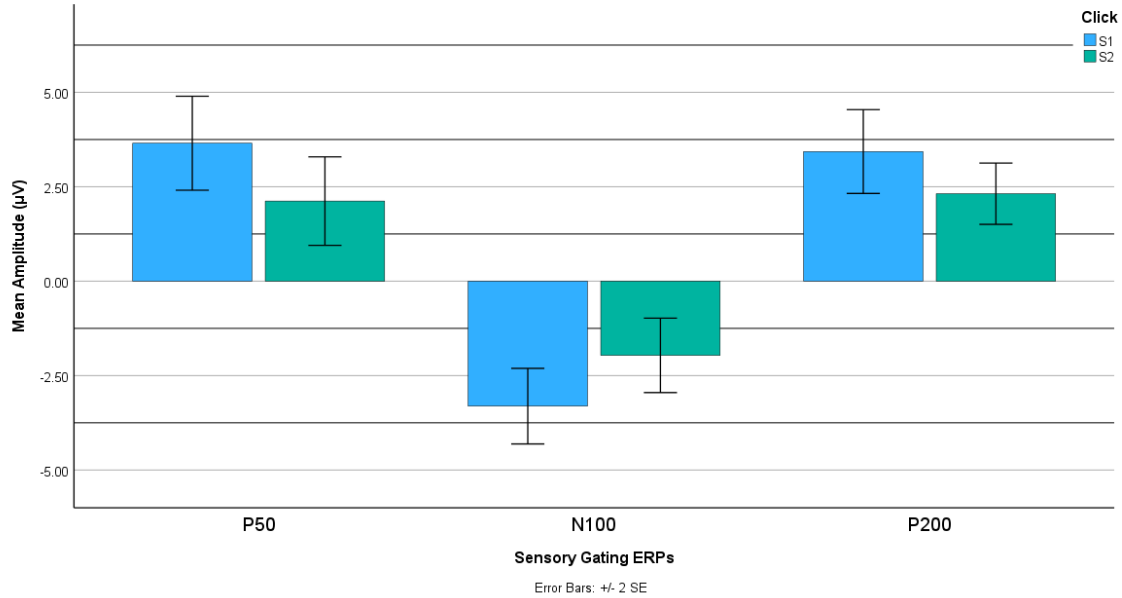
As Table 5.6 and the subsequent graphs (Figure 5.9, Figure 5.10, Figure 5.11) show, the P50 and P200 seem to mirror each other and show similar patterns in relation to the S1 and S2 amplitudes. Across all ISIs, the S2s in the P50 and P200 are significantly smaller than the S1s. In the N100, the S2 is only significantly smaller in the 800 ms ISI condition. Therefore, the P50 and P200 are more robust and reliable indicators of SG than the N100 in this dataset.

Figure 5.10 500 ms ISI of all three Sensory Gating ERPs: P50, N100, P200.



Note. (n = 27)

Figure 5.11 800 ms ISI of all three Sensory Gating ERPs: P50, N100, P200.



Note. (n = 27)

5.5.4 Sensory Gating Calculation

Following the ERP analyses, the suppressions of the P50, N100 and P200 were calculated using equation b from Figure 5.1. This was chosen because the higher the ratio, the better the SG abilities of the participant, and this was thought to make interpreting the results more logical. SG was calculated using the following equation (Figure 5.12):

Figure 5.12 The equation used to calculate the P50, N100 and P200 suppression ratio.

$$\frac{S1\ amplitude}{S2\ amplitude} \times 100$$

Note. This is subsequently used as an index measure for sensory gating abilities.

The bigger the value, the more effective the SG abilities of the individual, and we should be able to find effective SG ratios across participants. The suppressions of the P50, N100, P200 across all ISIs were calculated and are shown in the table below (Table 5.7).

Table 5.7 Results of Mean Suppressions of P50, N100 and P200 Across Participants.

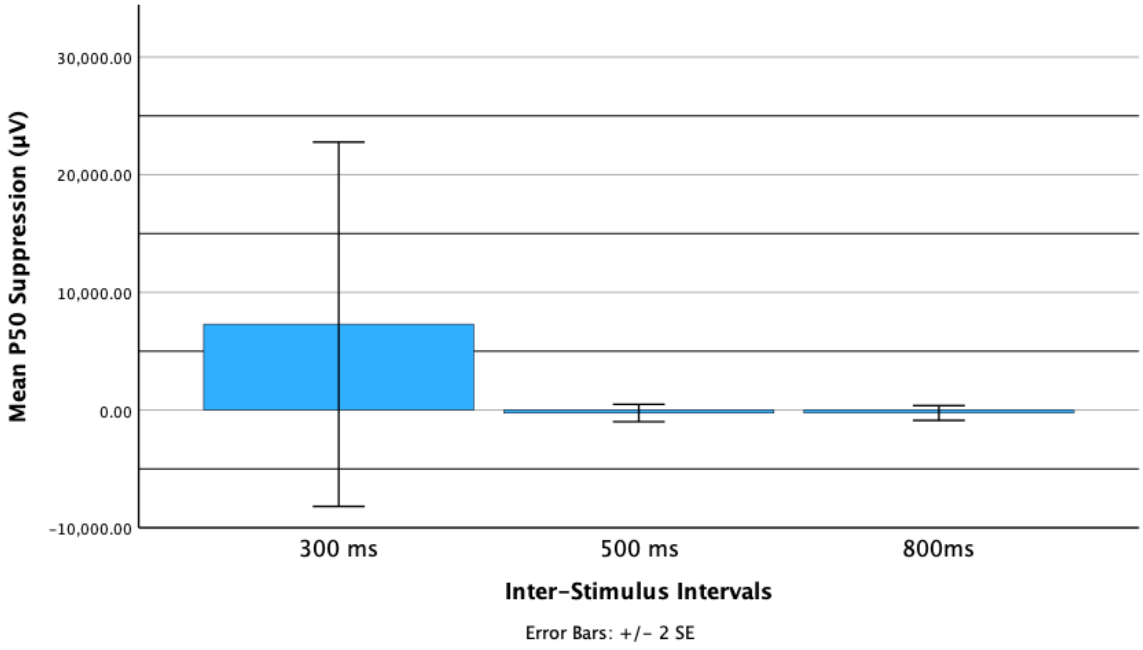
	Mean μV (SD)		
Sensory Gating Components	ISIs		
	300 ms	500 ms	800 ms
P50	7292.92 (40224.2)	-252.1 (1917.5)	-246.8 (1634.1)
N100	132.9 (164.0)	60.7 (248.8)	262.5 (932.7)
P200	9.14 (1607.9)	275.5 (502.6)	265.5 (731.0)

Note. Units are given in mean μV, with standard deviations in brackets (n = 27). ISI, Inter-Stimulus Intervals.

5.5.4.1 P50 Suppression

The mean P50 suppressions across 300ms, 500ms and 800ms ISIs were calculated across participants and are shown in Figure 5.13 below. Using a repeated measures ANOVA, with a Greenhouse-Geisser correction (Mauchley's Test $p > .05$), there were no significant differences between the mean P50 suppression potentials of 300ms, 500ms, and 800ms in participants (Greenhouse-Geisser: F (1.005,26.163) = .949, p = .339). The biggest difference was seen in the 300 ms ISI (see Figure 5.13) even though it is not significant. We did not find significant differences in how the brain modulated responses to sensory stimuli, as reflected by the P50 suppression component, across these specific ISIs.

Figure 5.13 P50 suppressions averaged across participants.



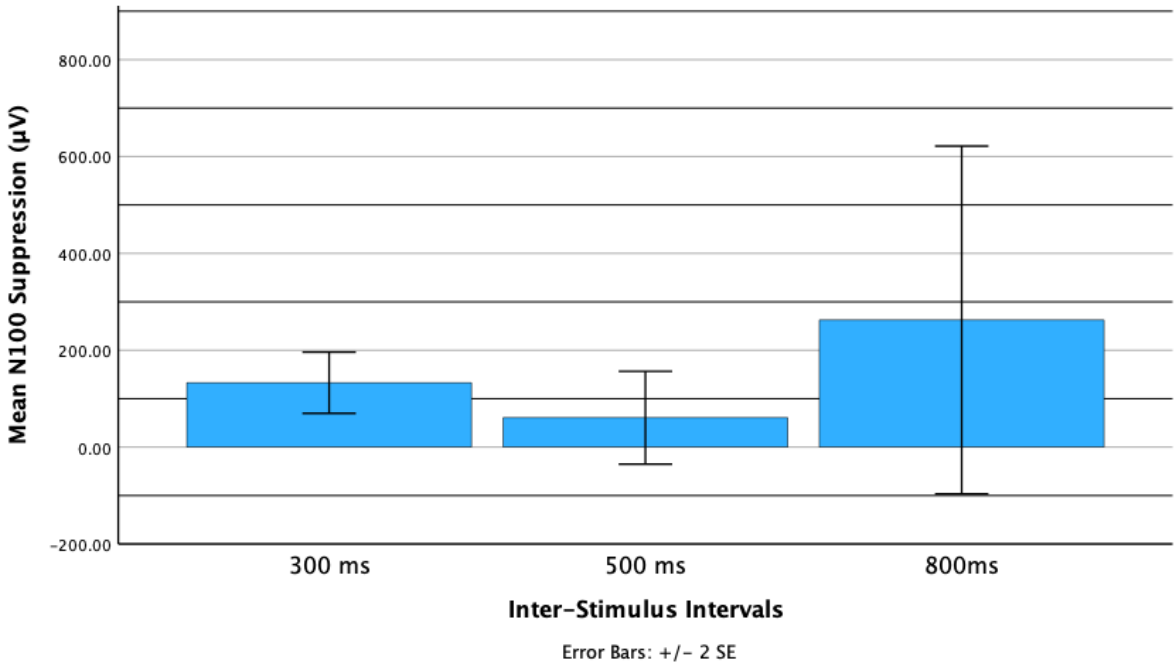
Note. The differences in ERP activity between the ISIs are all non-significant ($p > .05$).

5.5.4.2 N100 Responses

A repeated measures ANOVA with a Greenhouse-Geisser correction (Mauchley's Test $p > .05$) revealed no significant main effect of ISI on N100 SG potentials (F (1.146, 29.809) = 0.963, p = 0.347). Therefore, the varying ISIs did not significantly influence N100 SG responses based on the data collected (see The suppressions of the P50, N100, P200 across all ISIs were calculated and are shown in the table below (Table 5.7).

Table 5.7). Interestingly, the study did find that the most robust SG effect occurred at an ISI of 800 ms, as indicated in Table 5.6. This suggests that, in this study's context, the brain exhibited the most pronounced modulation of N100 responses when stimuli were presented with an 800 ms ISI (can also be seen in Figure 5.14). While we did not detect a significant impact of ISI on N100 SG potentials, it did observe that the most pronounced SG effect was evident at the 800 ms ISI, highlighting an optimal temporal interval for N100 SG.

Figure 5.14 N100 suppressions averaged across participants.

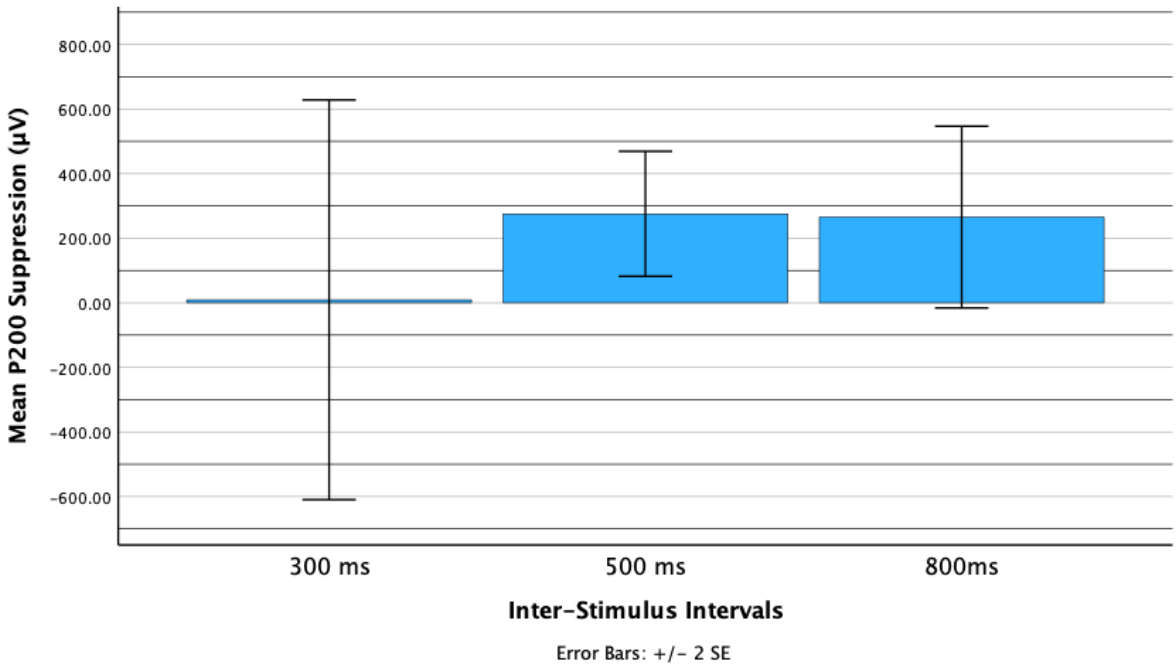


Note. The differences in ERP activity between the ISIs are all non-significant ($p > .05$).

5.5.4.3 P200 Responses

The mean P200 differences were calculated across participants considering inter-stimulus intervals (ISIs) of 300 ms, 500 ms, and 800 ms. After applying the Greenhouse-Geisser correction for violations of sphericity (Mauchley's Test $p > .05$), the analysis revealed no significant main effect of ISI (F (1.317, 34.23) = .468, p = .550). This means that, the duration of these ISIs did not significantly impact P200 responses, suggesting consistent neural and cognitive processes associated with the P200 component across these intervals. Figure 5.15 shows that the P200 500 ms and 800 ms ISI are the most similar in terms of amount of suppression.

Figure 5.15 P200 suppressions averaged across participants.



Note. The differences in ERP activity between the ISIs are all non-significant ($p > .05$).

5.5.5 Effects of ageing

There were no significant effects of age on the SG components and their respective ISIs ($p > .05$). Due to age not having an impact on SG, it is unlikely that we have to put in age as a covariate in the subsequent regressions with neuropsychological measures.

5.5.6 ERPs and Neuropsychological Tests

Stepwise multiple linear regression analyses were conducted for different neuropsychological measures on SG. All ISIs were used for each EEG component (P50, N100, P200) as the dependent variables, to investigate which one is the best candidate to associate with the measured neuropsychological variables; using the following variables used as predictors:

1. Anxiety (HADS A)
2. A6 (BMIPB inhibitory list recall)
3. CFQ (cognitive failures)
4. CTT SS form 2 (colour-number interference trails test scaled scores)
5. Verbal fluency (language inhibition and WM)
6. Story retained (%) (verbal long-term memory capacity)
7. Figure retained (%) (visual long-term memory capacity)

These variables were chosen based on the work of previous studies, as discussed in section 5.2.6.

5.5.7 Regression Analyses

Table 5.9 shows that the neuropsychological variables entered into the regression to predict the P50 response across all ISI (300, 500, 800 ms), did not significantly contribute towards any regression model involving the P50.

Table 5.10 shows that there was one variable which contributed significantly towards the N100 500 ms SG component (p = .008). The A6 inhibitory measure significantly contributed towards the N100 500 ms response (values from Table 5.12):

N100 500 ms = -416.77 (constant) + (46.20 * A6)

The analysis of P200 ISIs (see Table 5.11) indicates that Figure retained (%) significantly predicted the 300 ms response (p = .016), while Story retained (%) significantly predicted the 500 ms response (p = .038). The corresponding regression equations can be found below, with values extracted from Table 5.12:

P200 300 ms = 4365.41 (constant) + (-64.54 * Figure retained (%))

P200 500 ms = 2496.04 (constant) + (-23.43 * Story retained (%))

Table 5.8 Age predicting the sensory gating components and respective ISIs.

	P50											
Predictors	300 ms				500 ms				800 ms			
	B	*SE B*	*β*	*P*	*B*	*SE B*	*β*	*P*	*B*	*SE B*	*β*	*P*
(Constant)	21555.56	132726.09		.872	4499.22	6256.69		.479	-5580.15	5286.29		.301
Age (years)	-187.12	1738.22	-.022	.915	-62.34	81.94	-.15	.454	69.97	69.23	.198	.322
	N100											
	300 ms				500 ms				800 ms			
	B	*SE B*	*β*	*P*	*B*	*SE B*	*β*	*P*	*B*	*SE B*	*β*	*P*
(Constant)	-563.15	522.99		.292	492.34	816.60		.552	1799.64	3067.76		.562
Age (years)	9.13	6.85	.258	.194	-5.66	10.69	-.105	.601	-20.17	40.11	-.100	.620
	P200											
	300 ms				500 ms				800 ms			
	B	*SE B*	*β*	*P*	*B*	*SE B*	*β*	*P*	*B*	*SE B*	*β*	*P*
(Constant)	-6568.22	5140.57		.213	34.794	1658.20		.983	-3063.31	2318.60		.198
Age (years)	86.29	67.32	.248	.212	3.16	21.72	.029	.886	43.67	30.37	.276	.163

Note. Age was non-significant for all SG responses and ISIs ($p > .05$) (n = 27).

Table 5.9 P50 regression analyses incorporating all ISIs.

	P50											
Predictors	300 ms				500 ms				800 ms			
	B	*SE B*	*β*	*P*	*B*	*SE B*	*β*	*P*	*B*	*SE B*	*β*	*P*
(Constant)	-41510.85	168183.92		.81	4321.13	7928.62		.59	4022.59	6475.65		.54
Anxiety	-704.74	3231.78	-.05	.83	78.45	152.35	.12	.61	-105.73	124.43	-.18	.41
A6	-2747.42	4054.03	-.19	.51	23.05	191.12	.03	.91	-121.15	156.09	-.20	.45
Story retained (%)	-259.28	1076.21	-.06	.81	-47.03	50.74	-.21	.37	38.04	41.44	.20	.37
Figure retained (%)	616.30	859.86	.18	.48	-11.54	40.54	-.07	.78	-1.19	33.11	-.01	.97
CFQ	534.24	885.56	.15	.55	23.52	41.75	.14	.58	-18.79	34.10	-.13	.59
CTT SS Form 2	179.53	970.72	.05	.86	-29.07	45.76	-.17	.53	-26.19	37.38	-.18	.49
Verbal fluency	253.21	582.29	.11	.67	21.16	27.45	.20	.45	-24.51	22.42	-.27	.29

Note. All predictors entered into the regression were non-significant (> .05) (n = 27).

Table 5.10 N100 regression analyses incorporating all ISIs.

Predictors	N100											
	300 ms				500 ms				800 ms			
	B	*SE B*	*β*	*P*	*B*	*SE B*	*β*	*P*	*B*	*SE B*	*β*	*P*
(Constant)	483.08	594.40		.43	-163.14	829.30		.85	-1513.37	3723.07		.69
Anxiety	11.42	.30	1.51	.15	25.53	15.94	.29	.13	21.49	71.54	.07	.77
A6	14.33	-.12	-.53	.61	52.90	19.99	.58	.02*	45.49	89.74	.13	.62
Story retained (%)	3.80	-.20	-.99	.33	1.48	5.31	.05	.78	2.74	23.82	.03	.91
Figure retained (%)	3.04	-.33	-1.55	.14	-0.65	4.24	-.03	.88	-6.55	19.04	-.08	.74
CFQ	3.13	.31	1.46	.16	-6.43	4.37	-.29	.16	32.15	19.60	.38	.12
CTT SS Form 2	3.43	-.07	-.31	.76	-1.93	4.79	-.09	.69	1.65	21.49	.02	.94
Verbal fluency	2.06	.24	1.09	.29	-1.28	2.87	-.09	.66	-1.76	12.89	-.03	.89

Note. All predictors entered into the regression were non-significant (> .05) except for A6 predicting N100 500 ms (n = 27). *$p < .05$.

Table 5.11 P200 regression analyses incorporating all ISIs.

	P200											
Predictors	300 ms				500 ms				800 ms			
	B	*SE B*	*β*	*P*	*B*	*SE B*	*β*	*P*	*B*	*SE B*	*β*	*P*
(Constant)	5758.17	6021.17		.35	425.28	1738.42		.81	-2956.30	2860.77		.31
Anxiety	85.84	115.70	.15	.47	25.30	33.41	.14	.46	59.99	54.97	.23	.29
A6	-58.78	145.14	-.10	.69	75.43	41.90	.41	.09	-35.58	68.96	-.13	.61
Story retained (%)	-10.04	38.53	-.05	.80	-21.54	11.12	-.37	.07*	12.41	18.31	.15	.51
Figure retained (%)	-59.53	30.78	-.43	.07*	10.16	8.89	.23	.27	0.88	14.63	.01	.95
CFQ	-14.70	31.70	-.10	.65	1.24	9.15	.03	.89	16.78	15.06	.26	.28
CTT SS Form 2	-11.87	34.75	-.08	.74	10.00	10.03	.22	.33	15.09	16.51	.23	.37
Verbal fluency	11.90	20.85	.13	.58	-9.01	6.02	-.32	.15	-3.54	9.91	-.09	.73

Note. *Predictors were non-significant when entered in conjunction with the other predictors but were significant when entered using stepwise regression (see Table 5.12).

Table 5.12 Summary of Significant Stepwise Multiple Linear Regression Analyses for Variables Predicting P50, N100 and P200 Sensory Gating.

	Significant ERP and ISI Component											
	N100 500ms				P200 300ms				P200 500ms			
Predictors	*B*	*SE B*	*β*	*P*	*B*	*SE B*	*β*	*P*	*B*	*SE B*	*β*	*P*
(Constant)	-416.77	169.85		.021	4365.41	1701.48		.017	2496.04	1019.55		.022
A6	46.20	15.92	.502	.008								
Story retained (%)									-23.43	10.71	-.401	.038
Figure retained (%)					-64.54	24.86	-.461	.016				
R^2	.252				.212				.161			
Adj R^2	.222				.181				.127			
F	8.422**				6.738*				4.781*			

Note. Table only shows significant predictors determined by stepwise regression, and from the previous regression equations (n = 27) *$p < .05$; **$p < .01$.

5.6 Discussion

The current study tested the hypotheses that SG is related to higher-order cognitive functioning (Lijffijt et al., 2009) measured by performance on specialised neuropsychological tests. We hypothesised that the SG responses would be significantly related to neuropsychological measures, namely EF, and inhibition. Using a paired-clicks paradigm, we aimed to characterise the P50, N100 and P200 responses in a healthy older population.

In our investigation, we sought to explore the cognitive domains associated with SG by employing AERPs and administering neuropsychological tests designed to assess various facets of cognitive function. Our initial hypothesis was that SG would exhibit correlations with several measures related to inhibition and EF. We observed significant correlations between SG (N100 and P200) and memory measures suggesting that individuals with specific SG patterns may also exhibit distinct memory capabilities. This finding highlights the potential interplay between SG processes and memory function.

Additionally, significant associations were found between SG and measures of inhibition; we found a significant association between the N100 and our measure of inhibitory memory (A6). This implies that SG may be linked to the ability to inhibit or control certain cognitive processes, highlighting the relevance of SG in regulating cognitive functions.

Contrary to our initial hypothesis, we did not identify significant correlations between SG and measures of EF or language abilities. This suggests that while SG may play a role in memory and inhibition, its relationship with other cognitive domains, such as EF and language, may be less pronounced or not statistically significant in this particular study cohort.

The analysis did not reveal any significant associations between age and SG. This was not a primary hypothesis of ours to investigate, but it was important to rule age out as a potential confounder for our SG and neuropsychological measures associations. In this study, we found that age did not have a significant influence on SG patterns. However, it's important to note that previous research has demonstrated that the effects of age on SG can differ depending on the specific populations and contexts being studied (Brinkmann et al., 2021; Gmehlin et al., 2011).

In summary, our investigation sought to uncover the cognitive domains associated with SG using AERPs and neuropsychological tests. While we did not find significant correlations with EF or language abilities, our study did establish meaningful links between SG and memory measures as well as measures of inhibition. These findings shed light on the intricate relationships between SG processes and specific cognitive functions.

5.6.1 P50 Gating

The P50 SG mechanism, often considered a preattentional process, has been proposed in previous research as a potential protective shield for higher-order cognitive functions (Soshi et al., 2015). This protective role is thought to occur by preventing sensory flooding, where an overload of sensory information might overwhelm cognitive processes (Jerger et al., 1992; Lijffijt et al., 2009). The idea is that effective SG helps maintain CR by filtering out unnecessary or redundant sensory information, allowing cognitive resources to be allocated more efficiently to tasks requiring higher-level processing.

However, the current study's findings present a unique perspective. Despite the theoretical framework proposing a relationship between SG and cognitive functions, the study did not reveal a significant association between SG and neuropsychological variables. In other words, the effectiveness of SG, as measured in the study, did not appear to correlate with participants' cognitive performance on the assessed neuropsychological tests.

These results raise important questions about the specific nature and extent of the relationship between P50 SG and cognitive functions. While the theoretical framework suggests a protective role for SG in CR, the empirical findings in this study challenge the direct link between them. This discrepancy highlights the complexity of the relationship between SG mechanisms and higher-level cognitive processes and suggests that additional factors and interactions may influence the observed outcomes.

The literature is very conflicted regarding the relationship between memory and P50 suppression (discussed in section 5.2.6.2). We examined visual and verbal memory capacity, and visual memory to predict the P50 whereas other studies have used working memory indices (Jones et al., 2016). This could account for differences between our results and the literature. (L. A. Jones et al., 2016a)

Cognitive inhibition refers to the mental process of suppressing no longer relevant information that had already been encoded at an earlier stage (Jones et al., 2016). Our inhibition measure did not significantly positively predict P50 suppression as expected, we hypothesised that greater inhibition scores would lead to more effective SG. P50 gating is considered an inhibitory filter mechanism (Hermens et al., 2010), and previous studies have found significant

associations between the P50 and other inhibitory neuropsychological mechanisms (Jones et al., 2016).

5.6.2 N100 Gating

The current study showed a significant relationship between stronger N100 (500ms ISI) SG, and better inhibitory memory (A6). The N100 difference score positively correlated significantly with inhibitory WM recall scores, suggesting a relationship between N100 gating and the sensitivity of discriminating between lists A and B. Previous studies have suggested a relationship between N100 gating and WM. Participants with better N100 SG had better WM, which is consistent with previous research (Brumback et al., 2004), although differences in scoring of the N100 (~85-125ms post-stimulus) SG measure requires caution in interpretation.

Our study's results highlight the significant associations between N100 SG, particularly at 500ms ISI, and cognitive functions related to inhibitory memory and working memory, specifically within the verbal domain. These findings contribute to our understanding of the role of N100 SG in cognitive processes, particularly memory-related functions. However, further research and exploration are warranted to gain a more comprehensive understanding of the underlying mechanisms and implications of these observed associations.

