Neurocognitive and Electrophysiological Indices of Cognitive Performance in Ageing.

By

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A dissertation submitted for the degree of Doctor of Philosophy of the University of Dublin, Trinity College, Dublin 2, Ireland.

2011

DECLARATION

I declare that this thesis has not been submitted as an exercise for a degree at this or any other University. This thesis is entirely my own work. Trinity College library may lend or copy this thesis upon request.

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SUMMARY

Combining neuropsychological and electrophysiological methodologies this thesis investigates differential cognitive performance in ageing and attempts to identify neurocognitive and electrophysiological markers with the capacity to distinguish between age groups (young, old) and/or cognitive performance groups (old High performers, old Low performers). Chapter 1 introduces cognitive ageing, theoretical perspectives, markers of cognitive decline, and associated research issues. Chapter 2 describes the participant classification approach and behavioural testing methods, and presents results from neuropsychological assessment and experimental tasks. The older adults were assigned to sub-groups, and classified as High- or Low performers based on their memory performance relative to an estimate of their pre-morbid IQ. Significant age differences are evident across measures of executive function, memory and processing speed. In contrast, High performers are only distinguished from Low performers on measures of memory. Chapter 3 examines reaction time (RT) latency and intra-individual variability on tasks that assess cognitive and motor processing speed, attention, and memory. RT latency distinguishes age groups on processing speed and memory measures but not on a task that measures sustained attention. Variability measures distinguished groups on the basis of age and cognitive performance. The electroencephalogram (EEG) was used to assess cortical activity while participants rested and while they encoded and retrieved words during an experimental episodic memory task. Chapter 4 describes the EEG, Event-Related Potentials (ERPs) and the techniques employed for acquisition and analysis. Chapter 5 presents results from spectral analysis of the EEG and shows that resting alpha power distinguishes participants on the basis of age and cognitive performance. In Chapter 6 putative ERP modulations of familiarity, recollection, and post retrieval monitoring, are analysed. Significant age differences are reported for familiarity and recollection effects. In addition, Low performers demonstrate a different pattern of event-related neural activity associated with recognition than the High performers and the Young controls when ERP waveforms are analysed according to the type of encoding irrespective of response accuracy. A detailed analysis of the ERP activity recorded during the encoding phase of a novel experimental episodic memory task is presented in Chapter 7. Clear age differences are evident and during the task High performers demonstrate a pattern of neural activity that is qualitatively different from the pattern observed in the Young. In contrast, the Low performers engage in a similar, but attenuated, pattern as the Young. A general discussion of these findings is presented in Chapter 8.

Dedication

This thesis is dedicated to my dad. He was embarrassingly proud of my academic achievement and excited at the prospect of my PhD, unfortunately, he passed away a few months after I began my research. I miss you terribly dad. I know that you would have read every word.

Patrick O'Reilly

R.I.P

1st July 2008

Acknowledgements

First and foremost, sincere thanks must go to my supervisor, Professor Ian Robertson, not only for his advice, encouragement, support, and optimism, but also for allowing me the freedom to work at my own pace in my own way. I would like to express eternal gratitude to Paul Dockree for freely sharing his knowledge and his time with me. His advice was invaluable and his incredible patience and meticulous attention to detail inspiring. I would also like to thank the members of Ian's lab for their support and friendship. Laura McAvinue and Redmond O'Connell deserve special mention for answering many questions over the last three years. I also want to thank the girls in Room 3.08 who made coming into the office a pleasure and procrastination far too easy.

This research would not have been possible without participants or funding. I would like to say a heartfelt thank-you to all of my participants, particularly the older adults, their desire to make a selfless contribution to science and society was admirable. I would also like to thank the Irish Research Council for Science Engineering and Technology for funding this research through the Embark Initiative postgraduate scholarship scheme. Gratitude must also be extended to the TCIN/GSK Research Consortium on Neurodegeneration, being part of this team benefitted my research immeasurably.

Finally, I want to thank my family for their love, support, patience, and understanding. My brother John deserves a special mention for his ongoing encouragement and proofreading. I extend a huge thank-you to my husband, David, for everything, but most of all, for loving me. Doing a thesis is tough but somehow I suspect that being married to someone doing a thesis is tougher. To my sons, Darren and Gavin, you are my inspiration and my life, without you there is no meaning.

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List of Abbreviations

AAMI	Age Associated Memory Impairment
AD	Alzheimer's Disease
ADHD	Attention Deficit Hyperactivity Disorder
aMCI	amnestic Mild Cognitive Impairment
ANOVA	Analysis of Variance
APOE	Apolipoprotein E
BESA	Brain Electronic Source Analysis
CIND	Cognitive Impairment No Dementia
CNS	Central Nervous System
CR	Cognitive Reserve
CRs	Correctly Rejected items
CRTsr	Choice Reaction Time Task split response
CV	Coefficient of Variance
DTI	Diffusion Tensor Imaging
EEG	Electroencephalogram
EMG	Electromyogram
EOG	Electrooculograph
ERP	Event Related Potential
FLH	Frontal Lobe Hypothesis
GDS	Global Deterioration Score
HADS	Hospital Anxiety and Depression Scale
HAROLD	Hemisphere Asymmetry Reduction in Older Adults
IAF	Individual Alpha Frequency
IFB	Individual Frequency Band
ISD	Individual Standard Deviation
ISI	Inter-stimulus Interval
LE	Late Effect
LH	Left Hemisphere
LPC	Late Positive Component
MCI	Mild Cognitive Impairment
MEQ	Morning-Evening Questionnaire
MMSE	Mini Mental State Exam
ms	Millisecond
MTL	Medial Temporal Lobe
NART	National Adult Reading Test
PFC	Prefrontal Cortex

RH	Right Hemisphere
RT	Reaction Time/Response Time
SART$_{fixed}$	Sustained Attention to Response Task fixed
SD	Standard Deviation
SFB	Standard Frequency Band
SNR	Signal to Noise Ratio
SMS	Subsequent Memory Effect
SOP	Standard Operating Procedure
TBI	Traumatic Brain Injury
VEP	Visual Evoked Potential
WMS	Wechsler Memory Scale
WRAT	Wide Range Achievement Test

Chapter 1 **GENERAL INTRODUCTION**

"It's not how old you are, but how you are old"

- Maria Dressler

Cognitive decline has emerged as one of the greatest health threats of senescence (e.g. Bishop, Lu, & Yankner, 2010). Failing mental function is the single biggest obstacle to the social and economic integration of older people. Cognitive impairment that does not reach the threshold for dementia diagnosis is not only associated with increased risk for progression to dementia (Edland, Rocca, Petersen, Cha, & Kokmen, 2002; Petersen, 2004; Petersen et al., 2001), but also increased health care costs (Albert, Glied, Andrews, Stern, & Mayeux, 2002; Ernst & Hay, 1997), increased neuropsychiatric symptoms, and increased disability (Lyketsos et al., 2002; Tabert et al., 2002). The considerable prevalence of cognitive impairment with advancing age (Plassman et al., 2008), together with rapid demographic ageing, makes increasing understanding of the ageing brain and cognitive decline an imperative. Age differences in cognitive performance are well documented (Horn, 1986) and traditionally these age-associated cognitive deficits have been considered age-determined in the absence of identifiable pathology. The inevitability of cognitive decline is, however, brought into question by the existence of a significant proportion of elderly individuals who do not demonstrate decline and the considerable inter-individual variability in the nature and the severity of cognitive disturbances observed in those who do (Keller, 2006; Small, 2001). This thesis aims to illuminate differential cognitive decline and seeks neurocognitive and electrophysiological markers of that decline.

1.1 COGNITIVE DECLINE

Although normal ageing can be characterised by a gradual and progressive cognitive decline, it is important to note that cognitive performance is the outcome of dynamic interactions between multiple domains of cognition (Keller, 2006). Development of these interactions is ongoing across the lifespan (Keller, 2006). It is possible that a person's general cognitive function declines with age as a consequence of impairments in an individual domain (selective decline) or as a result of a generalised impairment in multiple domains (diffuse decline) (Keller, 2006). The way in which diffuse and selective disturbances mediate age-related decline in cognitive performance is not clear and remains open to debate (Craik & McDowd, 1987; Small,

2001; Youngjohn & Crook, 1993). Nonetheless, during normal ageing, selective domains appear to be preferentially affected (Salthouse, 1996b; Salthouse, Atkinson, & Berish, 2003). Age differences in episodic memory, executive function, and speed of processing are well documented (Horn, 1986), with cognitive functions that rely on the medial temporal lobe (MTL) and the prefrontal cortex (PFC) demonstrating particular vulnerability to age-related decline (Burke, 1997; Burke & Barnes, 2006).

While the myriad of cognitive changes associated with advancing age make a parsimonious explanation difficult to find, a distinction between the cognitive decline associated with attention and executive function and that associated with declarative memory is frequently drawn in the literature (Buckner, 2004). In the absence of dementia, difficulties in tasks that rely on attention and executive abilities are reported in ageing studies, in contrast, clinical impairment in Alzheimer's Disease (AD) initially manifests with deficits in declarative memory (Buckner, 2004; Buckner, Head, & Lustig, 2005). In later life, frontal-striatal systems show particular vulnerability to white matter alteration, atrophy, and some forms of neurotransmitter depletion. It has been proposed that these frontal-striatal changes not only result in reduced executive function in non-demented older adults, but may also underlie the relatively milder memory deficits observed in ageing because memory depends, in part, on controlled processing and executive functions (e.g. strategic elaboration during encoding and guiding search during retrieval) (Buckner, 2004). MTL and cortical networks are preferentially affected early in the progression of AD and it is thought that disruption of the MTL system leads directly to the memory impairment observed in AD. Figure 1:1 schematically illustrates the putative influence of the frontal-striatal and MTL systems on cognitive decline. Changes in frontal-striatal and MTL systems often co-occur but their degree of independence or interdependence currently remains unclear (for discussion see Buckner, 2004). There is evidence, both biological and psychological, to support the view that some cognitive functions not only gradually decline with age from early adulthood but also interact with diffuse neuronal damage (Stuss & Binns, 2001). General cognitive function reflects the interaction of multiple domains. In all likelihood, general cognitive decline is mediated by the integrity of, and interaction between, domains with known susceptibility to age-related and disease induced decline (e.g. memory, attention, executive function, and learning), together with progressive decline in the efficiency of neurophysiological systems (e.g. blood supply, neuronal connectivity, glucose metabolism etc.) and genetic risk factors (e.g. apolipoprotein E; APOE).

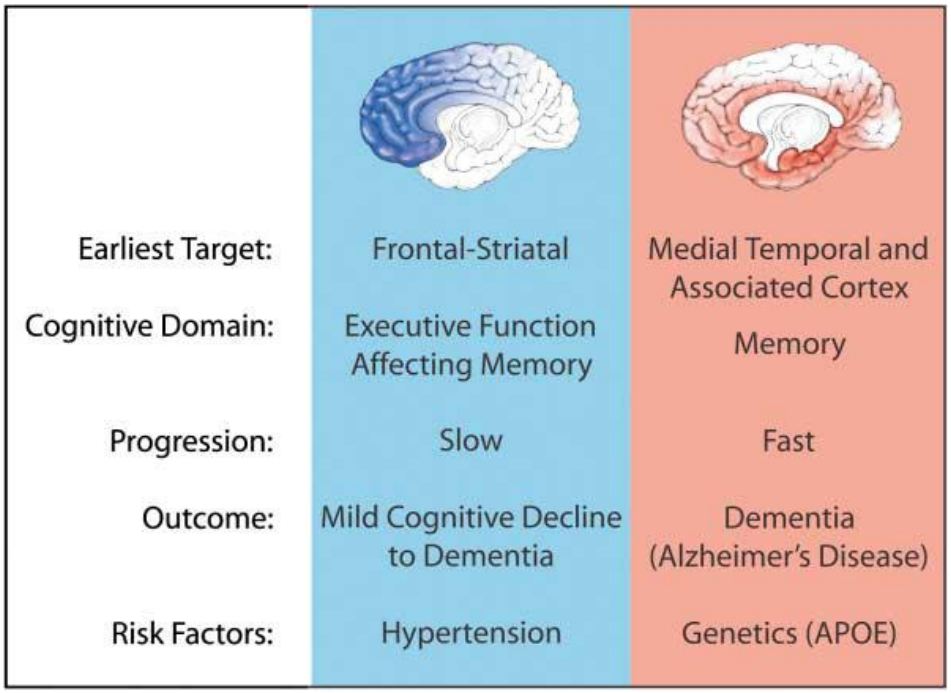

Figure 1:1 Schematic illustration of frontal-striatal and medial temporal factors

Note: (schematic from Buckner, 2004). Both factors have emerged as prominent candidates that directly or indirectly influence executive function and memory in ageing. Both factors may combine in some individuals and in all likelihood represent only a subset of factors that influence age-related cognitive decline (Buckner, 2004).

The evidence of different trajectories for different cognitive functions (Baltes, Staudinger, & Lindenberger, 1999; Horn & Cattell, 1967) suggests that the notion of gradual decline may be too simplistic. Raz offers this lyrical, but nonetheless, lucid description of the cognitive changes that occur with age:

> "Against the backdrop of generalized age-related deterioration, numerous differential changes loom, like multiple islands of relative preservation and decline" (2000a, p. 13).

A variety of labels have been used to describe the distinction between stable and declining cognitive abilities including the fluid-crystallized distinction adopted here (Baltes & Graf, 1996). Crystallized intelligence reflects accumulated knowledge and experience and fluid intelligence refers to the ability to use that knowledge in an adaptable and flexible fashion (Craik & Bialystok, 2006; Raz, 2000a). The former can be measured with tests of vocabulary or other knowledge-based activities and the latter with cognitive tasks that do not, for the most part, rely on general knowledge (Craik & Bialystok, 2006). Even though research suggests different trajectories for crystallised and fluid abilities across the lifespan, it is important to note that the two aspects of cognition may not be independent because, for example, the current level of crystallized intelligence may influence the effectiveness of fluid abilities and the acquisition of accumulated knowledge may be dependent on fluid abilities (Raz, 2000a). Across the lifespan, crystallised abilities show a tendency to increase up to the sixth and seventh decades and it is only in late old age that decline, if any, emerges

(Christensen, 2001). In contrast, continuous linear decline during early adulthood with later life acceleration is observed in memory function and cognitive speed (Hultsch, Hertzog, Dixon, & Small, 1998; Schaie, 1996). Figure 1:2 illustrates this differential decline using data from the Canberra Longitudinal Study (Christensen, 2001).

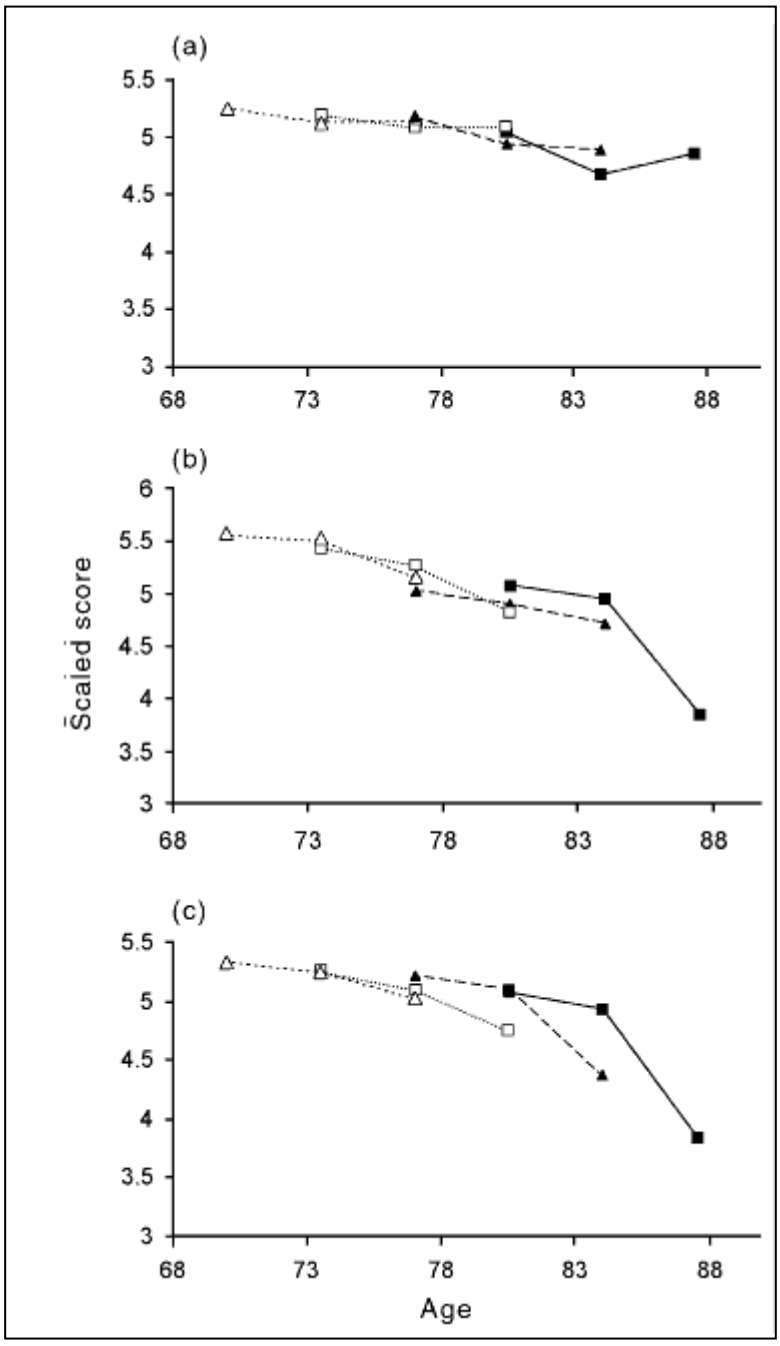

Figure 1:2 Mean scores on measures of intelligence, speed, and memory.

Note: a) crystallised intelligence, b) speed, and c) memory for four age groups across three occasions. Age groups are: --Δ-- = 70-74 year,; .. □.. = 75-79 years, --▲-- = 80-84, -■- = 85+ years at time of testing (Christensen, 2001).

Differential temporal patterns of age-related cognitive decline are also observed across the lifespan (Life-long decline, Late-life decline, Life-long stability).

Life-long decline has been observed in functions thought to represent the basic mechanisms of cognitive information processing (processing speed, working memory, encoding) (Craik, 1994). Habitual tasks or tasks that rely on knowledge tend to remain relatively stable until very late in life and so demonstrate late-life decline (Gregoire & Van der Linden, 1997; Park et al., 2002; Schaie, 1996). In contrast, autobiographical memory, and automatic memory processes demonstrate relative life-long stability (Fromholt et al., 2003; Happe, Winner, & Brownell, 1998; La Voie & Light, 1994).

Differential decline is not only evident across domains but is also obvious within the domain of memory. It has long been recognised that memory is a fractionated process and in the literature distinctions have been drawn between declarative (explicit) and non-declarative memory (implicit) (Squire & Zola-Morgan, 1991) and between long-term and short-term memory (Atkinson & Shiffrin, 1968). Five separate interacting sub-components have also been proposed; episodic memory (declarative), semantic memory (declarative), working memory (short-term), perceptual representation (priming), and procedural memory (non-declarative) (Tulving, 1987; Tulving, 1991). Procedural memory, semantic memory, and perceptual representation are described as proscopic (oriented towards the future with no need to travel back in time to a study episode). Working memory operates at the conscious level in the present. Episodic memory also operates at the conscious level and retrieval is explicit. However episodic memory is the only memory system that, at the time of retrieval, operates backwards in time. In order to access the information needed the person has to travel back in time to a study episode, which means that episodic memory is strongly dependent on contextual cues for proper access to the information to be remembered (Nilsson, 2003).

There are clear declines in episodic memory as a function of age that are not evident in semantic memory, short-term memory, or priming. Figure 1:3 illustrates this differential decline with data from a large longitudinal prospective study that echoes the data from other laboratories and studies (The Betula cohort study; Nilsson, Backman, & Erngrund, 1997). Although some semantic decline is evident on tasks requiring rapid retrieval it is thought that this reflects retrieval failures rather than semantic memory representation deficits (Zachs & Hasher, 2005). Generally speaking, semantic memory remains relatively spared in senescence. Findings for short-term memory are equivocal (see Hultsch, Hertzog, Small, McDonald-Miszczak, & Dixon, 1992). Mixed findings reported for procedural memory are thought to reflect lack of purity and inconsistency in procedural measures employed (Nilsson, 2003). However, clear age-related declines in episodic memory, that is explicit memory for recently experienced events, are repeatedly reported in both cross-sectional and longitudinal

studies, using a wide variety of tests and materials (Backman, Small, & Wahlin, 2001; Craik & Jennings, 1992; Hultsch & Dixon, 1990).

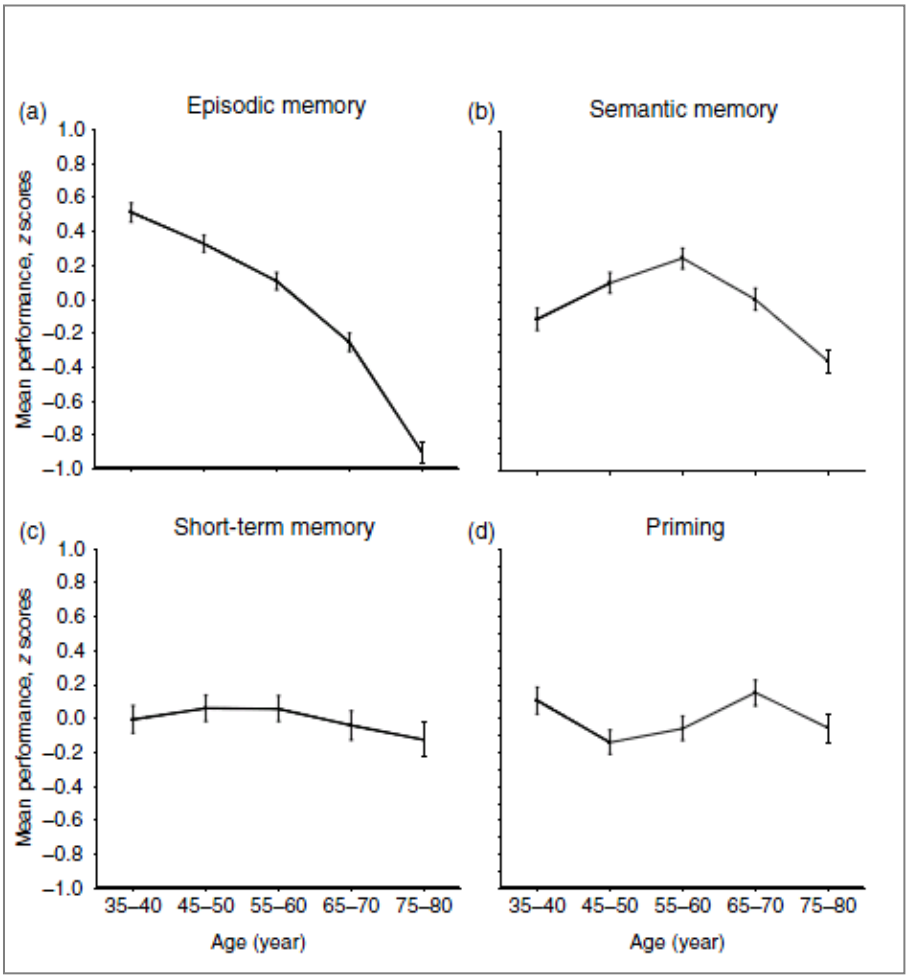

Figure 1:3 Mean memory performance as a function of age.

Note: tasks assess a) episodic memory, b) semantic memory, c) short-term memory and d) the perceptual representation system (Nilsson, 2003).

Differential age-trajectories within episodic memory are also evident and the overall pattern of poorer episodic memory performance with increasing age is complex. Data support a division of episodic memory into recall and recognition memory with the former demonstrating preferential susceptibility to age-related decline (Nyberg et al., 2003; Schonfield & Robertson, 1966). Although age-related decline in episodic memory performance is well documented it remains unclear whether these deficits are a consequence of encoding or retrieval failures or a combination of both but research is emerging that suggests that the two processes may be differentially affected and that encoding deficiencies may exert a larger influence (Friedman, Nessler, & Johnson, 2007). In addition, a number of theoretical models propose the fractionation of episodic retrieval into recollection and familiarity processes with the former showing greater age-related decline than the latter (for reviews see Rugg & Yonelinas, 2003; Yonelinas, 2002). Although incomplete and theoretically controversial (for discussion see Paller, Voss, & Boehm, 2007) findings

have associated familiarity with MTL structures, and recollection with both MTL structures and frontal lobe structures (Davidson & Glisky, 2002; Rugg & Yonelinas, 2003; Yonelinas, 2002).

Differential patterns of cognitive decline generally and memory decline specifically are not yet fully understood. Research that aims to illuminate differential decline, such as this thesis, may also help to distinguish age-related memory loss from pathological decline, assess the utility of memory loss as a diagnostic aid, and hopefully, ultimately facilitate prediction, early detection and intervention (Craik, 2008).

1.2 THEORETICAL PERSPECTIVES

1.2.1 Behavioural Perspectives

Four predominant theories of cognitive ageing have emerged from decades of behavioural research (Park, 2000). Each perspective explains age-related cognitive deficits by suggesting the impairment of an underlying mechanism. Thus the theories invoke the influence of either; a "general speed" factor (Salthouse, 1993; Salthouse, 1996a; Salthouse, 1996b), sensory functioning (Lindenberger & Baltes, 1994), depleted processing (attentional) resources (e.g. Baddeley, Logie, Bressi, Della Salla, & Spinnler, 1986; Craik & Byrd, 1982) or disinhibition (Hasher & Zacks, 1988).

1.2.1.1 Speed of Processing

Processing speed theory (Salthouse, 1991; Salthouse, 1996b) proposes generalised decreased speed of performing mental operations as the fundamental processing resource that accounts for age-related variance in cognitive performance. The effects of the slowed speed are hypothesised to be global and to have an impact on all aspects of cognition including those without an obvious speed element (Park, 2000).

1.2.1.2 Sensory Functioning

Lindenberger and Baltes (1994) propose that age-related variance in cognitive ability is mediated by sensory functioning that represents a more fundamental cognitive resource than speed of processing. Their 'common cause hypothesis' suggests sensory function as a general index of neurobiological architecture and a mediator of all cognitive abilities.

1.2.1.3 Processing Resources

In contrast, Craik & Byrd (1982) propose an age-related deficiency in on-line processing resources, attentional capacity, or mental energy (Baddeley, 1986a) and suggest that older adults are lacking in the ability to engage in "self-initiated processing". Self-initiated processes require conscious effort and are typically considered frontal lobe functions and so problems in this regard are thought to be mediated by declines in frontal lobe efficiency (Raz, 2000a). Although this theory proposes that working memory capacity declines with age, the Craik and Byrd model also suggests that the impact of limited capacity can be attenuated by environmental supports that decrease processing requirements.

1.2.1.4 Inhibition

Hasher and Zachs (1988) argue that the process of inhibition is fundamental to understanding cognitive ageing due to the fact that focussing on target information and

inhibiting attention to irrelevant material becomes more difficult with advancing age. They propose that the apparent losses in working memory associated with ageing can be explained by inefficient inhibitory function that allows goal irrelevant information into working memory resulting in the diffusion of attention across both relevant and irrelevant information (Hartley, 1993).

While there is currently little doubt that general slowing and diminished working memory can explain a large proportion of the variance in age-related changes in cognitive functioning, it should be acknowledged that reduced processing capacity theories have been accused of vagueness and although the speed of processing and sensory function theories have parsimony and may be basic indicators of neuronal integrity, their lack of specificity is seen by some as a limitation (Balota, Dolan, & Duchek, 2000; Park, 2000). It has also been argued that the theory of diminished inhibition is limited by the absence of an empirical definition and valid measures of inhibition (Burke, 1997; Mc Dowd, 1997).

Resource views of cognitive ageing generally agree that with age, the ability to perform mental tasks is constrained by diminished mental resources. However, it is the different conceptualisation of the nature of the mental energy underlying processing capacity that essentially sets the theories apart (Park, 2000). While each theory accounts for cognitive ageing in terms of a decline in a fundamental processing resource, it is also thought that the amount of cognitive processing resources that an individual has available for use in any given situation influences their everyday efficacy and so not everyone will manifest the same real world effects of cognitive ageing (Park, 1997, 1999). Evidence suggests that more educated individuals possess higher levels of cognitive resource (Baltes & Lindenberger, 1997) and so even significant age-related decline may leave them with sufficient cognitive resources to negotiate everyday living, In contrast, age-related decline may lead an individual with lower levels of cognitive resource to fall below some critical threshold of needed resources resulting in more obvious cognitive decline (Park, 2000).

Cognitive resource in ageing has generally been conceptualised as a single, undifferentiated resource pool (Sloane et al., 2002). The *differentiation / dedifferentiation hypothesis* suggests that the functional organisation of cognitive abilities is condensed in childhood and gradually unfurls (differentiates) (Garrett, 1946) as the individual matures and contracts again in old age (dedifferentiates) (Lindenberger & von Oertzen, 2006). Ageing is characterised by a reduction in the structural (Madden, Bennett, & Song, 2009; Sullivan & Pfefferbaum, 2006) and functional connectivity (Buckner et al., 2009; Grady et al., 2010; Madden et al., 2010), between different regions in the brain. In later life brain regions that emit specialised responses for specific cognitive processes in young adults generally become less

specialised and respond more similarly across a greater range of cognitive conditions with increasing age (Cabeza, 2002; Li & Sikstrom, 2002; Park et al., 2004). It has been suggested that age-related changes in neural connectivity and the organisation of these connections may be the underlying mechanisms for dedifferentiation (Goh, 2011). Although the common cause hypothesis of ageing, outlined above, does not address the issue of domain specificity it does support the idea of dedifferentiation of resources across the life-span because it argues that simple measures of visual and auditory acuity reflect the underlying neural integrity and predict cognitive performance (Sloane et al., 2002). However, although the differentiation / dedifferentiation hypothesis refers to the organisation of abilities within individuals, most of the empirical evidence supporting the hypothesis is gleaned from studies of inter-individual variability in different age groups sampled across individuals from childhood to adolescence and from adulthood to old age (e.g. Baltes & Lindenberger, 1997; Schaie, Maitland, Willis, & Ntieri, 1998).

1.2.2 Neurobiological Perspectives

Sophistication of methodology and developments in neurosciences have led to a convergence of knowledge that have improved understanding of the neural bases of cognition (Band, Ridderinkhof, & Segalowitz, 2002; Reuter-Lorenz, 2000). Given that theories of cognitive ageing are drawn largely from behavioural evidence, studies that combine cognitive and neural methods have the potential to evaluate the compatibility of psychological and physiological accounts of cognitive ageing (Reuter-Lorenz, 2000). Although there is value in relating function to structure, mapping cognitive operations onto neural circuitry is fraught with difficulty not only because cognitive theories can lack precision, but also due to the fact that correlations may involve one-to-many relationships (Valentine, 1997). In addition, although younger and older brains differ physically, regional physical dysfunction may not manifest in behavioural deficit due to reorganisation, compensation or strategic shifts (Band et al., 2002; Reuter-Lorenz, 2000).

1.2.2.1 Cognitive Reserve

The concept of cognitive reserve (CR) has been proposed to account for inter-individual variation in the clinical manifestation of neural changes associated with ageing and neurodegenerative disease (Stern, 2002, 2009; Stern et al., 2005). CR has been used to describe the capacity of an adult brain to sustain Alzheimer's disease (AD) pathology without manifesting clinical symptoms of dementia at a level that would be sufficient to cause clinical dementia in an individual with less cognitive reserve (Starr & Lonie, 2008; Stern, 2009). The CR concept suggests that the brain actively tries to cope with damage by employing pre-existing cognitive processes or

by engaging compensatory processes (Stern, 2009). CR postulates that individual differences in the cognitive processes or neural networks underlying task performance allow some people to cope better with brain changes incurred as a consequence of ageing, injury, or disease and goes some way towards explaining why: a) 25% of older adults with unimpaired neuropsychological testing prior to death meet full AD pathological criteria post mortem (Ince, 2001), b) a head injury of the same magnitude can result in different levels of cognitive impairment, and c) education and occupational exposure are associated with reduced risk of dementia and slower rate of memory decline in normal ageing. Two complementary facets to the neural implementation of CR have been proposed (Stern, 2002); neural reserve and neural compensation. Neural reserve may reflect inter-individual variability in brain networks or cognitive paradigms that underlie task performance in healthy individuals whereby greater processing efficiency, capacity, or flexibility facilitates better coping with increasing task difficulty, age-related change, or brain pathology (Stern, 2009; Stern et al., 2005). Neural compensation reflects differential ability to recruit alternative networks when standard processing networks have been disrupted by pathology or the physiological effects of ageing (Stern, 2002, 2009; Stern et al., 2005). Education and pre-morbid IQ have been proposed as useful proxy measures for CR.

1.2.2.2 Hemisphere Asymmetry Reduction in Older Adults (HAROLD)

Cabeza makes the observation that under similar circumstances older adults exhibit less lateralisation in prefrontal activity than younger adults (2002). It is proposed that that these hemispheric asymmetry reductions may reflect dedifferentiation or could have a compensatory function, may reflect regional or network mechanisms, and may have a cognitive or neural origin (Cabeza, 2002). The proposed mechanics for HAROLD may not all be mutually exclusive. Functional neuroimaging of episodic memory, working memory, and inhibitory control show less lateralisation in elders than in younger adults and Cabeza proposes that this represents a general ageing phenomenon, rather than a task specific occurrence.

1.2.2.3 The Frontal Lobe Hypothesis (FLH)

Non-pathological normal ageing is characterised by deterioration in frontal lobe function (Glisky, Polster, & Routhieaux, 1995; Parkin & Lawrence, 1994) and white matter degeneration (Guttmann et al., 1998; Raz et al., 2005). There is also evidence that deterioration of the brain begins primarily in the frontal regions (Raz, 2000a) and although the structural and functional disturbances associated with normal ageing are heterogeneous, neuroimaging evidence suggests that the prefrontal cortex (PFC) is more vulnerable to the effects of ageing than other cortical regions (Tisserand

& Jolles, 2003; West, 2000). It has been suggested that the traditional distinction between generalized and process-specific age-related cognitive decline is echoed in the distinction between the frontal-lobe hypothesis (FLH) and more differentiated views of neurocognitive ageing (Band et al., 2002)

The FLH is generally recognised as a neuropsychologically constrained model that provides a useful framework for understanding the pattern of spared and impaired cognitive functions observed in the cognitive ageing literature (West, 2000). According to this hypothesis, cognitive processes supported by the prefrontal cortex will manifest age-related decline at an earlier age and in greater magnitude than cognitive processes supported by non-frontal regions (West, 2000; West, 1996). While there is empirical support for these key assumptions (e.g. Petrides & Milner, 1982; Shimamura & Jurica, 1994) there is also criticism of the hypothesis and suggestion that the evidence is both weak and conflicting (Greenwood, 2000). West himself proposes that the FLH is in need of refinement following the identification of differential age-related decline within the PFC and suggests that future research should explore the differential effects of ageing on the various cognitive processes supported by this region (2000).

The PFC is a large heterogeneous region with functionally distinct sub-regions some of which have reciprocal connections to both sub-cortical centres and the secondary and association cortices of all modalities (Reuter-Lorenz, 2000; Tisserand & Jolles, 2003). Thus it is thought that the frontal lobes modulate neural operations in other brain regions in line with current goal-directed intentions and plans (Reuter-Lorenz, 2000). While age-related atrophy is most apparent within the PFC, it is also similarly apparent in the striatum and thalamus with which it has reciprocal connections (Gunning, Head, McQuain, Acker, & Raz, 1998). Therefore, while acknowledging that age-related cognitive changes are associated with alterations within the PFC, the neural networks and the functional activity of the circuitry interconnecting brain regions may be more important than specific cortical regions because cognitive performance is contingent on the integrity of all the brain structures and connections involved in any given function (Rubin, 1999; Tisserand & Jolles, 2003).

1.2.2.4 Unitary & Multiple Factor Frameworks

Several theories argue that age-related cognitive decline is due to changes in the functional properties of co-ordinated brain systems and from the anatomical disarticulation of brain systems that usually function together and support cognition, possibly as a consequence of white matter loss (Head et al., 2004; O'Sullivan et al., 2001; Salat et al., 2005). Diffusion tensor imaging (DTI) measures of white matter are

correlated with executive function, information processing and working memory which is thought to be particularly dependent on white matter connections (Charlton et al., 2006). Significant associations between episodic memory and measures of brain structural integrity but not hippocampal volume (after controlling for brain volume) found in normal older adults, suggest that memory deficits in normal ageing may be related to a reduction in the integrity of white matter connections in the prefrontal and temporal lobes that integrate memory processing (Charlton, Barrick, Markus, & Morris). Both unitary and multiple factor frameworks have been put forward to explain cognitive ageing. Within the former, cognitive decline is hypothesised to fall along a continuum whereby, for example, the memory deficits experienced in AD are considered an acceleration of the less dramatic cognitive changes associated with normal or non-pathological ageing (e.g. Huppert & Brayne, 1994). By contrast, a multiple factor framework proposes multiple slopes with varying trajectories that target different systems or functions and may vary in rates of progression across individuals (e.g. Albert, 1997; Gabrieli, 1996). Thus normal or non-demented cognitive decline may be mild because some individuals only experience the influence of some ageing processes while being spared from the devastating changes associated with others (Buckner, 2004). Evidence is accumulating in support of a multiple factor model whereby multiple cascades arising from distinct processes result in distinct cognitive outcomes (Andrews-Hanna et al., 2007). Salthouse and Ferrer-Caja propose the influence of one factor that leads to age-differences on many abilities including reasoning, memory, spatial processing, and speed, and another separate factor that influences additional age-related effects on memory (2003). A two factor model has also been proposed by Glisky et al. (1995) that draws a distinction between the cognitive decline associated with: a) executive and attentional dysfunction, and b) declarative memory disruption, with parallel functional disruptions observed in frontal-striatal systems and medial temporal and associated cortical networks.

1.3 MARKES OF COGNITIVE DECLINE

It is predicted that over 81 million people will have dementia by 2040 with 71% of those affected living in the developing world (Ferri et al., 2005). One of the greatest challenges facing researchers is to discriminate age-related change from disease induced decline, as a consequence much theoretical, clinical and empirical attention has focussed on the boundaries between normal ageing and pathological decline (Dixon et al., 2007). Understanding age-related cognitive decline will also help understanding of disease induced decline by providing a backdrop against which pathology can be assessed (Burke & Barnes, 2006). In the absence of a cure for dementia and in order to avert the catastrophic human and economic consequences of escalating impairment and disease, various strands of ageing and dementia research have focussed on earlier disease detection and/or the identification of biomarkers. It is important to note that at the time of writing there is no real consensus with regard to the attributes a neurocognitive/behavioural marker of cognitive ageing should have and currently there are no criteria or standardised measures against which putative markers can be assessed (Deary, 2010; McClearn, 1997). Detection of failing mental function at the earliest point possible together with the ability to distinguish disease-induced decline from age-related decline could facilitate prophylactic, or palliative intervention. This thesis aims to add to the growing body of cognitive ageing research by exploring a small number of possible neurocognitive indicators and electrophysiological markers of cognitive decline in healthy adults. Special attention will be paid to intra-individual variability in reaction time, spontaneous EEG rhythms, and event-related potentials (ERPs).

1.3.1 Neurocognitive Markers of Cognitive Decline

There is no dispute that processing speed, which is significantly correlated with higher-order cognitive functions, slows with age (Deary, 2001; Der & Deary, 2006). There is, however, debate as to whether processing speed represents just one of a number of domains of cognitive function that load on general cognitive ability, or a more fundamental construct that accounts for individual differences in cognitive ability (Deary, 2010). This debate is echoed in the cognitive ageing literature with one view proposing that processing speed is just one of many cognitive abilities that decline with age and another that it actually represents a fundamental cause of age-related decline in other cognitive abilities. Proponents of the latter view propose that processing speed represents an index of a fundamental capacity of the central nervous system (CNS) on which the efficient implementation of all other cognitive functions depend (Madden, 2001). Following on from this, processing speed has been proposed as a possible biomarker of cognitive ageing (Deary, 2010). Generally speaking

processing speed tasks usually assess the efficiency with which individuals complete task trials with simple cognitive content. Within experimental psychology, processing speed is generally measured with simple or choice reaction time tasks. Latency measures on choice reaction time tasks show age-related decline (Der & Deary, 2006), correlate with mortality and morbidity (Shipley, Der, Taylor, & Deary, 2006), and demonstrate stable individual differences over time in large adult samples (Deary, 2005), and so could offer useful information with regard to cognitive ageing (Deary, 2010). However, a measure that shows strong age-related mean changes does not necessarily inform about individual differences in ageing because, for example, age-related changes in choice reaction time may only provide information about cognitive variation in old age that has actually been stable across the lifespan (for discussion see Deary, 2010). Recently it has been proposed that the study of within-person performance variability on reaction time tasks could yield new information over and above that provided by the study of general mean level of performance.

Researchers interested in understanding human behaviour tend to investigate either group effects or individual differences. In general terms the former examines central tendency which indexes core ability while the latter explores variability in performance that assesses change (Stuss & Binns, 2008). An important distinction must be drawn between the variability that is observed within an individual (intra-individual variability) and the variability that is observed between individuals in a group (inter-individual variability).

Intra-individual performance variability has been proposed as a marker of brain, particularly prefrontal, pathology (Stuss, Murphy, Binns, & Alexander, 2003) and may represent an important index of the efficiency with that executive control processes are instantiated in the brain (Bellgrove, Hester, & Garavan, 2004). Increased intra-individual variability is commonly observed in ageing, dementia, and other brain disorders including schizophrenia, traumatic brain injury, and attention-deficit hyperactivity disorder (Bunce, MacDonald, & Hultsch, 2004; Hultsch, MacDonald, Hunter, Levy-Bencheton, & Strauss, 2000b; Hurks et al., 2005; Schwartz et al., 1989). Given the concurrent cognitive deficits that accompany the within-person variability exhibited by these diverse populations intra-individual variability in cognitive performance is thought to represent a behavioural proxy for neural changes underlying impairment (MacDonald, Li, & Backman, 2009). Intra-individual variability has been proposed as a disorder of control related to attentional lapses and/or attentional oscillations (Stuss & Binns, 2008) and a failure to maintain executive control (West, Murphy, Armilio, Craik, & Stuss, 2002). At the structural level, lesions of frontal grey matter (Sowell et al., 2003; Stuss et al., 2003) as well as changes to white matter (Anstey et al., 2007; Bunce et al., 2007; Walhovd & Fjell, 2007) have been correlated

with intra-individual variability. The developmental and degenerative trajectory of grey and white matter across the lifespan roughly correspond with increasing and declining intellectual functioning across the lifespan (Li, Lindenberger et al., 2004) and decreasing and increasing intra-individual variability observed across the lifespan (MacDonald, Hultsch, & Dixon, 2003). Immature or degraded white matter tracts may lead to disconnectivity in associative pathways, result in increased neural noise and give rise to poorer cognitive performance and increased performance variability (MacDonald et al., 2009).

Table 1:1Taxonomy of intra-individual variability in cognitive functioning across the lifespan.

	Scope	
Timescale	***Variations in single function (e.g. local, univariate)***	***Transformation in functional organisation (e.g. global, multivariate)***
Microgenetic *(e.g. across trials, sessions or weeks)*	Relatively reversible variations in one function (e.g. processing fluctuation)	Relatively reversible variations in functional organisation (e.g. shifts in resource allocation, co-ordination, & compensatory behaviour during multi-tasking.)
Ontogenetic *(e.g. across months, years or decades)*	Relatively permanent (cumulative, progressive) changes in one function. [e.g. progressive changes in a specific cognitive function for e.g. mechanics of cognition]	Relatively permanent (cumulative, progressive) alterations in functional organisation. [e.g. ability dedifferentiation from adulthood to old age].

Note: Table adapted from Lidenberger and von Oertzen (Lindenberger & von Oertzen, 2006)

Intra-individual change is fundamental to human development (Luszcz, 2004) and intra-individual variability is intrinsic to human functioning and inherent in human cognitive processes (Li, Huxhold, & Schmiedek, 2004). Nesselroade (2004a) proposes that intra-individual change refers to the kind of transformations associated with learning and development reflecting longer-term durable alterations in neurocognitive systems while, in contrast, intra-individual variability reflects shorter-term transient fluctuations that are usually reversible. Lindenberger and von Oertzen (2006) offer a similar taxonomy (Table 1:1) to explicate the neural and behavioural mechanisms that connect local to global variations and microgenetic variations to ontogenetic change. Currently there are a dearth of data on age differences in microgenetic variations (Lindenberger & von Oertzen, 2006). This may be explained by the fact that, historically, psychological ageing research focussed on long-term change in processes and behaviour, in this latter context researchers often characterised short-term variations as nuisance parameters and ascribed age-related increases in within-person variability in cognitive performance to poor instrument reliability and validity (Martin & Hofer, 2004).

Inter-individual Variability (Between Persons)

Inter-individual variability (diversity) considers the differences across people in performance measured on a single task on a single occasion (Hale, Myerson, Smith, & Poon, 1988). The bulk of the ageing literature examines inter-individual difference in cognition, showing increasing variability across people in performance on some cognitive variables with increasing age (Hultsch & Dixon, 1990; Nelson & Dannefer, 1992). Measures of memory, response time (RT) and fluid abilities appear to show increasing diversity while measures of crystallised intelligence do not (Morse, 1993). Diversity is generally assessed using the standard deviation (SD) of individual scores around the mean of the group (Shammi, Bosman, & Stuss, 1998). While some group variability is expected, excessive variability across individuals within a group may be indicative of inappropriate group composition (Stuss & Binns, 2008). It is, therefore, important to acknowledge, particularly within cognitive ageing research, that group heterogeneity may inflate variance and rather than reflecting random error, diversity could instead be related to a combination of one or more pertinent factors (see Stuss & Binns, 2008).

Intra-individual Variability (Within-persons)

Intra-individual variability can be exhibited across a broad spread of timescales ranging from milliseconds to months and can be defined as;

1. Profile of cognitive performance (scatter) within a person across different tasks at a single point in time also referred to as dispersion.
2. Fluctuations in performance on a single measure across trials within a task or across sessions spanning longer intervals (e.g. hours, days, weeks). This type of within-person variability is often referred to as intra-individual variability, inconsistency, and/or dispersion.

Short-interval trial-to-trial fluctuations may best capture intra-individual variability when it is theorised that endogenous sources (e.g. alterations in neurotransmitter efficiency) underlie cognitive variability, but when exogenous modulators (e.g. stress or fatigue) are postulated then intra-individual variability may be better indexed over days or weeks (MacDonald et al., 2009). The terms dispersion, inconsistency, and scatter are commonly used within the variability literature but their operational definitions can vary across research groups and publications. This thesis explores all three types of variability. Intra-individual variability can be assessed using the individual standard deviation (ISD), which measures the spread of a set of observations from an individual person. There is evidence from response time studies that suggests that the variance of a variable may be related to its mean (Jensen, 1992). The coefficient of variation (CV) is a summary measure that allows for this possibility

because it assumes a constant relationship between the mean and the standard deviation. Research that focuses on mean differences between young and old groups provides useful information when intra-individual variability is small but may lead to erroneous inference if increasing intra-individual variability represents systematic rather than random error (Nesselroade, 2004a). The study of intra-individual performance variability may produce new information over and above that provided by the study of general level of performance.

A small number of studies show that intra-individual variability is an integral phenomenon of cognitive functioning that demands further research in order to establish its importance at conceptual, theoretical, practical and clinical levels (Bunce et al., 2004). Intra-individual variability may represent a useful behavioural marker of some neurocognitive resource. Evidence suggests that inconsistency or consistency across trial performance on speeded tasks may respectively reflect compromised or available neural resources for related cognitive behaviour (Dixon et al., 2007; Hultsch, Hunter, MacDonald, & Strauss, 2005). This thesis measures reaction time intra-individual variability and latency on a number of experimental tasks in order to assess their ability to distinguish between age and cognitive performance groups and to ascertain their relationship with established neuropsychological indices of cognitive performance.

1.3.2 Electrophysiological Markers of Cognitive Decline

Recent years have seen increased interest in developing reliable markers of age-related and disease induced memory impairment. The working group on molecular and biochemical markers of Alzheimer's disease states that useful biomarkers should be inexpensive, simple to use and easy to implement (The Ronald and Nancy Reagan Research Institute of the Alzheimer's Association and the National Institute on Aging,1998). Recent improvements in acquisition technology and signal processing power mean that electroencephalography (EEG) now satisfies these criteria. Early age-related memory decline is not necessarily associated with clear structural lesions (Rapp & Gallagher, 1996). The observation that many age-related processes result in physiological dysfunction rather than neuronal loss (Gallagher, 1997) suggests that techniques that can assess neuronal physiological dysfunction independent of structure, such as EEG, may be best suited to detecting changes or dysfunction associated with age-related memory decline (Small, 2001). Given the observed overlap at the boundaries of normal ageing and early pathological decline, EEG may represent a non-invasive tool that could yield low-cost biomarkers for decline that may be capable of identifying subtle functional changes associated with normal ageing or

those that precede the structural or metabolic deficits of disease (Jackson & Snyder, 2008).

The use of electroencephalography to establish early biomarker of cognitive decline is not a novel concept. Although multiple candidate markers have emerged from years of research (for comprehensive reviews see; Jackson & Snyder, 2008; Rossini, Rossi, Babiloni, & Polich, 2007), the literature is fragmented due, in no small part, to the fact that research in this field spans several diverse disciplines (e.g. neural engineering, clinical neurophysiology, neuropsychology, psychiatry, cognitive neuroscience) and employs a wide spectrum of approaches (e.g. EEG power analysis, Event-Related Potential methods, coherence modelling, source reconstruction). This thesis will focus on analysis of alpha power in the ongoing EEG and will employ Event-Related Potential (ERP) methods to explore episodic memory. For a detailed description of EEG and ERP methodology please see Chapter 4.

EEG

Changes in the power spectra of the ongoing EEG are observed across the lifespan and are differentially affected, particularly at the boundaries of normal and pathological decline. EEG data recorded while participants are awake with their eyes open and/or closed represent an easy to obtain measure that has yielded a number of candidate markers, which may have particular utility in ageing research. In a healthy awake adult at rest with eyes closed, the most prominent component of the EEG is the 8-13 Hz background oscillation known as the alpha rhythm (Shaw, 2003). The 'power', i.e. the extent to which this frequency of alpha is present in the overall EEG, increases from childhood to adulthood (Breslau, Starr, Sicotte, Higa, & Buchsbaum, 1989), becomes more stable across middle age until later life when a pronounced drop in alpha power is observed (Klimesch, 1999). Alpha frequency also changes with age and decreases have been associated with slower cognitive speed and poorer memory performance (Klimesch, 1999). This thesis uses a number of methods to assess alpha power at rest and during a memory task in order to assess its ability to distinguish between age and cognitive performance groups and to ascertain its relationship to established neuropsychological indices of cognitive performance.

Event-Related Potentials.

Understanding age-related changes in ERP responding may have particular utility in elucidating differential decline and establishing whether differential responding across age and cognitive status groups reflects efficient or compensatory processes (Friedman, 2003). Age-related changes in episodic encoding and retrieval processes may also be illuminated by increased understanding of ERP responding during episodic tasks. It should be noted that although encoding and retrieval are separately operationalised in the laboratory, they may share processes and interact in

important ways (Rugg & Morcom, 2005). Age and cognitive performance differences have been reported for both early sensory and later cognitive ERPs, including those thought to reflect both executive and episodic memory processes (e.g. De Sanctis et al., 2008; Friedman, de Chastelaine, Nessler, & Malcolm, 2010; Rugg & Morcom, 2005; Wolk et al., 2009). These differences manifest in a variety of ways, for example components in old adults can be amplified or attenuated, activity can be more or less differentiated, more or less elaborate, or occur at earlier or later latencies relative to young adults. This thesis uses ERP methods to explore the encoding and subsequent retrieval stages of episodic memory separately in an attempt to identify differences between age groups and cognitive status groups with a view to illuminating differential decline.

1.4 RESEARCH ISSUES

Age-extrinsic factors that have been associated with cognitive performance in older populations include but are not limited to: education (Christensen, 2001) hypertension (Anson & Paran, 2005), blood pressure variability (Sakakura, Ishikawa, Okuno, Shimada, & Karia, 2007), heart rate variability (Kim et al., 2006), testosterone loss, (Moffat, 2005), endocrine fluctuations (see Ancelin & Ritchie, 2005); diabetes mellitus, chronic respiratory disease (Van Boxtel et al., 1998); and mild sensory impairment (Van Boxtel et al., 2000). The influence of these factors may account for discrepancies between results in cognitive ageing studies and should, where possible, be considered when interpreting empirical findings. The exclusion criteria implemented in this thesis were carefully chosen to limit, where possible, the impact of age-extrinsic factors known to affect or interact with cognitive performance. Furthermore, using older individuals who were well matched to young controls regarding educational history and indices of crystallised intelligence ensures that any age-differences observed most likely represent the lower bound of non-pathological ageing effects (Rugg & Morcom, 2005). A recent literature review has shown that cognitive performance on a wide range of tasks measuring attention, executive function and memory is affected by time of day modulations (Schmidt C, 2007). There is also evidence that cognitive performance is contingent on the chronotype of the participant particularly the synchronicity between the participant's peak circadian arousal period and the time of testing (Schmidt C, 2007; Yoon, May, & Hasher, 2000). Furthermore, clear age differences in circadian arousal patterns have been identified with older populations tending to reach their mental peak in the morning while younger adults tend to do so in the evening (Yoon et al., 2000). It is, therefore, possible that a lack of consideration of testing time could lead to an over estimation of age differences in cognitive ageing research (Hasher, Goldstein, & May, 2005). Interestingly, although both young and old populations show diminished inhibition at off-peak times (May, 1999), older participants show a larger influence of distraction in line with Hasher and Zachs, (1988) inhibitory-deficit model of ageing. In some instances differences in performance between young and old populations only appear when older populations are tested at their non-optimal time of day (Hasher et al., 2005). Conversely age differences on a number of performance measures are attenuated when older participants are tested during their optimal time and younger adults during their non-optimal time (Bunce, Warr, & Cochrane, 1993). In order to guard against bias the research reported in this thesis carefully controlled for individual and group differences in circadian arousal patterns by assessing participant chronotype and balancing testing times.

1.5 THESIS OUTLINE

By combining neuropsychological and electrophysiological methodologies this thesis aims to identify neurocognitive markers of age and/or cognitive performance. Chapter 2 describes participant classification and behavioural testing methods, and presents results from neuropsychological assessment and experimental tasks. Chapter 3 explores reaction time (RT) latency and intra-individual variability on experimental tasks that assess cognitive and motor processing speed, attention and memory. The electroencephalogram was used to assess cortical activity while participants rested and while they encoded and retrieved words during an experimental episodic memory task. Chapter 4 describes EEG and ERPs and the techniques employed for acquisition, and analysis. Chapter 5 presents results from spectral analysis of the ongoing EEG and Chapter 6 presents a detailed analysis of the ERP activity recorded during the recognition phase of a novel experimental episodic memory task. ERP components thought to reflect recognition and familiarity processes were analysed as was the impact of encoding level on ERP responding during retrieval. Chapter 7 presents a detailed analysis of the ERP activity recorded during the encoding phase of the same episodic memory task. A general discussion of these findings, their interpretation, implications and associated issues and limitations are presented in Chapter 8.

Chapter 2 **COGNITIVE PERFORMANCE**

2.1 INTRODUCTION

This thesis studies neurocognitive and electrophysiological markers that index cognitive decline. Neuropsychological tests that have long been used to assess age-related cognitive decline and pathological deterioration putatively have the capacity to detect cognitive changes many years before functional changes and prior to subsequent clinical diagnosis of Alzheimer's disease (AD) (Elias et al., 2000). Nonetheless, the increased heterogeneity of cognitive profiles in the elderly can make it difficult to distinguish between age-related deficits and those that represent preclinical AD. Combining neuropsychological testing with neuroimaging has been proposed as the best means of exploring the overlap observed at the boundaries of normal and pathological decline (Dubois & Albert, 2004). This thesis marries neuropsychological and electrophysiological methodologies with a view to explicating differential decline in the non-diseased population. One approach to capturing cognitive variability is to use contrasting psychological tests in order to identify sub-groups representative of different cognitive profiles and use neuroimaging methods, such as electroencephalography (EEG) to ascertain whether neurophysiological differences support these classifications (Jacobson, McEvoy, Dale, & Fennema-Notestine, 2009). Identifying sub-groups in elderly cohorts by defining asymmetric cognitive profiles that are based on dissociations between abilities, for example, based on contrasts between a domain known to be resistant to age-related decline and a second domain with known vulnerability to decline, has a number of advantages particularly for cross-sectional research (for review see: Jacobson et al., 2009). This chapter discusses sub-group classification, describes neuropsychological measures and methods, and reports cognitive performance results that will be referenced throughout the study. EEG methodology will be described in Chapter 4.