5.6.3 P200 Gating

The P200 is thought to reflect the early allocation of attention to the stimulus in a passive listening task (Näätänen et al., 2012); P200 gating could therefore be influenced by

distribution of attention and the initial conscious awareness of a stimulus (Gmehlin et al., 2011).

The P200 SG with 300 ms ISI was significantly predicted by long-term visual memory capacity (figure retained (%)). The relationship between the two was negative; the higher the percentage of memory retained from copying the image, the smaller the P200 300 ms suppression. Lijffijt et al. (2009) found the opposite relationship; they found that the stronger the P200, the better the participants did on a delayed memory task. The ISI used by the researchers was 500 ms, this may have influenced the results slightly, but this speculation wand would need to be investigated further.

The P200 500 ms was predicted by verbal long-term memory (story recall). This effect has been found in studies using verbal working memory, but not necessarily in verbal long-term memory as in this study. The relationship between the two was also negative; the better the long-term recall of the story, the smaller the P200 suppression at the 500 ms ISI.

5.6.4 Ageing

In our study, we observed significant negative predictions of ageing on various neuropsychological measures, including inhibitory WM, visual long-term memory, and verbal fluency. These results align with the well-established understanding that, in healthy adults, neuropsychological functioning tends to decline with age. These age-related cognitive changes are consistent with the framework outlined in the Frontal Hypothesis of Ageing (as mentioned in section 2.2), which postulates a decline in cognitive functions that rely on inhibitory or attentional regulation as individuals age. Additionally, ageing has been shown to affect

attentional networks (Mattson & Magnus, 2006). Interestingly, our study did not replicate the expected increase in P50 amplitude with normal ageing, a phenomenon reported in previous research (Golob et al., 2007). Instead, we found no significant association between P50, N100, and P200 components and the process of normal ageing in our sample of participants.

This lack of association with normal ageing may need further investigation. It's possible that conducting comparative analyses with younger participants could shed light on age-related differences in SG components. By contrasting the SG profiles of younger individuals with those of older adults, we might gain a more comprehensive understanding of how sensory processing changes across the lifespan and whether age-related differences are indeed present.

In summary, our study reaffirmed the well-established age-related decline in various neuropsychological functions. However, our findings did not replicate the typical change in P50, N100 or P200 amplitude associated with normal ageing. The suggestion to explore these effects in a comparative study involving younger participants highlights the potential for future research to uncover additional insights into age-related changes in SG and cognitive functions.

5.6.5 Limitations

Our study faced challenges in replicating various findings and associations between SG ERPs and cognitive profiles. Several factors may contribute to these discrepancies, and it's important to consider methodological differences as one possible explanation.

One potential source of disparity in our findings compared to previous studies is the formula used to calculate SG. In our study, we used the formula: S1/S2 * 100 to calculate SG scores (see Figure 5.12), whereas some prior research may have used the equation S2/S1 * 100.

This formulaic difference can lead to different SG scores and potentially alter the associations with cognitive profiles. The choice of formula can influence the interpretation of SG effects and their relationships with cognitive functions.

Another methodological difference involves the use of the S2 amplitude as a sole measure of SG. Some studies have exclusively used the S2 amplitude to assess SG. However, we did not use this approach as it may not provide a comprehensive understanding of SG. The S1 stimulus may not be consistent across individuals, making it challenging to accurately gauge the extent of SG based solely on the S2 amplitude. Our approach of considering the ratio between S1 and S2 amplitudes aims to account for individual variability in S1 responses, offering a more robust measure of SG.

Gating was assessed using AERPs, whereas cognitive functions were assessed using visual and verbal tests. Although this is a general limitation across most studies examining SG with cognition, it limits the generalisability of our findings, as we did not measure visual ERPs. While variations in methodology may account for differences in findings across studies, they also highlight the complexity of studying SG and its associations with cognitive profiles.

The challenges we encountered in replicating previous findings regarding ERPs and cognitive profiles highlight the need for methodological consistency and transparency in research. The choice of formulae and measures in SG studies can significantly impact the observed associations, emphasising the importance of clear reporting and careful consideration of measurement approaches. This study has several limitations that need to be addressed in future studies. First, the influence of N100 and P200 variables on task performance could not be separated adequately because of the high overlap between both components due to the

commonly applied procedure in SG studies to measure components peak to peak rather than baseline to peak.

5.6.6 Applications

P50 has been studied as a possible biomarker of early emerging AD pathology (Green et al., 2015), and it has significantly predicted which MCI patients will convert to AD, as they show significantly larger P50 amplitudes at baseline in comparison to non-converters (Golob et al., 2007; Mazaheri et al., 2018). P50 suppression could be a valuable predictive biomarker for detecting MCI or pre-symptomatic neuropsychiatric conditions such as AD. The fact that it can be recorded non-invasively and inexpensively may make it a practical diagnostic or screening tool that could help clinicians optimise therapeutic interventions or even help select additional costly or invasive tests (e.g., amyloid PET).

Many research studies use CSF biomarkers to find markers for neuropsychiatric disease (Gore et al., 2015; Neerland et al., 2016); this is a very invasive and sometimes painful procedure. ERPs can reveal abnormalities in brain activity that reflect underlying disease-related changes in the brain. Therefore, measuring ERPs may become a new clinical diagnostic tool for these types of disorders.

Future longitudinal studies can evaluate the utility of P50 to predict cognitive decline and conversion to dementia by tracking P50 changes in cognitively well and MCI individuals by measuring CR and neural reserve together.

5.6.7 Conclusions

This study investigated the interplay between SG components, including P50, N100, and P200, and cognitive functions. It highlights the role of methodological consistency in accurately interpreting research findings. Notably, N100, and P200 could show promise as non-invasive biomarkers for susceptibility for cognitive decline. Sensory gating ERPs could show diagnostic potential for susceptibility for a range of neuropsychiatric conditions. Their ability to reflect underlying abnormalities in brain activity offers a non-invasive and accessible opportunity for diagnosing such conditions. Future research should focus on the combined predictive power of P50, N100, and P200 in monitoring cognitive decline and susceptibility to future cognitive decline.

In summary, this study provides valuable insights into the complex interrelationships between SG components, cognitive functions, and their potential as diagnostic tools.

Chapter 6 Auditory Steady-State Responses and Neurocognition in a Healthy Ageing Population

Abstract

Sensory inhibition and processing can be studied through the Auditory Steady-State Response (ASSR). ASSRs are electrophysiological evoked oscillatory responses entrained to the frequency and phase of temporally modulated and periodically repeated (rapid) auditory stimuli. These ASSRs can be detected non-invasively using EEG recordings to measure the brain's responses to auditory stimuli. This study aimed to examine the relationship between ASSRs and neuropsychological test scores using the same healthy ageing population used in the previous chapter (section 5.4.1). However, due to technical issues with the recording setup only 14 datasets were usable. Three blocks of tones were presented: 2.5 Hz and 40 Hz, 2.5 Hz and 80 Hz, and 2.5 Hz and 40 Hz. The ASSR power response was calculated by subtracting the background power at 36 Hz from the 40 Hz entrainment. The power at 40 Hz was also analysed in relation to neuropsychological measures. Higher scores of verbal fluency were significantly associated with lower ASSR power response (p = .039), and with lower 40 Hz power response (p = .029). ASSR power responses were not significantly related to age or any other neuropsychological assessment. The ASSR's ability to be elicited without demanding active attention makes it a valuable tool for assessing cognitive function in older adults and individuals with cognitive vulnerabilities. More research in a larger sample is needed to deem it to be a robust measure of CR.

6.1 Introduction

Gathering research suggests that brain activity in the gamma range (30–80 Hz) of EEG reflects information processing in sensory and cognitive abilities (Parciauskaite et al., 2019). These include perception (Rodriguez et al., 1999), attention (Tiitinen et al., 1993; Villena-González et al., 2018), memory (Kucewicz et al., 2017), and language processing (Ford et al., 2005). The 40 Hz steady-state response (SSR), a sinusoidal response that mirrors the stimulus frequency and can be stimulated by simple sensory stimuli (Tallon-Baudry & Bertrand, 1999).

This gamma range brain activity plays a pivotal role in cognitive processing (Parciauskaite et al., 2019). These oscillations are crucial for various cognitive functions, including attention, memory, and information processing (Light et al., 2006). The synchronised firing of neurons at gamma frequencies serves as a binding mechanism, facilitating the integration of sensory input from different brain regions (Guan et al., 2022). Auditory Steady State Responses (ASSR) are neural responses to repetitive auditory stimuli (M. Spencer, 2012; Picton et al., 2003). Studying ASSRs provides valuable insights into the brain's ability to entrain or synchronise neural activity with external stimuli, shedding light on the mechanisms underlying cognitive function (Vohs, Andrew Chambers, et al., 2010). These responses are utilised as a tool to assess the brain's capacity to generate rhythmic responses, offering a view into normal brain function and its deviations in various neurological and psychiatric disorders (Hamm et al., 2012).

6.1.1 Auditory Steady-State Response Paradigm

The ASSR is an event-related potential (ERP) which represents neuronal activity in the brainstem, thalamocortical pathways, and the auditory areas (Masdeu et al., 2018; O'Donnell et al., 2013; Picton et al., 2009). In humans, the ASSR is most prominent for clicks or amplitude-modulated (AM) tones presented at 40 Hz (Picton et al., 2003; Rass et al., 2010). Even though gamma ranges from 30-80 Hz, 40 Hz remains the most mentioned elicited gamma response from auditory entrainment stimuli (Parciauskaite et al., 2019). Deficits of ASSR have been demonstrated in schizophrenia and early-onset or first-episode psychosis at 30 Hz (Friedrich et al., 2015; M. Spencer, 2012) and 40 Hz (Wilson et al., 2008).

The ASSR demonstrates the abilities of neurons to oscillate to the same frequencies as those presented by external stimuli (Kumar et al., 2008; Wang et al., 2020). MEG studies have located the ASSRs in the medial areas of the primary auditory cortex (Thuné et al., 2016). The thalamus and its cortical networks are involved in the generation of ASSRs (Reyes et al., 2004). However, the main contribution is from the medial auditory cortex (Pantev et al., 2007). Attention and arousal regulate the 40 Hz ASSR (Górska & Binder, 2019; Griskova et al., 2007; Skosnik et al., 2007). Intriguingly, the gamma-range ASSRs correlate with the degree of cognitive decline in Alzheimer's Disease (AD) and mild cognitive impairment (MCI) patients (Shahmiri et al., 2017). In schizophrenia, patients' ASSRs have been associated with various cognitive deficits (Light et al., 2006; Tada et al., 2016), which will be elaborated on in section 6.1.2.1.

6.1.2 Application of ASSR

At 40 Hz, the ASSR is thought to be due to an excitation/inhibition (E/I) imbalance among neurons, which serves as a crucial neurophysiological marker linked to various neuropsychiatric conditions (Tada et al., 2020). Disruptions in gamma oscillation bands, resulting from this E/I imbalance, are observed in conditions such as schizophrenia (Tada et al., 2016, 2020), bipolar disorder (Sivarao et al., 2016), autism (Ahmad et al., 2022), and AD (Babiloni et al., 2016; Osipova et al., 2006). Therefore, deficits within the 30–40 Hz range are likely to show an E/I imbalance, indicating potential disturbances in the auditory cortex (Grent-'t-Jong et al., 2023). These disturbances can have implications for cognitive processes and sensory gating mechanisms, particularly as similar circuits and brain areas are implicated in both ASSR and sensory gating areas (Grent-'t-Jong et al., 2023).

Synchronised neural activity is important for perceptual, cognitive, and motoric processes, and relies on the complex balance of oscillations (A.-K. R. Bauer et al., 2020). Deficits in these oscillations may signify a key mechanism for functional disconnection or integration (O'Donnell et al., 2013). Therefore, ASSRs not only provide insights into subtle neuronal changes indicative of neural dysfunction but also offer a potential avenue for understanding the interplay between neural function, and cognitive reserve, as previous research has determined them to be valuable translational biomarkers for risk of developing neuropsychiatric disorders (Grent-'t-Jong et al., 2023; Tada et al., 2020). This suggests that studying ASSRs could contribute to unravelling the complexities of ageing, cognitive resilience, and the regulation of sensory information in the brain (Hirst et al., 2022). Such

deficits may disrupt the coordinated functioning of neural networks, influencing cognitive reserve (CR) and the brain's resilience against age-related cognitive decline (Hirst et al., 2022).

In the context of ageing, understanding the neural markers presented by ASSRs becomes crucial for unravelling potential vulnerabilities (Tada et al., 2016). Cognitive reserve plays a pivotal role in bolstering cognitive resilience during the ageing process (Amodio et al., 2017; Perneczky et al., 2019). Investigating markers such as ASSRs provides valuable insights into early signs of cognitive decline and possibilities for developing strategies to support cognitive resilience in older adults.

6.1.2.1 ASSR in Schizophrenia

The ASSR can be applied to patients with neuropsychiatric disorders by examining their electrical gamma-band activity (Schuelert et al., 2018; Spencer et al., 2008). Impaired ASSRs are often found in schizophrenic patients and first-degree relatives of schizophrenic patients (O'Donnell et al., 2013). However, the research surrounding this is conflicted, as there are no certain conclusions on what the ASSRs represent. Some researchers argue it is a sensory response altered in patients with neuropsychiatric disorders (Ross et al., 2005; Wang et al., 2018), whereas others believe it represents higher-order cognitive functions (Parciauskaite et al., 2019).

People with schizophrenia consistently have a deficiency at the 40 Hz more than at any other frequency in the gamma range (Sivarao et al., 2016). ASSRs normally show decreased power or phase locking to stimulus onset when a 40 Hz tone is presented (Spencer et al., 2008). Kwon et al. (1999) first reported that schizophrenia patients showed a reduction in the ASSR.

Short, 500 ms click sequences were used to elicit the ASSR at three frequencies: 20, 30 and 40 Hz. Patients with schizophrenia showed a reduced power at 40 Hz but not at 20 or 30 Hz.

O'Donnell et al. (2013) measured ASSR in unmedicated patients during manic or mixed episodes of bipolar disorder and found reduced EEG signal power at stimulation frequencies of 20, 30, 40, and 50 Hz and diminished EEG wave uniformity at 20, 40, and 50 Hz. It's also been found that there is a significant reduction in the power and phase locked regularity in 40 Hz ASSR in schizophrenia patients (Brenner et al., 2009; Thun et al., 2016).

Numerous reports have confirmed deficits in ASSR in first-degree relatives of schizophrenia subjects (Brett et al., 1997), suggesting that such a deficit may be a trait marker. The 40 Hz ASSR deficit is not specific to schizophrenia and reaches various neuropsychiatric disorders, including bipolar disorder (Cheng et al., 2016; Rass et al., 2010) and autism spectrum disorders (Sussman & Shafer, 2014). It may be down to cortical N-methyl-D-aspartate (NMDA) transmission deficit, which may lead to the modulation of the ASSR (Sivarao et al., 2016); cortical NMDA transmission is impaired in a variety of disorders not limited to schizophrenia (Lau & Zukin, 2007). Sivaroa et al. (2016) argued that 40 Hz ASSR is an important marker for cortical NMDA function rather than just an SG marker.

Similar ASSR deficiencies have been recorded in bipolar disorder patients as in schizophrenia patients. These deficiencies include reduced EEG signal power at stimulation frequencies of 20, 30, 40, and 50 Hz and reduced EEG phase synchronisation at 20, 40, and 50 Hz (O'Donnell et al., 2004). Many researchers believe that the ASSR impairments in bipolar disorder may indicate dysfunctional Gamma-aminobutyric acid (GABA) neurotransmission within the auditory cortex and its circuits (Benes & Berretta, 2001). These GABA circuits and

neurotransmission modulate the generation and synchronisation of beta and gamma range oscillations (Maharajh et al., 2007). As a result, GABA dysfunction in bipolar disorder could alter the ASSR at 20, 30, 40 and 50 Hz frequencies (Sivarao et al., 2016).

Deficits in auditory processing, sensory gating (SG) and perception in both schizophrenia and bipolar disorder are seen in their clinical characteristics (e.g., auditory hallucinations) (O'Donnell et al., 2004; Rass et al., 2010) and abnormal auditory P50 SG measures (Cheng et al., 2016).

6.1.2.2 Mild Cognitive Impairment

Mild cognitive impairment is a condition outlined as cognitive deterioration greater than that expected for a person's age and education level, but not enough to restrict activities of daily life (Gauthier et al., 2006). MCI is an "at-risk" state of developing dementia, therefore, there is a demand for finding early biomarkers to identify subjects who could develop the disease (Mitchell & Shiri-Feshki, 2009; Moretti, 2015). Identifying patients early with MCI is crucial because interventions may help slow or prevent progression to AD (Shahmiri et al., 2017). This would be useful for early identification and effective prevention treatments (Green et al., 2015). It is becoming increasingly clear that incorporating a variety of biomarkers is an innovative method for a correct and early diagnosis of AD (Albert et al., 2011; Dubois et al., 2007).

Several studies have evaluated the 40 Hz rhythm responses in MCI patients using EEG, and although it is generally accepted that 40 Hz power increases with disease progression (van Deursen et al., 2011), the practical applications of using it to predict the progression of MCI to

AD remains uncertain (Shahmiri et al., 2017). The 40 Hz ASSR responses indicate early sensory processing (similar to sensory gating) (Van Deursen et al., 2011) and it's posited that sensory processing is one of the first compromised cognitive mechanisms within AD (Zhang et al., 2023). The study by Shahmiri et al. (2017) showed that ASSR responses can distinguish patients with AD from MCI patients and controls at two modulation rates, 40 and 80 Hz. They postulate that this could be due to more advanced neurodegeneration in patients with AD within the auditory cortex than in the MCI group (Shahmiri et al., 2017; van Deursen et al., 2011). Therefore, the ASSR may become a more reliable indicator for progressing cognitive decline from MCI to AD than previously thought.

6.1.2.3 Alzheimer's Disease Detection

ASSR can be used as a valuable neuro biomarker tool to detect AD. The ASSR using an 80 Hz modulation rate is thought to be acquired from brainstem activation, while the 40 Hz modulation rate may derive from the temporal cortex (Herdman et al., 2002; Usubuchi et al., 2014). The Temporal region is one of the initial areas impaired in AD (van Deursen et al., 2011; van Deursen et al., 2008). This is supported by an MEG study which confirmed that the 40 Hz ASSR power was increased in patients with AD due to reduced cortical inhibition (Osipova et al., 2006).

Several studies have suggested decreased inhibition and hyperexcitability of cortical responses in AD (Tada et al., 2020; van Deursen et al., 2011; van Deursen et al., 2008). Cortical disinhibition and hyperexcitability are often connected with glutamate and GABA neurotransmission dysfunction, a recognised characteristic of AD pathology (Francis, 2005). The role of GABA and glutamate in regulating gamma band has been shown to suggest

glutamate as a generator of gamma-band oscillations and GABA as an inhibitor (Kwon et al., 1999).

6.2 Ageing

Brain ageing is considered to be a decrease in regulation of cortical inhibition, which leads to a range of functional deficits (Cisneros-Franco et al., 2018). These include degraded temporal processing, reduced SG, sharp responses to noise, and reduced acclimatisation to repetitive stimuli (Lustig et al., 2009).

The ASSR has been found in research to change and vary with age. The 40 Hz ASSR was larger and less variable with increasing age (Poulsen et al., 2007). The increase in magnitude (and possible decrease in variability) of the 40 Hz ASSR with age indicates continued ability of the auditory cortex to synchronise its neuronal responses to modulated auditory stimuli (Yamasaki et al., 2005). Such resonant activity may play an essential role in identifying and isolating a stimulus, such as speech, from background noise (Dimitrijevic et al., 2004).

Cisneros-Franco et al. (2018) suggested that age-related inhibition reduction may cause reduced strength and increased variability in the cortex, as sensory processing is constantly biased by unconscious sensory stimulation. If the effects of age-related loss of inhibition observed during repetitive stimuli extend to higher order cognition, it is plausible that reduced inhibition might increase the likelihood of learning becoming more complex, slower, and more vulnerable to decline, as clinically observed in older patients (Boyke et al., 2008).

6.2.1 Section Conclusions

EEG biomarkers such as SG paradigms or ASSR can be elicited under conditions in which attention to stimuli is not required; these measures seem to be an ideal biomarker to test target-specific aspects of human psychiatric disorders by assessing the integrity of relevant neuronal circuits (Schuelert et al., 2018).

Research suggests that the ASSR could be a useful translatable brain marker. Translational neurological features can be taken from both human and animal disease models to help explain the pathophysiology by illuminating the producing mechanism of the marker (Tada et al., 2020). Multiple studies have examined the 40 Hz ASSR in individuals with MCI using EEG, and the 40 Hz power is thought to increase as the disease progresses (van Deursen et al., 2011). Early sensory processing indicated by the 40 Hz ASSR responses, akin to sensory gating, suggests a potential link to compromised cognitive mechanisms in AD, with sensory processing being one of the first affected cognitive functions (Zhang et al., 2023).

The ASSR can be measured through a passive listening auditory task; thus, it is easy to measure and quantify in patient populations and animal models. Various electrophysiological methods in the literature, including non-invasive recordings such as EEG and MEG (Thuné et al., 2016), have been used to detect the ASSR. However, EEG is much more portable and practical than MEG in such hospital settings.

6.2.2 Hypotheses

The present study aimed to relate the ASSR with neuropsychological measures in healthy older adults to see if it could be carried out in an unburdensome manner, and if it was

a robust measure that could be translated and used in preoperative patients in hospital settings. Therefore, we hypothesised that there would be a significant relationship between the ASSR and measures of memory, EF and inhibition using as few EEG channels as possible.

Ageing will also be analysed in the findings due to age-related cognitive and sensory variability, previously discussed in section 6.2.

6.3 Method

The following experiment was part of a more extensive study in addition with Chapter 5 for a PhD project. Therefore, the participants (5.4.1), method (5.4), EEG acquisition (5.4.5), procedure (5.4.4) were the same as in the previous chapter, but different stimuli were used to elicit another EEG paradigm.

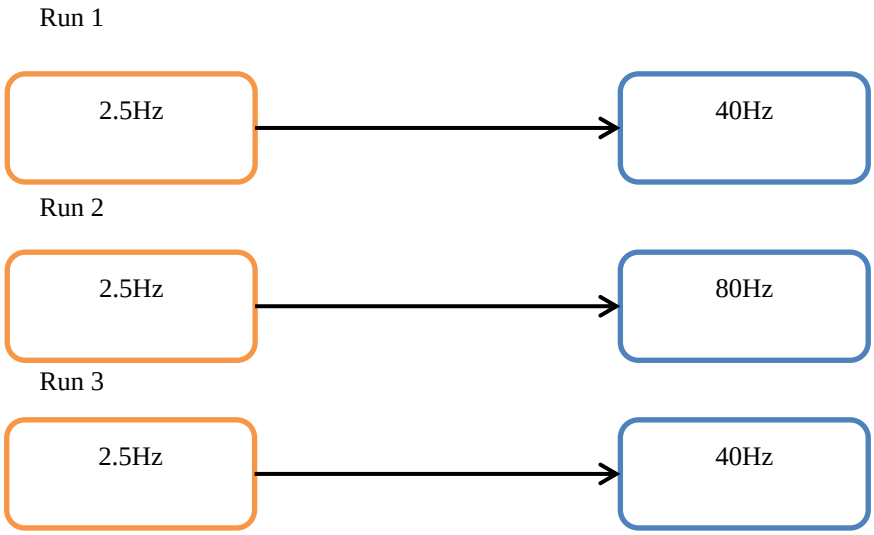
6.3.1 EEG Procedure

Once participants had completed the neuropsychological testing (~1 hour), they were offered a break and taken to our EEG lab where they were seated, and the EEG cap could be applied. After application of the EEG cap, participants received a brief explanation of the task: they were told to ignore the sounds from the headphones during the experiment and to just relax and watch a film of their choice with subtitles in a sound-proof booth. Once comfortable, noise cancelling headphones were placed on the EEG cap; subjects were asked to be relaxed and not produce large motor movements.

Within this experiment, subjects completed three blocks of approximately 15 minutes to measure the ASSR. To evoke the ASSR, we presented binaural 2.5 Hz, 40 Hz and 80 Hz frequency tones, as shown in Figure 6.1.

After each block, the experimenter (ES) went inside the booth to make sure the participants were feeling well and asked if they wanted a break in between the blocks.

Figure 6.1 The three different runs used to measure ASSR.



Note. Each run lasted 15 minutes, and participants were offered breaks between the blocks. A pure tone (10 ms duration) was used as the sound and presented during varying intervals.

6.3.2 Recording

The recording method for this experiment was the same as the one previously discussed in 5.4.5, but it is reiterated here for convenience. The EEG cap (WaveGuard^{TM} 10-20 system, ANT Neuro, 2016) with 32 Ag/AgCl electrodes was fitted to the participant, with impedance adjusted to be below 20 kΩ during the recording. EEG data were collected from five scalp sites

(Fp1, Fp2, GND, Cz, and Oz) referenced to the CPz electrode. The Oz served as reference, and the Fp1 and Fp2 electrodes recorded eye movements. The EEG was acquired using an 80 Hz low-pass filter, a 0.5 Hz high-pass filter and a 1,000 Hz sampling rate.

6.4 Results

6.4.1 ASSR Paradigm Analyses

6.4.1.1 Signal Processing

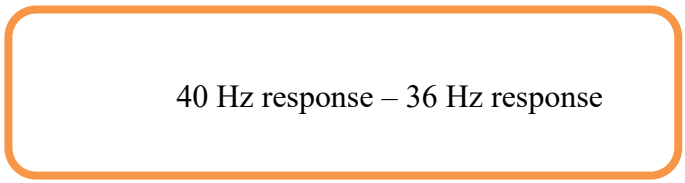
The signals were digitised for an epoch of 400 ms starting 200 ms before the presentation of each auditory stimulus. Individual trials were rejected when EEG voltage was greater than ± 35 μV, indicative of excessive muscle activity, eye movements, or other artefacts. Data were analysed offline: bandpass filtered (high-pass filtered from 0.5 and low-passed filtered at 80 Hz) and averaged. Before averaging, epochs were rejected if they were contaminated by substantial movement artefacts such as eye blinks. The EEG data were pre-processed using EEGLAB (Delorme & Makeig, 2004). Fieldtrip (Oostenveld et al., 2011) EEG epochs were locked to the onset of the stimuli and manually inspected for non-physiological artefacts. Independent component analysis was then applied to remove eye movement artefacts (Jung et al., 2001).

6.4.1.2 ASSR Calculation

The ASSR signals were epoched to the onset of the auditory stimuli (see Figure 6.1), and a Fourier transform was conducted on the ERP wave using the ‘mtmfft’ function of

Fieldtrip. The power of the frequency spectra at 40 Hz was obtained from this Fourier transform. The ASSR was calculated by subtracting the response at 36 Hz (which represented background activity) from the response at 40 Hz.