Although age is the single biggest risk factor for cognitive decline it is not, in itself, a sufficient explanatory variable. A number of factors have been identified that contribute to cognitive performance in later life (Glatt, Chayavichitsilp, Depp, Schork, & Jeste, 2007; Montross et al., 2006; Raz & Rodrigue, 2006; Rowe & Kahn, 1987). Considerable individual differences in cognitive performance have been reported in the non-diseased population and although research that delineates age-related and disease-induced decline is important it is limited and may be misleading because it fails to acknowledge this heterogeneity (Rowe & Kahn, 1987). Individual differences in cognitive performance generally and memory performance specifically increase from early to late adulthood (Small, 2001). Failure to acknowledge this increased

heterogeneity by conducting old versus young comparisons that focus only on average tendencies within the groups may also inaccurately assess the effects of ageing (Rowe & Kahn, 1987) or result in an under-assessment of impaired performance, not in the least, because most normal subject groups include incipient cases of dementia (Petersen, 2004). The distinction between normal age-related decline and the early, but abnormal state, of cognitive deterioration known as Mild Cognitive Impairment (MCI) is subtle. Considerable overlap observed at the boundaries of these two groups makes it likely that some elderly 'normative' samples inadvertently contain persons affected by pathological ageing (Dal Forno & Kawas, 1995; Lipton, Sliwinski, & Buschke, 1996; Sliwinski, Lipton, Buschke, & Stewart, 1996). This, in turn, means that the effects of age on cognition are overestimated and the true level of normal cognitive functioning is underestimated in ageing studies that assess cognitive performance relative to age-norms (Ylikoski et al., 1999). At the boundaries of normal and pathological ageing both clinicians and researchers are challenged by individuals of high intellect whose performance is within the normal range but at a level that represents change for them, (Petersen, 2004). Individuals with considerable cognitive reserve (CR; Stern, 2009) also represent a particular challenge due to their ability to mask age-related or disease-induced cognitive deficits.

A number of standards have been used for classifying memory impairment in the elderly (Howieson, Loring, & Hannay, 2004). For example Age Associated Memory Impairment (AAMI) requires one score at least one standard deviation (SD) below the young adult mean on an appropriate memory test (e.g. verbal memory test of the Wechsler Memory Scale; Wechsler, 1998 WMS), a scaled score of ≥ 9 on the Wechsler Intelligence Scale tests and scores ≥ 24 on the Mini Mental State Exam (Folstein, Folstein, & McHugh, 1975). The benign nature of this condition is suggested by the fact that people who satisfy the AAMI criteria demonstrate little or no change on a variety of memory tests (Youngjohn & Crook, 1993). Several standards have also been used for classifying early clinical memory impairment. The construct of MCI has come to represent a transitional state between the cognitive changes associated with normal ageing and those associated with very early dementia. Although cognitive function in some individuals diagnosed with MCI remains unchanged, some revert to normal levels and others decline further, eventually progressing to dementia. Differential decline within cognitive domains is also observed in MCI populations and this heterogeneity has been addressed by the identification of sub-categories (amnestic MCI single domain, amnestic MCI multiple domain, non-amnestic MCI single domain and non-amnestic MCI multiple domain) based on whether single or multiple domains are affected and the presence or absence of a memory impairment (Raz, 2000b). Within MCI populations, the amnestic subtype

(aMCI) may characterise individuals who are strongly predisposed to AD (Petersen, 2004). Individuals with aMCI are considered neither normal nor demented with regard to cognitive function, usually assessed using the Mini Mental State Exam (MMSE) (Folstein et al., 1975), but specifically show memory impairment in isolation (aMCI single domain) or in conjunction with impairment in other cognitive domains (aMCI multiple domain). Based on Peterson's criteria, people with aMCI must have objective memory impairment for their age but no particular test or cut-off score has been specified in the literature. Word list learning or paragraph recall tests have been suggested as a means of assessment and a cut-off score of 1.5 SD below age-mates is used by some investigators (Petersen, 2004) while others use 1SD below the group mean (Dixon et al., 2007). The mean performance of the original MCI cohort followed at the Mayo clinic was 1.5 SD below their age-mates. However, this was not a cut-off score and half of the group had memory performance scores $\leq$ 1.5 SD below the mean. How the memory impairment in aMCI should be measured remains contentious but what is clear is that the objective memory complaint is meant to represent a change for that person. Many older people with age-appropriate memory performance complain of poor memory relative to their ability when they were younger. Winblad (2004) suggests that individual slopes of decline may be a better measure of deterioration than deficits assessed according to age-specific norms.

Classifying individuals on the basis of their cognitive profile has been used to investigate sub-group associations with distinguishing characteristics in healthy elderly and to examine whether performance profiles can predict future cognitive decline (Hilborn, Strauss, Hultsch, & Hunter, 2008). The sub-group approach has also been used with individuals diagnosed with cognitive impairment no dementia (CIND: Ritchie & Tuokko, 2010) to ascertain whether membership of sub-groups based on distinct neuropsychological patterns at baseline was related to diagnosis at follow up (Peters, Graf, Hayden, & Feldman, 2005). Individuals who displayed a distinct weakness in the memory domain were more likely to receive a diagnosis of dementia at follow up (Peters et al., 2005). A number of memory studies that assess the impact of age (young/old) and level of memory performance (high/low) on electrophysiological measures sub-divide their old participants based on a median split of their performance on an experimental memory task (e.g. Wolk et al., 2009). However, the association of IQ and education level with differential susceptibility to age-related and disease-induced memory change highlights the need to benchmark an older adult's memory function to his or her global intellectual ability or cognitive reserve (CR) (Scarmeas, Albert, Manly, & Stern, 2006; Stern, 2009; Stern et al., 1994). In order to classify participants in a meaningful way, that could possibly tap change for an individual relative to their younger self, older participants in this study

were sub-divided on the basis of their performance on a memory task relative to an estimate of their pre-morbid IQ. The participants all completed a battery of neuropsychological assessments and experimental tasks that tap a variety of cognitive functions with known susceptibility to age-related change: global cognition, memory, executive function, and processing speed. This chapter describes these tests and the methods used to obtain them. Performance results are also presented and the effects of age and cognitive performance are discussed.

2.2 METHOD

2.2.1 Exclusion/Inclusion Criteria

Exclusion/inclusion criteria were given careful consideration. Within ageing research there is a dilemma with regard to the selection criteria used when sampling healthy older adults in relation to whether they should be perfectly healthy or more representative of the general population (Tisserand & Jolles, 2003). It would be impractical and prohibitive to apply all of the age-extrinsic factors that have been associated with cognitive performance in older adults as exclusion criteria. In addition, such an approach would arguably yield a population of what could be described as super-elderly. This study aimed for a balance between important and practical exclusion criteria. In consultation with clinical and academic ageing experts a decision was taken to exclude anyone with a history of head injury, epilepsy, stroke, and neurological conditions. Left-handed people were also automatically excluded. Additional exclusion criteria were discussed and a decision was taken to first survey 50 potential participants in order to provide information regarding the prevalence of possible exclusions. The findings of this initial screening were then used to inform the selection of additional exclusion criteria. To this end a screening questionnaire (Appendix A) designed to gather information relevant to age-related health and life-style exclusion criteria was devised.

Advertisements seeking volunteers aged 65-80 were placed in newsletters and on the websites of a number of retirement associations including; Ageing Matters, The Older Women's Network, The Irish Association of Older People, and Third Age. Twenty of the first seventy volunteers were automatically excluded due to history of head injury, epilepsy, stroke, neurological condition or left-handedness. The remaining 50 volunteers completed the screening questionnaire which was administered over the phone. The questionnaire which collected self-report information regarding neurological, cardiovascular, endocrinological, and respiratory health, current medications, vision, hearing, and smoking, alcohol and recreational drug use, took approximately 20 minutes to complete. The data collected was analysed and presented to a team of clinical and academic experts. After careful consideration the following exclusion/inclusion criteria were decided upon: participants should be right-handed, native English speakers who reported no history of epilepsy, stroke, neurological conditions, major psychiatric disorder, diabetes, or head injury. Participants with hypertension or thyroid problems were included if stable on medication for three months (self-report). Volunteers currently taking CNS (central nervous system) medication were excluded. Smokers and volunteers whose weekly

alcohol intake exceeded 28 units were also excluded. Participants were asked to refrain from consuming alcohol in the 24 hours preceding EEG testing.

2.2.2 Participants

Of the 70 people who responded to the initial advertisement 26 failed to satisfy the exclusion criteria. A further 16 were unavailable, not contactable, or declined to take part in the study. Twenty additional older adults aged between 65 and 80 were recruited from the Robertson Participant Panel[1] giving a total of 48 older participants. Twenty-two Young controls aged between 18 and 30 were recruited from the Robertson Participant Panel or through advertisement within the college. Four older adults failed to complete the entire test battery due to ill-health (n=2), personal problem (n=1), and voluntary withdrawal (n=1). In addition, one older adult disclosed taking CNS medication after testing and one young adult drank a substantial amount of alcohol in the 24 hours preceding EEG testing and so both were excluded. Data for forty-three (18 male) older adults (M= 69.95, SD ± 3.70) and 21 (9 male) young adults (M = 21.28, SD ± 2.97) were analysed. All of the participants gave written informed consent (Appendix B) before participating in the study, which was approved by the ethics committee at the Department of Psychology, Trinity College Dublin.

2.2.3 Classifying participants

The older adults in this study were assigned to sub-groups based on their memory performance relative to an estimate of their pre-morbid IQ. Z-scores were used to relate their performance on a standardised story recall memory test (Wechsler Memory Scale: Wechsler, 1998) to their NART (National Adult Reading Test: Nelson, 1982) estimated IQ. Pre-morbid IQ was favoured over education level in this study because it represents a more sensitive measure of CR than education level, which also has limited variance, especially in women (Starr & Lonie, 2008). Participants were defined as Low performers if they scored more than one standard deviation below their NART estimated pre-morbid IQ on the Wechsler Memory Scale logical memory delayed recall test (WMS-III UK: Wechsler, 1998). Logical memory delayed recall scores and IQ scores were first converted to Z-scores and then compared (Figure 2:1). Using scores from actual older participants, (Table 2:1) illustrates how participants with identical IQ scores or identical delayed recall scores can fall into different sub-groups.

[1] A computerised resource available to members of the Robertson research laboratory which contains contact details and basic demographic and medical information for volunteers interested in taking part in research studies conducted in Trinity College Institute of Neuroscience.

Table 2:1Sample group classification calculations

ID	NART-IQ	IQ Z-score	LM2 scaled score	LM2 Z-score	IQ Z-score minus LM2 Z-score
A	117.21	1.15	13	1.00	0.15 (High performer)
B	117.21	1.15	9	-.033	1.48 (Low performer)
C	104.76	0.32	9	-0.33	0.65 (High performer)

Note: NART-IQ = IQ estimated using the National adult reading test (Nelson, 1982). LM2 = logical memory 2 delayed recall subtest of the Wechsler Memory Scale III (Wechsler, 1998).

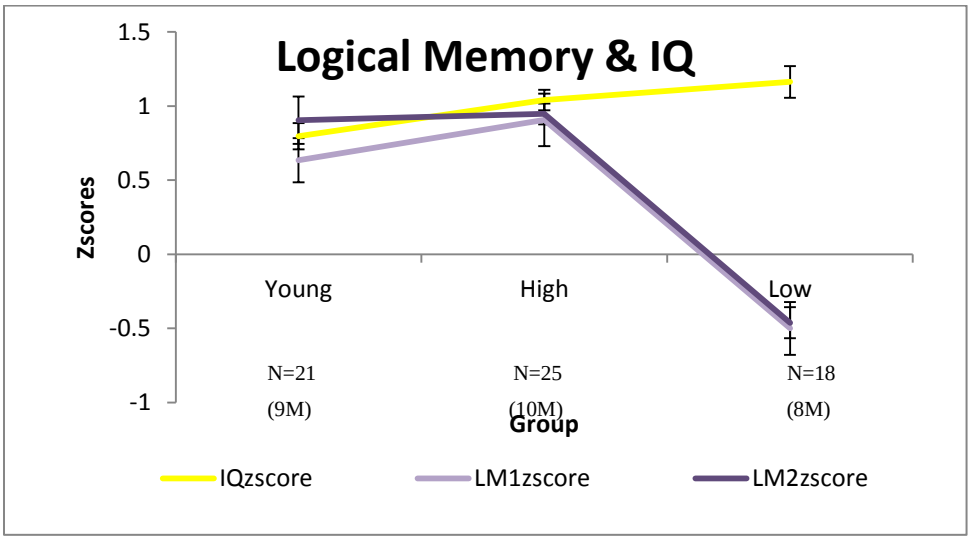

Figure 2:1 Group mean Z-scores for immediate and delayed recall

Note: (Wechsler Memory Scale III, scaled scores) and NART- IQ (National Adult Reading Test). LM1 = logical memory 1/immediate recall. LM2 = logical memory 2/delayed recall. Error bars represent one standard error. High = High performing old. Low = Low performing old.

Classifying older adults in this way yielded: a) 25 High performers (10 male, M=70.28, SD ± 3.39), and b) 18 Low performers (8 male, M=69.48, SD ± 4.15). Low performers had significantly poorer delayed recall scores (M=8.72, SD ±1.60) than both the Young (M=12.71, SD ± 2.19, $p \leq 0.0005$) and the High performers (M=12.84, SD=1.72, $p \leq 0.0005$) who did not differ significantly from each other $p=0.52$. All three groups had higher than average IQ: Young (M=111.95, SD ± 6.03); High performers (M=115.61, SD ± 5.29) and Low performers (M=117.44, SD ± 6.72). The mean level of education attained for participants at time of testing was Young (M=2.64, SD ± 0.73), High performers (M=2.54, SD ± 0.89) and Low performers (M= 2.55, SD ± .86) where level 1 = primary, 2 = secondary, 3 = third level/undergraduate and 4 = fourth level/post graduate. There was no significant difference in age or IQ between the two old groups or in education level between all 3 groups.

2.2.4 Materials

The materials used in this study were informed by the literature and chosen in consultation with a group of clinical and academic ageing experts. Experimental and neuropsychological measures were chosen based on their ability to tap a variety of cognitive functions with known susceptibility to age-related change. Measures that

screen for pathological cognitive decline, anxiety, depression, and reading difficulties were also incorporated into the protocol.

Pen and Paper Tests

2.2.4.1 Self-Report Measures

Participants completed a background questionnaire designed to collect pertinent medical and demographic information (Appendix A). Participants also completed the Morning-Evening Questionnaire (MEQ, Horne & Ostberg, 1976), which indentifies 5 chronotypes (definitely evening, moderately evening, neutral, moderately morning, and definitely morning) that in turn, reflect an individual's alertness and preference to be active early or late in the day. Participants also completed the Hospital Anxiety and Depression scale (HADs, Zigmond & Sims, 1983). Volunteers with scores ≥ 8 on the depression scale were excluded. Participants rated their overall memory on a five-point Likert scale (1 = very bad, 2 = not so good, 3 = neither good nor bad, 4 = good, and 5 = excellent) (Appendix C).

2.2.4.2 Neuropsychological Measures

All participants undertook the following neuropsychological tests: the Mini Mental State Exam (MMSE, Folstein et al., 1975) which screens for cognitive impairment, the National Adult Reading Test (NART, Nelson, 1982), which provides an estimate of pre-morbid intellectual ability; the Wide Range Achievement Test (WRAT, Wilkenson, 1993), which screens for reading achievement; Verbal fluency was assessed by asking participants to name as many animals as possible in 1 minute; and the Stroop test (Golden & Freshwater, 2002), which measures selective attention and cognitive flexibility.

2.2.4.3 Wechsler Memory Scale

Auditory and visual declarative and working memory abilities were assessed by the following subtests of the Wechsler Memory Scale (WMS-III – UK) (Wechsler, 1998); Logical Memory 1 and 2, Faces 1 and 2; Visual Reproduction 1 and 2 and Digit Span.

Experimental Tasks

Participants also completed computerised experimental tasks, which indexed memory (Learn Task), processing speed (Choice Reaction Time split response, $CRT_{sr)}$, and sustained attention (Sustained Attention to Response Task fixed, $SART_{fixed)}$. The $SART_{fixed}$ was programmed using the Presentation® software package (Version 0.75,

http://www.neurobs.com) all other experimental computerised tasks were programmed in E-Prime® (Version 2, http://www.pstnet.com).

2.2.4.4 Learn Memory Task (Cued Encoding & Delayed Recognition)

The experimental computerised Learn task was programmed in E-Prime® (Version 2, http://www.pstnet.com). All participants used the RB-530 Response box (Figure 2:2) and were instructed to respond using the index finger of their right hand.

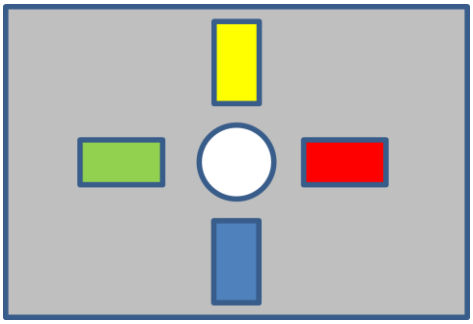

Figure 2:2 RB-530 Response box.

Encoding

For each trial a Cue (200ms), ISI1 (1200ms), Target (1500ms) and ISI2 (1200ms) were presented sequentially (Figure 2:3). In total, 126 trials were presented over a period ~ 8.5 minutes to all participants in the same order. The first six trials served as buffers and were not used in analysis. The inter-stimulus interval (ISI) in the memory task consisted of a fixation cross centred on a grey background. Targets were a set of 120 words, 4-6 letters in length, with concrete and imageable ratings of 300-700 and a written frequency of 2-60 (Francis & Kucera, 1982). The words, all nouns, were chosen from the psycholinguistic database (Coltheart, 1981). Half of the targets (L-Words) were preceded by the cue 'L' and half (X-Words) by the cue 'X'. Participants were instructed to silently read all of the words but to learn the words that followed the letter 'L'.

Between the encode and recognition phases of the Learn task participants completed a Choice Reaction Time task (CRTsr) and the Sustained Attention to Response Task ($SART_{fixed}$) (Robertson, Manly, Andrade, Baddeley, & Yiend, 1997).

Recognition

For each trial an ISI1 (100ms), a Target (500ms), an ISI2 (2,444ms) and an ISI3 (200ms) were presented sequentially. In total, 126 trials that comprised 6 buffers, 40 words that participants were instructed to learn at encoding (Learn Words), 40 words that participants were instructed only to read at encoding (Read Words), and 40

new-words, were presented to all participants in the same order over a period of ~ 8.5mins. Participants were instructed to press the green key on the RB-530 Response Box (Fig. 2.2) if they recognised the word from the encode phase regardless of whether it had been preceded by an 'L' or an 'X' and the red key if they did not. Responses were collected while the Target and ISI2 were on screen. All participants were instructed to use the index finger of their right hand when responding. ISIs consisted of a fixation cross centred on a grey background.

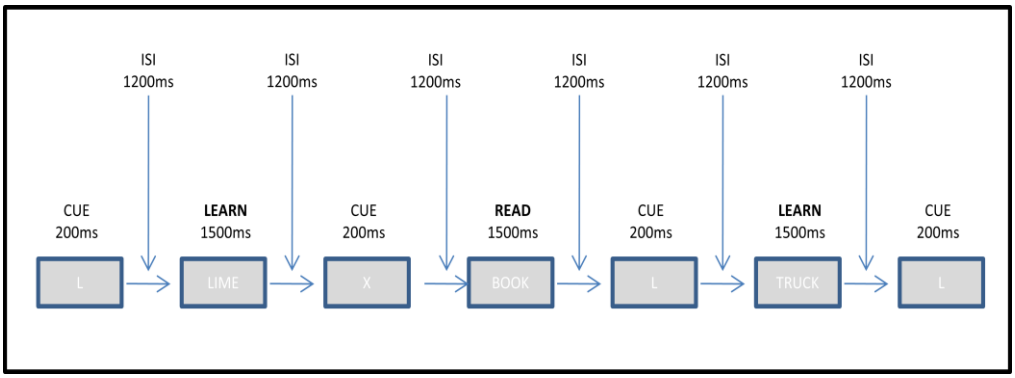

Figure 2:3 Schematic Encode Phase of Learn Memory Task.

Note: A series of words are presented on screen. Each word is preceded by a cue (L or X). Participants are instructed to learn the words that follow the 'L' cue and read the words that follow the 'X' cue.

2.2.4.5 Choice Reaction Time Task split response (CRTsr)

Speed of processing (Salthouse, 1985) has long been considered an important neurocognitive measure in cognitive ageing research (Gorus, De Raedt, & Mets, 2006). Processing speed can be measured using reaction time tests. There are 3 basic types: simple, choice, and recognition. Choice reaction times are the longest (Donders, 1868). Reaction times increase (Jevas & Yan, 2001) and become more variable with age (Hultsch, MacDonald, & Dixon, 2002). A reaction time (RT) consists of independent components: a decision element, which reflects the time necessary to initiate the response and the motor element, which reflects the time needed to execute the response (Roberts & Pallier, 2001). Although aggregate measures of variability across trials that produce a single summary measure for reaction time tasks have been investigated (e.g.Hultsch et al., 2002; Salthouse, 1993) little research attention has been paid to evaluating intra-individual variability in relation to the constituent components of reaction times. Nonetheless, two studies have attributed intra-individual variability in choice reaction time tasks to the decision rather than the motor component (Bunce et al., 2004; Gorus, De Raedt, Lambert, Lemper, & Mets, 2008). The choice reaction time task used in this study was developed in order to explore this relationship by splitting the response into decision and motor elements.

The CRTsr task was programmed in E-Prime® (Version 2, http://www.pstnet.com). Participants were instructed to hold down the central white button of the RB-530 Response Box to trigger target onset (See Figure 2:2 for key layout). Target offset was achieved by releasing the white key and by pressing either the green or the red key. Participants were instructed to press the 'green' key if the target 'YES' appeared on screen and the 'red' key if the target 'NO' appeared on screen. Participants were instructed to respond quickly and accurately and to hold down the white key after target offset to trigger the next target onset. As a safeguard against pre-emptive responding target offset could not be achieved if the white key was released before the target appeared on screen. In this task the interval between depression of the white trigger key and the target onset varied between 800ms and 1100ms. The task comprised 50 'NO' trials and 50 'YES' trials, which were presented in random order. This task was self-paced to guard against the interference that can occur when older people complete force paced tasks (Birren & Schaie, 1990). RT on this task was measured in milliseconds and divided into 'cognitive response' measured as time from target onset to trigger offset (release of white key) and 'motor response' measured as time from trigger offset to response selection (depression of green key or red key).

2.2.4.6 The Fixed Sequence Sustained Attention to Response Task (SART$_{fixed}$).

SART$_{fixed}$ (Robertson et al., 1997) assesses executive control of behaviour. It is particularly sensitive to transient lapses of attention, and challenges the ability to endogenously maintain an alert state (Manly, Davison, Heutink, Galloway, & Robertson, 2000). Performance on SARTfixed is prone to rapid automisation. SART activates the sustained attention network and is sensitive to frontal lobe dysfunction (Manly et al., 2003). The specificity of the SART for the sustained attention deficit of children with ADHD has been demonstrated (Shallice et al., 2002) as has its sensitivity for indexing self-report absent-mindedness in adults (Robertson et al., 1997). The reliability and validity of the SART as a measure of executive control of behaviour has been demonstrated in previous studies (Dockree et al., 2004; Manly et al., 2003; Robertson et al., 1997).

The digits '1' through '9' were presented sequentially. Over a period of ~5mins 225 digits that varied in size were presented (25 of each of the 9 digits). Participants were instructed to depress the left mouse button on presentation of each digit (go-trials) with the exception of the 25 occasions when the digit 3 (target / no-go trial) appeared where they were required to withhold their response (Figure 2:4). For each trial a digit was presented for 150ms followed by an inter-stimulus interval (ISI) that varied randomly between 1000 and 1500ms. This variable interval was introduced

to prevent participants from succumbing to a speed accuracy trade off that can occur when ISIs are evenly paced.

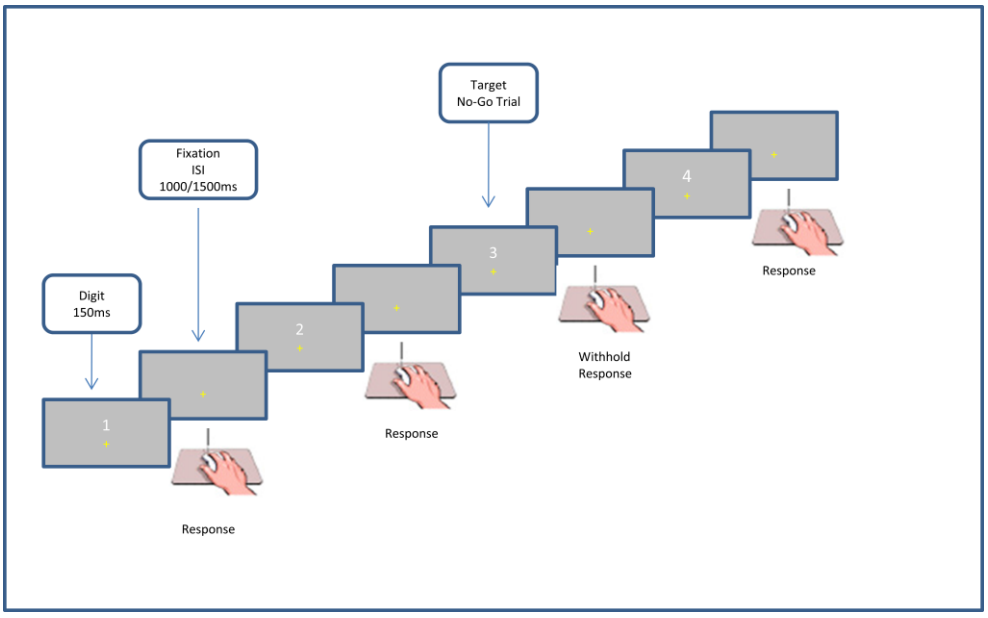

Figure 2:4 Schematic of the SARTfixed task showing three go-trials and one no-go trial.

Note: The numbers '1' through to '9' appear on screen in fixed sequence. Participants are instructed to press the mouse button to every number (go-trials) except the number 3 (no-go trial).

2.2.5 Procedure

Piloting was conducted to inform the design of the research protocol, assess whether the proposed protocol was realistic and workable, check the impact of the protocol on research participants, identify logistical problems, confounds, and floor and ceiling effects. Rigorous testing of the experimental tasks and the EEG equipment was conducted to check correct operation of the equipment and to ensure accurate recording and excellent temporal resolution of stimulus, response, and EEG signals. The information obtained on logistic issues was incorporated into the design of the study. Piloting revealed the need for two separate testing sessions in order to avoid participant fatigue. During Session 1 participants completed the neuropsychological assessments and memory tasks. Ordering of task administration was carefully considered and where appropriate timing of tests outlined in administration manuals were carefully incorporated into the protocol. During Session 2 EEG was recorded while participants completed the experimental tasks. Piloting revealed the need to train participants on two of these tasks and so training on the SART$_{fixed}$ and the CRTsr task were incorporated into Session 1. Pilot participants found the initial version of the Learn task, which was based on a task employed by Hogan et al. (2006) too difficult. To avoid floor effects, the task was revised and piloted again (for further details see chapter 6 section 6.2.2.1). Analysis of pilot EEG data revealed that the response box was generating 60Hz harmonics and interfering with the EEG signal recorded from

some of the pilot participants. After several attempts to eliminate the problem failed a decision was taken to purchase a different type of response box (RB-530) which worked perfectly when piloted. Standard operating procedures for Session 1 and Session 2 were developed to ensure consistency of administration across participants (see Appendices D and E).

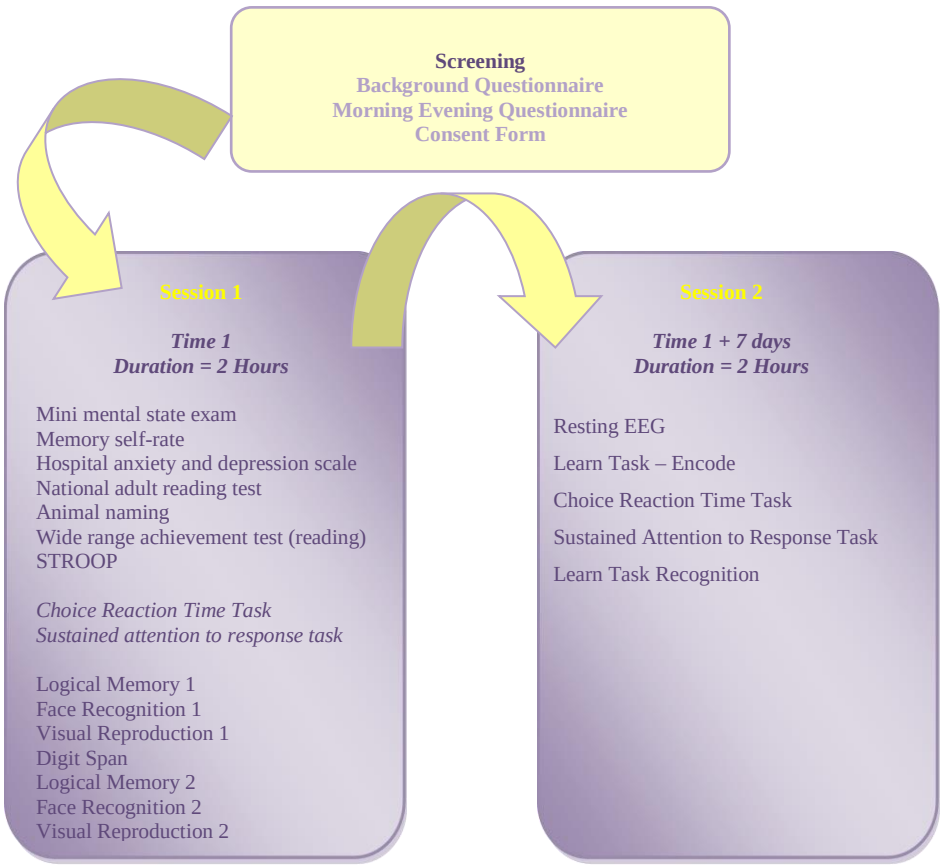

Figure 2:5 Schematic of testing protocol and order of test administration

Screening: The Background Questionnaire was completed over the phone. The Morning Evening Questionnaire and Consent form were then posted to the participants to be completed at home before Session 1. Session 1 took approximately two hours for older participants and 1.5 hours for young participants. During Session 1 participants were taught how to complete the Choice Reaction Time and Sustained Attention to Response Task. Session 2 took no more than 2 hours including application of electrodes.

All testing was conducted between September 2008 and May 2009. Figure 2.5 illustrates the testing protocol. The background questionnaire and the MEQ were completed off site prior to testing. Participants were assessed in two ~ 2hour sessions that took place approximately one week apart. Participants were allocated to either two morning (10am) testing sessions or to two afternoon (2pm) sessions. Approximately half of the participants from each group completed morning sessions. Chronotypes, as determined by MEQ scores, were also taken into consideration when allocating testing time to ensure a reasonably equal distribution of optimal, non-optimal, and neutral testing times within and across groups (see Table 2:2).

Table 2:2 Chronotype and Testing Time

	Young (21)		High (25)		Low (18)	
	AM-test	PM-test	AM-test	PM-test	AM-test	PM-test
Moderately Morning		1	7	8	5	5
Definitely Morning			3	1	2	2
Neutral	8	8	3	3	1	3
Moderately Evening	1	1				
Definitely Evening	1	1				
Session AM:PM	***10:11***		***13:12***		***8:10***	
Optimal: Non-Optimal	***2:3***		***10:9***		***7:7***	
Neutral	***16***		***6***		***4***	

Note: Table shows the testing times for each group by chronotype and the ratio of participants tested at optimal and non-optimal testing times. Chronotype reflects the time of day when an individual is most alert and runs along a continuum from morningness to eveningness. High = High performing old. Low = Low performing old. Green cells = optimal testing time. Optimal = when participant testing time coincides with their chronotype. Non-Optimal = when participant testing time differs from their chronotype.

During Session 1 participants completed the remaining self-report measures, and the neuropsychological tests. In order to familiarise participants with task instructions and response technology each individual completed the CRTsr and the SART$_{fixed}$ tasks. During this practice session participants were observed and made aware of the importance of limiting movements and speech in advance of completing the tasks in Session 2 during EEG acquisition. During Session 2 resting EEG was recorded for 3 minutes with eyes closed, and for 3 minutes with eyes open. Participants then completed the encode phase of the Learn task, the CRTsr, the SART$_{fixed}$, and the recognition phase of the Learn task.

2.3 RESULTS

Results will be reported under the following headings:

2.3.1 Pen and Paper Tests

2.3.1.1 Morning Evening Questionnaire (MEQ)
2.3.1.2 Hospital Anxiety and Depression Scale (HADS)
2.3.1.3 Memory Self-Rate
2.3.1.4 Mini Mental State Exam (MMSE)
2.3.1.5 National Adult Reading Test (NART)
2.3.1.6 Wide Range Achievement Test (WRAT3)
2.3.1.7 Fluency
2.3.1.8 Stroop

2.3.2Wechsler Memory Scale

2.3.2.1 Logical Memory
2.3.2.2 Face Recognition
2.3.2.3 Visual Reproduction
2.3.2.4 Digit span

2.3.3 Experimental Tasks

2.3.3.1 Learn Task performance accuracy
2.3.3.2 $SART_{fixed}$ performance accuracy
2.3.3.3 CRT_{sr} performance accuracy

Analysis Strategy

ANOVAs (mixed model and one-way) were used to test for interactions, main effects, and significant differences between groups. Effect sizes were calculated using eta^2 or partial eta^2 and were categorized as follows: small= 0.01, medium = 0.06 and large= 0.14 (Cohen, 1988). A robust test of equality of means (Brown-Forsythe) was used when the assumption of homogeneity of variances was violated. When variables were not normally distributed non-parametric equivalents were used. For post-hoc analysis Tukey's HSD test is reported unless stated otherwise.

2.3.1 Pen and Paper Tests

2.3.1.1 Morning/Evening Questionnaire (MEQ)

Scores on the MEQ scale range from 16 to 86 with lowest scores reflecting extreme eveningness and highest extreme morningness. Table 2:3 illustrates the frequency of chronotypes for the three groups using the MEQ classification system. The Young had MEQ scores that differed significantly from both High performers and Low performers' scores (Table 2:4). Both of the old adult groups were predominantly morning types while the Young were predominantly neutral.

Table 2:3 Frequency of Chronotype

Chronotype (score)	Young (n=21)	High (25)	Low (18)
Definitely Morning (70-86)		4	4
Moderately Morning (59-69)	1	15	10
Neutral (42-58)	16	6	4
Moderately Evening (31-41)	2		
Definitely Evening (16-30)	2		

Note: High = High performing old. Low = Low performing old.

2.3.1.2 Hospital Anxiety and Depression Scale (HADS)

This scale has two distinct elements that measure anxiety and depression. Higher scores on either element indicate higher levels of anxiety and depression respectively. There were no significant differences between the three groups on either element of the scale (see Table 2:4).

2.3.1.3 Memory Self-Rate

The Young had the highest mean subjective memory rating and Low performers the lowest. There was a statistically significant main effect of Group (Kruskal-Wallis; H=7.49, 2df, $p \leq 0.05$) and Mann-Whitney U post-hoc tests revealed that this was due to significantly lower memory self-ratings made by Low performers when compared with the Young ($p \leq 0.01$).

Table 2:4 Means, Standard Deviations, & p-values for self-report measures & pen & paper tests

Test	Young	High	Low	df	p-value
	(n=21)	*(n=25)*	*(n=18)*	*(2,61)*	
MEQ	46.24 (8.36)[1]	63.20(7.45)	62.17(7.89)	H=31.67	**p≤0.0005**
HADS (anxiety)	6.14 (2.11)	4.56 (3.19)	4.33 (2.25)	F=1.64	p>0.10
HADS (depression)	2.38 (2.11) [1]	2.12(1.69) [1]	2.89 (2.25)	H=1.13	p>0.10
Memory self-rate	3.76 (0.83) [1]	3.44 (0.92)[1]	3.11 (0.76) [1]	H=7.49	**p≤0.05**
MMSE	29.33 (0.80) [1]	28.84 (1.21) [1]	27.67 (1.33) [1]	H=17.4	**p≤0.0005**
NART	111.95 (6.04)	115.61 (5.29)	117.44 (6.72)	F=4.38	**p≤0.05**
Fluency	27.38 (6.90)	21.08 (3.83) [1]	19.33(7.51)	H=14.09	**p≤0.001**
	(n=20)	*(n= 25)*	*(n=18)*	*(2,60)*	
WRAT3	529.90 (12.65)	532.50 (10.60)	530.68 (8.21)	H=0.35	p>0.10
	(n=19)	*(n= 25)*	*(n=18)*	*(2,59)*	
Stroop	58.63 (9.34)	46.72 (4.90)	45.61(8.88)	F=17.19	**p≤.0005**

Note: Standard deviations are in parenthesis. High = High performing old. Low = Low performing old. MEQ = Morning-Evening Questionnaire (Horne & Ostberg, 1976). HADS = Hospital Anxiety and Depression Scale (Zigmond & Sims, 1983). Memory self-rate = 4 point Likert memory scale. MMSE = Mini Mental State Exam (Folstein et al., 1975). NART = National Adult Reading Test – full scale IQ (Nelson, 1982). Fluency = number of animals named in 60 seconds. WRAT3 = Wide Range Achievement Test – absolute score (Wilkenson, 1993). Stroop-t-score (Golden & Freshwater, 2002). [1] not normally distributed ∴non-parametric tests used (Kruskal-Wallis).

2.3.1.4 Mini Mental State Exam (MMSE)

The maximum score on the MMSE, which measures general cognitive function, is 30 and scores between 24 and 30 are considered within the 'normal range'. Young had the highest MMSE scores and Low performers the lowest. Minimum score was 25 for both High and Low performers and 27 for Young. Maximum score was 30 for all three groups. General cognitive function for Low

performers was significantly poorer than both High performers and Young. Cognitive performance in Young and High performers was not significantly different. Analyses of the individual sections of the MMSE revealed significant group differences only on the memory (Kruskal-Wallis; H=16.99, 2df, p≤0.0005) and orientation (Kruskal-Wallis; H=13.70, 2df, p≤0.001) elements of the test.

2.3.1.5 National Adult Reading Test (NART)

The mean full-scale IQ score for all three groups as predicted by participant's NART error scores were higher than average based on a mean of 100 and SD of 15 (NART manual; Nelson, 1982). Although the Young had significantly lower IQ than both High and Low performers, the IQ for the two older groups did not differ significantly (Table 2:5).

2.3.1.6 Wide Range Achievement Test 3 (WRAT3)

The means and standard deviations for WRAT3 absolute scores (raw scores transformed to scale scores with a mean of 500) are reported in Table 2:4. Absolute scores do not take account of education level or age. There was no significant difference in reading achievement scores across the three groups. While this measure was included to screen for adequate reading ability it is worth noting that the scores were highly correlated with NART scores (Young, r=0.84, p≤0.0005; Old r=0.76, p≤0.0005).

Table 2:5 Post-hoc comparisons for self-report measures and pen and paper tests

	Post-Hoc Tests		
	Young / Low	Young / High	High/ Low
	P-value	P-value	P-value
MEQ	**p≤0.0005**	**p≤0.0005**	p>0.10
Memory self-rate	**p≤0.01**	p>0.10	p>0.10
MMSE	**p≤0.0005**	p>0.10	**p≤0.01**
NART	**p≤0.05**	**p≤0.05**	p>0.10
Fluency	**p≤0.01**	**p≤0.001**	p>0.10
Stroop	**p≤0.0005**	**p≤0.0005**	p>0.10

Note: *High = high performing old. Low = low performing old. MEQ = Morning-Evening Questionnaire (Horne & Ostberg, 1976). Memory self-rate = 4 point Likert scale. .MMSE = Mini Mental State Exam (Folstein et al., 1975). NART = National Adult Reading Test – full scale IQ (Nelson, 1982). Fluency = number of animals named in 60 seconds. WRAT3 = Wide Range Achievement Test – absolute score (Wilkenson, 1993). Stroop-t-score (Golden & Freshwater, 2002).*

2.3.1.7 Fluency

Mean animal naming scores for all three groups were higher than average based on norms (Table 2:6) stratified by age and education reported by Tombaugh, Kozak and Rees (1999). Both High and Low performers had maximum scores of 34 animals named but the Low performers' group minimum score was 7 whereas the group minimum for High performers was 17. The Young had a range of 27 (min= 17 and max= 43). There was a main effect of Group (Table 2:4). Post-hoc (Mann-

Whitney U) revealed that Young named significantly more animals than both the High and Low performers (Table 2:5). Verbal fluency in the two older groups was not significantly different (Table 2:4).

Table 2:6 Norms for animal naming stratified for age and years of education.

	Age 16-59yrs		Age 60-79yrs	
Education	9-12yrs	13-21yrs	9-12yrs	13-21yrs
	19.8 (4.2)	21.9 (5.4)	16.4 (4.3)	18.2 (4.2)

Note: Normative data from (Tombaugh et al., 1999). All participants in the current study had > 8 years of education. Standard deviations are in parenthesis.

2.3.1.8 Stroop

The Young demonstrated significantly better cognitive flexibility and selective attention (as measured by the Stroop) than both the High and Low performers (Table 2:5). There was no significant difference between the two older groups.

2.3.2 Wechsler Memory Scale

Wechsler Memory Scale subtest raw scores for Logical Memory, Face Recognition, Visual Reproduction, and Digit Span are transformed to age-corrected scaled scores with a mean of 10 and a standard deviation of 3. The mean scores for the tests were above average for each group with the exception of the Low performers' Logical Memory scaled scores, which were below average, but still within one standard deviation of the mean (see Table 2:7). Mixed model ANOVAs with three levels of Group (Young, High, Low) and two levels of Recall (Immediate, Delayed) were conducted for Logical Memory, Face Recognition, and Visual Reproduction subsets of the WMS-III.[2]

Table 2:7 Wechsler Memory Scale, Mean Scaled Scores

WMS-III Sub-Test		Young (n=21)	High (n= 25)	Low (n=18)
		Mean (SD)	Mean (SD)	Mean (SD)
Logical Memory	Immediate	11.90 (2.05)	12.72 (2.67)	8.50 (2.26)
	Delayed	12.71 (2.19)	12.84 (1.72)	8.72 (1.60)
Face Recognition	Immediate	10.86 (2.56)	11.64 (3.70)	11.78 (3.24)
	Delayed	12.19 (2.87)	12.24 (3.37)	13.00 (2.87)
Visual Reproduction	Immediate	12.95 (2.87)	11.16 (3.02)	10.67 (3.48)
	Delayed	15.76 (2.59)	13.44 (2.53)	11.89 (4.15)
Digit Span		12.10 (2.59)	12.00 (2.80)	11.39 (2.06)

Note: High = high performing old. Low = low performing old. Immediate = immediate recall). Delayed = delayed recall. Standard deviations are in parenthesis.

2.3.2.1 Logical Memory (Immediate and Delayed Recall)

There was a significant Group effect, but no main effect of Recall and no significant interaction (Table 2:8). Post-hoc comparisons showed that the Low

[2] Non-parametric equivalents produced the same pattern of effects for the logical memory and visual reproduction measures.

performers had significantly poorer recall on the Logical Memory test than the Young ($p \leq 0.0005$) and the High performers ($p \leq 0.0005$) who did not differ significantly from each other $p > 0.10$.

2.3.2.2 Face Recognition

There was a significant effect of Recall, but no Group effect and no significant interaction (Table 2:8).

2.3.2.3 Visual Reproduction

There was a significant Group effect, a main effect of Recall, but no significant interaction (Table 2:8). Post-hoc comparisons revealed that Young differed significantly from both Low ($p \leq 0.005$) and High performers ($p \leq 0.05$). High and Low performers' scores were not significantly different ($p > 0.10$).

2.3.2.4 Digit Span

Digit span mean scaled scores are reported in Table 2:7 There was no significant difference between the groups for the digit span scaled score [$F(2,61)=0.44$, $p>0.10$], (partial eta squared = 0.01).

Table 2:8 Wechsler Memory Scale – Main Effects and Interactions

Logical Memory Immediate and Delayed Recall (WMS-III)		Partial Eta²	p-value
Story Recall (Logical Memory)			
Interaction (Recall x Group)	Wilks λ 0.96, $F_{(2,61)}=1.20$	0.04	p>0.10
Main Effect – Recall (Immediate, Delay)	Wilks λ 0.94, $F_{(1,62)}=3.69$	0.06	*p=0.06*
Main Effect Group (Young, High, Low)	$F_{(2,61)}=26.20$	0.46	**p≤0.001**
Face Recognition			
Interaction (Condition x Group)	Wilks λ 0.99, $F_{(2,61)}=0.38$	0.01	**p>0.10**
Main Effect – Recall (Immediate, Delay)	Wilks λ 0.89, $F_{(1,62)}=7.31$	0.11	**p≤0.01**
Main Effect Group (Young, High, Low)	F(2,61) 0.48	0.02	p>0.10
Visual Reproduction			
Interaction (Recall x Group)	Wilks λ 0.93, $f_{2,61}=2.44$	0.07	p>0.10
Main Effect – Recall (Immediate, Delay)	Wilks λ 0.53, $f_{1,62}=54.16$	0.37	**p≤0.001**
Main Effect Group (Young, High, Low)	$F_{(2,61)}=6.38$	0.17	**p≤0.001**

Note: High = high performing old. Low = low performing old.

2.3.3 Experimental Tasks

2.3.3.1 Learn Task

<u>*Method: Learn Task Recognition*</u>

In the recognition phase of this task participants are asked to discriminate between words that they encountered in the encode phase (old) and new words regardless of whether they had been instructed to learn the words (L-Words) or read the words (X-Words). Participants were instructed to make this distinction by pressing

the ‘green’ button of the RB-530 response box for old words and the ‘red’ button for new words (Figure 2:2). Percentage correct is not a very meaningful measure of discrimination accuracy in this task because pressing the green button in response to every item would result in a 100% correct score on the ‘old’ words. Percentage correct only becomes meaningful when the participant’s response tendency or bias is taken into account. Signal detection theory (MacMillan & Creelman, 2005) attributes responses to a combination of sensitivity and bias where sensitivity, broadly speaking, refers to detecting a signal against background noise or compared to another signal. The traditional way of viewing a discrimination task is represented in Table 2:9

Table 2:9 Possible Responses, Learn Task recognition phase.

Participant’s response Is this an old word?	Green Yes	Red No
Stimuli – Old Word	HIT (H)	MISS (M)
Stimuli - New Word	FALSE ALARM (F)	CORRECT REJECTION (C)

H is the proportion (P) of YES trials to which the participant responded ‘yes’ = P (‘yes’/YES) and F is the proportion (P) of NO trials to which the participant responded ‘yes’ = P (‘yes’/NO). D-prime represents a summary score of signal detection, and is derived by calculating the difference between the normalized values of the H and F. While a participant for whom H=F could be described as performing in a random manner no optimal cut-off has been described in the literature (McFall & Treat, 1999). Adopting a conservative d-prime cut-off score of .88 (H > 66% and a F ≤33%) has been used (Kates et al., 2007) to identify participants who perform poorly but not randomly.

$$d' = z(H) - z(F).$$

Results: Learn Task Recognition

Learn Task Accuracy

Figure 2:6 is a graphical illustration of the d-prime recognition scores for correctly identified old words that participants were instructed to Learn at the encode phase (Learn Words) and correctly identified old words that participants were instructed to Read at the encode phase of the task (Read Words). The Young had the best recognition scores and the Low performers the poorest for both Learn Words and Read Words. All three groups performed above chance for Learn Words. The Young also performed above chance for the Read Words. In contrast, the High performers responded poorly, but not randomly, for the Read Words. The Low performers’ response to the Read Words could be described as random or below chance.

A mixed model ANOVA with three levels of Group (Young, High, Low) and two levels of Condition (Learn/Read) revealed a significant Group effect, a main effect of Condition, but no significant interaction (Table 2:10). Figure 2:6 illustrates that all three groups benefitted from cued encoding. Post-hoc comparisons (LSD) indicated that Young word recognition scores were significantly better than Low ($p \leq .0005$) and High performers ($p \leq 0.05$). High performers also had significantly better recognition scores than Low performers ($p \leq 0.05$).

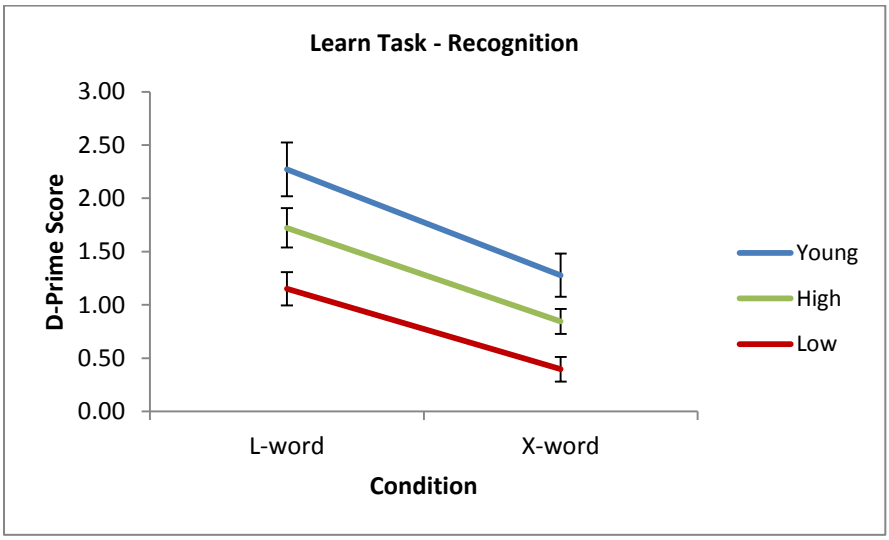

Figure 2:6 Mean recognition scores on the Learn task by word type and group

Note: Group = (Young, High performing old, and Low performing old). L-word = words participants had been instructed to 'Learn' during the encode phase. X-Word = words participants were instructed to 'Read' during the encode phase. Error bars represent one standard error of the mean.

Table 2:10 Learn Task Word Recognition Main Effects and Interactions

Logical Memory Immediate and Delayed Recall		Partial Eta²	p-value
Interaction (Condition x Group)	Wilks λ 0.97, F(2,54) 0.86	0.03	p>0.10
Main Effect – Condition (Learn, Read)	Wilks λ 0.27, F(1,54) 1.46	0.73	**p≤0.0005**
Main Effect Group (Young, High, Low)	F(2,54) 8.74	0.24	**p≤0.001**

2.3.3.2 Sustained Attention to Response Task – Fixed. (SART$_{fixed}$)

Method: SART$_{fixed}$

Extremely fast or extremely slow responses may reflect accidental key presses (e.g. 'double clicks') rather than true errors of omission or commission. To address this potential problem separate means and standard deviations were calculated for each individual based on their raw reaction times (RTs). The distribution of each individual's raw latency scores were examined for outliers, which were defined as responses that occurred more than 3SDs outside the individual's own mean RT. Presses on the target (no-go trial) were defined as commission errors and failure to respond to a go-trial were defined as errors of omission. However, if an omission on 4 was preceded by an error of commission on 3 that occurred at a latency more than

3SD above the individual's own mean RT then it was determined to be an early response to 4 and classified as a pre-emptive error. Similarly, if an error of omission was preceded by a double response to the preceding go-trial it was classified as a pre-emptive error rather than an error of omission.

Results: SARTfixed

SART$_{fixed}$ Accuracy

Descriptive statistics and p-values for accuracy scores are detailed in Table 2:11. There were no significant Group differences for errors of commission, or errors of omission. Pre-emptive errors did approach significance with the Young making more pre-emptive responses than both of the old groups (Kruskal-Wallis).

Table 2:11 SARTfixed means and standard deviations for errors.

Error Type	Young (17)	High (23)	Low (17)	df (2,57)	p-value
Commission	0.82(0.81)	1.13(0.92)	1.47(1.84)	H=0.08	p>0.10
Omission	1.82(2.67)	2.43(2.33)	2.35(3.90)	H=0.40	p>0.10
Pre-Emptive	2.76(2.68)	1.43(1.24)	1.35(1.84)	H=5.43	p=0.06

Note: High = high performing old. Low = low performing old. Commission: key press to no-go trial. Omission = failure to respond to go-trial. Pre-emptive: pre-stimulus response to a go-trial. Standard deviations are in parenthesis.

2.3.3.3 CRTsr

Young had the highest mean accuracy score and Low performers the lowest (Table 2:12). There was a statistically significant main effect of Group (Kruskal-Wallis; H=6.54, 2df, $p \leq 0.05$) and Mann-Whitney U post-hoc tests revealed that this was due to significantly greater accuracy in the Young when compared with both of the older groups ($p \leq 0.05$).

Table 2:12 CRTsr means and standard deviations for response accuracy.

CRTsr	Young	High	Low	p-value (df)
	n = 18	n = 23	n = 16	
Accuracy	99.83 (0.38)	99.74 (0.54)	99.25 (0.85)	**p≤0.05**(2)

Note: CRTsr= Choice Reaction time task split response. High = high performing old. Low = low performing old. Standard deviations are in parenthesis.

2.4 DISCUSSION

In this chapter membership of cognitive performance groups (High, Low) for older adults was established on the basis of asymmetry between their performance on a standardized memory test of verbal recall and their NART estimated pre-morbid IQ. All participants completed a battery of neuropsychological assessments and experimental tasks allowing a cognitive profile for each group to emerge. The pattern of significant differences that became apparent across the three groups (Young, High, Low) is interesting and suggests that classifying older adults in this way facilitates a meaningful exploration of differential decline in ageing and investigation of indices of such decline. Old participants were classified as High performers or Low performers based on a verbal memory measure relative to IQ but all three groups were significantly distinguished from each other by their level of performance on this memory recall measure independent of IQ. None of the other memory measures of the Wechsler memory scale (WMS; face recognition, visual reproduction, digit span) distinguished the High performers and Low performers suggesting that the cognitive performance group effect may be specific to verbal memory.

The literature supports a division of episodic memory into recall and recognition memory with the former demonstrating preferential vulnerability to age-related decline (Nyberg et al., 2003; Schonfield & Robertson, 1966). Interestingly, age and cognitive performance effects were also significant on a separate experimental measure (Learn task) of memory recognition, a process where the effects of age are usually less dramatic than those observed for memory recall. Importantly, general cognitive function (MMSE) for all participants was within the normal range but Low performers were functioning at a significantly lower level than both the Young and the High performers. Analyses of MMSE sub-components revealed that significant age and cognitive performance effects were only present in memory and orientation subsets, both elements that tap memory for recent events, suggesting differential performance in episodic memory only. Low performers also had the lowest mean subjective memory rating. Their mean was significantly different from that of the Young who had the highest, suggesting that perhaps Low performers had an awareness of problems with their memory above and beyond that of the High performers, who did not differ significantly from Young controls in how they rated their memory. The pattern of significant effects reported in this chapter reveal an interesting dissociation between performance on episodic memory measures and on established measures known to tap executive function or attention (fluency and stroop). While significant age effects were evident, performance on these tasks for the two older groups was on a par. Furthermore, there were no age or cognitive

performance effects for accuracy measures on the experimental task that assessed executive control of behavior ($SART_{fixed}$). Taken together this pattern of significant differences suggests that the group classification approach adopted here identified sub-groups with cognitive profiles that differed specifically in terms of episodic memory function.

Why the two older adult groups differ from each other in this way is a big question which is difficult to answer in the absence of longitudinal data. Since Rowe and Kahn (1987) first drew a distinction between usual, successful, and pathological ageing in their landmark paper, multiple biological, psychological, and social factors that influence individual trajectories of cognitive decline have been identified (Glatt et al., 2007; Montross et al., 2006; Raz & Rodrigue, 2006; Rowe & Kahn, 1987). Rowe and Kahn's model proposes that the most common pattern of cognitive decline (usual ageing) is determined by both age-intrinsic and age-extrinsic factors (e.g. lifestyle, diet), while successful ageing describes a pattern of age-determined cognitive decline where age-extrinsic factors play a neutral or positive role (Rowe & Kahn, 1987). Stringent exclusion criteria were imposed in this study to limit the effects of age-extrinsic factors and reduce participant heterogeneity in this regard. Nonetheless, not all factors can be accounted for and so the differences observed could reflect the influence of age-extrinsic factors not controlled for. It is, therefore, possible that successful cognitive ageing is reflected in the High performers who, although showing decline in memory performance relative to Young controls, demonstrate significantly better performance than the Low performers whose performance could well reflect usual decline. Given the considerable overlap observed at the boundary of normal and pathological decline, it is also possible that the Low performers may actually be on the threshold of pathological decline even though their memory performance was within the statistically normal range relative to age-mates. Nonetheless, it is interesting to note that their performance was below average. In contrast, the High performers' scores were above average as were the control's scores. Previous studies that have used a sub-group classification approach have shown that people who display a distinct weakness in the memory domain are more likely to receive a diagnosis of dementia at follow-up (Peters et al., 2005). The delayed memory subset of the MMSE, which specifically distinguished the groups in this study, has been shown to be a significant predictor of people who go on to develop AD irrespective of age, sex and years of education (Small, Fratiglioni, Viitanen, Winblad, & Backman, 2000). It is important of course to reiterate that all participants in this study had normal general cognitive function and performed within the expected range for their age. Furthermore, it is also important to note that classification of clinical impairment does not totally rely on performance on memory tests but importantly pivots on a

clinician's judgment. Finally, given the cross-sectional nature of this research it is possible that classifying participants in this way simply tapped into longstanding, possibly innocuous, group differences. Combining neuropsychological testing with neurophysiological measurement, as this study does, will not fully address this question, but may ultimately help to explicate differential decline.