Figure 6.2 ASSR power response calculation.



Note. The ASSR power is determined by subtracting the background activity from the 40 Hz response.

The calculation in Figure 6.2 was used to measure how well the brain can 'synchronise' to the presented binaural tone, compared to the natural background levels.

6.4.2 Descriptive Statistics

The data in

Table 6.1 show that the participants were on average in their mid-70s, and they were quite well-educated with the average years of education being more than 14 years.

Table 6.1 Demographic variables of included participants.

	Value
N	14
Gender (M/F)	5/9
Mean age (years)	76.92 (4.96)
Mean education (years)	14.31 (3.3)
Hearing aid (yes/no)	3/11
Urbanicity (1-3)	1.92

Note. Values and means given with standard deviations in brackets.

The neuropsychological variables for these participants are shown in Table 6.2. These results are different from the last chapter because these include only 14 of the previously used 27, which means that the means and standard deviations of this sample are different from the previous sample in Chapter 5.

Table 6.2 Neuropsychological descriptive statistics.

Neuropsychological Variables	Mean	SD	Skewness	Kurtosis	Shapiro-Wilk
NART					
Raw Score (/50)	43.8	3.3	-.697	-1.047	.867*
Pred. WAIS FSIQ	122.5	2.7	-.734	-1.179	.800**
WAIS Matrix Reasoning					
Raw Score (/20)	17.8	6.1	-.482	-.925	.937

Scaled Score	14.1	3.7	-.638	.490	.941
BMIPB					
List A1-5 Total (/75)	49.5	11.7	-.105	-.964	.958
A6 (/15)	10.8	2.4	.360	-1.564	.835*
Story Immediate Recall (/60)	33.7	8.2	.879	.602	.943
Story Delayed Recall (/60)	31.7	8.4	.752	-.527	.909
Story Retained (Del/Imm) (%)	93.9	8.2	-.434	-.582	.948
Figure Copy (/80)	79.0	1.1	-.938	-.078	.810**
Figure Immediate Recall (/80)	54.8	11.8	-.832	-.290	.901
Figure Delayed Recall (/80)	54.1	10.3	-.683	.142	.928
Figure Retained (Del/Copy) (%)	68.5	13.0	-.826	.400	.914
Verbal Fluency					
Letter Fluency (F, A, S)	56.0	13.3	.546	.018	.958
Category Fluency (Animals, Fruits)	38.6	7.3	.684	-.201	.932
Total	98	20.3	.728	.154	.957
Colour Trails Test					
Form 1 Raw (secs)	46.8	20.0	1.461	3.676	.867*
Form 1 Standard Score	102.7	15.0	-.327	-1.106	.928
Form 2 Raw (secs)	88.4	30.7	.429	-1.072	.931
Form 2 Standard Score	105.5	30.7	.429	-1.072	.926
CFQ					
Raw Score (/100)	40.0	12.1	-.198	.875	.947
HADS					
Anxiety (/21)	7.0	2.7	1.071	3.559	.841*
Depression (/21)	3.5	3.2	1.610	3.448	.858*

Note. The mean and standard deviation results for participants included in the chapter (n = 14), *p < .05, **p < .01

Table 6.3 shows that the mean 40 Hz power response was .0073 with a very small standard deviation of .01198. The mean ASSR power response was .007014, also with a very small standard deviation of .01137.

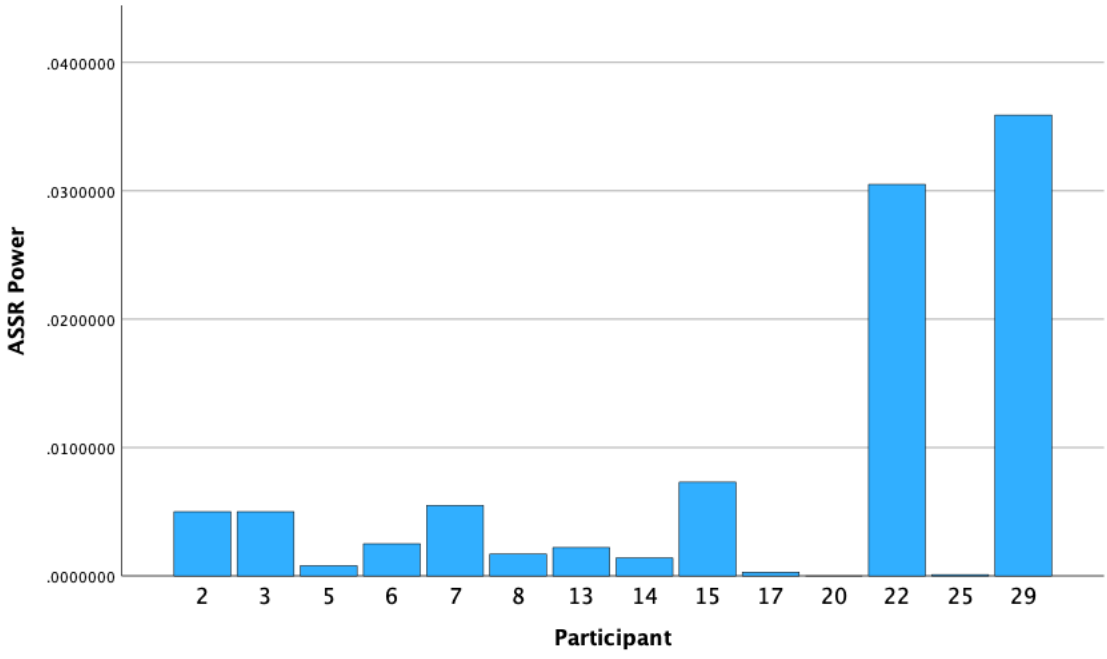
Table 6.3 ASSR descriptive results (n = 14)

	Mean	SD	Skewness	Kurtosis	Shapiro-Wilk
Power at 36 Hz	.000286	.00081	3.71	13.81	.357***
Power at 40 Hz	.007300	.01198	2.22	3.98	.613***
ASSR	.007014	.01137	2.12	3.57	.617***

Note. ***$p < .001$

The histogram in Figure 6.3 reveals that the 40 Hz responses were both small and variable. This suggests a lack of pronounced amplitudes in many participants, whilst the variation indicates fluctuations in response amplitudes across participants, prompting further investigation into potential influencing factors.

Figure 6.3 Individual ASSR power results for each participant



Note. Histogram made based on true values from each participant's ASSR, (n = 14).

6.4.3 Regression Analyses

Stepwise multiple linear regression analyses were conducted for different neuropsychological measures on SG in the previous chapter and we used the same neuropsychological variables here. ASSR results were used for the dependent variable, with the following variables used as predictors:

1. Anxiety (HADS A)
2. A6 (BMIPB inhibitory list recall)
3. CFQ (cognitive failures)
4. CTT SS form 2 (colour-number interference trails test scaled scores)
5. Verbal fluency (language inhibition and WM)
6. Story retained (%) (verbal long-term memory capacity)
7. Figure retained (%) (visual long-term memory capacity)

These variables were chosen based on the previous chapter (Chapter 5). We first did exploratory correlation analyses to find associations between the neuropsychological variables and the ASSR components. Due to previous research, we investigated the 40 Hz power response and the calculated ASSR power response (see Figure 6.2 for formula). The results from the non-parametric correlations are shown in Table 6.4 below. Table 6.4 shows that there is only one neuropsychological variable that is significantly associated with both/either of the ASSR components, which is the verbal fluency measure (total number of words said in five minutes based on letters and categories). Spearman's Rho shows that total verbal fluency was

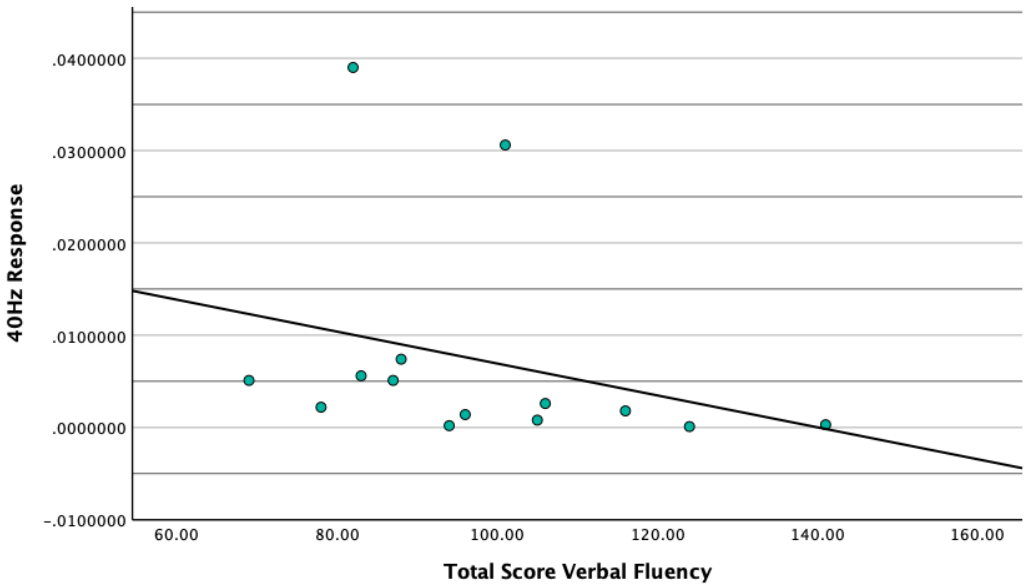
significantly associated with the 40 Hz (Spearman's R = -.583, p =.029) (Figure 6.4) and ASSR power response (Spearman's R = -.557, p = .039) (Figure 6.5) with a negative direction.

Table 6.4 Spearman's Rho exploratory correlations between neuropsychological variables and 40 Hz response and ASSR power.

Predictors	ASSR Components (n = 14)			
	40 Hz response		ASSR power	
	R	*P*	*R*	*P*
Anxiety	-.075	.798	-.060	.840
A6	-.371	.191	-.343	.229
Story retained (%)	-.130	.658	-.165	.573
Figure retained (%)	-.273	.345	-.255	.379
CFQ	.050	.866	.041	.890
CTT SS Form 2	-.337	.239	-.348	.223
Verbal fluency	-.583*	.029	-.557*	.039

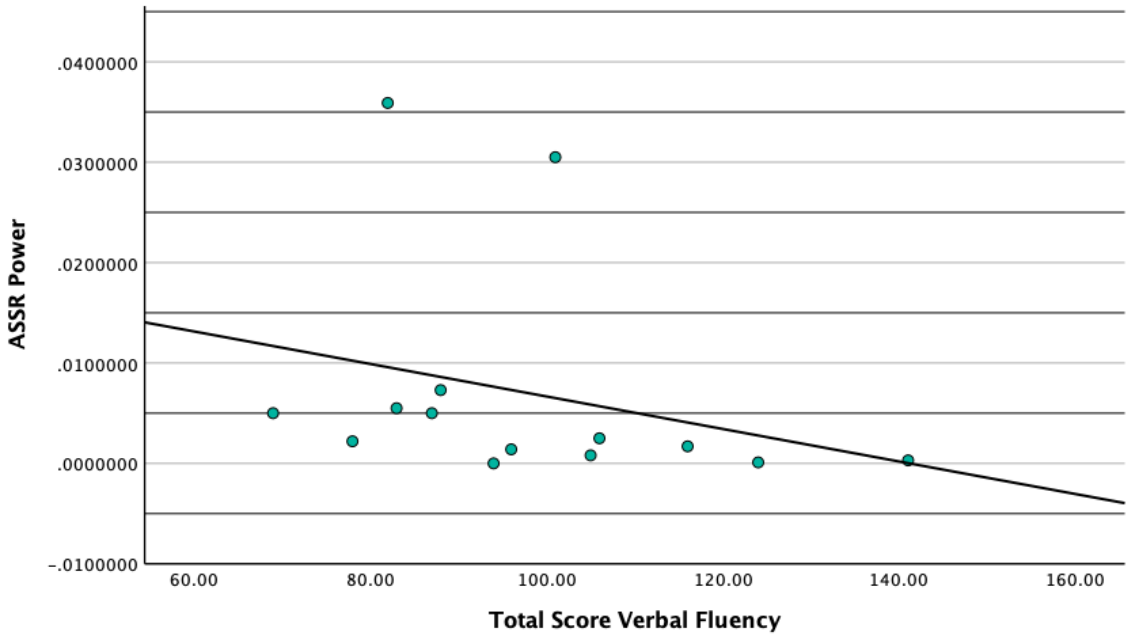
Note. Spearman's Rho is denoted by *R*. *p < .05.

Figure 6.4 Spearman's Rho correlation between Total Verbal Fluency and the 40 Hz Response



Note. Spearman's Rho R = -.583, p = .029 (n = 14).

Figure 6.5 Spearman's Rho correlation between Total Verbal Fluency and the ASSR Power Response



Note. Spearman's Rho R = -.557, p = .039 (n = 14).

We further explored these associations by carrying out a regression analysis. The neuropsychological variables (as mentioned above) were entered into a linear regression using the enter method, with the 40 Hz response as the dependent variable.

Table 6.5 shows that the significant association between total verbal fluency and the 40 Hz response were not strong enough (p = .231) to be able to predict the 40 Hz response within a regression.

A second linear regression was carried out using the enter method, the same neuropsychological variables as predictors before, and with the ASSR power response as the dependent variable.

Table 6.5 also shows that the significant correlation between the total verbal fluency and ASSR power was also not strong enough to be able to predict the ASSR power in a regression analysis (p = .262).

Table 6.5 Summary of stepwise multiple linear regression analyses for variables predicting ASSR power and 40 Hz response.

	ASSR Components (n = 14)							
Predictors	40 Hz response				ASSR power			
	B	*SE B*	*β*	*P*	*B*	*SE B*	*β*	*P*
(Constant)	.017	.076		.827	.021	.073		.782
Anxiety	-.002	.002	-.471	.407	-.002	.002	-.504	.379
A6	.000	.003	-.086	.899	-.001	.003	-.156	.820
Story retained (%)	.000	.000	.245	.506	.000	.000	.236	.524
Figure retained (%)	.001	.000	.718	.215	.001	.000	.730	.211

CFQ	.000	.000	.049	.891	.000	.000	.064	.861
CTT SS Form 2	.000	.001	-.185	.734	.000	.001	-.214	.697
Verbal fluency	.000	.000	-.732	.231	.000	.000	-.684	.262

Note. No predictors entered into either equation were significant (> . 05) (n = 14).

6.4.3.1 Ageing

An enter regression was carried out between age and the ASSR power response. Age did not significantly contribute towards the ASSR power:

ASSR power = -.051 (constant) + (.001*age).

This association was non-significant (F (1,12) = 1.358, p = .267).

A second enter regression was carried out between age and the 40 Hz power response. Age did not significantly contribute towards the 40 Hz power response:

40 Hz power response = -.055 (constant) + (.001*age).

This association was non-significant (F (1,12) = 1.394, p = .261).

From the previous chapter (5.5.1.1), we found that ageing significantly predicted the A6 measure (R = .541, R^2 = .293, Adj R^2 = .265, F (1,25) = 10.354, p = .004), but it did not predict the inhibitory memory measure (A6) in this dataset (R = .474, R^2 = .225, Adj R^2 = .154, F (1,11) = 3.185, p = .102), or the anxiety measure (HADS A) (R = .161, R^2 = .026, Adj R^2 = -.062, F (1,11) = .294, p = .598).

6.5 Discussion

The current study tested the hypotheses that the ASSR is related to higher-order cognitive functioning (Parciauskaite et al., 2019) measured by performance on specified neuropsychological tests. Using a passive auditory task, we aimed to characterise the ASSR power response in a healthy older population to see if it would be a suitable EEG measure to use in preoperative patients in hospital settings.

This study aimed to see if the ASSR correlated with neuropsychological and mental functioning results. We investigated the cognitive domains related to the ASSR using AERPs and neuropsychological tests that target different features of cognitive function and CR. We predicted that the ASSR could be predicted by several measures of inhibition and EF. We were unable to demonstrate a significant relationship between ASSR and inhibition, or memory. There was a significant correlation with verbal fluency, which is a measure of EF, cognitive flexibility, and frontal lobe functioning (Shao et al., 2014). This correlation was not strong enough to be able to predict the ASSR measure using verbal fluency, but it is clear that there is an association.

Verbal fluency and the ASSR can be linked through their shared association with cognitive and neural processes, particularly those related to language and auditory perception. Both verbal fluency and ASSR tasks involve cognitive processes, including attention, memory, and language-related functions. Studies have shown that ASSR is often impaired in schizophrenic subjects (Sivarao et al., 2016), as well as high-risk psychosis patients (Spencer et al., 2008), and these populations also have impaired verbal fluency and memory (Henry &

Crawford, 2005). Research by Kim et al. (2019) demonstrated a significant relationship between verbal fluency and ASSR power in schizophrenic subjects, but not in healthy controls, showing that the ASSR can be related to cognitive domains such as verbal fluency.

6.5.1 ASSR and Verbal Fluency

The limited research available on verbal fluency suggests a positive association between CR and verbal fluency. Moraes et al. (2013) explored the link between CR (measured by years of formal education and frequency of reading and writing) and performance on tasks involving semantic judgment, unconstrained verbal fluency, and constrained verbal fluency. Formal education emerged as the most reliable predictor for unconstrained verbal fluency, phonemic verbal fluency, and semantic verbal fluency. Additionally, Roldan-Tapia et al. (2012) found that a composite CR index (encompassing education, occupation, and vocabulary knowledge) exhibited a significant correlation with scores on phonemic and semantic verbal fluency tasks, such as the Controlled Oral Word Association Test (COWAT; Lezak et al., 2004). This reserve can potentially help them cope better with age-related cognitive decline or neurological conditions.

While ASSR is primarily used to study auditory processing, it is part of a broader context of cognitive function (O'Donnell et al., 2013; Parciauskaite et al., 2019). Cognitive reserve involves not only linguistic and executive functions but also sensory processing (Varela-López et al., 2022). Enhancing sensory processing abilities, as assessed by ASSR tasks, could contribute to CR by improving the brain's ability to efficiently process auditory information (Hirst et al., 2022). This, in turn, may support other cognitive functions.

Verbal fluency and ASSR assessments can be viewed as measures of cognitive and sensory processing abilities, respectively due to their inhibitory components. This is because the subject has to filter what words they say during the verbal fluency test (see section 5.4.3.1). They must begin using words with only the letters 'F,' 'A', 'S' followed by semantic fluency, fruits, and animals. This constrains the subject so they have to think and plan to see whether the words fit with the rules that they are constrained by during the test; therefore, they must filter their thoughts. Both verbal fluency and ASSR tasks require cognitive flexibility and executive function (Sugiyama et al., 2021). In verbal fluency tasks, individuals must switch between semantic categories or phonemic starting letters, demonstrating cognitive flexibility (Amunts et al., 2021). Similarly, in ASSR tasks, participants must attend to and process auditory stimuli with specific modulation frequencies, which also involves attention and executive functions (Ross et al., 2004; Tada et al., 2020). Verbal fluency is an important cognitive processing ability, and the ASSR is an important sensory processing mechanism which have been shown to link together especially in cognitively at-risk subjects and those with neuropsychiatric conditions (Kim et al., 2019).

Research examining the relationships between verbal fluency, ASSR, and CR can help us understand how distinct types of cognitive and sensory engagement contribute to maintaining cognitive function as individuals age. Research in this area can help elucidate the connections and implications for cognitive ageing and CR.

6.5.2 Executive Functioning

Research theorises that the 40 Hz ASSR reveals the neurons' ability to synchronise at a gamma band frequency elicited by an external sensory stimulus (Khaleghi et al., 2019; Wang

et al., 2020). Some investigators believe that NMDA receptor dysfunction could underlie the dysfunction of this gamma oscillatory process (Khaleghi et al., 2019). The normal function of NMDA receptors is relevant for healthy gamma modulation (Newcomer et al., 2000). Dysfunction of these receptors could pejoratively impact gamma amplitude and duration (Hamm et al., 2012). NMDA dysfunction is most likely to affect the GABAergic inhibition (Gonzalez-Burgos & Lewis, 2012). GABAergic inhibition is pivotal in neuropsychiatric disorders such as Bipolar disorder (Benes & Berretta, 2001) and schizophrenia (Vohs et al., 2010).

Cortical inhibitory function, mediated by GABAergic neurotransmission, is essential in gating sensory stimuli and leading to appropriate behavioural responses (Edden et al., 2012). Thus, disruption of inhibition could be due to GABAergic imbalances, particularly in the sensory cortices (Khaleghi et al., 2019), schizophrenia (Caspary et al., 2008) and dementia (Ford & Almeida, 2015).

However, other findings have suggested that ASSR measures have little or no correlation with neuropsychological tests of cognitive functioning (Rass et al., 2010). Researchers have posited that ASSR cannot be used to quantify cellular disruptions and compare them to cognitive deficiencies in bipolar disorder (Rass et al., 2010). The research appears to be conflicted on this view that the neural underpinnings in the ASSR are responsible for cognitive dysfunction. We only found a significant relationship between EF and the ASSR.

Parciauskaite et al. (2019) did find an association between EF and ASSR. There was a strong positive relationship between the delayed gamma response and the number of moves made to complete the Tower of London (ToL) task (Parciauskaite et al., 2019). The ToL task

measures planning and problem solving, as well as EF. However, the ASSR results did not correlate with performance on the Stroop test, which is a measure of inhibition and EF (Parciauskaite et al., 2019). Their results were also in accordance with Sun et al. (2018), who found a significant positive correlation between the Mazes test and the ASSR in both schizophrenics and controls. But we used different EF tests from the two discussed studies, making assumptions difficult.

6.5.3 Ageing

Many studies have stated that brain ageing is considered to decrease the regulation of cortical inhibition, which can cause a range of functional and neuropsychological deficits (Cisneros-Franco et al., 2018). It is therefore well documented that age and neuropsychological capabilities are closely linked (Cohen et al., 2019), but the literature on age and SG and ASSR remain divided. According to the Frontal Hypothesis of Ageing (section 2.2), we would expect to see a negative correlation between increasing age and ASSR efficiency, like in the findings of Goossens et al. (2016). We did not replicate this finding as there was no significant relationship between age and ASSR. This could be due to the small sample size, as other studies have a larger sample and more variation in ages, i.e., young, middle-aged, old (Goossens et al., 2016).

6.6 Limitations

This study has several limitations that need to be addressed in future studies. The ASSR was assessed using auditory stimuli, whereas cognitive functions were assessed using visual

and verbal tests. Although this is a general limitation across most studies examining the ASSR in relation to cognition, it limits the generalisability of our findings, as we did not measure it visually or use frequency tagging stimuli.

Our studies failed to replicate findings and associations between the ASSR and ageing and cognitive profiles. There may be reasons for this, such as whether our neuropsychological tests were scored similarly to previous studies or if our tests measured the same cognitive domains as previous ones.

We used an ageing sample, and typically models in previous research tend to be university students or patient groups. Due to ageing, our healthy participants may have already had reduced WM and attentional resources compared to participant groups used in previous research, so they may have been more vulnerable to the effects of age on cognition and gating mechanisms (Wetherell et al., 2002).

6.6.1 Applications

ASSR has been found to have practical implications for predicting transition to psychosis in clinical high-risk patient groups (Grent-‘t-Jong et al., 2020). The study used MEG to measure the ASSR and found that ASSR responses significantly predicted the patients’ transition to psychosis. This may also be possible using EEG alone in more neuropsychiatric disorders not isolated to schizophrenia.

Gathering research suggests that gamma (30–80 Hz) range activity in the brain is correlated with information processing of sensory and cognitive abilities (Parciauskaite et al., 2019). These include perception (Rodriguez et al., 1999), attention (Tiitinen et al., 1993;

Villena-González et al., 2018), memory (Kucewicz et al., 2017), and language processing (Ford et al., 2005). Previous research showing gamma range auditory entrainment in schizophrenia gives insight into how these electrophysiological mechanisms and neural imbalances can impact cognitive functioning (Vierling-Claassen et al., 2008). The ASSR was shown to be significantly correlated but not predicted by verbal fluency, but not with any other measure of cognitive ability. Therefore, the ASSR may not be a robust measure of cognitive functioning but rather a measure of neuron interaction and the effect this has on cognitive performance.

This follows from the fact that the ASSR is interpreted as a natural resonance frequency of the brain and is thought to be directly related to sensory processing (van Deursen et al., 2008). This could explain why ASSR deficiencies have been frequently reported in neuropsychiatric disorders that display perceptual disturbances in their symptoms, e.g., in schizophrenia (Griskova et al., 2007) and autism (Seymour et al., 2020). As activity in these EEG frequency bands is consistently implicated in cognitive impairment, the mechanisms that make up the ASSR could be of vital cognitive importance beyond schizophrenia and into less commonly researched disorders in the context of SG, such as delirium.

The ASSR can provide valuable insights into cognitive vulnerability, particularly in the context of neuropsychiatric and neurodegenerative conditions (Parciauskaite et al., 2019). Changes in the ASSR, such as alterations in amplitude, phase locking, or frequency following, can occur early in the progression of cognitive disorders, even before overt clinical symptoms are noticeable (Shahmiri et al., 2017). Monitoring these changes over time can serve as an early warning sign of cognitive vulnerability, allowing for interventions or treatment at an earlier stage of the condition.

The ASSR can assist in differentiating between various cognitive disorders that may present with similar symptoms but have distinct underlying neural mechanisms (Shahmiri et al., 2017). For example, Alzheimer's disease and schizophrenia may both affect cognitive function, but the patterns of ASSR abnormalities could differ between these conditions (Shahmiri et al., 2017). This differentiation is crucial for accurate diagnosis and tailored treatment approaches.

In some cases, the ASSR can be used to assess cognitive resilience or an individual's ability to maintain cognitive function in the presence of cognitive challenges or pathology (Grent-‘t-Jong et al., 2020; Shahmiri et al., 2017). Individuals with stronger ASSR responses may demonstrate greater cognitive resilience, while those with weakened ASSR may be more vulnerable to cognitive decline (Grent-‘t-Jong et al., 2020; Shahmiri et al., 2017).

Longitudinal assessments of the ASSR can track changes in cognitive vulnerability over time. This is especially valuable for monitoring the progression of neurodegenerative conditions like Alzheimer's disease, or even the vulnerability of patients needing major surgery, where cognitive abilities may deteriorate gradually. Early identification of changes in the ASSR can facilitate timely interventions and support, particularly in patients who may be at risk of postoperative cognitive decline after a delirium episode (Kotekar et al., 2018). The ASSR can be used to assess the effectiveness of interventions or treatments aimed at improving cognitive function. By measuring changes in the ASSR before and after an intervention, researchers and clinicians can determine whether the treatment has had a positive impact on cognitive vulnerability.

The ASSR can serve as a valuable tool for identifying cognitive vulnerability by detecting early changes in neural responses related to specific cognitive functions. It can aid in the early detection of cognitive impairment, differentiation between cognitive conditions, and monitoring cognitive changes over time. Additionally, it may assist in evaluating the effectiveness of interventions to mitigate cognitive vulnerability and promote cognitive resilience. These applications have significant implications for both research and clinical practice in the fields of cognitive neuroscience and neuropsychology, offering valuable tools for enhancing cognitive well-being and early intervention strategies.

6.6.2 Summary

The ASSR offers a unique benefit in cognitive research and clinical assessment due to its ability to be elicited under conditions where active attention to stimuli is not required. This is important, especially when working with older adults, vulnerable patients, or individuals with cognitive impairments, as it reduces the burden on participants compared to lengthy cognitive tasks that demand sustained focus and concentration. The less demanding nature of ASSR measurements can enhance participant compliance and minimise fatigue, making it an effective option for studying cognitive function in vulnerable populations.

One of the primary roles of ASSR measures is to assess the integrity of relevant neuronal circuits and neural reserve in older adults (Y. Wang et al., 2018). Neural reserve refers to the brain's ability to cope with age-related changes or pathological conditions without exhibiting overt cognitive deficits (Vohs, Andrew Chambers, et al., 2010). By examining ASSR responses, researchers gain insights into the functionality of these neural circuits, which are essential for various cognitive processes such as auditory perception, attention, and memory

(Gonzalez-Burgos & Lewis, 2012; D. C. Park & Reuter-Lorenz, 2009). While traditional diagnostic methods often rely on clinical symptoms or structural brain imaging, the ASSR offers a direct window into the brain's neural activity and processing capabilities. This can be particularly important for early disease detection or vulnerability when clinical symptoms may not yet be evident (Shahmiri et al., 2017; Sugiyama et al., 2021; Tada et al., 2016).

The potential applications of ASSR extend beyond cognitive ageing and into the realm of neuropsychiatric illnesses. Investigating ASSR mechanisms found in conditions such as Alzheimer's disease, schizophrenia, or depression and translating them into illnesses that occur after a big physical insult (i.e., delirium) could yield insights into the neural underpinnings of these disorders. It may uncover subtle neural abnormalities that precede clinical symptoms or provide a means of monitoring disease progression and treatment efficacy (Shahmiri et al., 2017; Sugiyama et al., 2021; Tada et al., 2016).

In conclusion, the ASSR's ability to be elicited without demanding active attention makes it a valuable tool for assessing cognitive function in older adults and individuals with cognitive vulnerabilities. It offers insights into neural circuit integrity and neural reserve, shedding light on the brain's ability to adapt and compensate. Additionally, the ASSR's potential as a neurophysiological marker in diagnosing and predicting neuropsychiatric diseases opens up exciting avenues for future research and clinical applications in the field of cognitive neuroscience and neuropsychology.

Chapter 7 Peak Alpha Frequency and Cognition

Roksana Markiewicz collected the results for the chapter, and the methodology sections were based on the paper (Markiewicz et al., 2021). The data were reanalysed by the current author and Ali Mazaheri and used with the authors' permission. The present author wrote the introduction, results and discussion, and the methods sections were repurposed from Markiewicz et al. (2021).

Abstract

Alpha frequency bands (8-13 Hz) are produced during relaxed wakefulness in occipital, central and parietal areas of the brain (Kropotov, 2016). Alpha frequency is thought to represent inhibiting irrelevant sensory pathways (Kropotov, 2009), and the peak frequency can be detected non-invasively using EEG. This study aimed to examine the influence of neuropsychological tests on the peak alpha occipital frequency in older ($\overline{x}$ = 73.62 years) and younger ($\overline{x}$ = 19.52 years) participants (n = 58). We extracted each participant's peak alpha frequency over the Oz electrode during EEG recording. Older participants had significantly lower peak alpha results than the younger participants (p = .023), and age significantly predicted the peak alpha frequency (p = .017). The peak alpha frequency was also significantly predicted by the WAIS full-scale IQ (p = .017) and a subtract two-digit span task (p = .039), but this was not seen when age was controlled for, implying that this relationship isn't robust. These are similar predictors found for sensory gating (SG) measures in our previous chapters, such as our inhibitory memory measures. Alpha can be predicted by attention and working

memory (WM), as well as intelligence and age, which makes it a valuable baseline predictor for future cognitive decline and complications.

7.1 Introduction

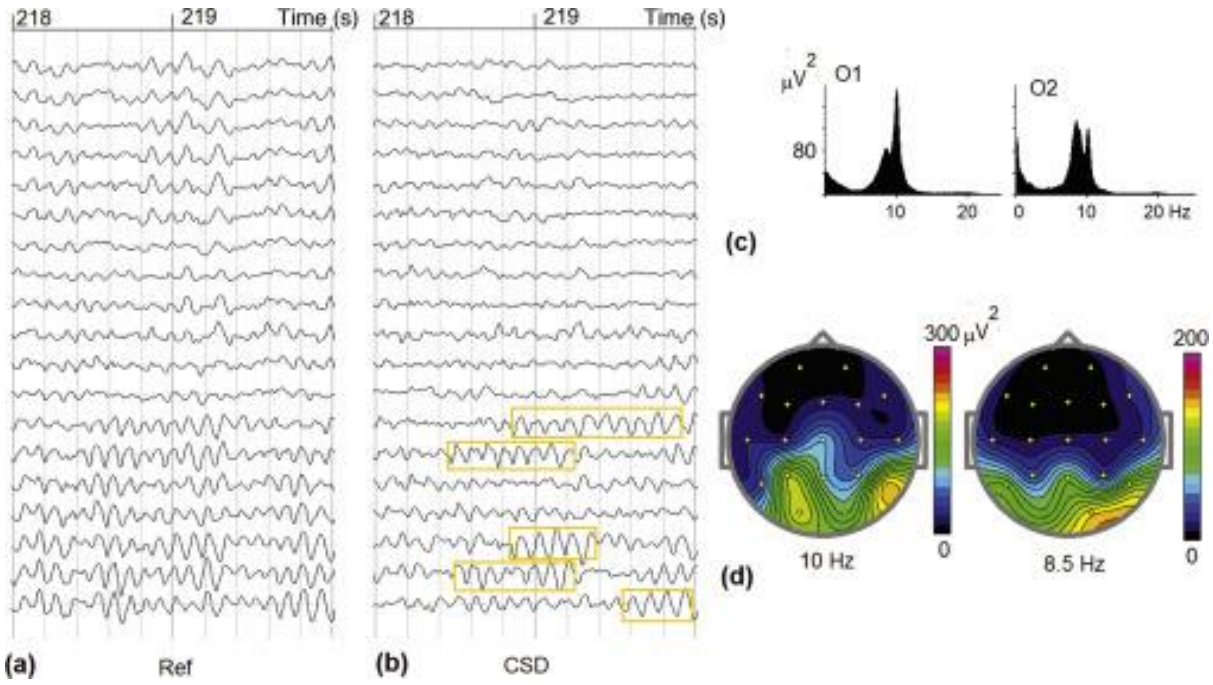
Hans Berger first observed the alpha rhythms in 1929 through EEG recordings of the human brain from human participants sitting relaxed with their eyes closed (Kropotov, 2009). He further demonstrated that alpha waves were suppressed when participants opened their eyes or performed cognitive tasks. These findings have been confirmed by many researchers who've discovered that different cortical areas show their own alpha rhythms when they are in a "resting state" (Kropotov, 2009).

Alpha frequency oscillations (8-13 Hz) are elicited during peaceful wakefulness in occipital, central and parietal areas of the brain (Kropotov, 2016). The alpha bands often depend on task load and vary in size and frequency (Kropotov, 2016). Alpha tends to represent the function of inhibiting irrelevant sensory pathways (Kropotov, 2009).

The alpha rhythm is the most prominent feature observed in EEG and is strongest when the subject is in an eyes-closed relaxed state (Niedermeyer & Lopes da Silva, 2004). Approximately 90% of healthy subjects show noticeable occipital alpha rhythms during recording when subjects have their eyes closed (Kropotov, 2016). The alpha rhythm represents the predominant oscillatory activity in the EEG, which is chiefly observed in primary sensory regions (e.g., vision, auditory) (Hanslmayr et al., 2011). Though previously thought of as a characteristic of cortical "idling," substantial data now propose that alpha signals play a top-down (TD) role in sensory gating (SG) information and inhibiting sensory overload (Jensen &

Mazaheri, 2010; van Diepen & Mazaheri, 2017). Figure 7.1 shows the alpha frequency in a healthy participant.

Figure 7.1 Alpha rhythms in a healthy subject



Note. From Kropotov (2016): "Posterior alpha rhythms in a 27-year-old healthy subject in eyes closed condition. (a) A fragment of EEG in the referential montage; (b) the same fragment in the CSD montage (posterior alpha rhythms are highlighted in boxes); (c) EEG power spectra at O1 and O2 (Occipital 1 and 2). Note two peaks at 10 and 8.5 Hz. and (d) spectra maps at 8.5 and 10 Hz."

Alpha frequencies are also present in arousal and sensory processing, and attentional processes (Foxe & Snyder, 2011). Alpha can be seen in EEG signals even when participants complete cognitively demanding tasks (Trammell, et al., 2017). Foxe, Simpson, and Ahlfors

(1998) have proposed that the amplitudes of N100 and P200 SG components are regulated based on the alpha amplitude preceding a stimulus.

While measuring alpha-band power (8-13 Hz), research discusses individual alpha frequency (IAF), which is the average of all an individual's recorded alpha-band power, or peak alpha frequency (PAF) which is the highest recorded frequency within the alpha-band (Rathee et al., 2020). Alpha-band power is thought to be genetic, demonstrating in an individual's cognitive functioning (Grandy et al., 2013). Research studies on typical adults undergoing standardised intelligence tests have indicated a positive correlation between their cognitive performance and both average and peak EEG alpha frequencies (Anokhin & Vogel, 1996).

Previous research has also shown that alpha oscillations relate to task performance of selective attention (Foxe & Snyder, 2011; Hanslmayr et al., 2011). Visual discrimination and detection negatively correlate with the alpha amplitude prior to the stimulus onset (Hanslmayr et al., 2011; Mathewson et al., 2009). Thus, processing and gating are less effective when the alpha amplitude is greater (Foxe & Snyder, 2011).

Studies have demonstrated that alpha oscillations are a prominent feature in filtering irrelevant stimuli (Bonnefond & Jensen, 2012; Freunberger et al., 2011). This is a crucial component in successful SG and filtering. However, these neural mechanisms during inhibition are not yet clear (Fodor et al., 2020; Gazzaley & Nobre, 2012).

7.1.1 Overlap with Sensory Gating

As alpha is involved in filtering out irrelevant stimuli. It can be seen as a form of SG, similar to the P50, N100 and P200 (Chapter 5). Some researchers have argued that relevant information is diverted by closing routes of irrelevant neural pathways – known as "gating through inhibition" (Jensen & Mazaheri, 2010). This gating inhibition is thought to be shown through the alpha oscillatory activity (Jensen & Mazaheri, 2010).

Brockhaus-Dumke et al., (2008) provided evidence for this using control and schizophrenic subjects. The researchers used a paired-click auditory experiment to measure alpha and theta oscillations, as well as the N100 and P50 paradigms. There was a diminished alpha increase after the second click compared to after the first click in both groups. In controls, habituation and SG were more prominent, whereas in schizophrenia patients, the responses to both clicks varied only marginally. N100 suppression was significantly reduced in schizophrenia patients, whereas there were no significant group differences in the P50 suppression (Brockhaus-Dumke et al., 2008).

Further support comes from Foxe and Snyder (2011), who suggested that alpha-band oscillations act as a way to block and mediate distracting information selectively. They found that the power was maximal over the cortical areas before an expected stimulus as a way of processing irrelevant information. These changes have been seen across a variety of selective attention tasks (Foxe & Snyder, 2011), including spatial attention in the visual (Mathewson et al., 2009), auditory, and somatosensory domains (Brandt, 1997). Increased alpha power signifies decreased cortical excitability and greater perceptual processing, which demonstrates better neural efficiency (Foxe et al., 1998; Foxe & Snyder, 2011).

7.1.2 Inhibition

Throughout the literature, alpha oscillations have been connected to having a role in inhibiting and filtering irrelevant stimuli, which is logical if they play a role in SG (Jensen & Mazaheri, 2010). Previous experiments have found that alpha oscillations increase when distractor stimuli are present compared to when there are no distractor stimuli (Banerjee et al., 2011). They have also been linked to TD modulation processing of attention (Sauseng et al., 2005) and expectations (Mayer et al., 2016). It has been implied that alpha oscillations maintain a crucial part in TD SG of task-relevant stimuli by inhibiting the task-irrelevant neurons (Fodor et al., 2020; Klimesch et al., 2007) through rhythmic synchronisation (Fries, 2015).

Supporting research demonstrated using EEG that the alpha-band power (8-13 Hz) decreases over areas associated with the task at hand (i.e., occipital areas for visual tasks) and increases over brain regions that represent distractors (i.e., auditory areas) (Payne et al., 2013; Sauseng et al., 2005). Some have also confirmed this causal relationship using transcranial magnetic stimulation (TMS) (Romei et al., 2010); stimulation of the occipitoparietal areas was shown to impair performance on visual tasks (Romei et al., 2010).

Payne et al. (2013) found that average alpha power increased over posterior brain areas when participants were asked to ignore a distractor stimulus. This confirmed many previous findings (Foxe & Snyder, 2011; Klimesch et al., 2007). This is because parietal regions are thought to be modulators of activity in the sensory cortices involved in the frontoparietal network of attention (ElShafei et al., 2020; Foxe & Snyder, 2011).

Consistent with posterior alpha power imitating an inhibitory mechanism, research indicates that attentional biasing in the visual cortex can suppress competing information (Kastner & Ungerleider, 2000) and task-irrelevant information (Waldhauser et al., 2012), which is in line with SG (Section 7.1.1.). In addition, this locus of alpha activity is observed throughout short-term memory maintenance tasks (Payne et al., 2013; Trammell et al., 2017). This is further posited to work as suppression of distracting and irrelevant stimuli during memory retention and can serve as a memory 'protector' (Bonnefond & Jensen, 2012).

7.1.3 Alpha in Ageing

Our alpha oscillations and alpha-band power can change as we age (ElShafei et al., 2020). An increase in behavioural inattentiveness due to decreased efficiency of TD cognitive processing and an increase in bottom-up (BU) processing is seen during ageing (ElShafei et al., 2020). This leads to attentional deficits, especially a reduced ability to inhibit extraneous information (Guerreiro et al., 2010). This impaired attention ability has been related to a deterioration in the brain's inhibitory mechanisms (Hasher & Zacks, 1988) and a decline in frontal lobe performance (Li, et al., 2022).

Subjects' PAF (the maximal power within the 8–13 Hz) has been found to change across the lifespan, increasing from childhood to adulthood and decreasing with age (Purdon et al., 2015). It is a genetic product of our nervous system, which is exposed to our cognitive abilities (Rathee et al., 2020). Previous research, including large sample sizes, discovered that the maximal power alpha frequencies decrease with age, even in healthy ageing adults (Chiang et al., 2011).

ElShafei et al. (2020) conducted an MEG study, collecting data from 14 older and 14 matched younger healthy subjects during the Competitive Attention Task. The older participants demonstrated increased behavioural inattention, reduced alpha oscillations in task-irrelevant brain regions, and reduced activation of prefrontal cortex areas. This shows that ageing affects TD and BU cognitive processes (ElShafei et al., 2020). During the expectation of visually cued sounds, the alpha power decreased in older adults, and the alpha increase in the irrelevant visual areas was reduced compared to younger adults.

The age-related decrease in alpha-band power, recorded via EEG, could result from an age-related reduction in synaptic density, alterations in dendritic dynamics, or a decline in the neurotransmitter synthesis (Purdon et al., 2015). Age can affect alpha band oscillations produced when undergoing anaesthesia (Purdon et al., 2015). There was a greater reduction in alpha frequencies (8-13 Hz) compared to other frequencies in older and younger patients. Older patients were also much more prone to demonstrate periods of burst suppression in relation to younger patients. These variations in EEG oscillations may be clarified by several neurobiological elements linked with ageing (Gmehlin et al., 2011).

7.1.4 Alpha in Cognitive Decline

These age-related changes in neuronal synapses and functional connectivity correlate with neurocognition, which alters in ageing (Murman, 2015). Previous research which reviewed the literature has found that critical regions such as the dorsolateral prefrontal cortex (dlPFC), an area responsible for executive function (EF) and working memory (WM), suffer dendritic loss in ageing (Morrison & Baxter, 2012). Morrison and Baxter (2012) have posited that these synapse changes correlate with neurocognitive function. An example is that during

ageing, the dlPFC suffers from a 46% loss of dendritic spines in the neurons, which are responsible for plasticity and are crucial in WM and EF tasks (Morrison & Baxter, 2012).

Subsequently, with the growth of a 'greying' population, the number of patients with clinical cognitive decline disorders is also likely to grow (Prince et al., 2016). Therefore, it would be in everyone's best interests to identify biomarkers that can register the beginning of cognitive decline and be measured throughout disease development (Lejko et al., 2020).

As neurocognitive function decreases and cognitive decline increases with age, so do alpha oscillations. Thus, alpha is often considered an essential role in cognition (Kropotov, 2016). Many researchers believe intelligence quotient (IQ) and alpha are closely linked; some even think higher IQ levels require higher alpha frequencies (Posthuma et al., 2001). Posthuma et al. (2001) observed 271 extended twin families (688 subjects). IQ was measured using the four dimensions (verbal comprehension, WM, perceptual organisation, and processing speed) from the Dutch version of the Wechsler Adult Intelligence Scale (WAIS-IIIR). The results suggested that PAF and WAIS-IIIR scales had high concordance rates (ranging from 66% to 83%), but no connection between alpha peak frequency and the four WAIS dimensions was confirmed.

Alpha power and synchrony are assuring neurophysiological indicators to measure various cognitive and motor processes (Başar et al., 2001; Ward, 2003). Dysfunctional activity in the different frequency bands (i.e., alpha, beta, gamma, delta, theta) has been linked with dementia (de Haan et al., 2008; Yener & Başar, 2010), and an ideal biomarker would accurately be able to discriminate between aetiologies of a decrease in neurocognitive functioning. Alpha is the most prominent rhythm during quiet/eyes-closed wakefulness (St. Louis et al., 2016).

Therefore, examining alpha activity in different settings such as hospitals is very practical as patients with cognitive decline or neurodegeneration do not have to complete complex or lengthy tasks during EEG recording (Lejko et al., 2020).

Decreases in power and synchrony of alpha oscillations have regularly been associated with neurological diseases, especially Alzheimer's Disease (AD) (Miraglia et al., 2016) and schizophrenia (Brockhaus-Dumke et al., 2008) and, more recently mild cognitive impairment (MCI) (Koenig et al., 2005). Reductions in alpha activity were associated with lower cognitive scores (Stam et al., 2006) and genetic predisposition for AD (Babiloni et al., 2006; Jelic et al., 1997). Resting-state eyes-closed alpha power was significantly lower in those who progressed from MCI to AD than in those who did not progress to develop AD (Miraglia et al., 2016). The research presents findings that functional connectivity levels in MCI patients are lower than in healthy older adults (Lejko et al., 2020), though the literature remains inconsistent. Thus, alpha power and synchronisation play a key role in the EEG activity accompanying cognitive dysfunction. Alpha is now acknowledged to have a pivotal role in inhibition, EF, and selective attention (Payne et al., 2013; Waldhauser et al., 2012).

7.1.5 Alpha and Cognitive Reserve

Studies using resting-state EEG (rsEEG) data tend to be conflicted when discussing the involvement of alpha rhythms (Babiloni et al., 2020), gamma rhythms (Yang & Lin, 2020), beta rhythms (Buján et al., 2022) and with little or no association with cognitive reserve (CR) (López et al., 2014). Many researchers have previously discussed that greater peak alpha is found in those with increased IQs (Posthuma et al., 2001). These subjects with higher IQs have shown higher alpha power at rest and during tasks (Jaušovec, 2000). Power has been stated to

be positively correlated with IQ in the alpha, theta and beta frequency bands in a rsEEG study with a sample size of 442 aged between 5–52 years (Thatcher et al., 2005).

Higher CR scores were also associated with greater power in the alpha and theta bands in a recent MEG study (Moezzi et al., 2019). It was found that the lower functional connectivity in the alpha band in participants with a higher CR was a marker of neural efficiency, as they showed less network connectivity while at rest. This suggests that these subjects use less of their attentional networks when it is not necessary at rest (Moezzi et al., 2019). Therefore, they have more efficient neural networks.

Other authors have found a highly significant association between spectral alpha and CR (estimated by past cognitively challenging events) (p = .001) (Griffa et al., 2021) and that better neuropsychological scores were associated with higher functional connectivity in the alpha band frequency. Lower CR participants showed decreases in the alpha band. AD patients did not show slower alpha rhythms in the occipital lobe in this study (Griffa et al., 2021), but they have in other research studies (Engels et al., 2017). Babiloni et al. (2021) also confirmed this as they showed that healthy high CR participants also demonstrated lower alpha source activations from posterior regions (Babiloni et al., 2021). However, in a previous study (Babiloni et al., 2020), they found using positron emission tomography (PET) scans that older participants with amyloid-β and high CR displayed lower alpha rhythms, which they claimed is a compensatory mechanism to preserve cognitive status.

There are a lot of conflicting findings regarding alpha rhythms and CR in older adults. Interestingly, alpha is related to IQ (a measure of CR) in healthy adults, but others have seen the opposite effect in participants with AD.

7.1.6 Hypotheses

In addition to Chapter 5 and Chapter 6, we wanted to investigate if peak alpha power in participants' occipital lobes can be associated with neuropsychological tests, namely EF, inhibition and language, as a measure of CR in a group of healthy older adults.

7.2 Method

The data was taken from Markiewicz et al. (2021) with permission from the authors, and the data were re-analysed for the alpha results with help from Dr Ali Mazaheri. The data is part of Open Access Science and is freely available from: https://www.biorxiv.org/content/10.1101/2021.01.15.426707v4. Therefore, the method is from this paper, and has been repurposed for this results chapter.

7.2.1 Participants

The participants included 33 young adults and 32 healthy older adults. Unfortunately, seven participants had to be removed from data analysis because of: (a) too many EEG artefacts while recording (n = 4) and (b) being a second language speaker (n = 3) (Markiewicz et al., 2021). Subjects incorporated in the analyses were 29 young adults and 29 healthy older adults (see Table 7.1 for more demographic information). All participants were native British monolingual speakers, right-handed with normal-to-corrected vision with no evidence of neurological, psychiatric or language impairments (Markiewicz et al., 2021). The older participants scored more than 26 out of 30 on the Montreal Cognitive Assessment test (MoCA)

(7.2.2.4) (M = 27.79, SD = 1.01). This is important as scores ≤ 26 suggest risk of MCI or dementia (Smith et al., 2007).

Participants in the young adult group consisted of undergraduate students recruited from the University of Birmingham Research Participation Scheme and completed the study in exchange for mandatory course credits (Markiewicz et al., 2021). The older adult participants were enrolled from the Patient and Lifespan Cognition Database and were reimbursed for their time with cash payments (Markiewicz et al., 2021). All participants signed consent forms, which adhered to the ethical guidelines made by the British Psychology Society, "and the experiment was approved by the Science, Technology, Engineering, and Mathematics (STEM) Ethical Review Committee for the University of Birmingham (Ethics Approval Number: ERN_15-0866)" (Markiewicz et al., 2021). Demographic information for participants is shown in Table 7.1.

Table 7.1 shows a balance in the number of participants in each group. There was no significant difference in the number of years spent in education between the younger and the older adults (p = .151).

Table 7.1 Participant demographics for young and old subjects.

	Young	Old	*t*	*p*	*Cohen's d*	*Glass' Delta*
N	29	29	-	-	-	-
Gender (M/F)	2/27	13/16	-	-	-	-
Age (years)	19.52 (1.5)	73.62 (5.8)	-48.703	<.001	4.23	5.79
Years of Education	14.52 (1.5)	15.45 (3.1)	-1.464	.151	2.42	3.08

Note. The results given are means with standard deviations shown in brackets.

7.2.2 Materials

The following neuropsychological testing materials were used in the experiment. They provide a brief overview of the participants' cognitive profiles, which we can then use alongside an analysis of their EEG results.

7.2.2.1 National Adult Reading Test (NART)

The NART involves participants reading 50 words of increasing difficulty aloud to the experimenter. Their pronunciation is marked and scored either 0 or 1, totalling 50. The predicted WAIS-IV Full-Scale IQ was calculated: 127.7 – (0.86*NART Errors). Seen in A.2.2.

7.2.2.2 WAIS-IV Processing Speed Index

The Wechsler Adult Intelligence Scale (WAIS) processing speed index (PSI) includes two tests, the Symbol Search and Coding. The Symbol Search (see A.4.1) involves participants matching the selected symbol with a choice of four other symbols. They have to do this 50 times in as little time as possible. The coding test (see A.4.2) has participants learning symbols for numbers one to nine, and they have to write the code for each number underneath in a random order. They must do as many as possible in under two minutes (Weschler, 2008).

7.2.2.3 Working Memory Tests

The backwards digit span task (see A.4.3) included strings of numbers being read aloud to the participants, and they had to repeat the numbers to the researcher in backwards order. If

they got one out of the two trials correct, they moved on to the next level of difficulty, where another number was added to the string length (Weschler, 2008).

In the subtract two-digit span task, participants had to listen to numbers being read aloud, only repeat the numbers that they had previously heard two trials previously and suppress what they had just heard (Waters & Caplan, 2003).

7.2.2.4 Montreal Cognitive Assessment (MoCA)

The MoCA (see A.4.4) is a 10-minute cognitive screening tool to assist in detecting MCI. It comprises different cognitive domains, such as EF, naming, WM, attention, language, abstract reasoning, delayed recall, and orientation (Nasreddine et al., 2005).

7.2.3 Procedure

At the beginning of the experiment, participants had a 64-channel EEG cap placed on their heads and electrode gel applied to the scalp at each of the 64-channel electrode sites. Participants then sat in a soundproof booth 70cm from a computer screen, where a computerised task took place (part of Markiewicz et al.'s 2021 experiment, but the results from this automated task will not be discussed or analysed). In the behavioural experiment run by Markiewicz et al. (2021), they aimed to investigate changes in oscillatory brain activity (i.e., theta (4-7 Hz), alpha (8-12 Hz), low beta (15-20 Hz), and high beta (20-25 Hz)) during semantic binding in participants (young vs old), using a two-word phrase paradigm. They presented target words (e.g., horse) in a semantic binding (e.g., swift horse) vs no semantic binding context (e.g., swrfeq horse). From this, the peak alpha frequencies were extracted from the subjects (8-12 Hz).

Following this, participants underwent various neuropsychological assessments, including WM tests (a backward digit span task and the subtract two-digit span task) (Waters & Caplan, 2003), the NART (Nelson & Willison, 1982), and two tests included in the WAIS-IV processing speed index (symbol search and coding) (Weschler, 2008). The older participants were screened for cognitive impairment using the MoCA (Nasreddine et al., 2005).