The importance of classifying sub-groups within research populations is highlighted by the observation that treating older participants in this study as a homogenous single group yielded no significant differences on verbal memory recall performance. A finding that confirms the suggestion made earlier that failure to acknowledge group heterogeneity by conducting old versus young comparisons that focus only on average tendencies within groups may inaccurately assess the effects of ageing and possibly even miss emerging impairment. The classification method chosen in this study is of course only one of many possible approaches to examining differential decline through sub-groups. Simply using a median split based on memory performance is, of course, also a valid approach that in this case would have yielded not entirely dissimilar groups. One distinct advantage of the approach used here is that it allows identification independent of research sample and therefore may have utility when pre-screening for participants with a particular cognitive profile in research situations, drug efficacy trials, intervention studies, or even in a clinical setting.

Many cognitive ageing studies suffer from cohort differences in education level that make it difficult to disentangle true age-related differences. This study consisted of older participants many of whom were retired professionals and well-matched to young university students in terms of educational level. Some refer to such individuals as *super-elderly* arguing that they are not typical of age-mates in the general population. But it can be equally argued that university students and graduates are not typical of their age-mates in the general population. One advantage of using relatively highly educated elderly participants is that any age-related differences that emerge represent the lower bound of effects that can be attributed to non-pathological ageing (Rugg & Morcom, 2005). One possible confound in this study is the fact that the Low performers had significantly higher IQ than the Young controls although this is likely to result in an underestimation of memory deficits rather than an overestimation particularly on tasks with a verbal element given the greater verbal facility of older adults compared with younger adults (Wingfield & Stine-Morrow, 2000). As discussed in Chapter 1 failure to control for testing time and time of day modulations may lead to an over estimation of age differences (Yoon et al., 2000). The fact that this study carefully controlled for such modulations by ensuring a balance of testing times across participants and chronotypes arguably yields results that more accurately reflect age differences than studies, for example, that hold testing time constant across

participants thereby testing young adults at their optimal time and old adults at their non-optimal time or vice-versa. It should be noted that the subjective memory test used in this study is rather limited not only because it simply asked participants to rate their memory on a five-point Likert scale but also because instructions failed to specify whether participants should rate their memory relative to other people in general, to their age-mates in particular, or indeed, to their younger selves.

To summarize significant age differences were evident across measures of executive function, memory, and processing speed. In contrast, High performers were only distinguished from the Low performers on measures of memory suggesting that we may have captured cognitive variability by identifying sub-groups representative of different cognitive profiles. The next step is to ascertain whether other putative and novel indices of age-related cognitive decline such as intra-individual variability in RT, EEG, and ERP measures support this classification. The next chapter examines intra-individual variability in RT.

Chapter 3 VARIABILITY IN REACTION TIME

3.1 INTRODUCTION

Within ageing research, processing speed is considered an important neurocognitive measure and possible marker of cognitive function with consistent age differences in reaction time repeatedly reported in the literature (see Chapter 1). Historically reaction time studies focused mainly on mean level of performance between groups across time but recently the importance of variability has been recognised. The relationship between age and intra-individual variability in cognitive performance across the lifespan is characterised by a U-shaped function that parallels the inverted U-shaped function observed for age-related changes in cognitive performance across the lifespan (for review see Li, Huxhold et al., 2004; Williams, Hultsch, Strauss, Hunter, & Tannock, 2005). Intra-individual variability in cognitive performance is initially high in childhood, decreases through adolescence only to increase again with senescence where clear links with concurrent cognitive impairments in attention, memory, and language are reported (Hultsch et al., 2002; Li, Huxhold et al., 2004; Nesselroade & Salthouse, 2004; Rabbitt, Osman, Moore, & Stollery, 2001). Cross-sectional studies reveal a negative correlation between intra-individual variability and performance on a wide range of cognitive tasks thought to reflect both crystallised, and fluid abilities (for review see MacDonald et al., 2009; MacDonald, Nyberg, & Backman, 2006). The magnitude of these correlations are both age and task dependent with older adults demonstrating larger associations than young adults irrespective of task complexity and although still negative, correlations in the young tend to be observed only in more demanding tasks such as those that require the engagement of frontal executive processes (Hultsch et al., 2002). Young and older adults demonstrate similar intra-individual variability in task conditions that require minimal executive control but older adults are more variable than younger adults in task conditions that require executive control (West et al., 2002). Associations between increases in intra-individual variability and cognitive decline demonstrated in longitudinal studies (e.g. Victoria Longitudinal Study) highlight the possible utility of behavioural intra-individual variability as a predictor of cognitive decline (MacDonald et al., 2009). For example, 6-year increases in reaction time (RT) intra-individual variability were associated with 6-year decline for various cognitive outcomes, including episodic memory and working memory (MacDonald et al., 2003). Intra-individual variability in cognitive performance has also been linked to fluctuations and impairment in a number of biomarkers of age including grip strength, sensory acuity, and forced expiratory volume (Anstey, Dear, Christensen, & Jorm, 2005; Li, Aggen,

Nesselroade, & Baltes, 2001; Strauss, MacDonald, Hunter, Moll, & Hultsch, 2002). In addition, greater intra-individual variability over and above mean level predicts risk of mortality from all causes (Shipley et al., 2006), and lower intra-individual variability predicts probability of survival independent of cognitive performance level, age, and cardiovascular health (MacDonald, Nyberg, Sandblom, Fischer, & Backman, 2008). In light of the foregoing, intra-individual variability in cognitive performance has been proposed as a behavioural marker of neurological dysfunction associated with impending death (MacDonald et al., 2009), and a behavioural indicator of central nervous system (CNS) integrity (Hedden & Gabrieli, 2004; Hultsch & MacDonald, 2004), specifically indexing frontal-cortex mediated processes (e.g. attentional lapses; Bunce et al., 1993; West et al., 2002).

Since Henry Head (1926) first proposed that "an inconsistent response is one of the most striking results produced by a lesion of the cerebral cortex" evidence for the prevalence of intra-individual cognitive performance variability in individuals with neurological disorder, disturbance, or injury has accumulated in the literature (Hultsch & MacDonald, 2004). Persons with schizophrenia, not only have slower reaction times than normal controls, but also consistently show higher intra-individual variability in RT (Schwartz et al., 1989; Vinogradov, Poole, Willis-Shore, Ober, & Shenaut, 1998). Similarly, significantly slower RTs and greater intra-individual variability in RT have been reported for both epileptic, and brain-injured (non-epileptic) patients compared to controls (Bruhn & Parsons, 1977). Although it can be said that greater inconsistency is observed in individuals with neurological disorders when compared with neurologically intact persons the evidence also suggests increased prevalence in some kinds of neurological damage compared to others (Hultsch & MacDonald, 2004). For example, while traumatic brain injury (TBI) has frequently been associated with slower and more variable responding (Burton, Hultsch, Strauss, & Hunter, 2002; Stuss, Pogue, Buckle, & Bondar, 1994) patients with focal frontal lesions exhibit higher intra-individual variability in RT than both patients with non-frontal lesions and healthy controls (Stuss et al., 1994). Increased intra-individual variability also characterises Attention Deficit Hyperactivity Disorder (ADHD, Hurks et al., 2005) and children with ADHD show greater response variability in RT tasks than children without ADHD (Westerberg, Hirvikoski, Forssberg, & Klingberg, 2004). Dementia is characterised by increased intra-individual variability and persons diagnosed with dementia show twice as much intra-individual variability as persons with arthritis or healthy adults (Hultsch et al., 2002), lending support to the suggestion that intra-individual variability reflects neurological compromise rather than general health decline (Hultsch, MacDonald, Hunter, Levy-Bencheton, & Strauss, 2000a; Williams et al., 2005). Increased intra-individual variability in RT is also observed in individuals

classified with mild cognitive impairment (MCI; Christensen et al., 2005). Furthermore, individuals diagnosed with frontal lobe dementia show greater intra-individual variability than patients with AD (Murtha, Cismaru, Waechter, & Chertkow, 2002). The prevalence of increased intra-individual variability in disorders of frontal and putatively frontal pathology such as schizophrenia (Vinogradov et al., 1998), ADHD (Westerberg et al., 2004), frontal dementia and focal frontal brain damage (Stuss et al., 2003) supports the suggestion that intra-individual variability represents an important index of the efficiency with which executive control processes are instantiated in the brain (Bellgrove et al., 2004; Stuss et al., 2003). This proposal is further substantiated by the finding that intra-individual variability is related to brain activation in frontal regions and associated with less efficient frontal responses during a response inhibition task (Bellgrove et al., 2004).

Intra-individual variability in cognitive performance is subject to the influence of both exogenous and endogenous factors including population variables, task demands and situational factors. The population variable that most commonly affects inconsistency is age but intra-individual variability has also been negatively correlated with education level and IQ (Christensen et al., 2005; Ram, Rabbitt, Stollery, & Nesselroade, 2005) with greater intra-individual variability associated with lower levels of education and lower IQ, both in the general population (Larson & Alderton, 1990) and in older adults, although the effect of intelligence held regardless of age (Rabbitt et al., 2001). While intra-individual variability increases in most populations with task difficulty (Stuss & Binns, 2008), as already discussed, the elderly seem to be particularly vulnerable (Bunce et al., 2004). It is also worth noting that in the elderly intra-individual variability is reduced in untimed tests (Hofland, Willis, & Baltes, 1981). Situational factors found to exert influence on variability of performance include, but are not limited to, blood pressure (Ong & Allaire, 2005), alcohol use, and sleep loss (Maruff, Falleti, Collie, Darby, & McStephen, 2005). Variability may also be affected by diurnal rhythms (Hockey, 1983) and optimal time of day (Murphy, West, Armilio, Craik, & Stuss, 2007) and Schmidt suggests (2007) that any studies investigating age-related variability should control for the testing time as a possible confound. For the most part ageing research focuses on the maladaptive nature of intra-individual variability but it should be acknowledged that intra-individual variability can also be adaptive depending on task characteristics (MacDonald et al., 2009). For example, intra-individual variability can be adaptive in children and is related to cognitive development when they try new strategies on complex tasks. In older adults positive associations between intra-individual variability and cognitive functioning have been reported in tasks that permit the implementation of new performance strategies and practice (Allaire & Marsiske, 2005).

In summary, intra-individual variability can differentiate among groups on the basis of age (Anstey, 1999; Nesselroade, 2004b), health status (Hultsch, MacDonald, Hunter, Levy-Bencheton, & Strauss, 2000c) and cognitive function, (Dixon et al., 2007) and putatively represents a neurocognitive predictor of cognitive decline and an index of neurological integrity rather than general health. The relatively recent interest in intra-individual variability within cognitive ageing research has given rise to a growing number of studies that have used a wide variety of tasks to assess intra-individual variability over a range of assessment frequencies in diverse populations. For the most part studies have used a variety of simple and choice reaction time measures with varying degrees of complexity and executive task load, ranging from tasks that assess RT to basic sensory targets (e.g. Gorus et al., 2006) to RT on n-back tasks (West et al., 2002) and RT on tasks involving semantic decisions (e.g. Dixon et al., 2007). The heterogeneity of tasks used makes it difficult to abstract findings and to make specific predictions particularly with regard to more complex tasks. Although studies have examined within-person variability in performance accuracy (e.g. Allaire & Marsiske, 2005) RT measures may be better suited to examining intra-individual variability because their potential large ranges make them more sensitive to individual differences than accuracy measures and RT tasks with multiple trials are amenable to multiple sample collection. In addition, RT measures may be more proximal indicators of basic functioning than accuracy and so are better suited to investigating the relationship between intra-individual variability and neural integrity in cognitive ageing (Allaire & Marsiske, 2005). Assessment frequencies have ranged from multiple trials within a task (Anstey, 1999) to single assessments conducted over months (Li et al., 2001). When endogenous sources such as alterations in neurotransmitter efficiency are theorised to underlie intra-individual variability then short-interval trial-to-trial assessments have been advised (MacDonald et al., 2009).

This chapter aims to extend the literature on intra-individual variability in cognitive ageing by examining RT variability and latency on a choice reaction time task (CRTsr), a memory word recognition task (Learn) and a sustained attention task ($SART_{fixed}$) in Young controls and older High and Low performers. The main purpose is to examine whether intra-individual variability in RT can distinguish the participant groups on the basis of age and cognitive performance. Response latency on the CRTsr task will be broken down into two stages or elements described in this thesis as cognitive response and motor response. These stages approximate the time required to initiate an appropriate response to stimuli (decision time) and the time associated with the sensory and motor control of movement (movement time, Roberts & Pallier, 2001). Young are predicted to have faster and more consistent RTs than both of the older groups. Faster and more consistent RTs are also predicted in the High

performers relative to the Low performers. Problems interpreting the degree of executive demand and strategy levels across structurally diverse tasks in the literature make predictions with regard to intra-individual variability on the memory and attention tasks used here difficult. Generally speaking, larger age-differences on more complex tasks relative to simpler tasks might be expected (e.g. Hultsch et al., 2002; Shammi et al., 1998; West et al., 2002). With regard to RT latency the Young are predicted to be faster than the older adults and High performers are predicted to be faster than Low performers on both the memory and attention task.

3.2 METHOD

3.2.1 Participants

Participants were recruited through public and college advertising and from the Robertson Participant Panel (see Chapter 2 for full details). Forty-eight older adults aged between 65 and 80 years and twenty-two Young controls aged between 18 and 30 years satisfied the eligibility criteria. Four older adults failed to attend for Session 2 due to ill health (n=2), personal problems (n=1) and voluntary withdrawal (n=1). In addition, one older adult disclosed taking CNS medication after testing was complete and one young adult drank a substantial amount of alcohol in the 24 hours preceding Session 2 and so both were excluded. Data for forty-three (18 male) older adults (M=69.95, SD ± 3.70) and twenty-one (9 males) young controls (M=21.28, SD ± 2.97) were analysed. The older participants were assigned to sub-groups based on their memory performance relative to an estimate of their pre-morbid IQ. Participants were defined as Low performers if they scored more than one standard deviation below their NART (National Adult Reading Test) estimated pre-morbid IQ on the Wechsler Memory Scale logical memory delayed recall test (for a full description of the classification procedure see Chapter 2 section 2.2.2). Classifying participants in this way yielded: a) 25 High performers (10 male, M=70.28, SD ± 3.39), and b) 18 Low performers (8 male; M=69.48 ± 4.14). In this chapter variability analysis is conducted on data from the three computerised tasks completed by participants during Session 2. Due to a technical error data for 4 High performers for the Learn task, and for 3 Young participants for the Learn task and for the CRTsr task was not suitable for analysis.

3.2.2 Procedure

Testing was conducted between September 2008 and May 2009. Participants were assessed in two ~2 hour sessions that took place approximately one week apart. During Session 1 participants completed the mini mental state exam, a memory self-rating scale, the Hospital Anxiety and Depression Scale, the National Adult Reading Test, animal naming, the Stroop task, and sub-sets of the Wechsler Memory Scale (Logical Memory 1 and 2, Face Recognition 1 and 2, Visual Reproduction 1 and 2 and Digit span). In addition, during Session 1 participants were taught how to perform the Choice Reaction Time split response task (CRTsr) and the Sustained Attention to Response Task fixed version SART$_{fixed}$. During Session 2 the electrical activity in participant's brains was recorded while participants rested (6 minutes) and while they performed three computerized experimental tasks: the Learn memory task, the CRTsr task, and the SART$_{fixed}$. The Learn task had an encoding and a delayed recognition phase which each took approximately 8.5 minutes to complete. Participants completed

the CRTsr (self-paced) and the SART$_{fixed}$ (~5 minutes) during the interval between the encoding and recognition phases of the Learn task. All materials and experimental tasks are described in detail in Chapter 2. Figure 3:1 highlights the tasks analysed in this chapter.

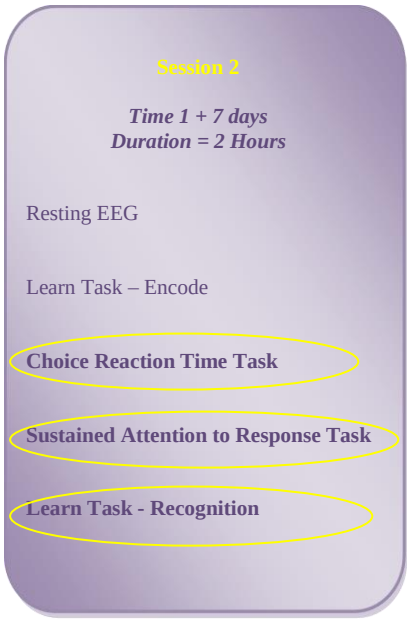

Figure 3:1 Variability Analysis.

Participant reaction times from the Choice Reaction Time Task split response, the Sustained Attention to Response Task and the Recognition Phase of the Learn task were subjected to latency and variability analysis.

3.3 RESULTS

Performance accuracy results for the CRTsr, SART$_{fixed}$ and the Learn task are presented in Chapter 2. Reaction time latency and variability analysis for the three tasks is presented below.

Analysis Strategy

Reaction time (RT) and reaction time variability measures for CRTsr, SART$_{fixed,}$ and the Learn task are presented in this chapter. Intra-individual variability was measured using intra-individual standard deviation (ISD) and the coefficient of variation (CV). The former represents the simplest measure of intra-individual variability and the latter is a normalised measure of variability that reflects the ratio of the standard deviation to the mean. Extremely fast or slow responses could be due to errors (e.g. accidental key presses). First the raw latency scores for each participant were examined and means and standard deviations (SDs) were calculated for each individual based on their raw RTs. The distribution of each individual's raw latency scores were examined for outliers, which were defined as responses that occurred more than 3SDs outside the participant's own mean RT. These single trial outliers were removed before ISD and CVs were calculated. Group means were then calculated and data for individuals with outlying RTs were also removed. This procedure reduces variability and so represents a conservative data preparation approach. Analyses were conducted on data from all trials irrespective of response accuracy as previous research indicates little difference in results of analysis conducted with data from all trials (correct plus incorrect) when compared to data from only correct trials (Burton, Strauss, Hultsch, Moll, & Hunter, 2006).

One-way ANOVAs were used to test for interactions, main effects, and significant differences between groups. Effect sizes were calculated using eta² or partial eta² and were categorized as follows: small = 0.01, medium = 0.14 and large = 0.14 (Cohen, 1988). A robust test of equality of means (Welch or Brown-Forsythe) was used when the assumption of homogeneity of variances was violated. When variables were not normally distributed non-parametric equivalents were used or when appropriate, variables were transformed. For post-hoc analysis Tukey's HSD test is reported unless stated otherwise.

3.3.1 Choice Reaction Time split response (CRTsr)

The CRTsr task is comprised of 100 trials. The response to each of these trials was broken down into two constituent components thought to reflect the decision element (cognitive i.e. the time necessary to initiate the response) and the movement

element (motor i.e. the time needed to execute the response) (Roberts & Pallier, 2001). Analysis of the total overall response is also presented. A relatively small number of trials were dropped as a consequence of the removal of individual trial outliers (Young, cognitive = 1%, motor 2.2%; High performers, cognitive = 1.8%, motor = 2% and Low performers, cognitive = 2.06% and motor = 2.3%). Two High performer group outliers and one Low performer group outlier were excluded from analysis. In addition, data from an additional Low performer was excluded due to the participant's repeated failure to hold down the white 'ready' key after target offset to trigger the next target onset. Data for 18 Young, 23 High performers, and 16 Low performers were subjected to analysis.

Means and standard deviations for RT latency and variability (ISD) measures are detailed in Table 3:1. The CV for the CRTsr task is illustrated graphically alongside the CV for the other RT tasks in Figure 3:2. RT latency and variability were examined using two one-way ANOVAs with cognitive response and motor response as the dependent variables. Young had the fastest mean cognitive and motor RTs and the Low performers the slowest (see Table 3:1). Higher ISD and CV scores indicate more inconsistent performance across trials while lower scores indicate relatively consistent performance. The Low performers' RTs were the least consistent and the Young the most consistent for both the cognitive and motor elements of the response. There was a significant main effect of Group for mean cognitive RT [$F(2, 54)=33.74$, $p\leq0.0005$] ($eta^2=0.47$) and mean motor RT [$F(2, 54)=11.92$, $p\leq0.0005$] ($eta^2= 0.42$). Post-hoc tests indicated that for the cognitive mean RT latency measure this was due to significantly faster responding in the Young when compared with both older groups ($p\leq0.0005$). Post hoc tests for the motor mean RT latency measure also indicated significantly faster responding in the Young when compared to the High performers ($p\leq0.05$) and the Low performers ($p\leq0.0005$). The High and Low performers did not differ significantly from each other for either the cognitive or the motor RT ($p>0.10$).

Table 3:1 CRT Task: Means and standard deviations for latency & intra-individual variability.

CRTsr	Young (18) Mean (SD)	High (23) Mean (SD)	Low (16) Mean (SD)
Cognitive RT (ms)	340.76 (52.27)	471.17 (54.23)	486.76 (99.97)
Cognitive ISD	60.29 (10.03)	110.95 (32.65)	215.22 (205.21)
Motor RT (ms)	149.03 (34.67)	206.16 (56.77)	257.87 (120.36)
Motor ISD	36.11 (12.81)	61.45 (26.37)	131.28 (135.34)

Note: CRTsr = Choice reaction time split response task. High = high performing old. Low = low performing old. RT = reaction time. RT on this task was measured in milliseconds and divided into 'cognitive response' measured as time from target onset to trigger offset (release of white key) and 'motor response' measured as time from trigger offset to response selection (depression of green key or red key).The RB-530 response box used in this task is illustrated in Chapter 2. ISD = individual standard deviation.

There was a strong main effect of Group across all variability measures: cognitive ISD [$F(2,54)=33.74$, $p\leq0.0005$] ($eta^2=0.42$), cognitive CV [$F(2,54)=11.71$,

p≤0.0005] (eta²=0.46), motor ISD [H (2,54)=10.56, p≤0.0005] (eta²=0.25), and motor CV [F (2,54)=3.69, p≤0.05][3] (eta²=0.11). For the cognitive ISD measure post-hoc tests revealed that this was due to a more consistent performance in the Young relative to both of the older groups (p≤0.0005). The High performers were also significantly more consistent than the Low performers (p≤0.05). When variability for the cognitive response element was measured relative to the individual's own level of performance (CV) the Young were significantly more consistent than both the High (p≤0.05) and the Low performers (p≤0.0005), the High performers were less variable than the Low performers and this difference approached significance (p=0.057, LSD). For the motor response ISD the Young were significantly more consistent than both the High performers (p≤0.05) and the Low performers (p≤0.0005) who did not differ significantly from each other (p>0.10). For the motor response element CV post-hoc tests revealed that the Young were significantly more consistent than the Low performers (p≤0.05). The High performers did not differ significantly from the Young or the Low performers (p>0.10).

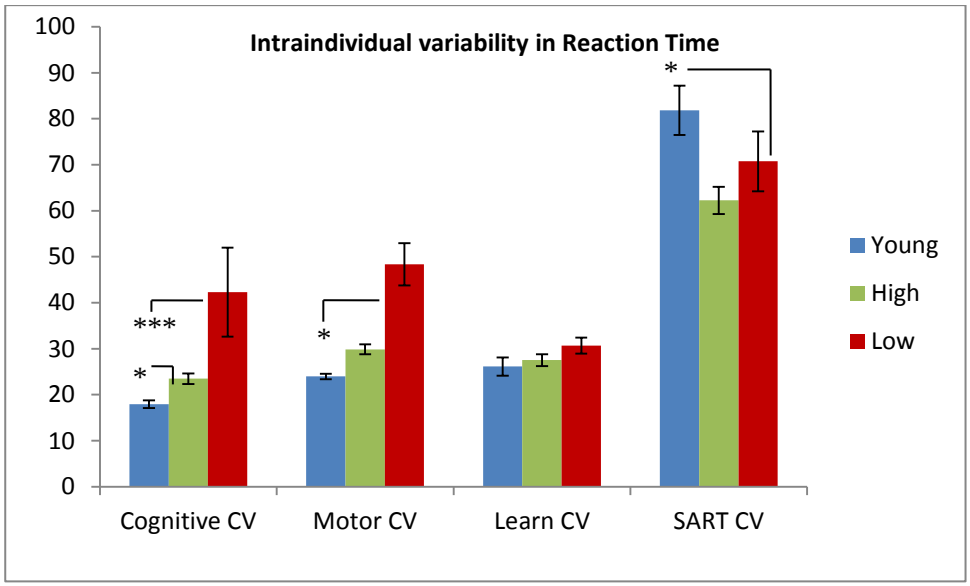

Figure 3:2 Intra-individual variability in reaction time.

*Note: the graph shows variability in reaction time on the choice reaction time (CRTsr), recognition memory (Learn) and sustained attention (SARTfixed) tasks as measured by the coefficient of variation (CV) which is expressed as a percentage. The response on the CRTsr task is split into cognitive (decision time) and motor (movement time). Error bars represent one standard error of the mean. *= p≤0.05, *** = p≤0.0005.*

For the overall response the Young had the fastest RT and the Low performers the slowest. The Low performers RTs were the least consistent and the Young the most. There was a main effect of Group for the overall RT [F (2,54)=26.25, p≤0.0005]

[3] Measures were not normally distributed and so the following actions were taken; cognitive ISD – log transformed, cognitive CV – inverse transformed, motor CV – inverse transformed. Normality could not be achieved for the motor ISD through transformation so non-parametric (Kruskal Wallace) tests were used. The assumption of homogeneity of variances was violated so robust test of equality of means (Welch) are reported.

(eta^2 = 0.49). Post-hoc tests revealed that this was due to significantly faster responding in the Young when compared with both older groups ($p \leq 0.0005$) who did not differ significantly from each other ($p > 0.10$). There was a strong main effect of Group for the overall ISD [H (2, 54)=31.90, $p \leq 0.0005$] (eta^2=0.22) and CV [F (2,54)=12.78, $p \leq 0.0005$][4]. For the ISD Mann-Whitney U tests revealed that the Young were significantly more consistent than both of the older groups ($p \leq 0.0005$) who did not differ from each other $p > 0.10$. Similarly post-hoc tests for the CV revealed that the Young were significantly more consistent than both of the older groups ($p \leq 0.0005$) who did not differ from each other $p > 0.10$.

3.3.2 Learn Task

The recognition phase of the Learn task comprised 126 trials including 6 buffer trials, which were excluded from analysis. A relatively small number of trials were dropped as a consequence of the removal of individual trial outliers (Young = 2.3%, High performers = 1.78%, and Low performers = 1.99%). There were no group outliers.

Table 3:2 Learn Task, Means & standard deviations for RT latency & intra-individual variability

Learn Task	Young (18) Mean (SD)	High (21) Mean (SD)	Low (18) Mean (SD)
Mean RT	1019.42 (173.12)	1221.45 (235.21)	1255.85 (262.40)
ISD	270.90 (111.76)	338.64 (103.77)	381.99 (114.41)

Note: High = high performing old. Low = low performing old. Mean RT = mean reaction time latency to all response trials irrespective of response accuracy. ISD = individual standard deviation of reaction time. CV = coefficient of variation of reaction time.

Means and standard deviations are detailed in Table 3:2. The CV is illustrated graphically alongside the CV for the other RT tasks in Figure 3:2. The Young were the fastest and the most consistent while the Low performers had the slowest and most variable RTs. There was a significant main effect of Group for RT [F (2, 55)=5.78, $p \leq 0.005$] (eta^2=0.18). Post-hoc tests revealed that this was due to significantly faster RTs in the Young relative to the High ($p \leq 0.05$) and the Low performers ($p \leq 0.01$) who did not differ significantly from each other ($p > 0.10$). There was also a significant difference between the Group's RT intra-individual variability as indexed by the ISD [F (2, 55)=4.69, $p \leq 0.01$] (eta^2=0.15). This Group effect was the result of greater intra-individual variability in the Low performers when compared with the Young ($p \leq 0.01$).

[4] Measures were not normally distributed and so the following actions were taken; Normality could not be achieved for the ISD through transformation so non-parametric (Kruskal Wallace) tests were used. The assumption of homogeneity of variances was violated so robust test of equality of means (Welch) are reported.

3.3.3 Sustained Attention to Response Task fixed

The SARTfixed is comprised of 225 trials, of which 25 are 'no-go' trials where the participants were instructed to withhold their response. The remaining 200 'go-trials' were subjected to mean RT and variability analysis (ISD and CV). A relatively small number of trials were dropped as a consequence of the removal of individual trial outliers (Young = 1.32%, High performers =1.58%, and Low performers =1.94%). Three Young, one High performer, and one Low performer group outliers were excluded from analysis. In addition, data from an additional High performer and a Young participant were excluded due to their failure to execute the task correctly. Data for 17 Young, 23 High performers, and 17 Low performers were subjected to analysis.

Table 3:3 SART: Means & standard deviations.