7.2.3.1 EEG recording

EEG was gathered using a 64-channel Waveguard^{TM} with Ag/AgCI electrodes in a 10-20 layout (plus left and right mastoids) (Markiewicz et al., 2021). Two electrodes located on the outer left and right canthi measured horizontal eye movements (Markiewicz et al., 2021). Two other electrodes placed above and below the right eye recorded vertical eye movements. The EEG recording was obtained with the CPz channel as a reference (Markiewicz et al., 2021). The ANTneuro EEGosports amplifier system was used to amplify the recorded signal, and this was recorded using EEGo software (Advanced Neuro Technology) (Markiewicz et al., 2021). The signal was acquired using a 30 Hz low-pass filter, a 0.05 Hz high-pass filter and a 500 Hz sampling rate. The impedances of the applied electrodes were kept below 100 kΩ (Markiewicz et al., 2021).

7.2.3.2 EEG analysis

The data were pre-processed using EEGLAB 14.1.2b (Delorme & Makeig, 2004). Fieldtrip (Oostenveld et al., 2011) was used to inspect for non-physiological artefacts manually. Independent component analysis was then used for eye movement artefacts removal (Delorme & Makeig, 2004). The average number of removed components was 2.52 (SD =

1.00) across 58 participants due to eyeblinks and line noise. The peak alpha was then calculated by extracting the maximum peak frequency between 8-12 Hz from the electrode Oz (occipital lobe) from the data; this then gave us the peak alpha (Hz) for each participant.

7.3 Results

7.3.1 Descriptive Statistics

The neuropsychological results for both groups are shown in Table 7.2 below. Between-subjects t-tests were calculated to find significant differences between both groups and effect sizes.

Table 7.2 Cognitive results from young and old participants

	Young (n = 29)	Old (n = 29)	*t*	*p*	*Cohen's d*	*Glass' Delta*
WAIS-IV Processing Speed Index	81.46 (11.6)	65.00 (13.3)	5.027	<.001	12.49	13.34
NART Average Score	25.8 (5.1)	37.05 (4.6)	-8.829	<.001	4.85	4.62
Pred. WAIS-FSIQ	107.72 (4.2)	117.00 (3.8)	-8.829	<.001	4.00	3.81
Average WM Score	4.42 (.67)	4.97 (.92)	-2.621	.011	.80	.92
Backwards digit span	4.41 (.80)	5.07 (1.06)	-2.656	.010	.94	1.06
Subtract 2-digit span	4.34 (.71)	4.88 (.86)	-2.145	.036	.79	.86

Note. The results are means with standard deviations in brackets (n = 58), from Markiewicz et al., (2021).

Table 7.2 shows that the young participants outperformed the older subjects in processing speed scores (WAIS-IV processing speed index), whereas older adults did better on the NART than the younger participants; subsequently, they also had higher Predicted WAIS Full-Scale IQ (Pred. WAIS-FSIQ; calculated in the same method as in Section 5.4.3.2). Unexpectedly, older adults scored higher in the WM tasks (i.e., the average joint score of the backward digit span and subtract two-digit span tests).

7.3.2 EEG Alpha Analysis

The Oz electrode was chosen to measure the peak alpha frequency due to the documented strong prominence of Oz together with Pz electrodes in EEG alpha research (Klimesch, 1999; Tröndle et al., 2021), and together with age effects being found in alpha power in these particular electrodes (Polich, 1997). Many researchers believe that the occipital lobe generates the alpha signal (St. Louis et al., 2016). Alpha can be primarily recorded and measured from the occipital lobes while participants are relaxed with their eyes closed (Kropotov, 2009). These occipital alpha waves during eyes-closed recordings are one of the strongest EEG brain signals (St. Louis et al., 2016). Oscillations in the alpha band (8-13 Hz) are involved in the SG of information from the occipital lobe to the ventral stream (Zumer et al., 2014).

In addition, in line with previous research (above), the alpha power suppression from the two-word paradigm experiment peaked at approximately 0.5 sec post word onset and was greatest over the Oz channel (Foxe & Snyder, 2011; Furman et al., 2018). This was what our peak alpha frequency was extracted from. Table 7.3 below shows the EEG results for both groups.

The results in Table 7.3 show no significant differences between groups regarding how many EEG components were removed during independent component analyses (p = .295), which means differences between alpha peaks cannot be attributable to this.

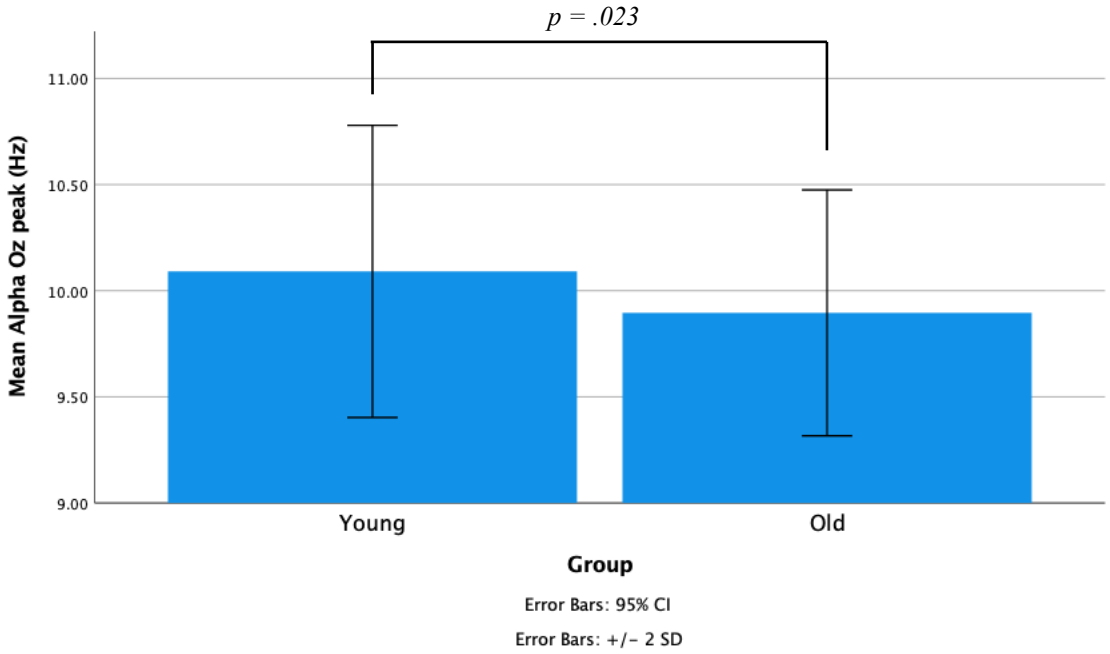
Table 7.3 EEG Descriptive Statistics

	Young (n = 29)	Old (n = 29)	*t*	*p*	*Cohen's d*
No. of EEG Components Removed	2.66 (.97)	2.38 (1.01)	1.056	.295	.99
Peak Alpha Oz Frequency (Hz)	10.09 (.34)	9.89 (.29)	2.338	.023	.32

Note. Mean results are given, and standard deviations are in brackets.

There was a significant difference in the peak alpha frequencies between the older and younger participants (p = .023), which means the older participants had significantly lower peak alphas than the young participants. These differences are illustrated in Figure 7.2.

Figure 7.2 Young vs Old Alpha Peak Frequency



Note. Results are taken from the occipital electrode (Oz), n = 58.

Figure 7.2 shows a more significant reduction in the Oz peak alpha frequency in the older participants than in the younger participants. A linear regression using the enter method was conducted to see if age could predict the peak Oz alpha. The results were significant (R = .313, R^2 = .098, Adj R^2 = .082, F (1, 56) = 6.079, p = .017), which produced the equation: Alpha Oz peak = 10.168 + (-.004 * Age).

7.3.2.1 Alpha Oz Peak and Neuropsychological Results

Further examining the neuropsychological outcomes of both older and younger participants, the aim was to predict the peak alpha frequency at Oz. Utilising regression

analysis with the enter method, the study investigated associations between neuropsychological variables and the peak alpha frequency at Oz, as shown in Table 7.4.

Table 7.4 Summary of enter linear regression analyses for variables predicting Alpha Oz Peak (Hz).

Predictors	Alpha Oz peak (Hz)			
	B	*SE B*	*β*	*P*
(Constant)	11.657	1.003		< .001
Average WM Score	-.039	.059	-.099	.510
NART Pred. WAIS FSIQ	-.014	.009	-.252	.127
WAIS-IV Processing Speed Index	.001	.003	.027	.192
R^2		.105		
Adj R^2		.005		
F		2.102		

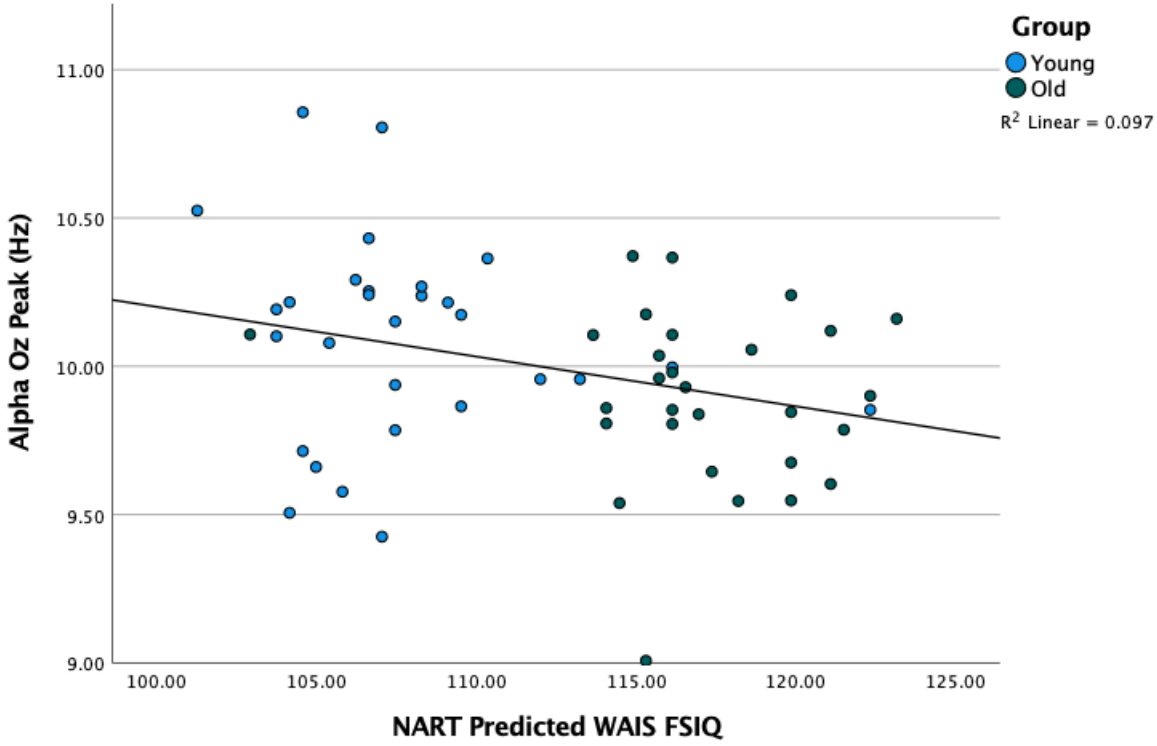
Note. (n = 58)

Table 7.4. shows that when all the neuropsychological variables are entered into the equation, the model including all the variables is non-significant (p = .111), however, they may be significant when entered as separate predictors.

We then ran a stepwise linear regression with the peak Oz alpha as the dependent variable and the neuropsychological results (i.e., WAIS-IV processing speed index, Pred. NART WAIS-FSIQ and WM scores). The NART Pred. WAIS FSIQ significantly negatively predicted the outcome of the Oz alpha peak in both groups, shown in

Figure 7.3 below.

Figure 7.3 Relationship between the Pred. WAIS FSIQ and Peak Oz Alpha (Hz)



Note. (n = 58), $R = .312$, $R^2 = .097$, Adj $R^2 = .081$, $F\ (1,56) = 6.022$, $p = .017$.

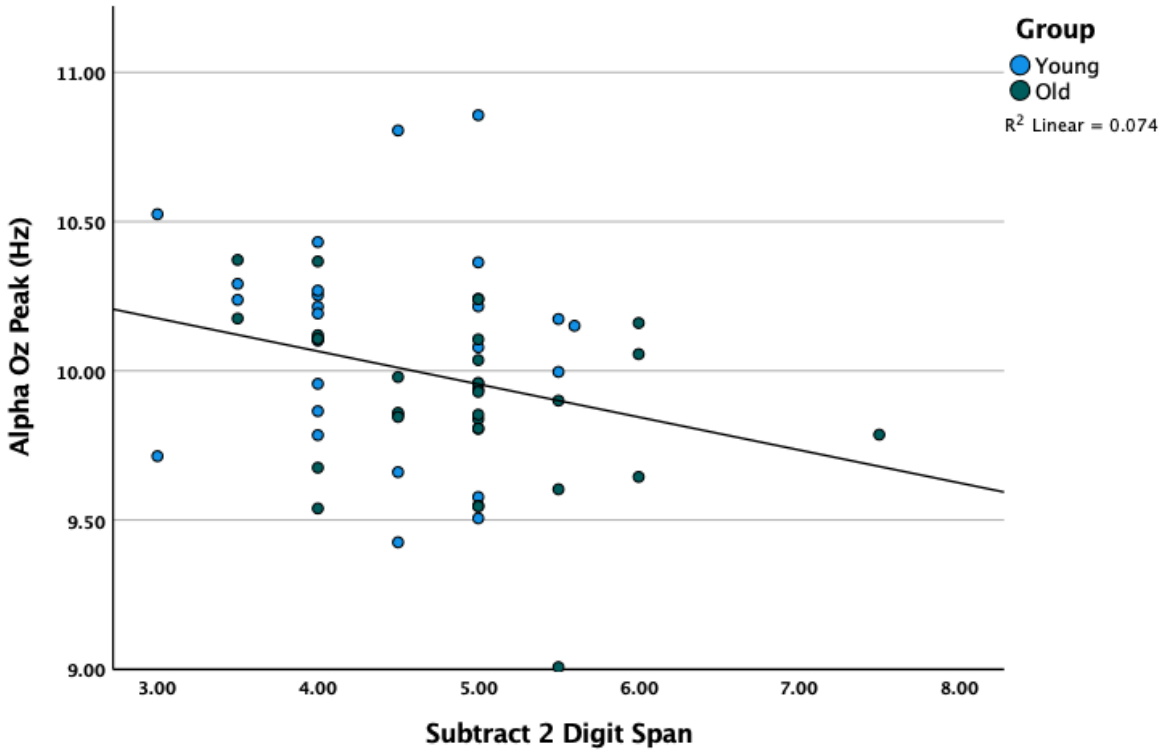
From the regression, we received the following equation:

Alpha Oz peak = 11.877 + (-.017 * NART Pred. WAIS FSIQ)

A second regression was carried out with the WM score, but this was non-significant ($p = .092$), so we decided to investigate the individual WM tests that made up this score. Backwards digit span was entered as a predictor variable, this was also non-significant ($p = .243$). Subsequently, the subtract two-digit span was entered in as a predictor of alpha Oz peak

frequency as a separate predictor variable. This was a significant negative predictor of alpha Oz peak frequency. This relationship is shown in Figure 7.4.

Figure 7.4 Relationship between the Subtract Two-Digit Span and Peak Oz Alpha (Hz)



Note. (n = 58), R = .272, R^2 = .074, Adj R^2 = .057, F (1,56) = 4.470, p = .039

The regression equation for this model is: Alpha Oz peak = 10.507 + (-.110 * subtract two-digit span).

The subtract two-digit span and the NART Pred. WAIS-FSIQ were not significant predictors when entered together into the peak Oz alpha frequency equation (p > .05). Therefore, the alpha Oz peak frequency could be significantly predicted by Pred. WAIS FSIQ

and subtract two-digit span separately. The former is a measure of intelligence, and the latter is a measure of attention together with inhibition.

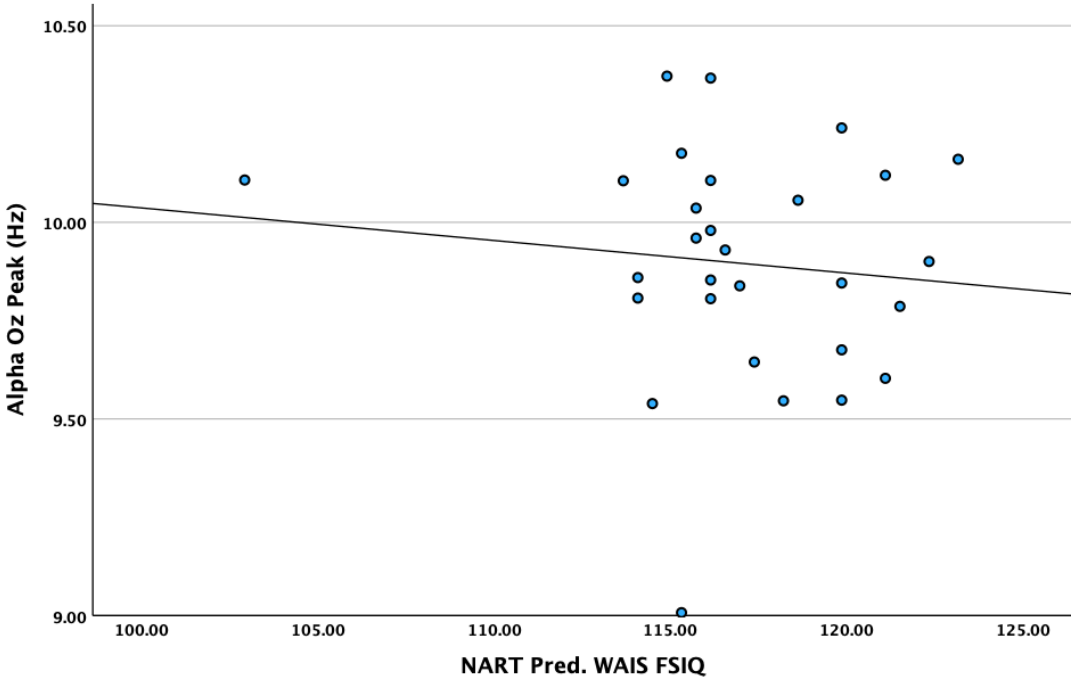
7.3.2.2 Controlling for Age

Further analysis was conducted to see if partialling out the effect of age would still produce the significant relationship between the NART Pred. FSIQ and the Alpha Oz peak. This is because the NART Pred. WAIS FSIQ is age standardised, the NART itself is not, but when used in conjunction with the WAIS, this produces an assumed FSIQ based on age. Therefore, a follow-up partial correlation was performed between NART Pred. WAIS FSIQ and Alpha Oz peak, controlling for age. We found a non-significant correlation between these two when age was controlled for (R = -.114, p = .399).

This is not surprising, particularly as the Oz Alpha peak also had a significant relationship with age (p = .017). Subsequently, we analysed the older groups peak Oz alpha in relation to the NART Pred. WAIS FSIQ. These participants were of a similar age (> 65 years) to those included in the previous two chapters, so they would be more likely to show comparable results.

A linear regression using the enter method was conducted to see if the NART Pred. WAIS FSIQ could predict the peak Oz alpha in the older group (n = 29). The results were non-significant (R = .109, R^2 = .012, Adj R^2 = -.025, F (1, 27) = .325, p = .574), which shows that when we only use the older participant group, we lose the relationship between NART Pred. WAIS FSIQ and the Oz alpha peak. This non-significant relationship can be seen in Figure 7.5 below.

Figure 7.5 Relationship between the Pred. WAIS FSIQ and Peak Oz Alpha (Hz) in Older Participants.

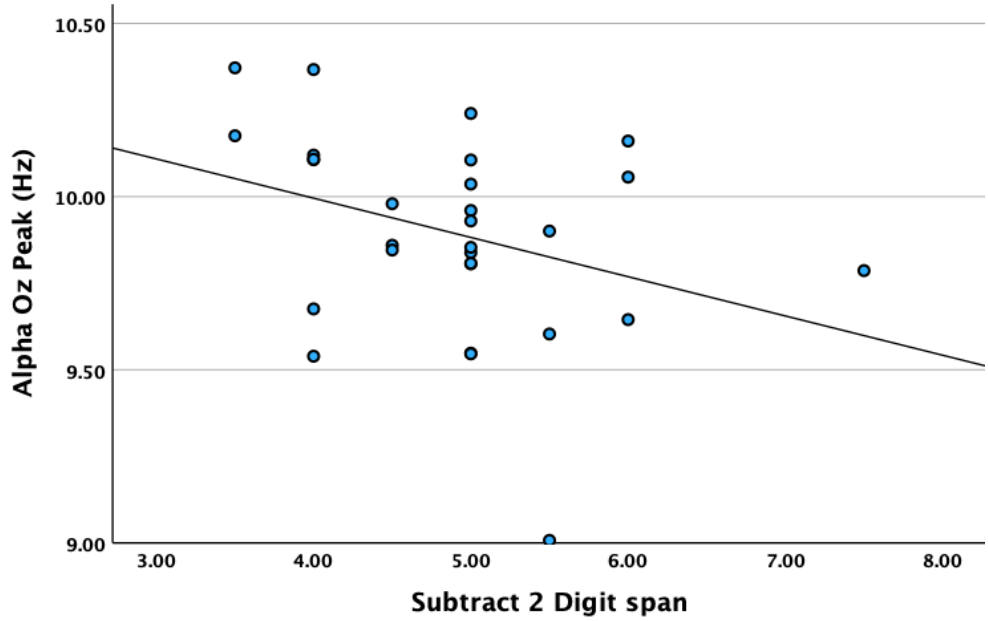


Note. Only older participants are shown in the graph, (n = 29), relationship is non-significant (p = .574).

A second regression was carried out with the subtract two-digit span as a predictor of alpha Oz peak frequency as a separate predictor variable (see Figure 7.4). Further analysis was conducted to see if partialling out the effect of age would still produce the significant relationship between the subtract two-digit span and the Alpha Oz peak. This is because the older participants performed significantly better on the subtract two-digit span than the younger participants (see Table 7.2). Therefore, a follow-up partial correlation was performed between subtract two-digit span and Alpha Oz peak, controlling for age. We found a non-significant correlation between these two when age was controlled for (R = -.212, p = .114).

Consequently, we analysed the older groups peak Oz alpha in relation to the subtract two-digit span. A linear regression using the enter method was conducted to see if the subtract two-digit span could predict the peak Oz alpha in the older group (n = 29). The results were non-significant (R = .337, R^2 = .114, Adj R^2 = .081, F (1, 27) = 3.470, p = .073), which shows that when we only use the older participant group, we lose the relationship between the subtract two-digit span and the Oz alpha peak. This non-significant relationship can be seen in Figure 7.6 below.

Figure 7.6 Relationship between the Subtract Two-Digit Span and Peak Oz Alpha (Hz) in Older Participants.



Note. Only older participants are shown in the graph, (n = 29), relationship is non-significant (p = .073).

7.4 Discussion

The current study tested the hypotheses that the peak alpha frequency of subjects can be predicted by neuropsychological functioning (Posthuma et al., 2001) and change with age (Lejko et al., 2020). We aimed to characterise the peak alpha frequency in a healthy older population and to see if it decreases with age by comparing their results with younger participants.

This study aimed to see if the peak alpha correlated with neuropsychological and mental functioning results. We investigated different cognitive domains using various neuropsychological tests that target additional features of cognitive function. We predicted that attention, inhibition, and EF measures could predict the alpha. We demonstrated a significant relationship between peak alpha, concentration, intelligence, and age. EF and peak alpha were non-significant.

We discovered that a measure of attention and WM significantly predicted the peak alpha. This aligns with the results from Chapter 4 and Chapter 5; WM and attention measures also predicted the P50, N100 and P200 SG responses and the ASSR. Alpha signals are thought to play a TD role in SG information and inhibiting sensory overload (Jensen & Mazaheri, 2010; van Diepen & Mazaheri, 2017). In addition, they are involved in general alertness and sensory processing (Foxe & Snyder, 2011). Foxe et al. (1998) proposed that the amplitudes of N100 and P200 SG components are regulated based on the alpha amplitude preceding a stimulus. Therefore, it is not unexpected that similar neuropsychological tests predict the alpha peak that also indicates the P50, N100, P200 and ASSR responses.

7.4.1 Alpha and Ageing

The results demonstrated that the participants' age could predict the peak alpha frequency. The older the participants were, the lower their peak alpha. This is consistent with previous research, which states that peak alpha frequency changes across the lifespan, increasing during childhood to adulthood, and then decreases with age (Purdon et al., 2015). This maximal alpha power has reduced with age, even in healthy older participants (Chiang et al., 2011).

Previous research has posited that ageing can be acknowledged by increased behavioural inattention and reduced cognitive processing, which leads to attentional deficits (Guerreiro et al., 2010). However, it was found that the older participants outperformed the younger subjects in nearly all aspects of neuropsychological testing. This unexpected result did not confirm previous findings that cognition worsens with age alongside peak alpha frequency reduction. A potential explanation for this could be that the older adults were more motivated; they were compensated for their time with cash payments and participated because they were interested in helping academic research and their cognitive health. In contrast, the younger participants were rewarded with course credits, a requirement for passing their modules during their degree. Therefore, they may have been less motivated and did not give as much effort as the older adults. This would have affected their neuropsychological results but not their peak alpha frequency.

This age-related decrease in peak alpha frequency could result from an age-related reduction in synaptic density, dendritic dynamics, or a decline in neurotransmitter synthesis (Purdon et al., 2015). However, we could not see the effects of such changes in the participants'

neuropsychological scores, only in their peak alpha frequencies. Previous studies have shown that individual peak alpha frequencies have been positively correlated with AD patients' encoding abilities and memory retrieval (Puttaert et al., 2021). Evidence for this comes from the peak alpha being positively associated with the patients' hippocampal volume and the "regional glucose consumption in the posterior cingulate cortex" (Puttaert et al., 2021, p. 1). The authors posited that the ability to learn and store/manipulate information in a short time period could be correlated with alpha slowing and peak alpha decrease. They considered the decreased alpha peak to accompany ageing (pathological or otherwise), which would explain the reduced alpha in our sample, but not their neuropsychological scores.

7.4.2 Alpha and Attention

Our results demonstrated a significant link between the peak alpha frequency and the subtract two-digit span score; the better the participants did on the task, the lower their peak alpha. However, this may have been affected by the fact that the younger participants were not as motivated, so they did worse on the task and already had higher alpha peaks. Furthermore, this has also been confirmed by previous research. Many papers have found that higher alpha peaks have been associated with inattention, decreased perception of stimuli and mind wandering episodes (Deiber et al., 2020; Sigala et al., 2014). Our results support this; the higher the alpha peak, the worse participants do on the subtracting two-digit span test.

However, other studies argue that the higher the alpha peak, the better the performance on demanding tasks. Rathee et al. (2020) found that participants with higher peak alpha scored significantly higher on reading comprehension tests. Klimesch (1997) also found that the peak alpha frequency is 1 Hz higher on average for those performing better on memory tests than

those who performed poorly. This difference is most pronounced in memory retrieval tasks and smaller during memory encoding and resting state alpha. Klimesch (1997) argued that the EEG frequencies within the alpha band partly originate from the thalamus. The neuronal activity within the thalamocortical networks suggests mechanisms for accessing and retrieving information from semantic long-term memory.

However, this peak alpha frequency is inconsistent across the lifespan or even during the same task, be it a memory task or resting state alpha (Puttaert et al., 2021). Throughout cognitive tasks, the peak alpha could alter between higher or lower frequencies and may change across brain regions, i.e., thalamus or occipital areas (Haegens et al., 2014; Romei et al., 2010). Haegens et al. (2014) discovered that the average posterior peak alpha increased when participants were doing the n-back WM task compared to resting state alpha. The results suggest that peak alpha increased during more cognitively demanding tasks.

Our results do not support this; lower peak alpha led to higher results during cognitive tasks. This may be because the older participants were more motivated to help with research than the younger participants who were obliged to participate in their degree courses. Therefore, the older participants would have tried harder during the assessments and performed better, but because of their age, they have lower peak alpha than the younger participants. However, our results support those of Deiber et al. (2014); thus, we have an unclear picture of the role of peak alpha in attention and cognitive tasks.

7.4.3 Limitations

There are several limitations to this experiment which need to be addressed. Firstly, there were significant differences in the cognitive performances of the older and younger participants, making it more difficult to compare the participants directly. Younger participants outperformed the more senior participants on processing speed assessments, while older adults outperformed them on memory and language tests. Therefore, it may be more challenging to say that these participant groups were evenly matched in cognitive abilities and that the differences in peak alpha could be purely down to age. Both groups had a similar level of education, so they should have had similar levels of cognitive performance.

Secondly, it could be argued that the younger participants were less motivated, so they did not try as hard during the more demanding cognitive tasks. The older adults were volunteers and were monetarily compensated. In contrast, the younger participants were obliged to take part in their degree course and were not monetarily compensated but were compensated in terms of course credits. Therefore, it could explain why we had a negative correlation between peak alpha and cognitive performance.

Thirdly, our results did not confirm the majority of previous findings. However, the literature is very inconsistent on peak alpha's role in cognition, mainly resting state peak alpha. This makes it very difficult to draw conclusions based on previous literature. We only analysed the peak alpha at resting state with eyes closed. What may have been more effective in analysing the alpha during cognitively demanding tasks is to uncover more of the peak alpha's role during cognitive tasks. However, the object was to be able to link resting state peak alpha with subjects' cognition and to be able to use it as a marker of overall cognitive health.

7.4.4 Applications

Together with the SG measures from Chapter 5 and Chapter 6, sensory processes measured using EEG can be a valuable biomarker for predicting the development of neuropsychiatric illnesses and cognitive deficiencies. EEG biomarkers such as P50, ASSR and peak alpha can be elicited under conditions where attention to stimuli is not required. These measures can be an ideal biomarker to test relevant neuronal circuits (Schuelert et al., 2018). Specifically, ASSR has been found to have practical implications for predicting transition to psychosis in clinical high-risk patient groups (Grent-‘t-Jong et al., 2020). This may also be possible using EEG alone for more neuropsychiatric disorders not isolated to schizophrenia. Mazaheri et al. (2018) used background alpha frequency to predict conversion from MCI to AD. More research has also used peak alpha frequency to distinguish between AD, Parkinson’s disease, and Lewy Body Dementia (Meghdadi et al., 2019) when cognitive tests such as the MMSE were unable to determine specific biomarkers. These uses may not only be isolated to the studies mentioned above but also for more complex inflammatory acute conditions.

7.4.5 Summary

To summarise, the peak alpha frequency was negatively predicted by the Full-Scale WAIS IQ calculated from the NART and by subtracting the two-digit span test. These results were similar to the P50 and ASSR results, where the EEG results were related to memory measures requiring inhibition. These have also been found in previous research examining CR. These can be helpful markers when measuring the susceptibility for low CR in older adults.

We showed that we could measure the peak alpha in participants with one electrode (Oz) and extract the alpha after four minutes with their eyes closed, which is a low-burden experiment.

Chapter 8 General Discussion

8.1 Research questions

In this thesis, I aimed to investigate the role of sensory gating (SG) and neural inhibition in relation to cognitive reserve (CR) in healthy older adults. What we really aimed to do was to create an EEG and neuropsychological preoperative protocol, which would be able to be carried out during preoperative hospital visits, in hospital settings, with as little burden on the patient as possible. We wanted to be able to measure patients' preoperative vulnerability in the context of CR before their major abdominal oncology surgery and be able to predict their development of postoperative delirium and clinical outcome. However, as previously stated in Chapter 1, this was not possible due to the outbreak of COVID-19. Therefore, the pilot data, which was collected on healthy older participants, made up the data bulk in this thesis. We piloted whether the SG, ASSR and alpha indices that we had chosen could be done using a skeleton EEG system and be related to our neuropsychological measures.

Chapter 2 was concerned with the general introduction of why we were interested in measuring CR in older populations, and what this could mean in the context of a traumatic physical event, such as major surgery. Some patients have very different outcomes post-surgery, and our hypothesis was that it was because of their levels of preoperative functioning. We chose to use EEG in conjunction with neuropsychological tests, purely because EEG is an objective measure of the patient's physical brain state, and it is one side of CR – neural reserve, neural capacity, efficiency, and compensation. We wanted to relate it to the patient's

neuropsychological functioning, which is heavily subjective, and we could possibly only need to do an EEG during patients' preoperative visits. Therefore, because we wanted to use EEG in our study, Chapter 3 investigated the inner workings of EEG, and how it would help us in the context of clinical biomarkers investigating preoperative patient vulnerability.

In Chapter 4, we were interested in what the previous research had stated on this topic and, mainly, what EEG setup was used, how they measured CR, and what their results were. Chapter 5 was written to test the ERPs P50, N100, and P200 and relate these to measures of neuropsychological functioning. These paradigms are well-documented in the literature and are the best ways to measure SG in older adults. We wanted to investigate more measures of inhibition and SG to strengthen our conclusions, so we included the ASSR in the experiment. The results of the ASSR were also related to cognitive tests in older adults in Chapter 6. In Chapter 7, we examined the peak alpha frequency in both young and old participants to see if there was a significant difference between their peak alpha frequencies and the CR built up over their lifespan. The results will be discussed as per chapter.

Our research questions were to see if we could link the sensory and neural processing of the brain to CR in healthy older adults. We focused on inhibitive and executive functioning (EF) measures, such as working memory (WM) and planning tasks. These questions were based on previous research, which states that EF is the first cognitive domain to reduce ageing due to decreased functioning of the prefrontal cortex (PFC) and that this has never been linked to SG or inhibitory EEG measures in research.

8.2 Results Summary

8.2.1 Chapter 4

In the literature review, we examined 23 relevant studies examining EEG, MEG, or event-related potentials (ERPs) and relating them to measures of CR. The majority used EEG with ERPs in their methodology. The most common ERP was the M/P300 and occasionally the N200 during inhibition and verbal task recognition tasks, reaction time and n-back tasks. The rest measured resting-state brain rhythms using EEG while participants were in a relaxed state with their eyes closed or one with their eyes open. The mode number of electrodes used in these studies was 64, with the second most common (excluding MEG) being 32, and then 129. The lowest number of electrodes was two (bispectral EEG). The mode method of CR used the CRIq (Nucci et al., 2012), with the next most common being to make an index incorporating various factors such as years of education, job attainment, and verbal IQ. Others used standardised subtests from neuropsychological assessments. Looking back at previous research, we could show in the following chapters that we still measured good enough signals by using fewer electrodes and the P50, N100, P200 and ASSR paradigms in relation to CR. This is valuable and saves time for potential clinical populations in the future.

8.2.2 Chapter 5

Chapter 5 showed that P50 SG was not related to any neuropsychological test in our study. However, stronger N100 SG led to better inhibitory memory, this suggested a relationship between N100 gating and inhibitory memory, including sensitivity of

discriminating between lists A and B. Previous studies have presented a relationship between N100 gating and WM. Participants in this chapter, with better N100 SG had better WM, consistent with previous research (Brumback et al., 2004).

The P200 SG was significantly predicted by visual and verbal long-term memory, suggesting that individuals with specific SG patterns may also exhibit distinct memory capabilities. This finding highlights the potential interplay between SG processes and memory function. Contrary to our initial hypothesis, we did not identify significant correlations between SG and measures of EF or language abilities. This suggests that while SG may play a role in memory and inhibition, its relationship with other cognitive domains, such as EF and language, maybe less pronounced or not statistically significant in this particular study cohort.

8.2.3 Chapter 6

Chapter 6 demonstrated a significant relationship between ASSR and verbal fluency. There were no significant correlations between inhibition and memory. Age and ASSR were also non-significant. Verbal fluency significantly predicted the ASSR; an inhibitory prefrontal task which constricts the participants to saying words constricted to letters and categories. This aligns with the 40 Hz and ASSR response being deficient in patients/populations with dysfunctioning of the PFC.

8.2.4 Chapter 7

We discovered that a measure of attention and WM significantly predicted the peak alpha in Chapter 7. This aligns with the results from Chapter 5 and 6; WM and attention

measures also predicted the N100 and P200 SG responses, and an inhibitory measure predicted the ASSR.

Our results demonstrated a significant link between the peak alpha frequency and the subtract two-digit span score; the better the participants did on the task, the lower their peak alpha. However, this may have been affected by the fact that the younger participants were not as motivated, so they did worse on the task and already had higher alpha peaks.

8.2.5 Overall Results

To summarise our findings, we found that EF was unrelated to SG paradigms (P50, N100, P200) or the ASSR. However, a measure of EF used in Chapter 7, the subtract two-digit span, was significantly associated with peak alpha frequency.

Inhibition was related to SG and ASSR in Chapters 5 and 6. The subtracting two-digit span could also be considered an inhibition measure because the participants must suppress the last two numbers they heard and state the previous number. Therefore, they must inhibit their initial response, which was significantly related to the subjects' alpha power. Unfortunately, anxiety measures were not taken from these participants in Chapter 7.

As measured by IQ, CR was not associated with neural or sensory functioning in Chapters 5 and 6. However, it was related to peak alpha power; the higher the subjects' IQ, the lower their peak alpha. Based on previous literature, it could be argued that the higher IQ subjects showed lower alpha at rest, which may indicate compensatory neural mechanisms in older adults.

Based on previous research into CR and alpha frequency, our results were consistent with the fact that intelligence is negatively correlated with peak alpha across young and old groups. However, there is the issue that older adults had a significantly higher IQ than younger participants. In addition, peak alpha is well-known to decrease with age, particularly in older adults, so it may be difficult to make causal conclusions due to the collinearity of the variables involved.

Previous research has examined the relationship between IQ and SG (Lijffijt et al., 2009). Still, it has not examined CR from a neural or neuropsychological point of view regarding ageing. We examined IQ, EF, and memory as measures of CR and found a relationship between inhibitory memory and verbal and visual long-term memory in SG.

8.2.6 Big Picture

The big picture presented in this passage revolves around the investigation of SG and neural inhibition in relation to CR in healthy older adults. The overarching goal was to develop an EEG and neuropsychological preoperative protocol that could be implemented efficiently during preoperative hospital visits, particularly for major abdominal oncology surgeries. The initial plan was to predict postoperative delirium and clinical outcomes based on preoperative vulnerability assessments.

However, due to unforeseen circumstances, specifically the outbreak of COVID-19, the planned patient data collection had to be halted. Consequently, the thesis predominantly relies on pilot data collected from healthy older participants. The focus shifted to examining whether

selected SG indices and neuropsychological measures could be effectively implemented using a skeleton EEG system.

Chapters 2 to 7 provide a comprehensive exploration of the background, methodology, literature review, and empirical findings. The research questions centred on linking sensory and neural processing to CR, with a specific focus on inhibitive and EF measures such as WM and planning tasks.

Results from each chapter contribute to the overall understanding of the relationships between SG, neural measures, and CR in healthy older adults. Notably, the thesis finds that EF is unrelated to SG paradigms, but inhibition is related to SG and ASSR. Moreover, a measure of EF, the subtract two-digit span, is significantly associated with peak alpha frequency.

In the big picture, the thesis emphasises the potential clinical significance of using an EEG setup with fewer electrodes and a passive listening task. This approach allows for a faster setup, reducing burden on patients, and provides insights into possible neural vulnerability before cognitive symptoms manifest. The findings suggest that measuring cognitive vulnerability, especially in older adults, is crucial in clinical settings, offering support before major healthcare events such as planned major surgery.

8.3 Limitations

There are several limitations to the experiments included, which will be discussed. The first is that small sample sizes were used in all three chapters, particularly Chapter 6. This makes the data underpowered and challenging to draw conclusions in terms of the general older

population. A sample size of 60 older participants would have been more appropriate for Chapters 5 and 6. This would have reduced the risk of us making a type 1 error from the results.

Secondly, the neuropsychological tests used in Chapters 5, 6 and 7 were not computerised and so could have been biased unconsciously by the test administrator, particularly the scoring of the BMIPB figure and story, NART and verbal fluency. These tests require some interpretation from the administrator, which may have biased the results collected from the participants. This was reduced in Chapter 7, as the NART was recorded and marked independently by two raters. Unfortunately, this method was not used in the other chapters, which reduces the consistency of the methods. Still, inconsistency across the different tests used in neuropsychology is a well-documented problem (Overton et al., 2016).

Thirdly, although we wanted to carry out a less burdensome experiment on participants using EEG and neuropsychological measures as CR, the procedure still took around 2.5 hours for participants to complete. The EEG paradigm we used did not require conscious effort from the participants as they did not have to complete any tasks whilst being measured. The neuropsychological aspect required a great deal of cognitive effort, which may have led to neural fatigue during the EEG part of the experiment (Dmitrieva & Aleksandrov, 2015), so this may have reduced SG functioning compared to how it would normally function. An improvement to solve this issue would be to reduce the time for neuropsychological assessment and to counterbalance the procedure to avoid and prevent and order effects.

Fourthly, a standardised CR was not used in the experiments. However, only 42% of the studies in the literature review (Chapter 4) used a standardised CR questionnaire (i.e., the CRIq) to determine CR; the rest used various measures of cognitive domains (e.g., EF,

memory, language) to determine CR. That is what we did here. We used a detailed range of assessments to investigate the complete picture of the participants' CR. This may have been the reason for inconsistencies in findings relating to previous research because it is a different way of measuring CR in participants.

8.3.1 Unforeseen Circumstances

Some unforeseen circumstances occurred during data collection in this PhD. We began collecting patient data in September 2019, but, unfortunately, was stopped in March 2020 because of the coronavirus pandemic. We managed to collect preoperative and postoperative data on eight patients (five complete datasets), but this was not warranted to be enough for a standalone PhD chapter. In the event of this, we reanalysed a dataset that was already collected for Chapter 7, which examined the peak alpha frequency in older adults, and I was able to link these to CR.

8.4 Future directions

Based on the current research, future investigations should include a larger sample of participants. This would give the data more power and show more variations in participants' SG, ASSR and peak alpha frequencies. A more comprehensive range of ages in healthy older adults would also make the data more useful. Then we would be able to see how the inhibition measures on the EEG change over time in adults increasing in age. This would increase the usefulness and meaning of the data.

To increase the clinical implications of the data, future experiments on SG and peak alpha should be done on patients in hospital settings in a quick setup. As far as we know, this has yet to be done. Measuring a patient's brain integrity to protect itself from sensory overload in relation to their CR could be very important in protecting patients from high-risk situations, such as planned major surgery. The setup should be more mobile and streamlined, reducing patient time and burden.

Another consideration to streamline the process would be to use the standardised CRIq (Nucci et al., 2012), as it was designed and validated for the specific purpose of being a single questionnaire to specifically measure CR in subjects. If the neuropsychological tests were replaced with the CRIq, this would further reduce the time taken to do the experiment, reducing the burden on patients in the future. It may even increase the usefulness of the research, as it would follow previous research in this area more closely in terms of materials, which would improve consistency and reliability.

8.5 Conclusions

This thesis aimed to investigate the SG and oscillatory mechanisms and the relationships with CR in healthy older adults. Results suggest that individuals with increased CR have more efficient SG abilities and have increased alpha bands, which are thought to be neural protective factors. This fits with previous research and provides a new paradigm of only using six electrodes, and participants can passively listen to sounds and watch a film of their choice. This is a low-burden method; if made portable in the future, it could be used in other clinical settings for vulnerable adults. This could support clinical populations by measuring

their cognitive vulnerability before a major healthcare event, such as planned major surgery. We preoperatively measure everything else in the body but the brain and cognitive functioning, even though these are the most traumatic results for patients. EEG is an objective measure of neural reserve and vulnerability, and it can help support unknowingly vulnerable older adults in the future.

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Appendix A

A.1 Participant Information Sheet

UNIVERSITY OF BIRMINGHAM

INFORMATION SHEET

Project title: Exploring preattention mechanisms and related neuropsychological factors in healthy subjects

You are being invited to take part in a research study carried out by researchers from the University of Birmingham. Before you decide about taking part, it is important for you to understand why the research is being done, and what it will involve. Please take some time to read the following information carefully. Please ask the researcher who gave you this sheet if there is anything that is not clear or if you would like more information.

Thank you

Researcher: Emma Staley
Supervisor: Dr Ali Mazaheri

Contact details:
Dr Ali Mazaheri
A.Mazaheri@bham.ac.uk

I would like to invite you to take part in a study that I am conducting as part of my PhD at the University of Birmingham, under the supervision of Dr Ali Mazaheri. The study has been approved by the Department of Psychology Ethics Committee.

Before you decide whether to agree to take part it is important for you to understand why the research is being done and what your participation will involve. Please read the following information carefully. Please contact me or my supervisor on the contact details shown above if there is anything that is not clear or if you would like more information.

What is the purpose of the study?

The aim of this study is to collect standardised norms for novel EEG mechanisms, and to collect neuropsychological profiles in healthy controls to allow comparison in patients suffering from postoperative delirium. Delirium is a serious complication sometimes occurring after surgery. Delirium is when a person has a rapid deterioration in their mental functioning often becoming agitated or drowsy.

You will be part of the control group, where we can compare results with patient scores. You won't have any history of neurological or psychiatric conditions.

Do I have to take part?

Your participation is voluntary and you do not have to agree to take part. You can withdraw, without giving a reason, at any time if you decide you would no longer like to take part. You can also withdraw your data by contacting either myself or my supervisor.

What will I do if I take part?

A researcher will ask you to sign a consent form.

We will then:

1. Conduct mental functioning tests which will take about 90 minutes
2. Run an EEG experiment, which will take around 45 minutes and involves watching a silent film of your choice

If you do not wish to answer questions presented, then you can withdraw from the study at any time. The EEG setup involves several electrodes placed on the scalp, and is shown in the picture below.

The skin is firstly cleansed with alcohol swabs and the EEG cap is secured on the head. A drop of electrode gel is administered at each electrode, and this assures good electrode skin conductance.

Will my data be kept confidential?

All information obtained during the study will be kept confidential and if the data is published it will not be identifiable as yours. You will be allocated an anonymous number for data collection (e.g. C_001), which will not be connected to your name or identity. Details will be kept in a locked filing cabinet in a locked office and only accessed by the researchers conducting the study.

Thank you for reading this information and considering taking part in this study.

Emma Staley
(EKS710@student.bham.ac.uk)

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A.2 Neuropsychological Test Materials

A.2.1 Verbal Fluency

Participant no. _____ Date: _____ Researcher: _____

Verbal Fluency

Words beginning with ' F'	
Words beginning with ' A'	
Words beginning with ' S'	

Participant no. _____ Date: _____ Researcher: _____

Category: Animals	
Category: Fruits	

A.2.2 National Adult Reading Test

NHS
University Hospitals Birmingham
NHS Foundation Trust

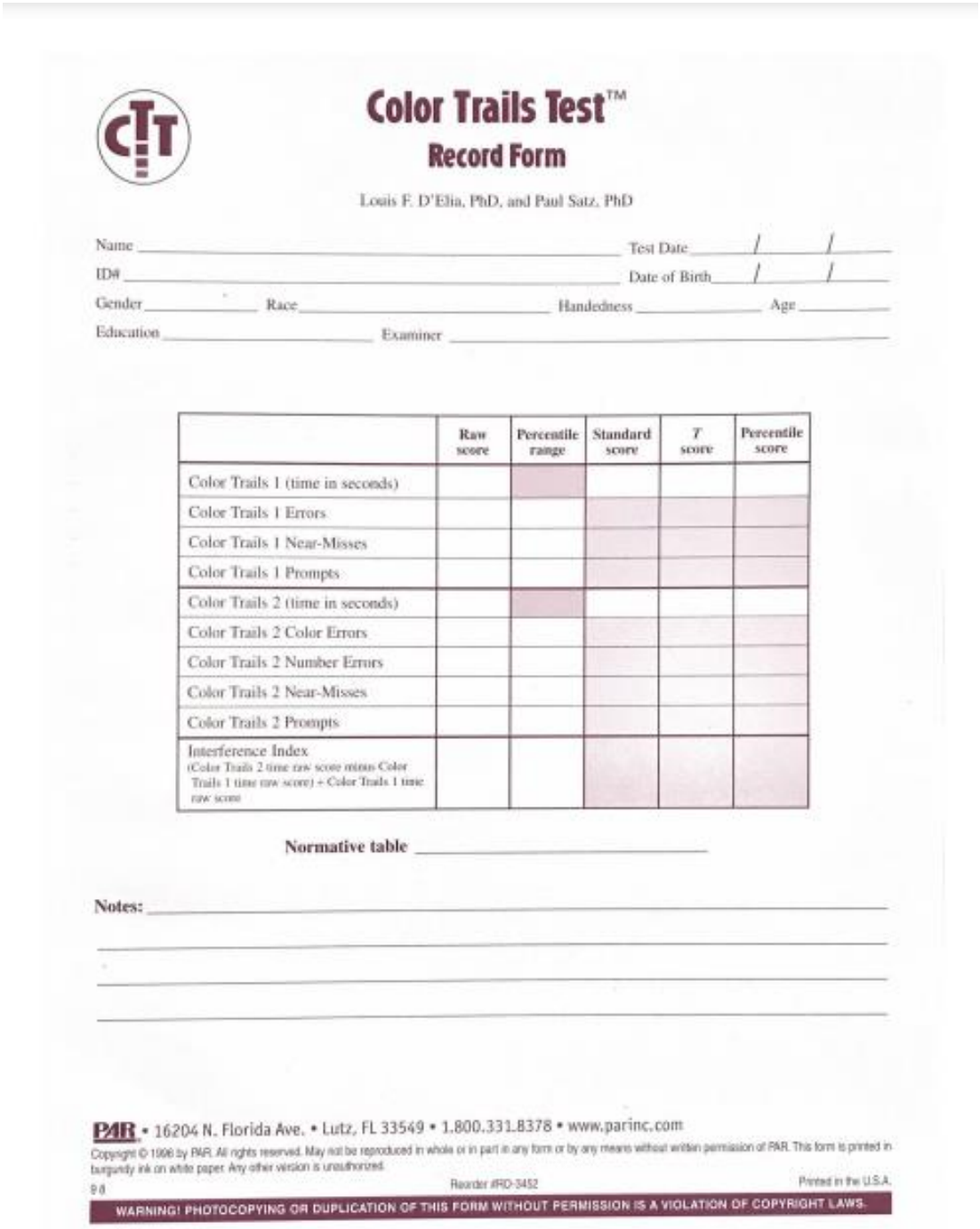
UNIVERSITY OF BIRMINGHAM | INSTITUTE OF INFLAMMATION AND AGEING

National Adult Reading Test (NART)

CHORD	SUPERFLUOUS
ACHE	SIMILE
DEPOT	BANAL
AISLE	QUADRUPED
BOUQUET	CELLIST
PSALM	FAÇADE
CAPON	ZEALOT
DENY	DRACHM
NAUSEA	AEON
DEBT	PLACEBO
COURTEOUS	ABSTEMIOUS
RAREFY	DÉTENTE
EQUIVOCAL	IDYLL
NAÏVE	PUERPERAL
CATACOMB	AVER
GAOLED	GAUCHE
THYME	TOPIARY
HEIR	LEVIATHAN
RADIX	BEATIFY
ASSIGNATE	PRELATE
HIATUS	SIDEREAL
SUBTLE	DEMESNE
PROCREATE	SYNCOPE
GIST	LABILE
GOUGE	CAMPANILE

Participant no. _____ Date: _____ Researcher: _____

A.2.3 Colour Trails Test



Color Trails Test™

Record Form

Louis F. D'Elia, PhD, and Paul Satz, PhD

Name _____ Test Date ___/___/___

ID# _____ Date of Birth ___/___/___

Gender _____ Race _____ Handedness _____ Age _____

Education _____ Examiner _____

	Raw score	Percentile range	Standard score	*T* score	Percentile score
Color Trails 1 (time in seconds)					
Color Trails 1 Errors					
Color Trails 1 Near-Misses					
Color Trails 1 Prompts					
Color Trails 2 (time in seconds)					
Color Trails 2 Color Errors					
Color Trails 2 Number Errors					
Color Trails 2 Near-Misses					
Color Trails 2 Prompts					
Interference Index (Color Trails 2 time raw score minus Color Trails 1 time raw score) ÷ Color Trails 1 time raw score					

Normative table _____

Notes: _____

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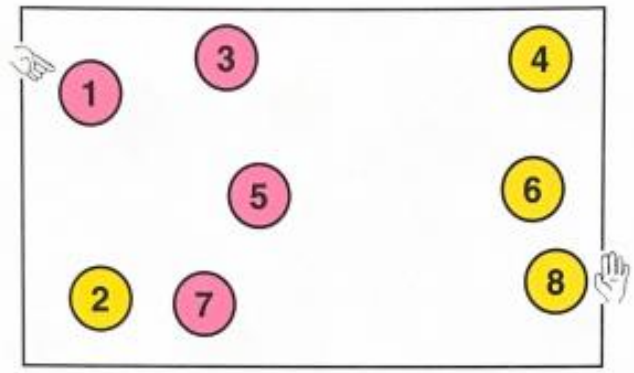
Color Trails 1