SARTfixed	Young (17) Mean	High (23) Mean (SD)	Low (17) Mean (SD)
Go-Trials RT	79.73 (24.08)	92.25 (27.38)	102.89 (35.79)
Go-trials ISD	65.32 (33.14)	56.51 (18.91)	74.90 (55.91)

Note: Means & standard deviations for go-trial mean RT latency & intra-individual variability SARTfixed = sustained attention to reaction time task. High = high performing old. Low = low performing old. Go-trials RT = reaction time latency to trials for which a response was required (1, 2, 4, 5, 6, 7, 8, 9). ISD = individual standard deviation for go-trial RTs.

Means and standard deviations for mean RT and variability (ISD and CV) measures are detailed in Table 3:3. The CV is illustrated graphically alongside the CV for the other RT tasks in Figure 3:2. The Young had the fastest mean RT and Low performers the slowest RTs. Higher ISD and CV scores indicate more inconsistent performance across trials while lower scores indicate relatively consistent performance. When intra-individual variability was measured relative to a participant's own performance the Young demonstrated the greatest variability while the High performers were the most consistent. There was no significant difference in RT [$F(2, 56)=2.67$, $p=0.08$], or ISD [$H(2, 56)=2.35$, $p>0.10$] between the three Groups. There was a significant difference when variability was measured using the CV [$F(2, 56)=4.25$, $p\leq0.05$] ($eta^2 = 0.14$). Post-hoc tests (LSD) revealed that this was due to significantly more variable performance in the Young when compared with the High performers ($p\leq0.05$).

Correlational Analysis

Spearman's rank order correlation coefficient was used to explore the relationship between reaction time (latency and variability) measures, and key neuropsychological test scores that measure memory and executive function (Table 3:4) for Young and Old participants separately. Correlations are reported in Table 3:5 for the old adults and Table 3:6 for the young adults. All neuropsychological tests are described in detail in Chapter 2.

Table 3:4 Measures used in correlational analysis

Neuropsychological Measures	Memory Self-Rate Recall Memory (LM1 & LM2, WMS-III) Recognition Memory (Learn Task, d-prime L & X) Working Memory (Digit Span, WMS-III) Executive function (Fluency & Stroop)
RT Measures	CRTsr– cognitive RT latency, ISD, CV CRTsr – motor RT latency, ISD, CV SART*fixed* – go-trial RT latency, ISD, CV Learn Task – RT latency, ISD, CV

Note. SARTfixed = sustained attention to response task fixed. Memory self-rate = 5-point Likert memory self-rate score.LM1 = immediate recall standardised score, LM2 = delayed recall, standardised score, digit span (WMS-III, Wechsler, 1998). Fluency = number of animals named in 60 seconds. Stroop (t-score; Golden & Freshwater, 2002). Mean RT = mean reaction time latency to all response trials irrespective of response accuracy. ISD = individual standard deviation of reaction time. CV = coefficient of variation of reaction time. RT on the CRTsr was measured in milliseconds and divided into 'cognitive response' measured as time from target onset to trigger offset (release of white key) and 'motor response' measured as time from trigger offset to response selection (depression of green key or red key). The RB-530 response box used in this task is illustrated in Chapter 2. Go-trials for the SARTfixed = (1, 2, 4, 5, 6, 7, 8, 9).

3.3.4 Choice Reaction Time - Correlations

3.3.4.1 Cognitive Response

In the Old adults ISD for the cognitive element of the response was significantly correlated with Stroop scores ($p \leq 0.05$) with greater variability associated with poorer cognitive flexibility. In addition, in the Old adults greater variability as measured by the CV was significantly correlated with poorer memory self-rate scores ($p \leq 0.05$). In the Young RT latency for the cognitive element of the response was significantly correlated with Digit span ($p \leq 0.01$), with slower response times associated with shorter digit span. In the Young the cognitive ISD was correlated with the Stroop score ($p \leq 0.05$) with greater variability associated with poorer cognitive flexibility.

3.3.4.2 Motor Response

In the Old adults motor response ISDs were significantly correlated with digit span ($p \leq 0.05$) and Stroop scores ($p \leq 0.05$) with greater variability associated with shorter span and poorer cognitive flexibility. In the Old adults the motor CV was also significantly and negatively correlated with digit span ($p \leq 0.05$) and the Stroop

($p \leq 0.01$). In the Young greater intra-individual variability (ISD and CV) was also significantly correlated with poorer cognitive flexibility as assessed by the Stroop ($p \leq 0.05$).

3.3.5 Learn Task - Correlations

In Old adults RT latency in the Learn task was correlated with Fluency ($p=0.055$) scores with slower reaction times associated with less animals named. There was also a borderline correlation between ISD and Learn Word recognition scores ($p=0.068$) with greater consistency in RT associated with better Learn Word recognition scores. When intra-individual variability was assessed relative to the individual's own level of performance (CV) there was a strong correlation between variability and Learn Word recognition scores ($p \leq 0.01$) with greater variability associated with poorer recognition scores. In the Young greater variability was associated with poorer recall. Specifically CV was significantly correlated with both immediate and delayed story recall (WMS-III; $p \leq 0.05$) and the ISD measure was also correlated with immediate recall ($p \leq 0.05$).

3.3.6 Sustained Attention to Response Task - Correlations

In the Old adults both SART intra-individual variability measures (ISD and CV) were significantly correlated with memory self-rate scores ($p \leq 0.05$) with greater variability associated with poorer self-ratings (see Table 3:5). In contrast, in the Young variability measures were not correlated with any of the measures of interest but RT latency scores were significantly correlated with immediate recall scores on the WMS story recall task ($p \leq 0.05$) with slower reaction times associated with poorer recall. Correlations with delayed recall (WMS-III) and digit span also approached significance ($p \leq 0.06$) with slower reactions associated with poorer delayed recall and shorter digit span.

Table 3:5 Correlations Old Adults.

	Spearman's rho	Memory Self-Rate	Immediate Recall	Delayed Recognition	Learn Word Recognition	Read Word Recognition	Digit Span	Fluency	Stroop
CRT		39	39	39	35	35	39	39	39
CRT Cognitive RT	r	.059	.019	.083	-.022	.074	-.115	-.070	-.285
	p-value (2-tailed)	.721	.910	.616	.900	.671	.486	.674	.079
CRT Cognitive ISD	r	-.285	-.048	.023	-.148	.033	-.248	-.078	-.392*
	p-value (2-tailed)	.079	.771	.888	.397	.849	.128	.635	.013
CRT Cognitive CV	r	-.366*	-.126	-.091	-.160	-.028	-.227	-.110	-.283
	p-value (2-tailed)	.022	.446	.583	.359	.874	.165	.506	.081
CRT Motor RT	r	-.076	-.093	.021	-.056	-.073	-.285	-.088	-.223
	p-value (2-tailed)	.646	.575	.901	.748	.676	.078	.595	.173
CRT Motor ISD	r	-.129	-.207	-.192	-.131	-.199	-.388*	-.226	-.398*
	p-value (2-tailed)	.435	.206	.241	.452	.252	.015	.166	.012
CRT Motor CV	r	-.088	-.138	-.172	-.148	-.132	-.317	-.296	-.415
	p-value (2-tailed)	.595	.402	.296	.396	.450	.050	.068	.009
Learn		*39*	*39*	*39*	*39*	*39*	*39*	*39*	*39*
Learn RT	r	.166	.003	.064	.016	-.169	-.016	.310	-.111
	p-value (2-tailed)	.312	.984	.698	.922	.303	.921	.055	.500
Learn ISD	r	-.075	-.120	-.130	-.295	-.267	-.019	.068	-.169
	p-value (2-tailed)	.648	.466	.429	.068	.100	.911	.681	.304
Learn CV	r	-.274	-.221	-.269	-.431**	-.250	-.076	-.133	-.166
	p-value (2-tailed)	.091	.177	.098	.006	.126	.645	.419	.312
SART		*40*	*40*	*40*	*36*	*36*	*40*	*40*	*40*
SART RT	r	-.055	-.040	-.063	.105	.166	-.087	.144	-.168
	p-value (2-tailed)	.735	.804	.700	.543	.332	.592	.377	.300
SART ISD	r	-.354*	-.124	-.102	.007	.093	-.183	-.050	-.193
	p-value (2-tailed)	.025	.445	.530	.967	.589	.257	.757	.234
SART CV	r	-.348*	-.259	-.139	-.165	-.116	-.106	-.199	-.010
	p-value (2-tailed)	.028	.106	.393	.336	.501	.515	.219	.952

Note: CRT=Choice Reaction Time Task. SART = sustained attention to response task. RT=reaction time, ISD = individual standard deviation. CV= coefficient of variation. Memory self-rate – 5-point Likert. Immediate story recall (WMS-III, standardised scores). Delayed story recall (WMS-III, standardised scores). Learn Recognition Task (D-prime scores). Digit Span (WMS-III). Fluency = number of animals named in 60 seconds. Stroop (t-score; Golden & Freshwater, 2002). Mean RT = mean reaction time latency to all response trials irrespective of response accuracy. ISD = individual standard deviation of reaction time. CV = coefficient of variation of reaction time. RT on the CRTsr was measured in milliseconds and divided into 'cognitive response' measured as time from target onset to trigger offset (release of white key) and 'motor response' measured as time from trigger offset to response selection (depression of green key or red key).The RB-530 response box used in this task is illustrated in Chapter 2. Go-trials for the SARTfixed = (1, 2, 4, 5, 6, 7, 8, 9).

Table 3:6 Correlations Young Adults

	Spearman's rho	Memory Self-Rate	Immediate Recall	Delayed Recognition	Learn Word Recognition	Read Word Recognition	Digit Span	Fluency	Stroop
CRT		*18*	*18*	*18*	*17*	*17*	*18*	*18*	*18*
CRT Cognitive RT	r	.180	-.227	-.123	-.113	.009	-.635**	-.052	-.199
	p-value	.474	.365	.626	.666	.974	.005	.839	.428
CRT Cognitive ISD	r	.065	-.318	-.070	-.188	-.109	-.327	-.256	-.462
	p-value	.797	.198	.782	.471	.677	.185	.304	.054
CRT Cognitive CV	r	-.142	-.117	.039	-.050	-.074	.319	-.264	-.247
	p-value	.574	.645	.879	.848	.779	.197	.290	.323
CRT Motor RT	r	.093	-.087	.239	-.206	-.130	-.432	-.299	-.251
	p-value	.715	.731	.341	.428	.619	.073	.228	.314
CRT Motor ISD	r	-.204	-.181	-.021	-.140	-.022	-.313	-.355	-.537*
	p-value	.418	.473	.934	.593	.933	.206	.149	.022
CRT Motor CV	r	-.392	-.229	-.129	.069	.269	-.049	-.219	-.622**
	p-value	.107	.361	.361	.793	.297	.848	.382	.006
Learn		18	18	18	18	18	18	18	18
Learn RT	r	-.132	-.091	.152	-.151	-.335	-.077	-.007	-.456
	p-value	.601	.719	.548	.550	.175	.762	.977	.057
Learn ISD	r	-.193	-.467	-.322	-.034	-.140	.030	-.006	-.263
	p-value	.444	.051	.193	.893	.578	.906	.981	.292
Learn CV	r	-.287	-.509*	-.467	-.174	-.103	-.039	-.013	-.210
	p-value	.248	.031	.051	.491	.683	.877	.958	.403
SART		17	17	17	15	15	17	17	15
SART RT	r	-.375	-.498*	-.464	-.070	.146	-.457	-.338	-.043
	p-value	.137	.042	.061	.805	.603	.065	.185	.879
SART ISD	r	-.400	-.337	-.328	.029	.025	-.154	-.263	.018
	p-value	.112	.187	.199	.919	.930	.556	.308	.949
SART CV	r	-.148	.103	.344	.159	-.143	.272	.279	-.043
	p-value	.571	.695	.177	.571	.612	.292	.279	.879

Note: CRT=Choice Reaction Time Task. SART = sustained attention to response task. RT=reaction time, ISD = individual standard deviation. CV= coefficient of variation. Memory self-rate – 5-point Likert. Immediate story recall (WMS-III, standardised scores). Delayed story recall (WMS-III, standardised scores). Learn Recognition Task (D-prime scores). Digit Span (WMS-III). Fluency = number of animals named in 60 seconds. Stroop (t-score; Golden & Freshwater, 2002). Mean RT = mean reaction time latency to all response trials irrespective of response accuracy. ISD = individual standard deviation of reaction time. CV = coefficient of variation of reaction time. RT on the CRTsr was measured in milliseconds and divided into 'cognitive response' measured as time from target onset to trigger offset (release of white key) and 'motor response' measured as time from trigger offset to response selection (depression of green key or red key).The RB-530 response box used in this task is illustrated in Chapter 2. Go-trials for the SARTfixed = (1, 2, 4, 5, 6, 7, 8, 9).

3.4 DISCUSSION

This chapter examined whether reaction time (RT) latency and RT intra-individual variability, a putative index of neural integrity and possible marker of emerging cognitive impairment, could distinguish participant groups on the basis of age and cognitive performance. As predicted, the Young had faster RTs than both of the older groups for the CRTsr, the least cognitively demanding of the three tasks examined. The Young were also significantly more consistent than both of the older groups for the cognitive element of this task even after controlling for processing speed. The Young were also significantly more consistent than both of the older groups for the motor element however, after controlling for processing speed, only the Low performers remained significantly more variable than the Young. Contrary to our prediction the High performers were not significantly faster than the Low performers, however the Low performers were more variable (ISD) than the High performers for the cognitive but not the motor element of the task and this difference approached significance after controlling for processing speed (CV). Accuracy scores reported in Chapter 2 distinguished groups on the basis of age but not cognitive performance status. Therefore, while there are significant differences in level of performance (accuracy and RT latency) and variability measures (ISD, CV) only the cognitive variability measure discriminated the High and Low performers.

The age effects reported in this chapter for the CRTsr task are in line with general expectations of slower responding and increased variability with increasing age (Hultsch et al., 2002). A search of the cognitive ageing literature revealed only two studies (Bunce et al., 2004; Gorus et al., 2006) that examined the effects of age on the cognitive and motor sub-components of RT intra-individual variability. Although generally speaking findings are similar, it is difficult to interpret the Bunce et al. findings relative to the present study due to differences in operationalisation of the sub-components.[5] Although the Gorus et al. study used comparable operationalisation of sub-components to examine age effects they did not distinguish between High and Low performers. In line with the findings presented here, Gorus et al. (2006) report significant age differences on both the cognitive and motor elements when variability is measured using the ISD in normal elderly and Young controls. However, once processing speed is controlled for with the CV measure, Gorus et al. report that it is only the cognitive component of RT intra-individual variability that is influenced by age. Significant age differences also remain for the cognitive element in the present study after controlling for processing speed. However, the motor element in the

[5] Bunce labels decision time as the time between stimulus onset and stimulus offset and motor time as the time between stimulus offset and return to the home key. In the present study the time between stimulus offset and return to the central button is not considered.

present study for the Low performers remains significantly more variable than the motor element for the Young even after controlling for processing speed. Distinguishing between High and Low performers may account for this different finding. In addition to treating their older participants as a homogenous group some other important differences between the present study and the Gorus et al. study may have influenced differential findings. Firstly, the mean age of old participants in the present study differed from the Gorus study (present study = 69.95 ± 3.7 years vs. Gorus study = 75± 5years). Young-old adults demonstrate different patterns of variability than adults over the age of 75 classified as old-old (Hultsch et al., 2002) and so it is possible that this differentially effects the sub-components of the RT. Secondly, although the CRTsr task is not a lexical task per se the target stimuli, ('yes', 'no'), were lexical and so arguably were more complex than the purely sensory stimuli (light/tone) used by Gorus et al. In addition, structural differences in the response devices used across studies possibly interfere with comparability of findings.

As already discussed intra-individual variability in overall RT has distinguished groups on the basis of age (e.g. young/old Anstey, 1999; Nesselroade, 2004b), health status (healthy/patient e.g. Hultsch et al., 2000c), cognitive impairment, (normal/mild-moderate cognitive impairment e.g. Dixon et al., 2007), and type of dementia (AD / frontal lobe Murtha et al., 2002). The present study is of interest because it shows that intra-individual variability (ISD) in the cognitive component of RT on the CRTsr task can discriminate High performers from Low performers and this difference approaches significance even after controlling for processing speed. The fact that the observed effect is specific to the cognitive component of the task could be interpreted as meaning that it more likely reflects the integrity of neural processes or availability of neural or cognitive resources rather than a decline in general sensory functioning. Participants in this study were classified as High performers or Low performers on the basis of the memory performance scores on a standardised memory test relative to an estimate of their pre-morbid IQ. In a study examining the effects of cognitive deterioration (normal, aMCI, mild AD, moderate AD) on the sub-components of RT intra-individual variability Gorus et al. (2008) concluded that the effects of cognitive deterioration on variability in AD patients when compared to healthy controls were specific to the cognitive element. Intra-individual variability in RT has been proposed as a possible marker of emerging cognitive impairment. This study demonstrates that intra-individual variability in cognitive RT warrants further research with larger samples as it may have the power to differentiate cognitive profiles within the normal population and so could have particular utility in explicating differential decline in normal ageing. Given that subjective memory complaints are criteria for MCI diagnosis it is interesting to note that intra-individual

variability in cognitive RT in the older adults in this study is correlated with subjective memory rating scores.

Intra-individual variability has been proposed as an important index of the efficiency with which executive control processes are instantiated in the brain (Bellgrove et al., 2004). This chapter demonstrates the ability of intra-individual variability in cognitive RT (ISD) on a relatively straight forward choice reaction time task to distinguish cognitive performance groups that differed on the basis of memory performance but did not differ from each other on measures of executive function. One important point to remember in teasing this apparent contradiction out is that many acts of remembering including the story recall task used to classify groups in this study rely on controlled processes and executive function, for example for strategic elaborations during encoding (Buckner, 2004). Furthermore, it should also be remembered that participants were not simply either low or high memory performers but had cognitive profiles wherein their performance on the memory task was discrepant relative to an estimate of their IQ which also acts as a proxy for cognitive reserve. It is interesting to note that while intra-individual variability (ISD) in cognitive RT is negatively correlated, in both Young and Old adults, with scores on the Stroop task, a frontal measure thought to reflect selective attention and cognitive flexibility, this correlation falls away when processing speed is controlled for (CV). In contrast, the negative correlation between the same executive measure and intra-individual variability in motor RT remains in both the older adults and in the Young, after controlling for processing speed.

A different pattern of results was observed for the memory recognition task. Chapter 2 showed that accuracy measures on this task discriminated groups on the basis of age and cognitive performance. RT latency measures reported in this chapter distinguish on the basis of age but not cognitive performance. Although measures of RT variability across groups were in the expected direction, only the difference between Young and Low performers reached significance but even this fell away when processing speed was controlled for. The difference observed across the CRTsr and word recognition tasks in the ability of variability measures to distinguish groups may possibly be related to greater verbal facility of older adults when compared to young adults (Wingfield & Stine-Morrow, 2000). In the light of similar findings, Hultsch has suggested that verbal ability in older adults may facilitate compensation on tasks in the lexical domain reducing relative inconsistency and that compensatory mechanisms may be more easily engaged for multi-component tasks, than for more primitive tasks (2002). The findings reported here support the view that age-related variability is not a unitary phenomenon and increasing variability with increasing age and increasing task complexity is not necessarily the case (Shammi et al., 1998). This

may also be true of the relationship between cognitive deterioration and RT variability as evidenced by the finding that aMCI patients were significantly more variable than healthy controls on simple but not more complex tasks (Gorus et al., 2008). Greater RT intra-individual variability (CV) on this memory recognition task was moderately and significantly correlated with memory accuracy measures in both the Old (Learn Words correctly identified as old) and the Young (immediate and delayed story recall).

Chapter 2 reported that accuracy measures on the SART$_{fixed}$ task failed to discriminate groups on the basis of age or cognitive performance. RT latency also failed to discriminate the groups on the basis of age and cognitive performance. Although there were no significant differences, the pattern of RTs across groups was similar to that found on the other two measures (i.e. Young = fastest RTs and Low = slowest). Interestingly the Young were significantly more variable than the High performers on this task. No other variability effects were significant. This apparent flip in age effects may be an artefact of the nature of the task. Variability in this task can be broken down into three components: a) sequence specific variance; which is a measure of the distinctiveness and consistency of a particular pattern, b) gradual variability; which has a slow temporal characteristic, and c) trial to trial variability; which has a fast temporal characteristic (for full description see Johnson et al., 2007). The latter was measured in this study and represents the combined influence of all three components and so it is quite possible that age effects may be more apparent in the other two types of variability not examined here. On the view that intra-individual variability indexes attentional lapses (Bunce et al., 1993) and fluctuations of executive control (West et al., 2002), it is plausible to propose that the greater intra-individual variability observed in the Young relative to the High performers, reflects lapses of attention that could somehow be related to the fact that Young made more pre-emptive errors than the older participants. Of course, it is quite possible that this task elicits more variable responding in young adults although increased variability in older adults would be expected on tasks with increased executive demand.

It is worth noting that the data preparation approach adopted here represents a conservative approach to examining within-person variability, because it reduces the observed intra-individual variability. Intra-individual variability is also reduced in the elderly in untimed tasks (Hofland et al., 1981) such as the CRTsr task used here. While the self-paced nature of the CRTsr task may have helped to guard against the interference that can occur when older people complete force paced tasks it should be acknowledged that the other two tasks were not self-paced and so this may have contributed in some way to the differential results reported across tasks. This study controlled for a number of exogenous factors, such as time of testing and alcohol

consumption, known to affect intra-individual variability and so should provide a truer reflection of age effects on variability than studies that fail to control for such influences. Informed by the literature (Burton et al., 2002) this study examined intra-individual variability on all responses irrespective of response accuracy on the CRTsr on all three tasks. Errors on the CRTsr task were negligible and by definition all responses to go-trials are accurate. However, there were significant group differences in accuracy levels across the three groups on the memory recognition task and it is, therefore, possible that a different profile of variability may emerge if only accurate responses were assessed. This chapter has shown that intra-individual variability measures on a relatively straight forward choice reaction time task can distinguish age groups and shows real promise for distinguishing groups on the basis of cognitive performance status. In addition, the results demonstrate that there is value in splitting a RT into its cognitive and motor components.

Chapter 4 **METHODS**

4.1 HUMAN ELECTROENCEPHALOGRAPHY

Electroencephalography involves placing electrodes on the scalp over multiple areas of the brain in order to detect and record the patterns of electrical activity generated by neurons by means of an instrument called an electroencephalograph. The electroencephalogram (EEG) is a graphical record of the pattern of voltage variation that is revealed over time in the output from a differential amplifier that has been attached to a pair of electrodes that are, in turn, attached to the human scalp. Action potentials and postsynaptic potentials are the two main types of electrical activity associated with neurons. Due to the timing and the physical arrangement of action potentials, it is not possible to detect them at the scalp surface. However, there is a general acceptance that the ongoing EEG recorded on the scalp surface derives from summated postsynaptic potentials (Davidson, Jackson, & Larson, 2000). This view is supported by evidence from animal studies that compare intracellular recordings and scalp recorded EEG (Davidson et al., 2000; Thatcher & John, 1977). Postsynaptic potentials are the voltages that arise when neurotransmitters bind to receptors on the membrane of the postsynaptic cell. Postsynaptic potentials are generally confined to the dendrites and cell body, occur instantaneously, and last for tens or hundreds of milliseconds. When postsynaptic potentials summate it is possible to record them at the scalp. Although the exact biophysical events involved are not known, it is thought that current flows from the extracellular space when a neurotransmitter is released, for example, at the apical dendrite of a cortical pyramidal cell, yielding a net negativity in the region of the apical dendrite. The circuit is completed when current also flows out of the cell body and the basal dendrites, producing a net positivity in this area. Together, the negativity and the positivity create a tiny dipole (a pair of positive and negative electrical charges separated by a small distance). The dipoles from many neurons with a similar orientation (e.g. cortical pyramidal cells) must summate in order to be recordable at the scalp. The voltage present at any point on the scalp is dependent upon the position and orientation of the generator dipole and on the resistance and shape of the brain, skull, and scalp. Electricity spreads out through the brain, and laterally when it encounters the skull leading to a blurring of the surface distribution of voltage and poor spatial resolution. In contrast, because electricity travels at the speed of light, the voltage recorded at the scalp reflects the activity of the brain with millisecond accuracy. This excellent temporal resolution makes the EEG an ideal choice for studying the neural correlates of behaviour that dynamically change over time.

The electrical activity of the brain can be described at multiple levels ranging from the currents within a single dendrite to the activity measured by the electroencephalograph, which aggregates the electrical voltage fields from millions of neurons. Different types of EEG oscillatory activity can be characterised according to whether the rhythms are spontaneous, induced or evoked (Galambos, 1992). This classification is based on the degree to which the oscillations are time locked to a stimulus. Evoked activity is time-locked to the onset of an experimental condition across trials and has the same phase in every trial, induced activity is correlated with experimental conditions but not locked to its onset and spontaneous activity is not correlated with the occurrence of an experimental condition (Herrmann, Grigutsch, & Busch, 2005). Evoked activity or electrical potentials that show a stable relationship to a definable reference event are called Event-Related Potentials (ERPs, Luck, 2005). ERP analysis involves increasing the discrimination between the ERP and the background EEG and averaging samples of the EEG that are time-locked to an event such as the presentation of a stimulus. These ERPs are small in comparison to the ongoing EEG in which they are embedded. Electrical activity reflected in the ongoing or background EEG can be spontaneous or induced. Ongoing spontaneous (resting) and induced (task) EEG analyses are reported in Chapter 5. ERP stimulus evoked data analyses are reported in Chapters 6 and 7.

4.2 EEG

The first recording of electrical activity in the human brain was reported by Berger in 1929 (Gloor, 1969) who observed regular waves, subsequently named "alpha', at about 10Hz that 'blocked' when an individual opened their eyes. Berger went on to make recordings directly from the cortical surface during neurosurgery that allowed him to confirm that scalp and cortical recordings were identical with the exception that the amplitude of scalp recordings were attenuated (Davidson et al., 2000). The adult EEG is often decomposed into four frequency bands, which in turn, are associated with various states of consciousness, depending on the relative contribution of each frequency component to the entire EEG signal (see Table 4:1).

Table 4:1 Frequency Bands

Frequency	Name	State
Delta	0-4Hz	Deep sleep
Theta	4-8Hz	Drowsiness
Alpha	8-12 or 13Hz	Relaxed wakefulness
Beta	12-30Hz	Alert Attentiveness

A fifth band, (Gamma, >30Hz) has been associated with certain cognitive and motor functions. In a healthy awake adult at rest with eyes closed the most prominent component of the EEG is the alpha rhythm (Shaw, 2003). Analysis of the ongoing EEG (resting and task) in this thesis is confined to alpha activity.

4.2.1 Alpha Rhythm

The original definition of alpha rhythm proposed by the International Federation of Societies for Electroencephalography and Clinical Neurophysiology in 1951 was updated in 1999 by Deutschl & Eisen who gave the following definition;

"Alpha rhythm: Rhythm at 8-13Hz occurring during wakefulness over the posterior regions of the head, generally with maximum amplitudes over the occipital areas... best seen with eyes closed and during physical relaxation and relative mental inactivity. Blocked or attenuated by attention, especially visual, and mental effort. Comment: use of the term alpha rhythm must be restricted to those rhythms that fulfil these criteria. Activities in the alpha band which differ from the alpha rhythm as regards their topography and/or reactivity should either have specific appellations (for instance mu rhythm) or should be referred to as rhythms of the alpha frequency or alpha activity"

A classical view of alpha activity is that it reflects a passive, or idling state, that facilitates a rapid return to goal oriented behaviour (Adrian & Matthews, 1934). The putative consistency of the brain's activity patterns and its metabolic properties has led

to the proposition that resting state activity reflects a ‘default mode’ of brain function (Gusnard & Raichle, 2001). [For an alternative view see (Nunez, Wingeier, & Silberstein, 2001)]. The notion of an activated standby state is supported by recent imaging studies that describe a network of activation that diminishes during goal oriented tasks, relative to resting state (Gusnard & Raichle, 2001; Raichle et al., 2001). Increased alpha power in posterior regions during eyes closed, meditation, and other relaxation states also lend support to this classical view (Travis & Wallace, 1999), as does the negative correlation between alpha and individual arousal levels (Barry, Clarke, Johnstone, Magee, & Rushby, 2007). However, alpha has also been assigned a more active role in inhibitory control (for hypothesis outline see; Klimesch, Sauseng, & Hanslmayr, 2007) and brain functions, including sensory, motor, and memory processes (Basar, Schurmann, Basar-Eroglu, & Karakas, 1997; Schurmann & Basar, 2001). Spontaneous network correlations are not confined to the default network and five resting state networks, that include distinct sensory, motor, and cognitive brain systems, have been identified, demonstrating that the brain contains organized, spontaneous patterns of functional activity (Buckner & Vincent, 2007; De Luca, Beckmann, De Stefano, Matthews, & Smith, 2006). Multiple origins of alpha have been suggested including: one which is spontaneous, endogenous, and has a distributed source, and another which is more localized and induced by exogenous stimuli (Basar, Basar-Eroglu, Karakas, & Schurmann, 2001; Basar, Schurmann et al., 1997). In line with this view, studies that combine EEG and fMRI suggest two simultaneous processes that characterize the brain at rest: one that is related to expected change in sensory information and another that is endogenous and independent of stimulus change (Ben-Simon, Podlipsky, Arieli, Zhdanov, & Hendler, 2008).