Louis F. D'Elia, PhD, and Paul Satz, PhD

Form A

Name: _____

ID#: _____ Date: _____



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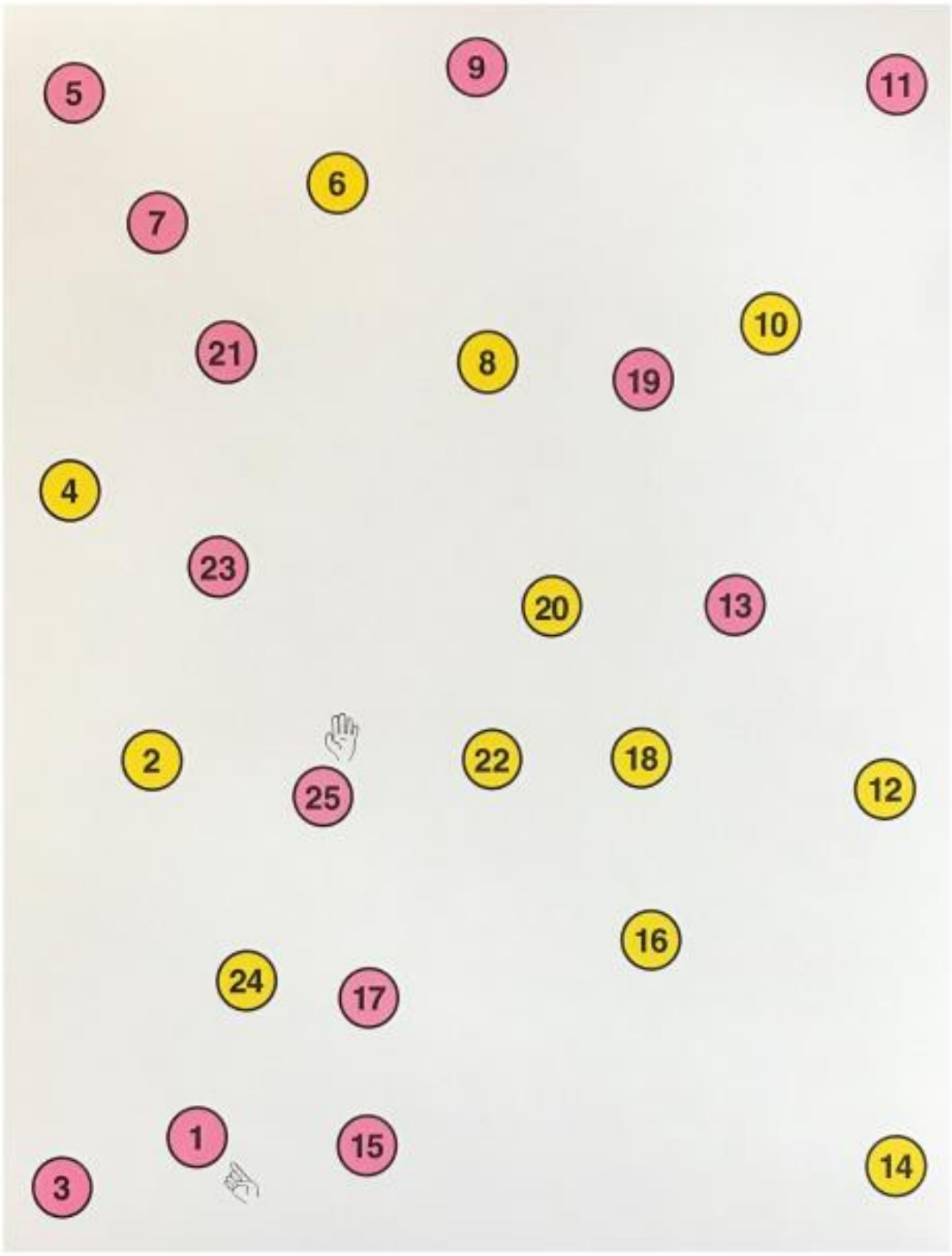
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1
15
14
3

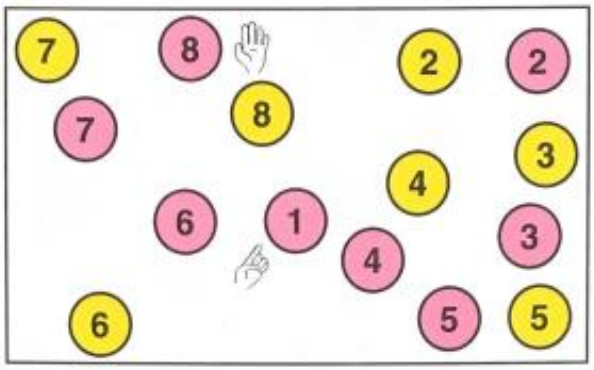
Color Trails 2

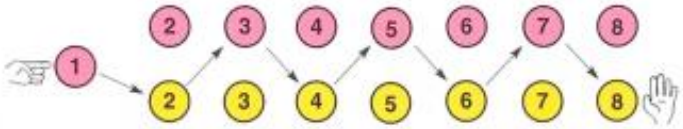
Louis F. D'Elia, PhD, and Paul Satz, PhD

Form A

Name: _____

ID#: _____ Date: _____





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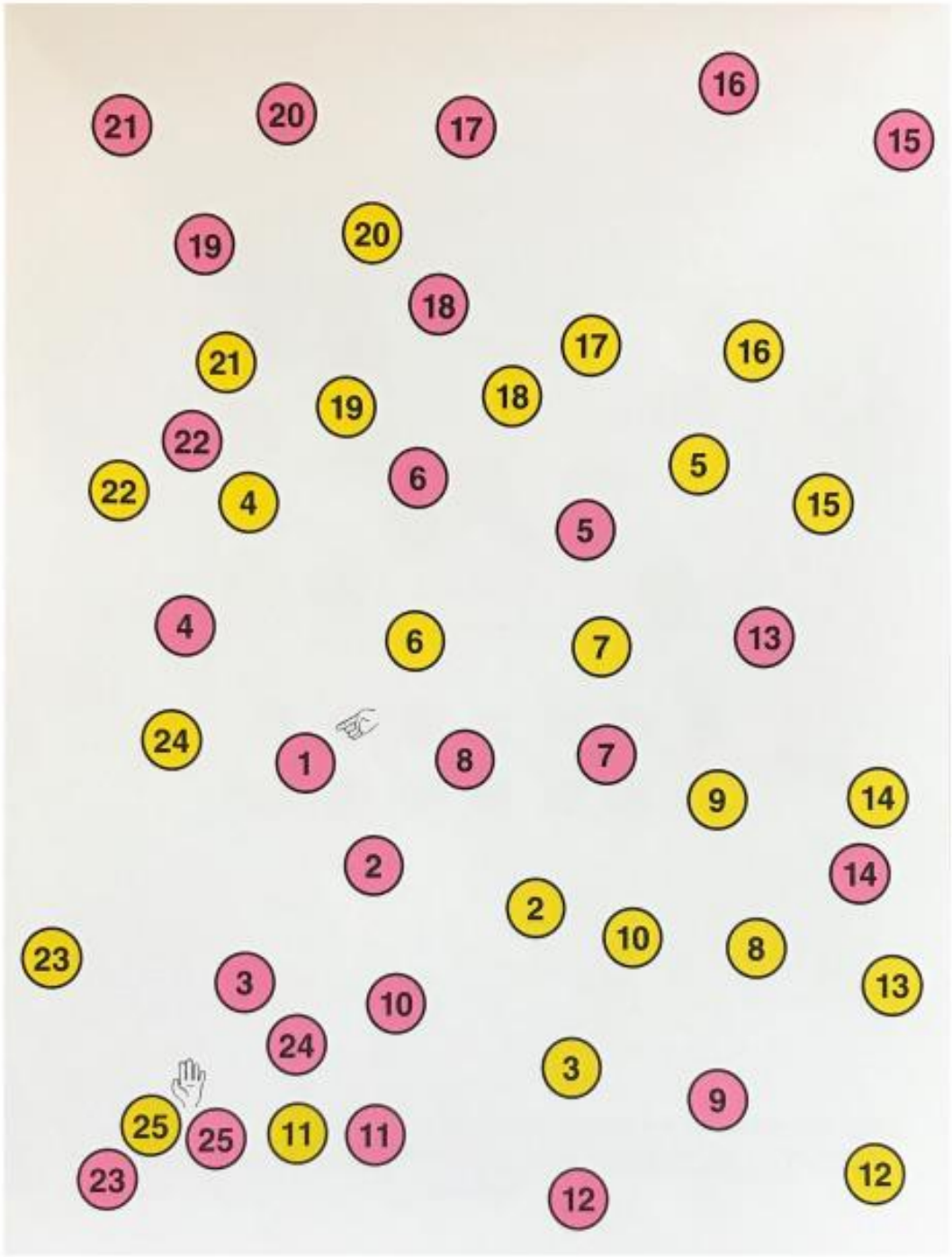
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9
14
2
14
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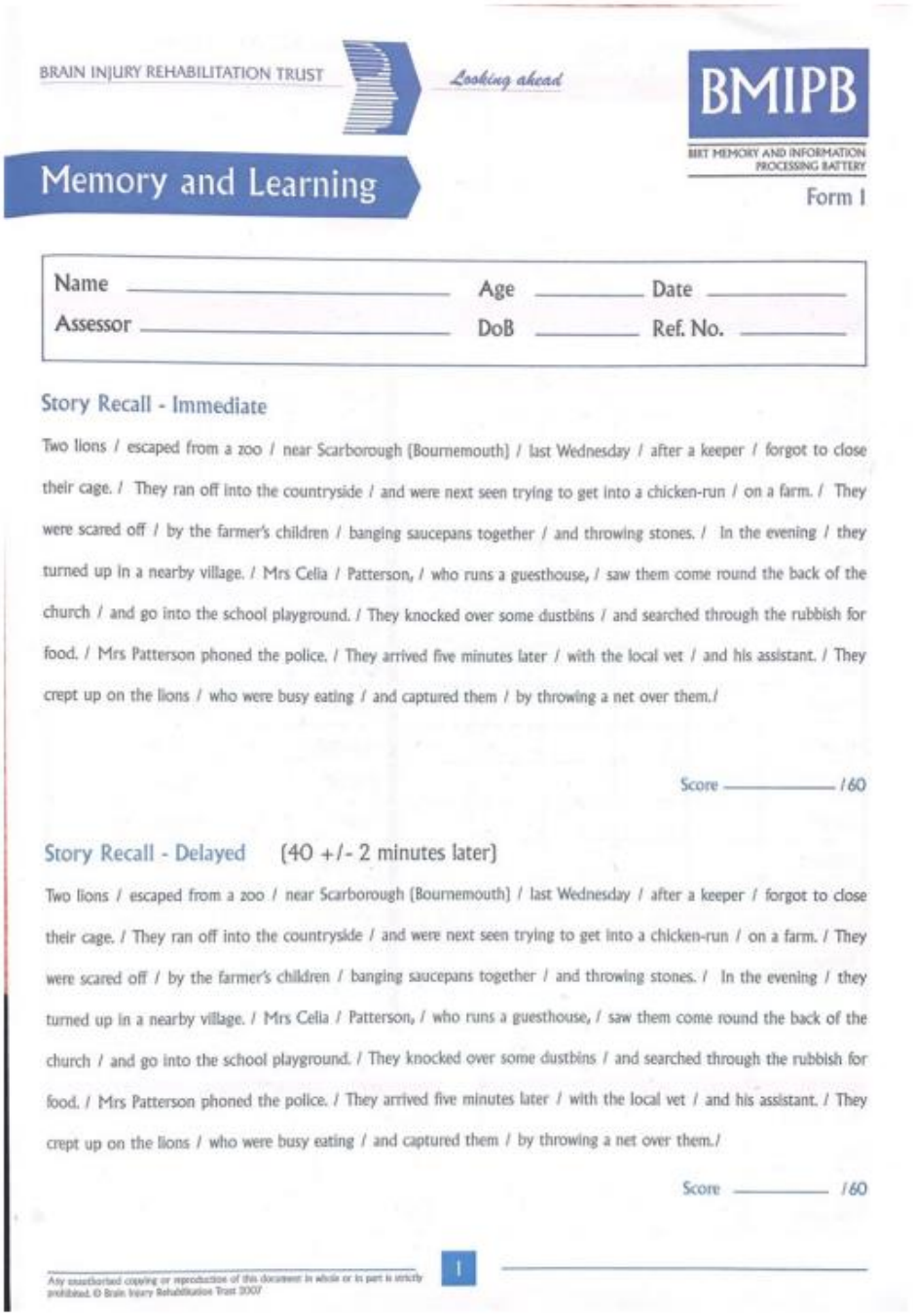
23
12
12

A.2.4 BMIPB Story



BRAIN INJURY REHABILITATION TRUST *Looking ahead*

BMIPB
BRIT MEMORY AND INFORMATION PROCESSING BATTERY

Memory and Learning

Form I

Name _____ Age _____ Date _____

Assessor _____ DoB _____ Ref. No. _____

Story Recall - Immediate

Two lions / escaped from a zoo / near Scarborough (Bournemouth) / last Wednesday / after a keeper / forgot to close their cage. / They ran off into the countryside / and were next seen trying to get into a chicken-run / on a farm. / They were scared off / by the farmer's children / banging saucepans together / and throwing stones. / In the evening / they turned up in a nearby village. / Mrs Celia / Patterson, / who runs a guesthouse, / saw them come round the back of the church / and go into the school playground. / They knocked over some dustbins / and searched through the rubbish for food. / Mrs Patterson phoned the police. / They arrived five minutes later / with the local vet / and his assistant. / They crept up on the lions / who were busy eating / and captured them / by throwing a net over them./

Score _____ /60

Story Recall - Delayed (40 +/- 2 minutes later)

Two lions / escaped from a zoo / near Scarborough (Bournemouth) / last Wednesday / after a keeper / forgot to close their cage. / They ran off into the countryside / and were next seen trying to get into a chicken-run / on a farm. / They were scared off / by the farmer's children / banging saucepans together / and throwing stones. / In the evening / they turned up in a nearby village. / Mrs Celia / Patterson, / who runs a guesthouse, / saw them come round the back of the church / and go into the school playground. / They knocked over some dustbins / and searched through the rubbish for food. / Mrs Patterson phoned the police. / They arrived five minutes later / with the local vet / and his assistant. / They crept up on the lions / who were busy eating / and captured them / by throwing a net over them./

Score _____ /60

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A.2.5 BMIPB List Learning

STORY RECALL – Form 1

	Score	Percentile Range
Immediate (I)		
Delayed (D)		
Retained% (D/I)		

FIGURE RECALL – Form 1

	Score		%	Percentile Range
Copy (C)		*	Copy% (C/80)	
Immediate (I)		*	Immediate% (I/C)	
Delayed (D)		*	Delayed% (D/C)	
Retained%			Retained% (D/I)	

*Max = 80

LIST LEARNING SCORE SHEET

	A1	A2	A3	A4	A5	A6		B	
VILLAGE						VILLAGE		DRINK	
DUST						DUST		SWING	
FROG						FROG		PLUM	
COAT						COAT		MONEY	
TICKET						TICKET		DESK	
TAXI						TAXI		RATTLE	
FRIEND						FRIEND		GIRL	
SHADOW						SHADOW		BASKET	
KETTLE						KETTLE		STAIN	
CHAIR						CHAIR		BOOK	
POWDER						POWDER		SAILOR	
STATUE						STATUE		VELVET	
OFFICE						OFFICE		MOON	
CREAM						CREAM		SHELL	
GHOST						GHOST		COTTAGE	
Score									
Intrusions									

LIST LEARNING – Form 1

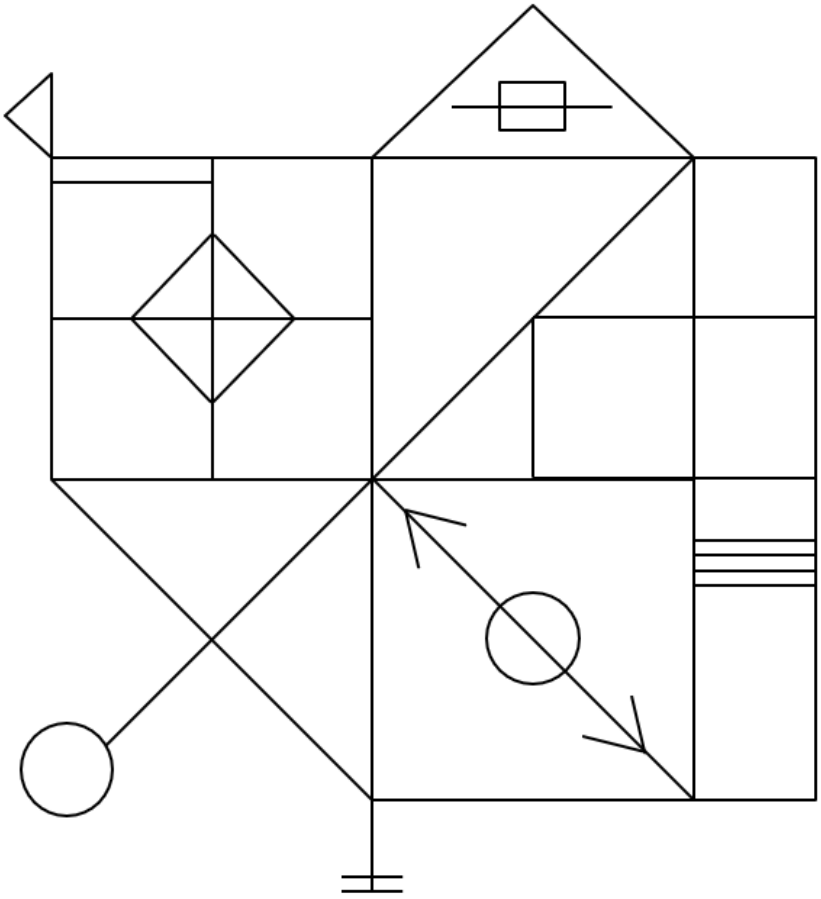
	Score	Percentile Range
Total A1-A5		
A6		
B		
Intrusions		

DESIGN LEARNING – Form 1

	Score	Percentile Range
Total A1-A5		
A6		
B		
Intrusions		

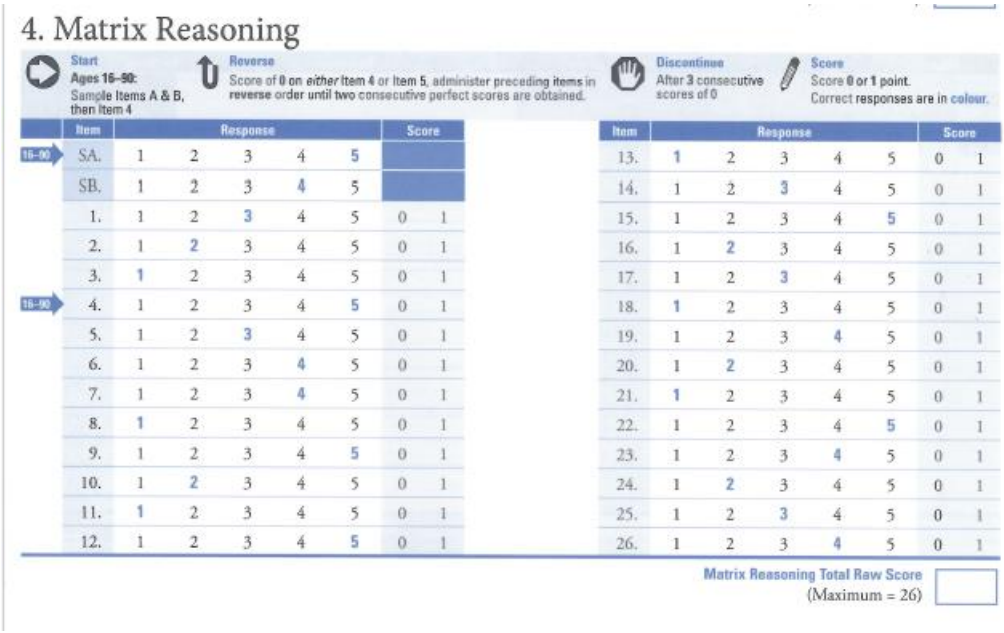
2

A.2.6 BMIPB Figure



A.2.7 WAIS-IV Matrix Reasoning

A.2.7.1 Report Form



4. Matrix Reasoning

Start
Ages 16–90:
Sample Items A & B, then Item 4

Reverse
Score of 0 on *either* Item 4 or Item 5, administer preceding items in reverse order until two consecutive perfect scores are obtained.

Discontinue
After 3 consecutive scores of 0

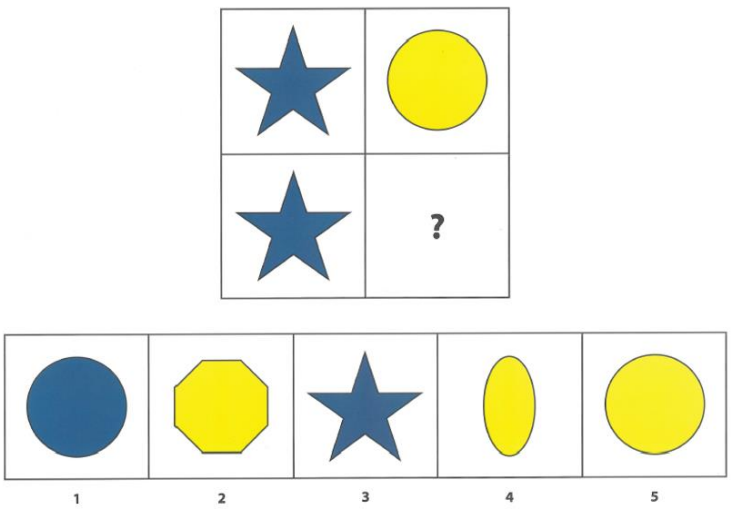
Score
Score 0 or 1 point.
Correct responses are in colour.

	Item	Response					Score	
16–90	SA.	1	2	3	4	5		
	SB.	1	2	3	4	5		
	1.	1	2	3	4	5	0	1
	2.	1	2	3	4	5	0	1
	3.	1	2	3	4	5	0	1
16–90	4.	1	2	3	4	5	0	1
	5.	1	2	3	4	5	0	1
	6.	1	2	3	4	5	0	1
	7.	1	2	3	4	5	0	1
	8.	1	2	3	4	5	0	1
	9.	1	2	3	4	5	0	1
	10.	1	2	3	4	5	0	1
	11.	1	2	3	4	5	0	1
	12.	1	2	3	4	5	0	1

Item	Response					Score	
13.	1	2	3	4	5	0	1
14.	1	2	3	4	5	0	1
15.	1	2	3	4	5	0	1
16.	1	2	3	4	5	0	1
17.	1	2	3	4	5	0	1
18.	1	2	3	4	5	0	1
19.	1	2	3	4	5	0	1
20.	1	2	3	4	5	0	1
21.	1	2	3	4	5	0	1
22.	1	2	3	4	5	0	1
23.	1	2	3	4	5	0	1
24.	1	2	3	4	5	0	1
25.	1	2	3	4	5	0	1
26.	1	2	3	4	5	0	1

Matrix Reasoning Total Raw Score
(Maximum = 26)

A.2.7.2 Example Stimulus



A.2.8 Hospital Anxiety and Depression Scale

NHS
University Hospitals Birmingham
NHS Foundation Trust

UNIVERSITY OF BIRMINGHAM | INSTITUTE OF INFLAMMATION AND AGEING

Hospital Anxiety and Depression Scale (HADS)

Clinicians are aware that emotions play an important part in most illnesses. If your clinician knows about these feelings he or she will be able to help you more.

This questionnaire is designed to help your clinician to know how you feel. Read each item below and underline the reply which comes closest to how you have been feeling in the past week. Ignore the numbers printed at the edge of the questionnaire.

Don't take too long over your replies; your immediate reaction to each item will probably be more accurate than a long, thought-out response.

A	D		A	D
		I feel tense or 'wound up'		
3		Most of the time		
2		A lot of the time		
1		From time to time, occasionally		
0		Not at all		
		I still enjoy the things I used to enjoy		
	0	Definitely as much		
	1	Not quite so much		
	2	Only a little		
	3	Hardly at all		
		I get a sort of frightened feeling as if something awful is about to happen		
3		Very definitely and quite badly		
2		Yes, but not too badly		
1		A little, but it doesn't worry me		
0		Not at all		
		I can laugh and see the funny side of things		
	0	As much as I always could		
	1	Not quite so much now		
	2	Definitely not so much now		
	3	Not at all		
		Worrying thoughts go through my mind		
3		A great deal of the time		
2		A lot of the time		
1		Not too often		
0		Very little		
		I feel cheerful		
	3	Never		
	2	Not often		
	1	Sometimes		
	0	Most of the time		
		I can sit at ease and feel relaxed		
0		Definitely		
1		Usually		
2		Not often		
3		Not at all		
		I feel as if I am slowed down		
		Nearly all the time		3
		Very often		2
		Sometimes		1
		Not at all		0
		I get a sort of frightened feeling like 'butterflies' in the stomach		
		Not at all	0	
		Occasionally	1	
		Quite often	2	
		Very often	3	
		I have lost interest in my appearance		
		Definitely		3
		I don't care as much as I should		2
		I may not take quite as much care		1
		I take just as much care as ever		0
		I feel restless as if I have to be on the move		
		Very much indeed	3	
		Quite a lot	2	
		Not very much	1	
		Not at all	0	
		I look forward with enjoyment to things		
		As much as I ever did		0
		Rather less than I used to		1
		Definitely less than I used to		2
		Hardly at all		3
		I get sudden feelings of panic		
		Very often indeed	3	
		Quite often	2	
		Not very often	1	
		Not at all	0	
		I can enjoy a good book or radio or television programme		
		Often		0
		Sometimes		1
		Not often		2
		Very seldom		3

Participant no. _____ Date: _____ Researcher: _____

A.2.9 Cognitive Failures Questionnaire

NHS
University Hospitals Birmingham
NHS Foundation Trust

UNIVERSITY OF BIRMINGHAM | INSTITUTE OF INFLAMMATION AND AGEING

Cognitive Failures Questionnaire (CFQ)

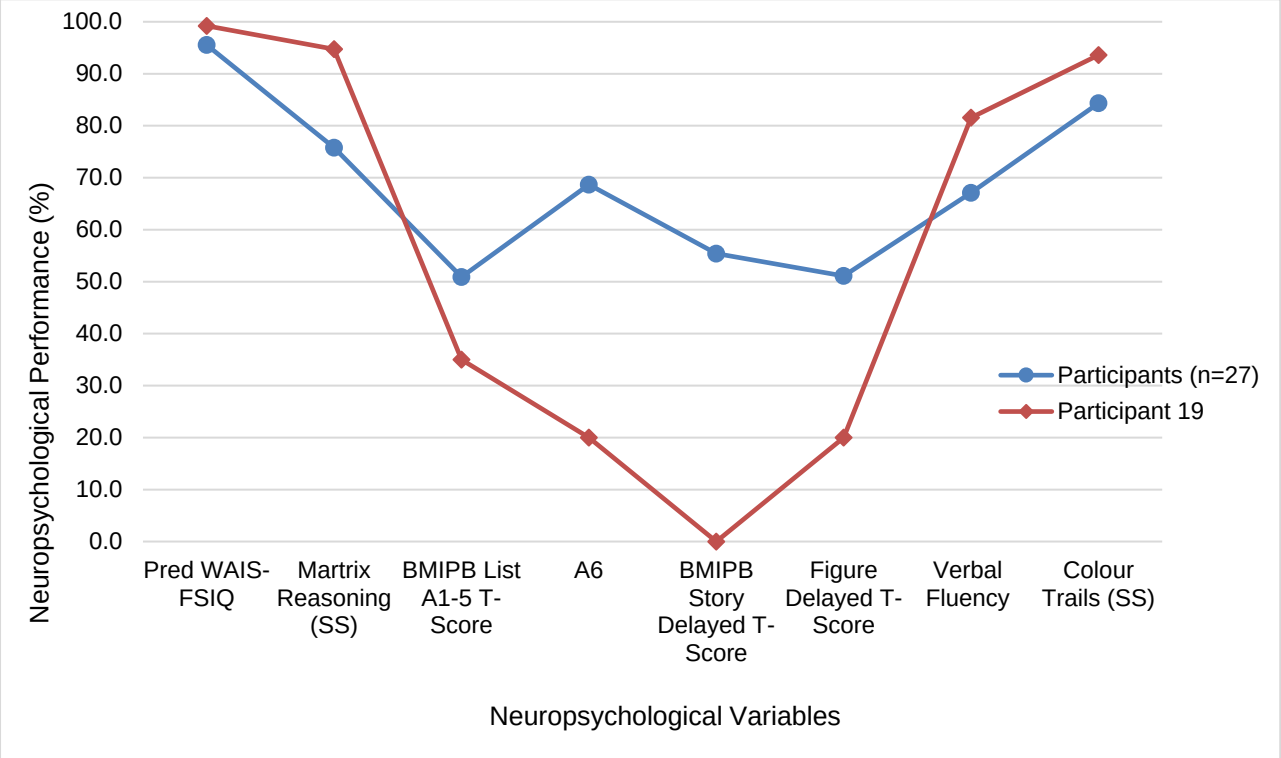
		Very often	Quite often	Occasionally	Very rarely	Never
1	Do you read something and find you haven't been thinking about it, and must read it again?	4	3	2	1	0
2	Do you find you forget why you went from one part of the house to the other?	4	3	2	1	0
3	Do you fail to notice signposts on the road?	4	3	2	1	0
4	Do you find you confuse right and left when giving directions?	4	3	2	1	0
5	Do you bump into people?	4	3	2	1	0
6	Do you find you forget whether you've turned off a light, or a fire, or locked the door?	4	3	2	1	0
7	Do you fail to listen to people's names when you are meeting them?	4	3	2	1	0
8	Do you say something and realise afterwards that it might be taken as insulting?	4	3	2	1	0
9	Do you fail to hear people speaking to you when you are doing something else?	4	3	2	1	0
10	Do you lose your temper and regret it?	4	3	2	1	0
11	Do you leave important letters unanswered for days?	4	3	2	1	0
12	Do you find you forget which way to turn on a road you know well but rarely use?	4	3	2	1	0
13	Do you fail to see what you want in a supermarket (although it's there)?	4	3	2	1	0
14	Do you find yourself suddenly wondering whether you've used a word correctly?	4	3	2	1	0
15	Do you have trouble making up your mind?	4	3	2	1	0
16	Do you find you forget appointments?	4	3	2	1	0
17	Do you forget where you put something like a newspaper or a book?	4	3	2	1	0
18	Do you find you accidentally throw away the thing you want, and keep what you meant to throw away?	4	3	2	1	0
19	Do you daydream when you ought to be listening to something?	4	3	2	1	0
20	Do you find you forget people's names?	4	3	2	1	0
21	Do you start doing one thing at home and get distracted into doing something else (unintentionally)?	4	3	2	1	0
22	Do you find you can't quite remember something, although it's on the 'tip of your tongue'?	4	3	2	1	0
23	Do you find you forget what you came to the shops to buy?	4	3	2	1	0
24	Do you drop things?	4	3	2	1	0
25	Do you find you can't think of anything to say?	4	3	2	1	0

Participant no. _____ Date: _____ Researcher: _____

A.3 Participant 19's Cognitive Profile

Participant 19 was excluded from the analysis of the results in Chapters 5 and 6, as they were suspected of having a cognitive profile indicative of MCI. Their complete cognitive profile is shown below in Figure A.1 Figure A.1 shows that participant 19's cognitive profile reflects MCI.

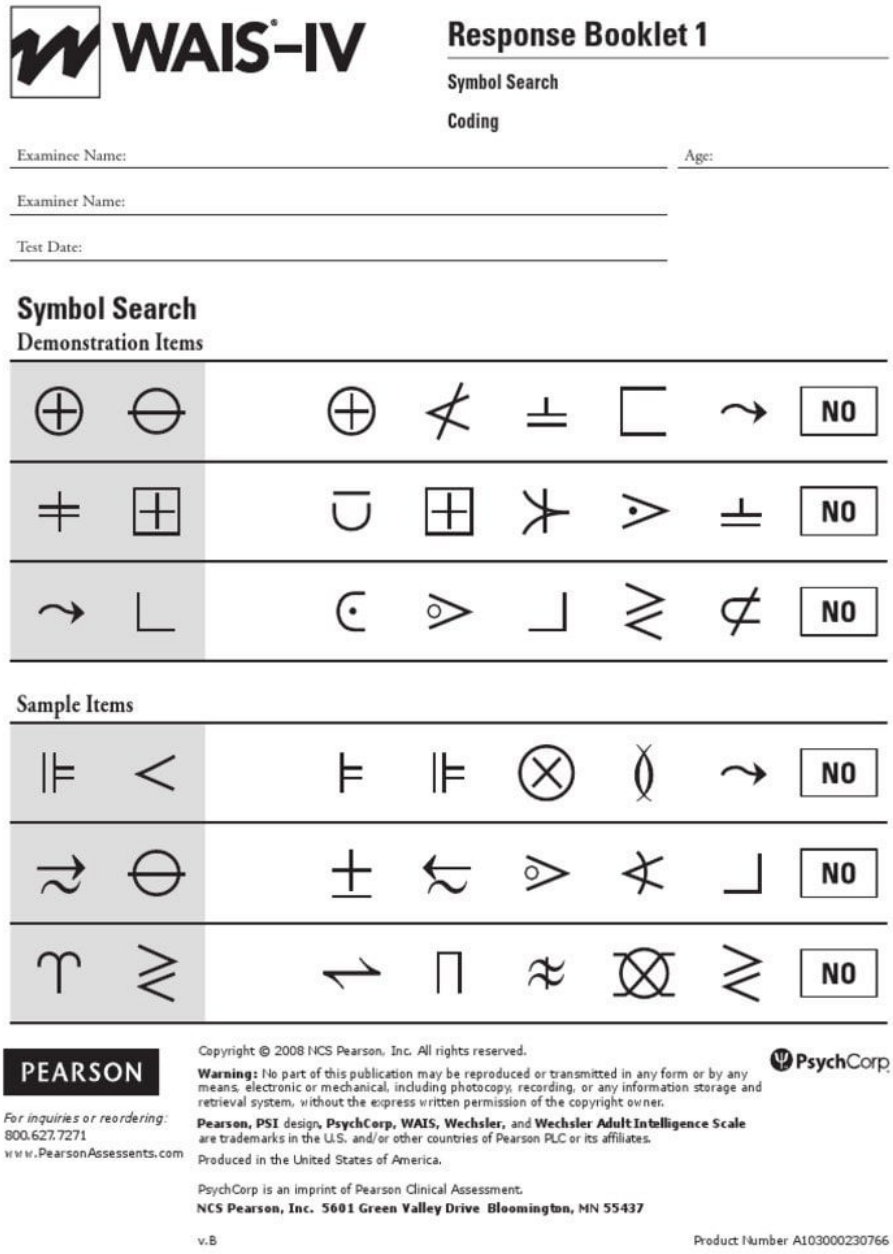
Figure A.1 Participant 19's neuropsychological profile compared with the average results of other participants.



Note. Percentages were made of participants' results divided by the biggest possible test score to allow for test comparison on the same axes. SS, Scaled Score.

A.4 Chapter 7 Additional Tests

A.4.1 WAIS-IV Symbol Search



WAIS®–IV

Response Booklet 1

Symbol Search

Coding

Examinee Name: Age:

Examiner Name:

Test Date:

Symbol Search

Demonstration Items

Sample Items

PEARSON

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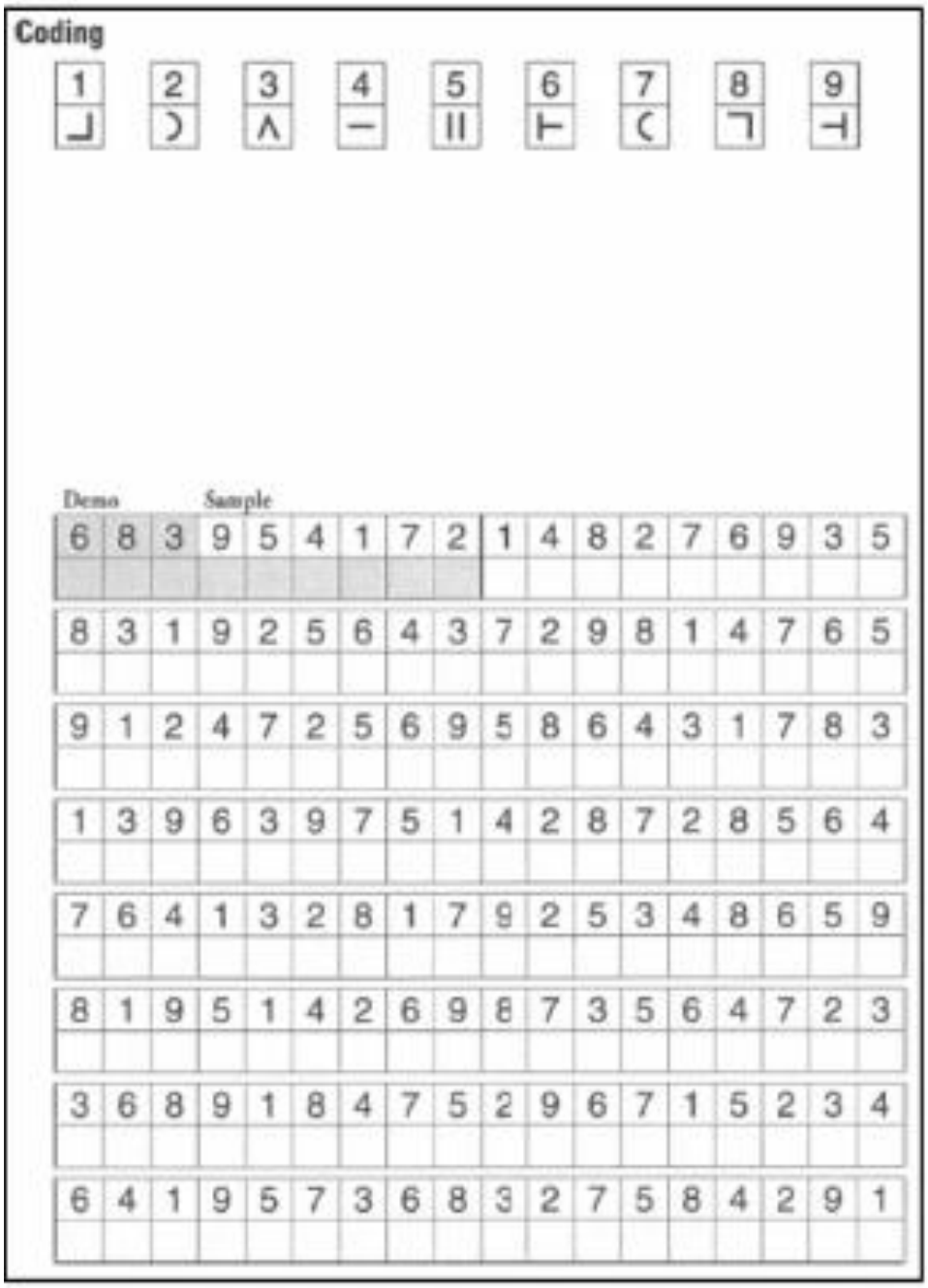
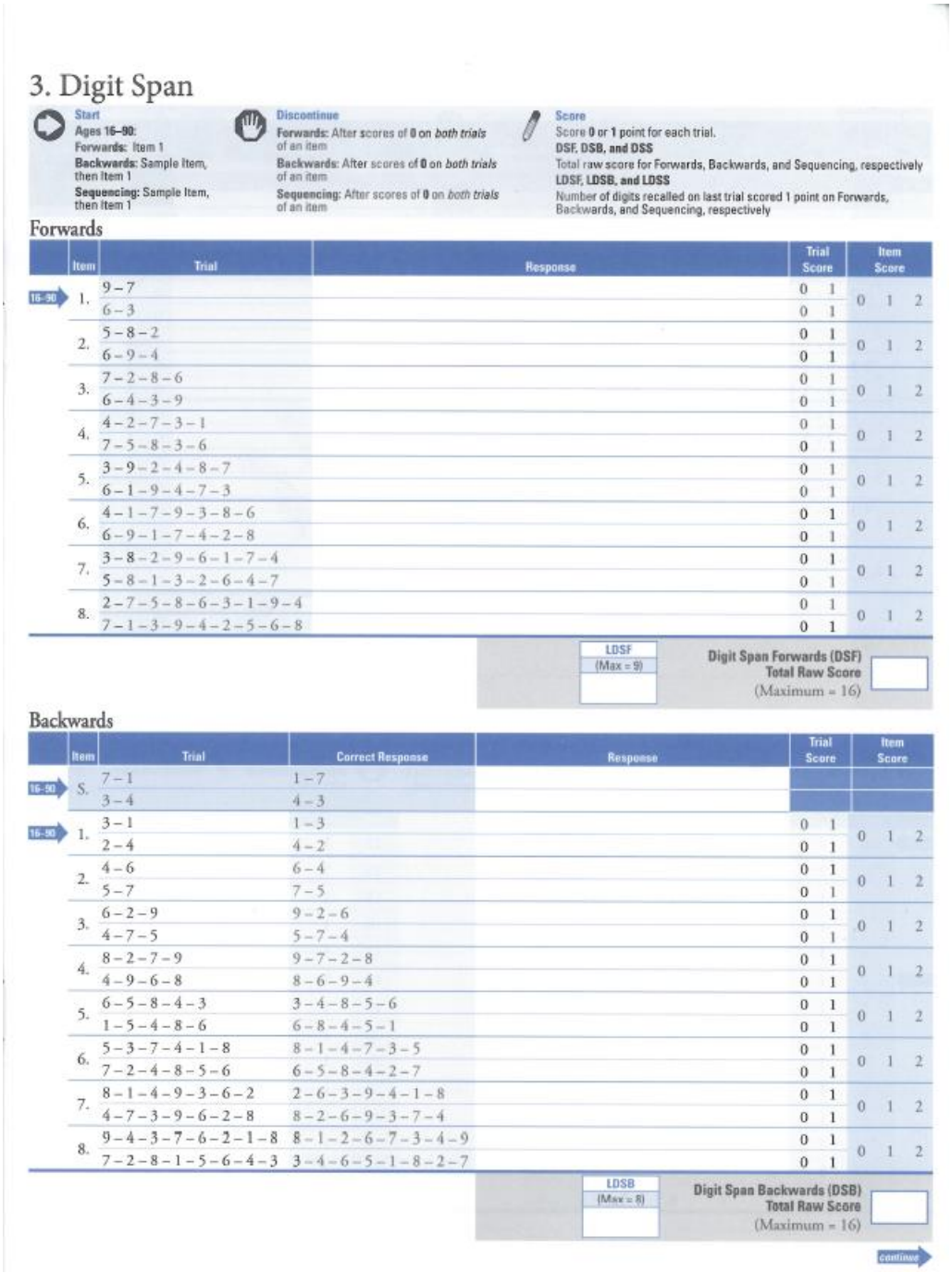
A.4.2 WAIS-IV Coding



A.4.3 WAIS-IV Digit Span



3. Digit Span

Start
Ages 16–90:
Forwards: Item 1
Backwards: Sample Item, then Item 1
Sequencing: Sample Item, then Item 1

Discontinue
Forwards: After scores of **0** on *both trials* of an item
Backwards: After scores of **0** on *both trials* of an item
Sequencing: After scores of **0** on *both trials* of an item

Score
Score **0** or **1** point for each trial.
DSF, DSB, and DSS
Total raw score for Forwards, Backwards, and Sequencing, respectively
LDSF, LDSB, and LDSS
Number of digits recalled on last trial scored 1 point on Forwards, Backwards, and Sequencing, respectively

Forwards

	Item	Trial	Response	Trial Score	Item Score
16–90	1.	9 – 7		0 1	0 1 2
		6 – 3		0 1	
	2.	5 – 8 – 2		0 1	0 1 2
		6 – 9 – 4		0 1	
	3.	7 – 2 – 8 – 6		0 1	0 1 2
		6 – 4 – 3 – 9		0 1	
	4.	4 – 2 – 7 – 3 – 1		0 1	0 1 2
		7 – 5 – 8 – 3 – 6		0 1	
	5.	3 – 9 – 2 – 4 – 8 – 7		0 1	0 1 2
		6 – 1 – 9 – 4 – 7 – 3		0 1	
	6.	4 – 1 – 7 – 9 – 3 – 8 – 6		0 1	0 1 2
		6 – 9 – 1 – 7 – 4 – 2 – 8		0 1	
	7.	3 – 8 – 2 – 9 – 6 – 1 – 7 – 4		0 1	0 1 2
		5 – 8 – 1 – 3 – 2 – 6 – 4 – 7		0 1	
	8.	2 – 7 – 5 – 8 – 6 – 3 – 1 – 9 – 4		0 1	0 1 2
		7 – 1 – 3 – 9 – 4 – 2 – 5 – 6 – 8		0 1	

LDSF (Max = 9)

Digit Span Forwards (DSF) Total Raw Score (Maximum = 16)

Backwards

	Item	Trial	Correct Response	Response	Trial Score	Item Score
16–90	S.	7 – 1	1 – 7			
		3 – 4	4 – 3			
16–90	1.	3 – 1	1 – 3		0 1	0 1 2
		2 – 4	4 – 2		0 1	
	2.	4 – 6	6 – 4		0 1	0 1 2
		5 – 7	7 – 5		0 1	
	3.	6 – 2 – 9	9 – 2 – 6		0 1	0 1 2
		4 – 7 – 5	5 – 7 – 4		0 1	
	4.	8 – 2 – 7 – 9	9 – 7 – 2 – 8		0 1	0 1 2
		4 – 9 – 6 – 8	8 – 6 – 9 – 4		0 1	
	5.	6 – 5 – 8 – 4 – 3	3 – 4 – 8 – 5 – 6		0 1	0 1 2
		1 – 5 – 4 – 8 – 6	6 – 8 – 4 – 5 – 1		0 1	
	6.	5 – 3 – 7 – 4 – 1 – 8	8 – 1 – 4 – 7 – 3 – 5		0 1	0 1 2
		7 – 2 – 4 – 8 – 5 – 6	6 – 5 – 8 – 4 – 2 – 7		0 1	
	7.	8 – 1 – 4 – 9 – 3 – 6 – 2	2 – 6 – 3 – 9 – 4 – 1 – 8		0 1	0 1 2
		4 – 7 – 3 – 9 – 6 – 2 – 8	8 – 2 – 6 – 9 – 3 – 7 – 4		0 1	
	8.	9 – 4 – 3 – 7 – 6 – 2 – 1 – 8	8 – 1 – 2 – 6 – 7 – 3 – 4 – 9		0 1	0 1 2
		7 – 2 – 8 – 1 – 5 – 6 – 4 – 3	3 – 4 – 6 – 5 – 1 – 8 – 2 – 7		0 1	

LDSB (Max = 8)

Digit Span Backwards (DSB) Total Raw Score (Maximum = 16)

continue

3. Digit Span *(continued)*

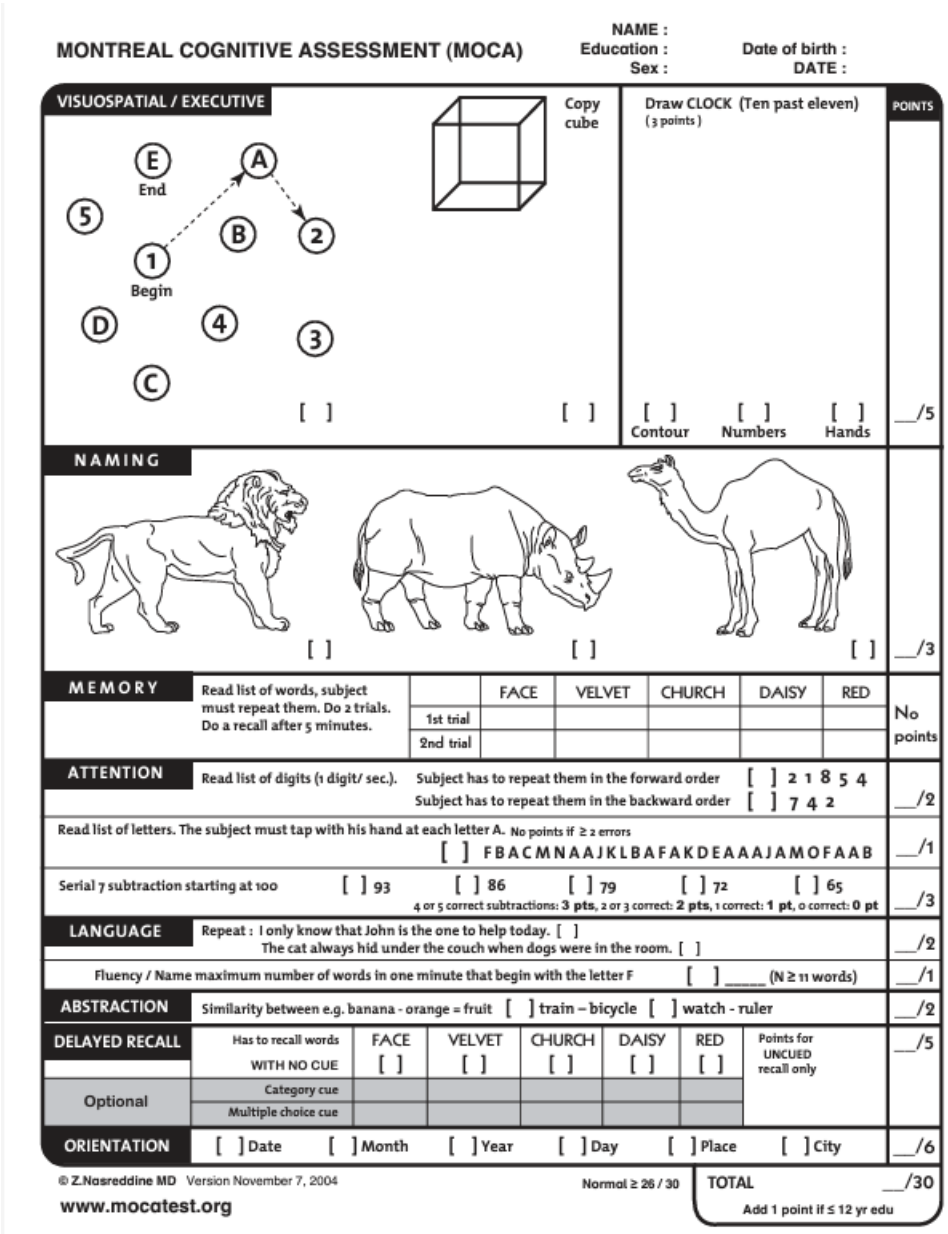
Sequencing

Discontinue after scores of 0 on *both trials* of an item.

	Item	Trial	Correct Response	Response	Trial Score	Item Score
16–90	S.	2 – 3 – 1	1 – 2 – 3			
		5 – 2 – 2	2 – 2 – 5			
16–90	1.	1 – 2	1 – 2		0 1	0 1 2
		4 – 2	2 – 4		0 1	
	2.	3 – 1 – 6	1 – 3 – 6		0 1	0 1 2
		0 – 9 – 4	0 – 4 – 9		0 1	
	3.	8 – 7 – 9 – 2	2 – 7 – 8 – 9		0 1	0 1 2
		4 – 8 – 7 – 1	1 – 4 – 7 – 8		0 1	
	4.	2 – 6 – 9 – 1 – 7	1 – 2 – 6 – 7 – 9		0 1	0 1 2
		3 – 8 – 3 – 5 – 8	3 – 3 – 5 – 8 – 8		0 1	
	5.	2 – 1 – 7 – 4 – 3 – 6	1 – 2 – 3 – 4 – 6 – 7		0 1	0 1 2
		6 – 2 – 5 – 2 – 3 – 4	2 – 2 – 3 – 4 – 5 – 6		0 1	
	6.	7 – 5 – 7 – 6 – 8 – 6 – 2	2 – 5 – 6 – 6 – 7 – 7 – 8		0 1	0 1 2
		4 – 8 – 2 – 5 – 4 – 3 – 5	2 – 3 – 4 – 4 – 5 – 5 – 8		0 1	
	7.	5 – 8 – 7 – 2 – 7 – 5 – 4 – 5	2 – 4 – 5 – 5 – 5 – 7 – 7 – 8		0 1	0 1 2
		9 – 4 – 9 – 7 – 3 – 0 – 8 – 4	0 – 3 – 4 – 4 – 7 – 8 – 9 – 9		0 1	
	8.	5 – 0 – 1 – 1 – 3 – 2 – 1 – 0 – 5	0 – 0 – 1 – 1 – 1 – 2 – 3 – 5 – 5		0 1	0 1 2
		2 – 7 – 1 – 4 – 8 – 4 – 2 – 9 – 6	1 – 2 – 2 – 4 – 4 – 6 – 7 – 8 – 9		0 1	

LDSS (Max = 9)	Digit Span Sequencing (DSS) Total Raw Score (Maximum = 16)	
	Digit Span Total Raw Score (Maximum = 48)	

A.4.4 Montreal Cognitive Assessment (MoCA)



MONTREAL COGNITIVE ASSESSMENT (MOCA)

NAME :
Education :
Sex :
Date of birth :
DATE :

VISUOSPATIAL / EXECUTIVE — POINTS

Copy cube

[ ] [ ]

Draw CLOCK (Ten past eleven) (3 points)

[ ] Contour [ ] Numbers [ ] Hands

__/5

NAMING

[ ] [ ] [ ]

__/3

MEMORY — Read list of words, subject must repeat them. Do 2 trials. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION — Read list of digits (1 digit/ sec.).

Subject has to repeat them in the forward order [ ] 2 1 8 5 4

Subject has to repeat them in the backward order [ ] 7 4 2

__/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

__/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**

__/3

LANGUAGE — Repeat : I only know that John is the one to help today. [ ]

The cat always hid under the couch when dogs were in the room. [ ]

__/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words)

__/1

ABSTRACTION — Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler

__/2

DELAYED RECALL

	Has to recall words WITH NO CUE	FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [ ]	Points for UNCUED recall only
Optional	Category cue						
	Multiple choice cue						

__/5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City

__/6

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Normal ≥ 26 / 30

TOTAL __/30

Add 1 point if ≤ 12 yr edu