The physiological substrates of EEG are not yet clear but as early as the 1930s a thalamo-cortical reverberating theory of rhythmicity was proposed. Based on their work with anaesthetised animals Anderson and Anderson became champions of the view that the thalamus is a major contributor to cortical rhythmic activities (1968). This thalamic model has been updated by Steriade and colleagues who, based on their work with animals, propose the nucleus recticularis, within the thalamus, as a pacemaker that imposes its rhythmic oscillation on other thalamic nuclei and thalamo cortical cells (Steriade, Deschenes, Domich, & Mulle, 1985). Physicist Paul Nunez, challenges the view that the thalamus represents the primary regulator of cortical rhythmicity and argues against dismissing alpha, which he describes as a complex brain phenomena, with generic labels like ‘pacemaker’ and ‘idling’ (Nunez et al., 2001). In two theoretical books Nunez (1981, 1995) highlights intrinsic properties of intra-cortical interaction in the production of cortical rhythmicity. Inter-connections

among cortical neurons, the majority of which are pyramidal cells, are either short range (< 1mm) or cortico-cortical, which can be described as long-range, because they extend up to several centimetres (Davidson et al., 2000). There are considerably more cortico-cortical connections than there are afferent connections to the cortex or efferent connections from the cortex. Although the most extensive sub-cortical input to cortex of any structure comes from the thalamus, it only provides ~1% of fibres entering any given region of cortex (Davidson et al., 2000). Nunez argues that EEG frequencies are particularly sensitive to long-range cortico-cortical connections and suggests that white matter plays a role in determining the frequency of cortical source oscillations (Nunez, 1981). The presence of multiple alpha rhythms have been taken by some as evidence for multiple isolated generators (local interpretation), but Nunez considers this isolated source view to be a special case of a more general picture that consists of local, regional, and general mechanisms, where interactions between non-local sources may be an essential aspect of dynamics, contingent on brain state (for discussion see Nunez et al., 2001). It is possible that local neural networks[6] can influence global dynamics (bottom up) and global systems can influence local networks (top down) (Nunez, 1995; Nunez et al., 2001). Nunez speculates that the neocortex determines the resonant rhythmic activity of the brain while the thalamus adjusts its oscillatory activity to be synchronous with the neocortical frequency.

Alpha synchronisation describes an increase in alpha power wherein large populations of neurons fire with the same phase and frequency producing oscillations that can be measured at the scalp surface and has been associated with a non-sleep resting state in the brain (Pfurtscheller, 1999). In contrast, desynchronisation (blocking), the decrease in power that occurs when local neuronal generators start to oscillate independently at the micro-scale, is linked to increased cognitive demand (Klimesch, 1999). The pattern of the EEG signal varies both across and within individuals depending on a number of factors including health, state of consciousness, and age (for discussion see; Shaw, 2003).

4.2.2 Alpha Frequency

In healthy adults the alpha rhythm is characterised by a bell-shaped curve with an average peak of ~ 10Hz (Angelakis, Lubar, Stathopoulou, & Kounios, 2004). Alpha frequency is defined in terms of peak frequency within the standard alpha frequency range (8-13Hz). Peak frequency is the spectral component that shows the largest power estimate. Alpha frequency varies as a function of age, neurological disease, and

[6] Neural networks are defined as strong preferential connections, strengthened by Hebbian mechanisms, and continuously reformed on millisecond time scales (Gevins, Morgan, Bressler, Doyle, & Cutillo, 1986; Nunez, 1995; Nunez et al., 2001)

task demands (Klimesch, 1999) and so it has been argued that the analysis of fixed frequency bands (e.g. 8-13Hz) could blur the real alpha peak masking age-related or disease induced change (Moretti et al., 2004). It has been suggested that adjusting frequency bands individually for each subject could reveal additional information (Klimesch, 1999; Köpruner, Pfurtscheller, & Auer, 1984). This thesis investigates alpha activity using both individual frequency bands and standard fixed frequency bands.

4.2.3 Relative Alpha Power

The power spectrum provides information on the contributions of each frequency to the entire EEG spectrum and alpha power refers to the extent to which the frequency of alpha is present in the overall EEG. Absolute power values are sensitive to confounds of head volume conduction and so to counteract this problem the use of relative power measures has been recommended (Hogan, Swanick, Kaiser, Rowan, & Lawlor, 2003; Moretti et al., 2004; Nuwer, 1988). Expressing alpha power as the ratio of absolute power within the alpha frequency band divided by absolute power for 1.0 – 30Hz yields a relative alpha power measure that demonstrates less inter-individual variability than absolute power measures, thus controlling for group differences in total spectral power. Resting EEG changes with age and gradual alterations in the spectral power profile are observed (Rossini et al., 2007). In the main, studies report a general slowing of the EEG with power increases in frequency ranges below 7Hz and decreases in frequencies above 7Hz (Markand, 1990; Ogilvie, A, Kuderian, T, & Rustenburg, 1991). In particular an age-related power decrement of low frequency alpha (8-10Hz) in occipital, parietal, and temporal regions has been reported (Babiloni, Frisoni et al., 2006).

4.2.4 Alpha Reactivity

The alpha rhythm suppresses or desynchronizes with visual stimulation and mental activity (Gloor, 1969). Alpha reactivity usually reflects this power difference between two waking resting periods, one with eyes closed the other with eyes open, but can also be used to compare resting power with power recorded during a memory task (Klimesch, 1999; van der Hiele, Vein, Kramer et al., 2007; van der Hiele, Vein, Reijntjes et al., 2007). Alpha reactivity increases during childhood (Somsen, van't Klooster, van der Molen, van Leeuwen, & Licht, 1997), decreases with age (Duffy, Albert, McAnulty, & Garvey, 1984), and with neurological impairment (Alloway, Ogilvie, & Shapiro, 1997; Besthorn et al., 1997).

4.3 EVENT-RELATED POTENTIALS

Event-Related potentials (ERPs) are small fluctuations in the electrical activity of the brain recorded from the scalp that are associated in time with specific sensory, cognitive, and motor events (Coles & Rugg, 2002; Luck, 2005; Otten & Rugg, 2005; Picton et al., 2000). Conceptually ERPs are regarded as manifestations of specific psychological processes that occur in preparation for, or in response to, discrete internal or external events (Fabiani, Gratton, & Coles, 2000). Recording EEG during a defined epoch that is time locked to the presentation of a stimulus reveals voltage changes that are specifically linked to the brain's response to that stimulus (Coles & Rugg, 2002). These voltage changes constitute the scalp recorded ERPs. It is generally held that most ERPs are the summation of postsynaptic rather than presynaptic potentials (Fabiani et al., 2000). ERPs recorded at the scalp are thought to represent net electrical fields associated with the activation or inhibition of large populations of neurons. The voltage changes reflected in the ERP are primarily generated by the large pyramidal neurons in the cerebral cortex that are aligned in parallel and are located relatively near the scalp. In order to be detected at the scalp these populations of neurons must be synchronously active (Coles & Rugg, 2002). In addition, the neurons must have an open field configuration, that is their individual electrical fields must summate to give rise to a dipolar field (i.e. a field with a pair of charges with opposite signs between which a current flows) that usually involves neurons aligned in a parallel orientation (Coles & Rugg, 2002). Therefore, when interpreting ERP data it is important to acknowledge that a considerable portion of the brain's electrical activity cannot be recorded at the scalp.

Because ERPs are small relative to the EEG in which they are embedded signal processing techniques are necessary to extract the time-locked ERP (signal) from the background EEG (noise). ERPs can be extracted from the ongoing EEG by means of filtering and averaging. Analog or digital filters can be used at the time of recording and/or at the time of analysis to attenuate activity outside the frequency of interest. Averaging involves the summation of a number of EEG epochs (or trials) that are time-locked to repeated occurrences of a particular event or class of event. These EEG epochs are considered the product of both the ERP and other voltage variations that are not time-locked to the event. The number of samples used in the average is related to the signal-to-noise ratio. With conventional averaging the size of the signal remains constant with the addition of trials but the size of the noise decreases. A single vector of values that represent the average activity at each time point are produced when the digital EEG values for each time point in the epochs are averaged. On the assumption that EEG activity that is not time-locked to the event varies randomly

across epochs, the background EEG averages to zero leaving a residual waveform that reflects electrical activity that has a fixed temporal relationship to the event across epochs (Coles & Rugg, 2002; Fabiani et al., 2000). The resulting averaged ERP waveforms contain a number of positive and negative voltage deflections known as *peaks, waves, or components* that can then be subject to a variety of measurement operations.

4.3.1 ERP Components

Peaks and components are not the same thing and so it is important to draw a distinction between the observable peaks in a waveform and the unobservable latent components (Otten & Rugg, 2005). The voltage deflections observed in an ERP waveform reflect the sum of several relatively independent underlying components, in the absence of direct access to these latent components researchers can only make inferences about them from the observed waveforms (Otten & Rugg, 2005). Figure 4:1 illustrates the relationship between examples of latent components and observable peaks.

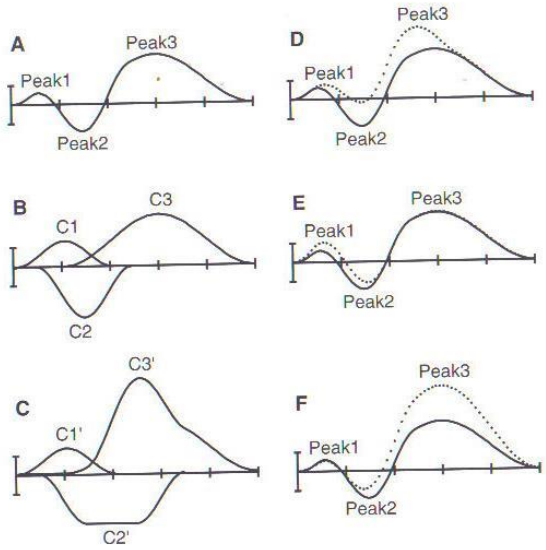

Figure 4:1 Latent components that may sum together to form an observed waveform.

Note: Illustration taken from Otten & Rugg (2005). B and C represent two different sets of latent components that could underlie the ERP waveform in A. The effects of decreasing component C2 by 50% (broken line) on the ERP waveform compared to the original line (solid line) is represented in D. The effect of increasing the amplitude of component C1 (broken line) relative to the original waveform (solid line) are represented in E. Illustration F shows the effects that an increase in component C3 (broken line) would have relative to the original waveform (solid line).

The concept of the component facilitates communication across experiments, paradigms and scientific fields, allows the integration of ERP data with other measures of brain activity and can act as a marker of cognitive processes (Otten & Rugg, 2005). However, there is no universally accepted definition of what constitutes an ERP component. The voltage deflections observed in a waveform may be the

summation of contributions from a variety of origins and may reflect functionally heterogeneous neural or cognitive sources (Otten & Rugg, 2005). A number of approaches to component definition that span the extremes of physiological and functional viewpoints have emerged from ERP research. Physiological proponents (Naatanen & Picton, 1987) advocate the definition of ERP components in terms of their anatomical source within the brain, an approach that necessitates the isolation of cerebral sources underlying ERP waveforms in order to facilitate component measurement. In contrast, a functional approach (Donchin, 1981) requires that the component be defined predominantly in terms of the functional processes with which it is associated. This view makes it irrelevant whether the component reflects the activity of one or multiple generators within the brain as long as these generators constitute a functionally homogenous system (Fabiani et al., 2000; Otten & Rugg, 2005). Physiological and functional/psychological approaches are not mutually exclusive and in practice components can be defined operationally as a part of a waveform with a delineated scalp distribution and delineated relationship to experimental variables (Otten & Rugg, 2005). A classic approach (Donchin, Ritter, & McCallum, 1978) defines a component by a combination of its polarity, characteristic latency, scalp distribution, and its sensitivity to characteristic experimental manipulations.

The letters *P* and *N* traditionally designate positive-going and negative-going peaks respectively. At present there is no universally agreed convention for plotting ERP waveforms with some researchers plotting negative voltages up and others plotting positive voltages as up. This study adopts the latter approach because the wider scientific community uses a positive-up convention. It is important to note that the polarity of an ERP effect has no particular physiological or functional significance because it is contingent on a number of neurophysiological and non-neurophysiological factors including the baseline against which the effect is compared, the location and orientation of intra-cerebral sources, whether input is inhibitory or excitatory, or whether input is received via synapses distal or proximal to the cell bodies (Otten & Rugg, 2005; Wood, 1987). Peaks can be labelled according to their ordinal or temporal latency. When the letters P and N are followed by a single digit (e.g. N1, P3) the number simply refers to the peak's ordinal position within the waveform. However, it is also common to label components according to their exact latency (e.g. P225) or approximate latency (e.g. N100, P300). The latency of a component can vary across experiments, across conditions of an experiment and within conditions across electrodes. The final two descriptors used to define components refer to the scalp location (e.g. frontal P300) or the experimental manipulation (e.g. novelty P3 or readiness potential).

Components can also be distinguished according to whether they reflect sensory or cognitive processing. From a psychological perspective components can be characterised along a continuum that runs from exogenous, through mesogenous, to endogenous (Fabiani et al., 2000). Obligatory responses that are primarily influenced by the physical properties of an external eliciting event are referred to as exogenous or 'sensory'. In contrast, endogenous potentials are thought to reflect information processing in the brain that may or may not be invoked by the event (Picton et al., 2000). These components are influenced by factors such as attention, task relevance, and type of processing required by the stimulus and can even be elicited in the absence of an event, for example, when an expected target doesn't appear (Coles & Rugg, 2002). Although sensory components in all modalities are considered obligatory because they are elicited in all individuals with intact sensory systems, on all occasions, they are also modifiable because they are modulated by attentional and task parameters (Coles & Rugg, 2002; De Sanctis et al., 2008; Dockree, Kelly, Robertson, Reilly, & Foxe, 2005). Scalp voltage oscillations elicited by the presentation of stimuli in visual, auditory, and somatosensory modalities are thought to be related to the transmission of the signal generated at peripheral receptors to the cortex and/or the arrival of that information in the cortex (Coles & Rugg, 2002; Fabiani et al., 2000). It is thought that extremely short deflections (e.g. <10ms) reflect the transmission of sensory information in the sensory pathways while later deflections (e.g. up to 100ms) reflect the arrival of the information in the modality relevant areas of the cortex (Coles & Rugg, 2002). Only later deflections are evident in the visual modality, most probably due to the closed field configuration of the sensory relay nuclei (Coles & Rugg, 2002).

Potentials that are sensitive to both the physical properties of the stimulus and the nature of the participant event interaction can be referred to as mesogenous (Fabiani et al., 2000). The exogenous-endogenous continuum can be described as roughly coextensive with time wherein components that occur within the first 100ms post-stimulus tend to be more exogenous and those that occur later tend to be more endogenous in nature. However, it should be noted that recent evidence suggests that endogenous processes can affect visual components as early as the C1 (~50ms), a component that up until very recently was thought to be purely exogenous and impenetrable to endogenous processes (Kelly, Gomez-Ramirez, & Foxe, 2008). Sensory components tend to have less individual variability when compared to later more cognitive processes which tend to demonstrate greater spatial variability across subjects (Handy, 2005). It is important to note that although components are labelled according to their polarity and position within the waveform sensory components from different modalities given the same label are not usually functionally related (Luck,

2005). Even within a modality components given the same label in different experiments may not be the same. Components can also be classified based on their relationship to a response or on whether they precede or follow events. Placing a bar over the latency component represents a convention that facilitates the distinction between a theoretical entity (e.g. $\overline{\text{P300}}$) and the observed polarity and latency of a peak from a particular experiment. Finally, it is important to note that cognitive electrophysiologists tend to examine differences waves (e.g. ERPs to incongruent minus congruent ERPs) because it reduces the contribution of irrelevant ERP differences. However, this approach overlooks differences due to individual variability, modality, stimulus characteristics, and so on, resulting in a residual problem of non-identity between ERPs that makes it difficult, for example, to know the extent of the relationship between two effects (Kutas, 1997).

4.3.2 Components of Interest

P1 Component

The visual evoked **P1** is largest at lateral occipital electrode sites, has an onset of 60-90ms post stimulus, a peak at 100-130ms and is sensitive to stimulus parameters, spatial attention, and arousal (Luck, 2005). A number of studies show age-related enhancement of early visual evoked potentials (VEPs), such as the P1 and N1 (Falkenstein, Yordanova, & Kolev, 2006; Kolev, Falkenstein, & Yordanova, 2006), contradictory reports of age-related decreases in VEP amplitude (Czigler & Balazs, 2005) may be due to differences in task parameters (De Sanctis et al., 2008).

N1 Component

The P1 is followed by the **N1**. There are several visual N1 components. The earliest subcomponent peaks at 100-150ms post stimulus at anterior sites. Two posterior N1 components peak at 150-200ms post-stimulus from the parietal and lateral occipital cortex (Luck, 2005). The lateral occipital component is larger when subjects perform a discrimination task than when they perform a detection task (Luck, 2005). The N1 is also thought to be modulated by attention and other task parameters (Dockree et al., 2006). Processing of orthographic stimuli during the N1 timeframe is left lateralised (Allison, McCarthy, Nobre, Puce, & Belger, 1994). Substantially increased N1 amplitudes have been reported in healthy elderly when compared to young controls, which is driven by additional N1 activity in the elderly over the right lateral occipital area (De Sanctis et al., 2008). The functional significance of age-related N1 enhancement is as yet unclear but could be indicative of resistance to cognitive decline or may reflect inefficient inhibitory processing in normal ageing (De Sanctis et al., 2008).

P2 Component

The **P2** component follows the N1 and precedes the N200. Two different visually evoked P2 components that may have different functional significance have been identified (Riis et al., 2009), one with an occipito-parietal distribution and the other with a more anterior scalp distribution. The latter has been proposed as a marker of the motivational salience of a stimulus based on task relevance (Potts & Tucker, 2001). This anterior visual P2 is sensitive to specific stimulus attributes marked out as significant in task instructions (Luck & Hillyard, 1994). The P2 is larger for stimuli with target features, and is enhanced for infrequent targets (Luck, 2005). At posterior sites the P2 can be difficult to distinguish from N1, N2, and P3 waves. There is little research examining the generation mechanisms, functional significance or cognitive correlates of the P2 (Crowley & Colrain, 2004).

P300 Component

The **P300** (Sutton, Braren, Zubin, & John, 1965) is one of the most well researched components. The component, which is generally elicited using an 'Oddball' paradigm, is maximal over the parietal/central region and has a latency of at least 300ms and at most 900ms. The P300 has been linked to memory processes and is sensitive to attentional resources allocated to task (Gonsalvez & Polich, 2002). It has been proposed that the P300 reflects context updating of neural representations as a function of incoming information (Dochin & Coles, 1988). P300 amplitude declines with age and peak latencies increase linearly with age (Polich, 1997). The P300 may reflect the activity of a widely distributed system within which the coupling of constituent parts are situation contingent (Coles & Rugg, 2002). The P300 is also known as the P3b to distinguish it from the frontal P3 or P3a that is elicited if a third 'novel' event is introduced into an oddball task. This P3a is thought to reflect involuntary attentional response to salient events (Coles & Rugg, 2002).

N400 Component

The **N400** is generally largest over central and parietal scalp regions with slightly enhanced amplitude observed in the right hemisphere relative to the left hemisphere. This negative going wave**,** which is one of the most studied language components, is sensitive to deviance in relation aspects of the eliciting stimulus such as meaning (Coles & Rugg, 2002). Some N400 activity is elicited by any content word but relatively infrequent words elicit larger N400s than relatively frequent words. The amplitude of the component is inversely related to the congruity of a word within a sentence context (Coles & Rugg, 2002). Large N400s are elicited when isolated words are processed to the level of their identity (Coles & Rugg, 2002).

FN400 & Late Posterior Component (LPC)

ERP correlates of recognition memory have generally been employed in paradigms in which participants decide whether test items were on a previous study list. Studied items correctly endorsed as 'old' (Hits) are more positive going than those elicited by correct endorsements of 'new' items (correct rejections, CR's) starting about 300ms post test stimulus and the effect last several hundred milliseconds (Rugg, 1995). Topographically distinct modulations within this old/new effect have been identified and are thought to be associated with different retrieval processes (Rugg & Curran, 2007). The **FN400** and **LPC** (late posterior component) old/new effects are postulated to correlate with familiarity and recollection respectively. The FN400 (~300-500ms) also known as the frontal-EM (episodic memory) effect is maximal over frontal sites and is associated with an enhanced positivity for correct endorsement of old items. The LPC (~500-700/800ms) also known as the parietal-EM effect, takes the form of a phasic, positive, parietally maximal ERP modulation, that often demonstrates a left-hemisphere bias (De Chastelaine, Friedman, Cycowicz, & Horton, 2009; Rugg & Curran, 2007). There is limited research that explores the impact of age on these putative correlates of familiarity and recognition but recent studies have reported that the FN400 and LPC were absent or attenuated in older adults (Wolk et al., 2009).

4.3.3 Quantifying Waveform Components

The electrode site chosen for analysis should accurately reflect where the component of interest manifests its maximum or minimum amplitude. Individual ERP components can be quantified with regard to the amplitude or peak of the component in (μV), the latency of the peak (ms) or the onset latency for the peak. Most commonly, measures of ERP components focus on differences in amplitude between experimental conditions. The amplitude of an ERP component is commonly measured in one of two ways. One, known as *peak amplitude measure*, measures the amplitude at the peak latency, the other called, *mean amplitude measure*, computes the average amplitude over a time window that contains the component of interest. The mean amplitude measure is the arithmetic average of all time points within the time window, which is usually centred on the peak latency and sufficiently constrained so as to avoid including time points from adjacent components in the waveform. There are advantages and disadvantages to each method. Because peak amplitude measures are particularly sensitive to noise in ERP waveforms, mean amplitude measures are preferable when noise is a concern especially when making comparisons between

conditions with unequal number of trials or between groups where the data from one group might be more noisy than the data from another. It is also possible to use an area amplitude measure, which is calculated by multiplying the mean amplitude by the number of points in the measurement window. Amplitude must be measured relative to some zero point, usually this baseline is based on the mean of the waveform calculated across a pre-stimulus time window in that same waveform (e.g. -100 to 0ms pre-stimulus).

4.4 ISSUES

Age-related morphological and topographical differences in ERP waveforms are frequently observed. It is not yet known whether these differences have functional significance or simply reflect age-related changes in brain structure (Rugg & Morcom, 2005). Differences in scalp distributions could reflect age-related differences in the geometry of generators that is secondary to changes in brain morphology rather than the engagement of different neural systems (Rugg & Morcom, 2005). It has been argued that focusing on age by condition interactions rather than main effects of age may minimize the impact of this issue (Rugg & Curran, 2007).

Age-differences in signal-to-noise (SNR) ratio is of particular relevance to ERP studies of memory. Event-related responses (correct responses) are likely to be estimated from fewer trials in older adults when compared to young controls due to the likely greater incidence of error trials in older adults. Although this will not systematically bias response estimates it will result in across group differences in their reliability (standard error), due to the fact that the SNR is proportional to the square root of the number of trials over which a response is estimated. Because response times (RTs) show more intra-individual variability with increasing age (Hultsch et al., 2002) more temporal jitter may be evident in older participants in neural responses that are correlated with RT, which in turn will lead to an underestimation of the amplitude of older participants averaged responses (Picton et al., 2000). Greater incidence of movement artifacts and a signal that may be inherently nosier or more variable with increasing age are also likely to reduce SNR in older adults (D'Esposito, Zarahn, Aguirre, & Rypma, 1999).

4.5 PROCEDURE

EEG data were collected during Session 2. See Appendix E for standard operating procedures (SOP).

4.5.1 Fitting Participants with Cap and Electrodes

Participants were seated in a comfortable chair ~65 cm from a computer screen in a dimly lit EEG testing room. The circumference of the participant's head was measured just above the eyebrows and over the inion at the back of the head. This circumference was used to guide selection of appropriate cap size. The distance from the nasion to the inion was then measured and divided by two to determine the proper location of the Vertex electrode (CZ). The mastoid electrodes were then attached to the participant. The cap was carefully placed on the participant's head in such a way as to ensure that the midline of the cap lined up with the nose and the vertex electrode was in the correct location. The chin strap was then fitted to ensure that the cap remained in a secure position. After each electrode holder was filled with gel the remaining electrodes were attached. The electrodes were then plugged into the A/D box. Using the Actiview software the trace for each electrode was examined to check for impedance. Once any problems with poor connections were rectified testing began. Participants were made aware of artefact-related problems induced by blinks, other facial movements, head, and neck movements and other twitches. They were asked to keep such movements to a minimum.

4.5.2 EEG Acquisition

Continuous EEG was acquired through the ActiveTwo Biosemi electrode system from 64 scalp electrodes, digitized at 512 Hz. Individual electrodes (see Figure 4:2) are identified by brain hemisphere (odd numbers = left, even numbers = right) and general cortical zone (F = frontal, C = central, T = temporal, P = parietal and O= occipital). Vertical eye movements were recorded with two vertical electrooculogram (EOG) electrodes placed below the left and right eye, while electrodes at the outer canthus of each eye recorded horizontal movements. All electrode channels were subjected to an artefact criterion of ±100 mV to reject trials with excessive EOG or other noise transients.

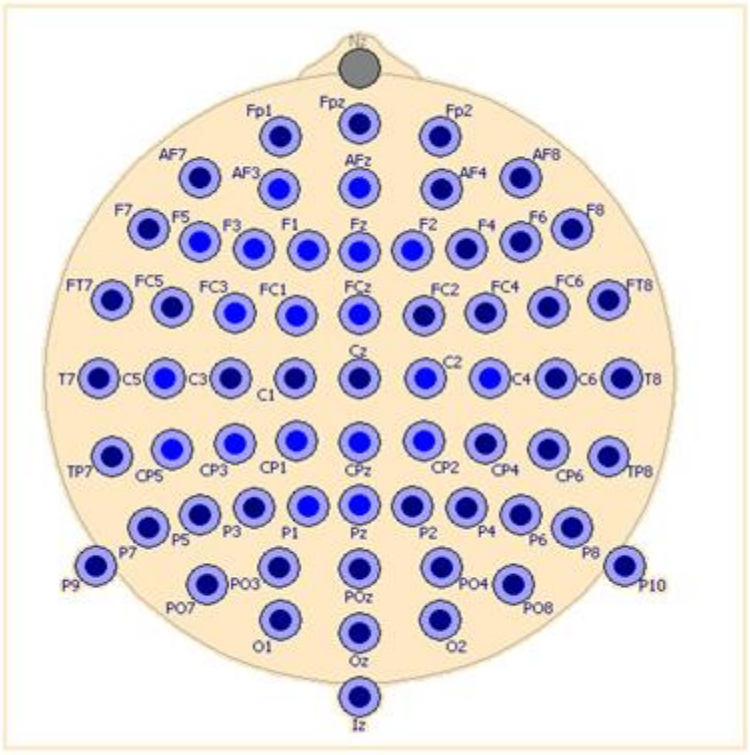

Figure 4:2 Location of Electrodes on the scalp.

Chapter 5 AN EEG STUDY OF ALPHA ACTIVITY

5.1 INTRODUCTION

The human electroencephalogram (EEG) and its most prominent component, the alpha rhythm, are described in Chapter 4. This thesis seeks markers that may index cognitive decline and this chapter specifically investigates the ability of resting and task related alpha measures to distinguish participant groups, on the basis of age and cognitive performance. Although the special significance of resting brain activity has been challenged (for commentary see Morcom & Fletcher, 2007), an exclusive focus on task-evoked brain activity is arguably limited because it may miss important neural processes, neglects cognitive, behavioural, and functionally relevant processing events that are not directed to immediate task demands, and may lead to erroneous conclusions if brain processes persist, or only occur independent of engaged task events (Buckner & Vincent, 2007). Resting state activity may reflect spontaneous cognition and could be linked to planning and imagination (Esposito et al., 2006; Fransson, 2006), it may also play a role, beneath awareness, in consolidation and setting the context for future information processing (Raichle, 2006). Recently it has been speculated that lifelong resting state electrophysiological activity may play a direct, or indirect, role in the development of Alzheimer's disease (AD) pathology (Buckner & Vincent, 2007). Differences in resting state activity have been found in autism (Kennedy, Redcay, & Courchesne, 2006), depression (Anand et al., 2005), multiple sclerosis (Lowe et al., 2002), and attention deficit disorder (Tian et al., 2006). Clinical diagnosis of AD is correlated with differences in resting activity (Lustig et al., 2003; Wang et al., 2006). Such findings make it clear that understanding resting state activity may be central to understanding individual differences in cognition, the physiology of brain disease, and the risk for disease (Buckner & Vincent, 2007). Using variance in spontaneous activity patterns, as a basis for exploring functional differences among individuals, has recently been advocated as an important area for future research (Buckner & Vincent, 2007; Hampson, Driesen, Skudlarski, Gore, & Constable, 2006). This chapter examines alpha frequency, power, and reactivity at rest with eyes closed, at rest with eyes open, and during the encoding phase of the Learn memory task described in detail in Chapter 2.

Alpha Frequency

The peak of the spectral distribution of the alpha rhythm usually occurs around 10-11Hz in healthy adults but is slower in children and the elderly (Clark et al., 2004; Roubicek, 1977). The variation of the spectral distribution within the alpha range (8-13 Hz) can be quantified in a number of ways: for example, peak alpha frequency,

which measures the discrete frequency with the greatest magnitude within the alpha range, or individual alpha frequency, which measures the centre of gravity, rather than the peak, for each individual. It has been argued that the latter represents a more accurate measure of spectral distribution than the former (for discussion see; Klimesch, 1997). There is a linear relationship between alpha peak frequency and age across adulthood (alpha peak frequency = 11.95 - 0.053 x age), such that the expected peak frequency for a 20 year old is 10.89 Hz and for a 70 year old is 8.24 Hz (Köpruner et al., 1984). However, it should be noted, that there is considerable inter-individual variability in alpha frequency even for age-matched individuals (Klimesch, Schimke, Ladurner, & Pfurtscheller, 1990; Köpruner et al., 1984). In fact, inter-individual alpha frequency differences in age-matched subjects are as large as age-related differences (Klimesch, 1999).

Peak alpha frequency has been associated with various cognitive functions including attention, arousal, anticipation, and memory in healthy individuals and has been related to task demand (Angelakis et al., 2004; Basar, Yordanova, Kolev, & Basar-Eroglu, 1997; Klimesch, 1997). It has been argued that intra-individual variability in peak alpha frequency reflects arousal and/or attentional demands (Klimesch et al., 1990). It has also been argued that alpha peak frequency reflects speed of processing in the thalamo-cortical networks (Klimesch, 1997; Steriade, Jones, & Llinas, 1990). Alpha frequency is significantly correlated with the speed of information processing as measured by reaction time (RT) (Klimesch, Doppelmayr, Schimke, & Pachinger, 1996; Surwillo, 1961, 1963). In contrast, to inter-individual differences in alpha frequency, intra-individual, or task related shifts, in alpha frequency do not appear to be related to processing speed (Klimesch, Doppelmayr, Russegger, & Pachinger, 1996). There is a positive relationship between alpha peak frequency and working memory performance as measured by digit span (Clark et al., 2004). Good memory performers demonstrate higher alpha frequency than age-matched samples of poor performers (Klimesch, 1996; Klimesch, Pfurtscheller, & Schimke, 1993; Klimesch et al., 1990). Individual alpha frequency has been proposed as an index of memory ability (Klimesch et al., 1990). In individuals with lower memory performance and lower alpha frequency than higher performing cohorts, alpha frequency decreased with increasing memory demand, in contrast, in higher performers, frequency remained constant in the face of the same cognitive load (Klimesch, Schimke, & Pfurtscheller, 1993).

There is clinical evidence that indicates that a number of brain diseases reduce alpha frequency (Köpruner et al., 1984), leading some to argue that the decrease in alpha frequency observed with increasing age is not a consequence of the ageing process itself, but rather a consequence of age-related disease (Hubbard, Sundae, &

Goldensohn, 1976; Torres, Faoro, Löwenson, & E. Johnson, 1983). Decreased peak alpha frequency has been observed in hemispheric stroke patients (Juhasz, Kamondi, & Szirmai, 1997). The peak alpha frequency decreases in the stroke patients are observed in the affected hemisphere within 48 hours of the acute episode and return to normal within 2 to 4 weeks (Juhasz et al., 1997). When compared to age-matched controls individuals with Alzheimer's disease (AD) have reduced peak alpha frequency (Passero, Rocchi, Vatti, Burgalassi, & Battistini, 1995) or individual alpha frequency (Klimesch et al., 1990). Klimesch has also reported a significant correlation between individual alpha frequency and memory performance on the Weschler Memory Scale in AD patients (1990). In contrast, no significant correlations between peak alpha frequency and cognitive impairment were reported in the Passero et al. study. Discrepant findings across studies may be a consequence of different methods used to quantify alpha frequency. Another study shows that a decrease in individual alpha frequency and a decrease in the transition between alpha and theta bands characterizes patients with vascular dementia but not patients with AD (Moretti et al., 2004).

Relative Alpha Power

From a physiological perspective EEG power reflects the number of neurons that discharge synchronously. Alpha power, the extent to which the frequency of alpha is present in the overall EEG, increases from childhood to adulthood (Breslau et al., 1989), becomes more stable across middle age, until later life, when a pronounced drop is observed (Klimesch, 1999). Alpha power has been related to cognitive and memory performance. During resting state there is a positive relationship between alpha power and memory performance with high alpha associated with good performance (for review see Klimesch, 1999). Klimesch argues that upper alpha oscillations reflect memory processes, including the encoding of new information, and lower alpha oscillations reflect attentional processes (1999). The modulation of alpha activity by thalamo-cortical and cortico-cortical interactions is thought to facilitate, or inhibit, the transmission of sensorimotor information and the retrieval of semantic information (Brunia, 1999; Pfurtscheller & Lopes da Silva, 1999; Steriade & Llinas, 1998). Over the course of 'natural' ageing, the power decrease observed in the occipital alpha rhythm may be related to alterations in the cholinergic basal forebrain system, which sustains the excitatory activity in the cholinergic brainstem pathway (Davies & Maloney, 1976; Sarter & Bruno, 1998a, 1998b). EEG power changes may, therefore, reflect cortical atrophy and/or cortical reorganization (Hogan et al., 2003).

It is worth noting that there is considerable overlap in EEG parameters at the boundaries of normal ageing and mild cognitive impairment (MCI), as well as at the

boundaries of MCI and AD (Jeong, 2004). Generally speaking EEG parameters for MCI subjects are intermediate between those of controls and dementia patients. Compared to healthy elderly, individuals with MCI exhibit reduced alpha power, In addition, reduced global cognitive function in individuals with MCI is associated with lower alpha (Huang et al., 2000; Jelic V et al., 1996). People with MCI who progress to AD within 2 years show decreased alpha compared to those who remain stable (Huang et al., 2000). It has recently been shown that EEG power markers can discriminate among different sub-groups of MCI patients (Moretti et al., 2009). A number of recent studies have disclosed EEG power changes during a memory activation task in individuals with MCI that were not evident in the resting EEG (Jiang, 2005; Pijnenburg et al., 2004; van der Hiele, Vein, Kramer et al., 2007). Correlations between lower alpha activity and decreased MMSE or Global Deterioration Scores (GDS) scores have been reported in cross-sectional studies of older adults with different levels of cognitive impairment (Brenner et al., 1986; Jiang, 2005; Princhep et al., 1994). Abnormalities in the alpha rhythm of early AD patients were first reported more than 50 years ago (Gordon & Sim, 1967; Letemendia & Pampiglione, 1958). Since then decreased alpha activity in AD patients has been repeatedly observed (Babiloni et al., 2004; Brenner et al., 1986; Coben, Danziger, & Berg, 1983; Dierks, Ihl, Frolich, & Maurer, 1993; Huang et al., 2000). In addition, when compared to age-matched controls, people with probable AD exhibit alpha anteriorisation (i.e. alpha activity shifts from posterior to more anterior sites), which is correlated with the degree of cognitive impairment as measured by MMSE (Chiaramonti et al., 1997). Resting EEG abnormalities observed in AD may originate from impairment in the cholinergic neural projections from the basal forebrain (Mesulam, 2004). While brainstem cholinergic innervations of the thalamus remain relatively spared in AD, degeneration of cholinergic neurons of the basal forebrain is a neuropathological feature of AD (Auld, Kornecook, Bastianetto, & Quirion, 2002; Mesulam, 2004). Interestingly, increased cholinergic tone is related to restoration of alpha rhythms in AD responders to cholinesterase inhibitors (Babiloni, Cassetta et al., 2006; Tanaka, Hanyu, Sakurai, Takasaki, & Abe, 2003).

Alpha Reactivity

The alpha rhythm suppresses or desynchronizes with visual stimulation and mental activity (Gloor, 1969). Alpha reactivity usually describes the power difference between two waking resting periods, one with eyes closed, and the other with eyes open, but can also be used to compare resting power with power recorded during a task. Decreases in alpha power are observed when EEG, recorded during a rest condition, is compared with EEG recorded during a task (Klimesch, 1996; Klimesch,

1997; Pfurtscheller & Lopes da Silva, 1999). Strong age-related increases in alpha reactivity are reported in childhood (Somsen et al., 1997), while decreases in alpha reactivity are reported in late life (Duffy et al., 1984), and neurological impairment (Alloway et al., 1997) (Besthorn et al., 1997). Decreased alpha reactivity has been associated with poorer memory performance and positive correlations have been reported between alpha reactivity and measures of executive function and, to a lesser degree, measures of global cognition (Klimesch, 1999; van der Hiele, Vein, Kramer et al., 2007). For event-related changes recorded during a task, decreased alpha is negatively associated with good cognitive and good memory performance (Klimesch, 1999). Decreased alpha reactivity has been reported in MCI patients during a memory task (van der Hiele, Vein, Kramer et al., 2007). AD patients demonstrate decreased alpha reactivity compared with controls and this decrease is related to poorer performance on tests of global cognition, memory and executive function (van der Hiele, Vein, Reijntjes et al., 2007). Significantly higher Wechsler Adult Intelligent Scale performance IQ scores have been reported in AD patients with normal alpha that suppresses during eyes open than AD patients with irregular alpha that does not, or only slightly suppresses during eyes open (Sheridan, Sato, Foster, & Bruno, 1988).

This chapter aims to extend the literature on alpha activity in cognitive ageing by examining alpha frequency, alpha power, and alpha reactivity measures in the Young controls, High performers, and Low performers described in Chapter 2. The main purpose is to examine whether any of these measures of alpha activity can distinguish participant groups on the basis of age and cognitive performance. Alpha frequency, power, and reactivity measures are commonly used in the EEG literature, but their operational definitions vary considerably across research groups and publications. As already discussed, some studies use peak alpha frequency and others individual alpha frequency, but even within these different quantification approaches standardization is lacking. This study uses the method outlined by Dockree and colleagues (2007) to calculate individual alpha frequency. Some studies report absolute alpha power and others relative alpha power. In order to reduce inter-individual variability this study uses relative alpha power (for discussion see Chapter 4). The majority of studies use standard frequency bands but some research groups advocate the use of individualised frequency bands. Given the putative importance of calculating individualised frequency bands in cognitive ageing research individualised frequency bands are used to examine frequency, power, and reactivity. In addition, in line with more traditional approaches, this study uses the 8-13Hz standard alpha frequency band to assess both alpha power and reactivity at rest. Most studies treat alpha as a single band but others advocate parcelling alpha into two or even three sub-bands. In order to restrict the number of EEG parameters and to avoid limiting the

ability to generalise, this study will adopt the more traditional single band approach rather than identifying separate sub-bands as they are not consistently used in EEG research. Based on the linear relationship between alpha frequency and age reported in the literature Young are predicted to have higher alpha frequencies than both of the old groups. Individual alpha frequency has been proposed as an index of memory and so positive correlations with memory performance is predicted. It has also been argued that alpha frequency reflects processing speed so a positive correlation with RT is also predicted. Young are predicted to have higher relative alpha power than both of the old groups. In addition, a positive relationship between resting alpha power and memory performance measures is predicted and a negative relationship between task relative alpha power and memory performance measures is also predicted. Young are predicted to have greater alpha reactivity than both of the old groups. Lower memory performance is expected to be correlated with decreased reactivity and increased reactivity is expected to be correlated with better executive function. Correlations between the alpha measures and intra-individual variability measures on CRTsr (Choice Reaction Time split response task; see Chapter 2 for description) will also be explored.

5.2 METHOD

5.2.1 Participants

Participants were recruited through public and college advertising and from the Robertson Participant Panel (see Chapter 2 for full details). Forty-eight older adults aged between 65 and 80 years and twenty-two Young controls aged between 18 and 30 years satisfied the eligibility criteria. Four older adults failed to attend for Session 2 due to ill health (n=2), personal problems (n=1) and voluntary withdrawal (n=1). In addition, one older adult disclosed taking CNS medication after testing was complete and one young adult drank a substantial amount of alcohol in the 24 hours preceding Session 2 and so both were excluded. Data for forty-three (18 male) older adults (M=69.95, SD ± 3.70) and twenty-one young (9 males) controls (M=21.28, SD ± 2.97) were analysed. The older participants were assigned to sub-groups based on their memory performance relative to an estimate of their pre-morbid IQ. Participants were defined as Low performers if they scored more than one standard deviation below their NART (National Adult Reading Test) estimated pre-morbid IQ on the Wechsler Memory Scale logical memory delayed recall test (for a full description of the classification procedure see Chapter 2 section2.2.2). Classifying participants in this way yielded; a) 25 High performers (10 male, M=70.28, SD ± 3.39 and b) 18 Low performers (8 male, M=69.48 ± 4.14).

5.2.2 Procedure

5.2.2.1 Testing Protocol

Testing was conducted between September 2008 and May 2009. Participants were assessed in two ~2 hour sessions that took place approximately one week apart. During Session 1 participants completed the mini mental state exam, a memory self-rating scale, the Hospital Anxiety and Depression Scale, the National Adult Reading Test, animal naming, the Stroop task, and sub-sets of the Wechsler Memory Scale (Logical Memory 1 and 2, Face Recognition 1 and 2, Visual Reproduction 1 and 2 and Digit span). In addition, during Session 1 participants were taught how to perform the Choice Reaction Time split response task (CRTsr) and the Sustained Attention to Response Task fixed version $SART_{fixed}$. During Session 2 the electrical activity in participant's brains was recorded while participants rested (6 minutes) and while they performed three computerized experimental tasks: the Learn memory task, the CRTsr task, and the $SART_{fixed}$. The Learn task had an encoding and a delayed recognition phase which each took approximately 8.5 minutes to complete. Participants completed the CRTsr (self-paced) and the $SART_{fixed}$ (~5 minutes) during the interval between the

encoding and recognition phases of the Learn task. All materials and experimental tasks are described in detail in Chapter 2. Analysis of EEG data collected during Session 2 while participants rested and while they completed the encoding phase of the Learn task is presented in this chapter (see Figure 5.1).

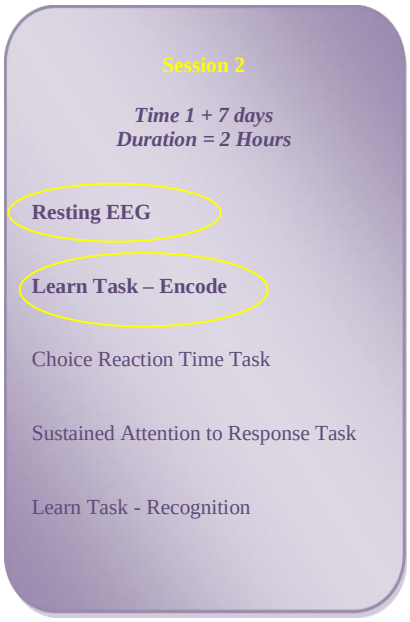

Figure 5:1 Analysis of Alpha Activity

Electrical activity recorded during Session 2 while participants rested and while they completed the encode phase of the Learn task were subjected to EEG analysis.

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5.2.2.2 Fitting Participants with Cap and Electrodes

During Session 2 participants were seated in a comfortable chair ~65 cm from a computer screen in a dimly lit EEG testing room. The circumference of the participant's head was measured just above the eyebrows and over the inion at the back of the head. This circumference was used to guide selection of appropriate cap size. The distance from the nasion to the inion was then measured and divided by two to determine the proper location of the Vertex electrode (CZ). The mastoid electrodes were then attached to the participant. The cap was carefully placed on the participant's head in such a way as to ensure that the midline of the cap lined up with the nose and the vertex electrode was in the correct location. The chin strap was then fitted to ensure that the cap remained in a secure position. After each electrode holder was filled with gel the remaining electrodes were attached. The electrodes were then plugged into the A/D box. Using the Actiview software the trace for each electrode was examined to check for impedance. Once any problems with poor connections were rectified testing began. Participants were made aware of artefact related problems induced by blinks, other facial movements, head, and neck movements and other twitches. They were asked to keep such movements to a minimum.

5.2.2.3 Individual Alpha Frequency (IAF)

Alpha frequency changes with age. Using standard frequency bands could blur the real alpha peak masking age-related or disease-induced change (Moretti et al., 2004). This study calculated peak alpha frequency on an individual basis for each participant and then calculated subject specific frequency bands centred on this peak. The term individual alpha frequency (IAF) is used here to denote the individual dominant (peak) EEG frequency in the alpha band (8-13Hz) (Dockree et al., 2007). IAF varies from subject to subject in scalp location and size. Alpha rhythm occurs over the posterior regions of the head, generally with maximum amplitudes over the occipital areas (Deutschl & Eisen, 1999), therefore, in order to calculate IAF the site of maximum alpha was determined for each participant from posterior electrodes (see Figure 5.2). This was achieved by recording resting EEG from all participants while they had their eyes closed and selecting the appropriate electrode site for each individual. The same procedure was then followed for the eyes open condition. Eyes closed and eyes open were then averaged to produce a single resting IAF.

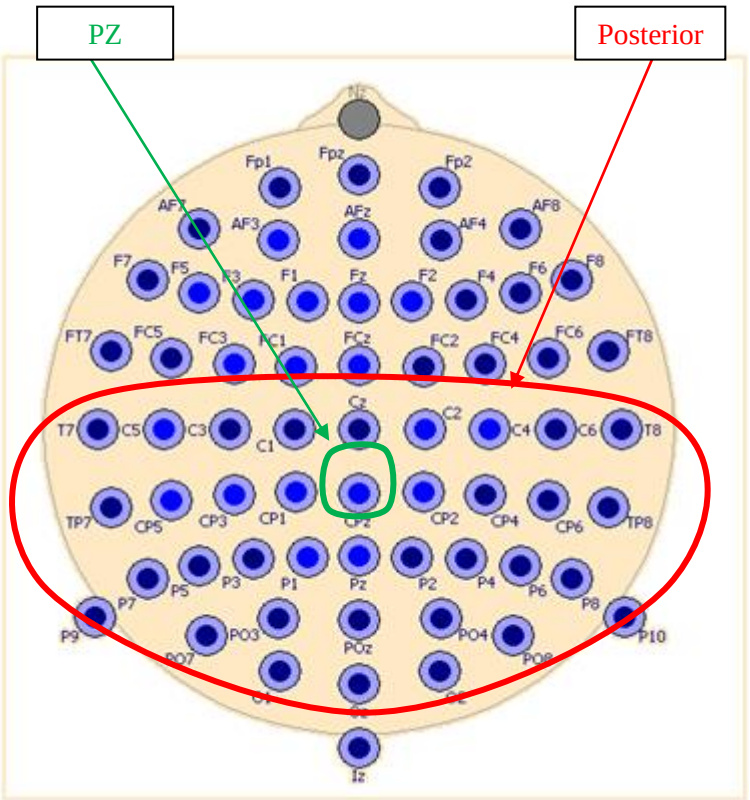

Figure 5:2 Location of Electrodes on the scalp.

Note. Posterior electrodes used to calculate individual alpha frequency are circled in red. Electrode PZ circled in green is used to calculate alpha measures using standard frequency bands.

5.2.2.4 Relative Alpha Power

5.2.2.4.1 Relative Alpha Power – Individual Frequency Band (IFB)

Calculating individual frequency bands for each subject has been advocated given the extent to which alpha frequency varies as a function of age, neurological disease and task demands (Klimesch, 1999). Once an IAF has been calculated for each participant, a 4Hz Individual Frequency Band (IFB) that centres on their IAF can be determined (Dockree et al., 2007). The peak EEG frequency in the alpha range identified for each participant was used to define a subject-specific alpha band. This was done by bandpass filtering the EEG data at the site of maximum alpha power from 2Hz below the participant's IAF to 2Hz above their IAF. The average absolute alpha power for the eyes closed condition was extracted by applying the standard formula for average power in a real signal.

$$\textit{Average Power} = \frac{1}{N}\sum_{n=1}^{N}[x(n)]^2 \qquad \textbf{Equation 1}$$

'x' is the signal being examined and N is the length of the signal in samples.

For example average absolute alpha power for someone with an IAF of 9Hz was calculated using an IFB of 7-11Hz. Relative alpha power was calculated by dividing each individual's average absolute alpha power by the average power in the total band (1-30Hz) at the same electrode site. Frequencies above 30Hz were not used as these can be easily contaminated. This procedure was repeated using EEG data recorded while the participant was at rest with their eyes open.

5.2.2.4.2 Resting Relative Alpha Power – Standard Frequency Band (SFB)

Using a standard frequency band and an identical electrode for all participants is less labour intensive than identifying each participant's site of maximal alpha power, peak alpha frequency, and individual frequency band. Therefore, in this study in addition to using individual frequency bands for each participant, a standard frequency band (8-13Hz) was used to calculate absolute alpha power for all participants at electrode PZ for both Eyes Closed and Eyes Open resting conditions. Relative alpha power was calculated for PZ for both resting EEG conditions (Closed, Open) by dividing absolute alpha power by total band power (1-30Hz).

5.2.2.4.3 Task Relative Alpha Power – Individual Frequency Band

The encode phase of the Learn task is described in detail in Chapter 2. For ease of reference the task is illustrated in Figure 5:3. Four conditions of interest were identified within the task: L-Cue (defined as the L-Cue + L-ISI1, 1400ms), X-Cue (defined as X-Cue + X-ISI1, 1400ms), L-Word (1500ms) and X-Word (1500ms).

Epochs for each condition were extracted for each of the 126 trials. Absolute and relative alpha power were extracted for each condition, after identifying subject specific frequency bands by bandpass filtering the EEG data at the site of maximum alpha power from IAF -2Hz to IAF +2Hz as described above.

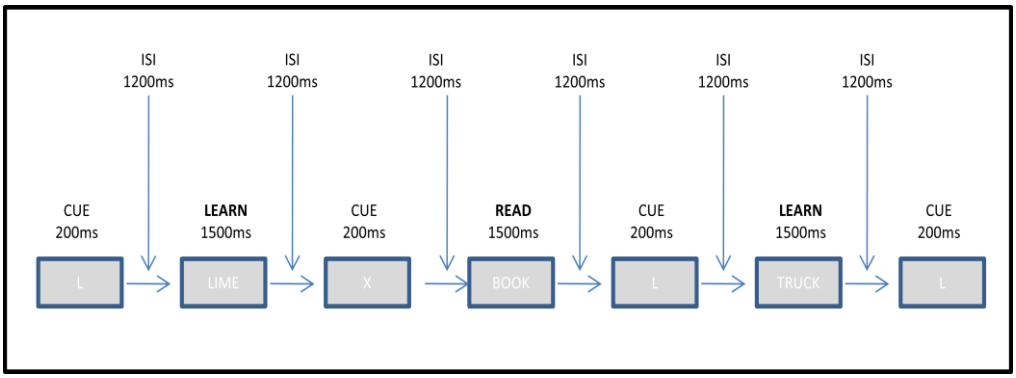

Figure 5:3 Learn Task Sequence – Encode Phase.

Note: Participants were instructed to Learn words preceded by the letter 'L' and Read words that were preceded by the letter 'X'.

5.2.2.5 Alpha Reactivity

The alpha rhythm suppresses with visual stimulation. Measures of alpha reactivity are often used to assess this power difference between two waking resting periods, one with eyes closed the other with eyes open, but can also be used to compare resting power with power recorded during a memory task. This study uses alpha reactivity to assess resting power differences based on individual frequency bands and standard frequency bands. In addition, the difference between resting power and task power are also measured using individual frequency bands.

5.2.2.5.1 Resting Alpha Reactivity - Individual Frequency Bands

Alpha reactivity was calculated for resting EEG based on both individual and standard frequency bands and for the encode phase of the Learn task. The resting alpha reactivity reported reflects the alpha power decrease from eyes closed to eyes open and task alpha reactivity reflects the alpha power decrease from eyes closed to task. The method used to calculate individual frequency bands is described in 5.2.2.4.1 above. Alpha reactivity is the difference in absolute alpha power between eyes closed and eyes open, expressed as a percentage of absolute alpha power recorded during eyes closed.

5.2.2.5.2 Resting Alpha Reactivity Standard Frequency Band

A standard frequency band (8-13Hz) was used to calculate absolute alpha power for all participants at PZ for both eyes open and eyes closed resting conditions. Alpha reactivity is the difference in absolute alpha power between eyes closed and

eyes open expressed as a percentage of absolute alpha power recorded during eyes closed.

5.2.2.5.3 Task Alpha Reactivity Individual Frequency Bands

The methods used to calculate individual frequency bands and task alpha power are detailed in 5.2.2.4.1 and 5.2.2.4.3 above. Task alpha reactivity reflects the alpha power decrease from eyes closed to task, based on the average of each of the four task conditions (L-Cue, X-Cue, L-Word, X-Word).

5.3 RESULTS

Results will be reported under the following headings;

Comparative Analysis

5.3.1 Individual Alpha Frequency (IAF)

5.3.2 Relative Alpha Power

5.3.2.1 Resting - Individual Frequency Band

5.3.2.2 Resting - Standard Frequency Band

5.3.2.3 Task - Individual Frequency Band

5.3.3 Alpha Reactivity

5.3.3.1 Resting - Individual Frequency Band

5.3.3.2 Resting - Standard Frequency Band

5.3.3.3Task - Individual Frequency Band

Correlations

5.3.4 IAF & neuropsychological, RT and variability measures

5.3.5 Relative Alpha Power & neuropsychological, RT latency & variability measures

5.3.6 Alpha Reactivity and neuropsychological, RT latency & variability measures

Comparative Analysis

ANOVAs (mixed model and one-way) were used to test for interactions, main effects and significant differences between groups. Effect sizes were calculated using eta ² or partial eta² and were categorized as follows; (.01=small, .06 = medium, .14 = large: Cohen, 1988). A robust test of equality of means (Brown-Forsythe) was used when the assumption of homogeneity of variances was violated. The non-parametric Kruskal-Wallis test was used when variables were not normally distributed. For post-hoc analysis Tukey's HSD test is reported unless stated otherwise.

5.3.1 Individual Alpha Frequency

The mean resting IAFs for each of the three groups are graphed in Figure 5:4, Panel A. There was a statistically significant main effect of Group (Kruskal-Wallis; $H(2, 61)=15.47$, $p\leq0.0005$). Mann-Whitney U post-hoc tests revealed that the Young had significantly higher IAF than High ($p\leq0.0005$) and Low performers ($p\leq0.05$). High and Low performers did not differ significantly from each other ($p>0.10$).

5.3.2 Resting Relative Alpha Power

5.3.2.1 Resting Alpha Power – Individual Frequency Band

There was a reduction in relative alpha power, calculated using individual alpha frequency (IFB), across the three groups in both the Eyes Closed and Eyes Open conditions (Figure 5:4, Panel B). Young demonstrated the highest power and Low performers the lowest power in both resting conditions (Closed, Open). Alpha suppression to visual stimulation was evident in all three groups. A mixed model ANOVA with three levels of Group (Young, High, Low) and two levels of Condition (Closed, Open) revealed a significant Group effect, a main effect of Condition, but no significant interaction (Table 5:1). Post-hoc comparisons (LSD) showed that Young differed significantly from Low ($p \leq 0.0005$) and High performers ($p \leq 0.05$). Low and High performers also differed significantly from each other ($p \leq 0.05$).

5.3.2.2 Resting Relative Alpha Power for PZ – Standard Frequency Band

There was a systematic reduction in mean relative alpha power using standard frequency bands across the three groups in both resting conditions (Closed, Open) with the Young displaying the highest relative alpha power and Low performers the lowest (Figure 5:4, Panel C). Alpha suppression to visual stimulation was evident in all groups.

A mixed model ANOVA with three levels of Group (Young, High, Low) and two levels of Condition (Closed, Open) revealed a significant Group effect, a main effect of Condition, but no significant interaction (Table 5:2). Post-hoc comparisons indicated that Low performers had significantly lower relative alpha power than both Young ($p \leq 0.0005$) and High performers ($p \leq 0.05$). The High performers' relative alpha power was also significantly lower than the Young ($p \leq 0.05$).

Table 5:1 Main Effects and Interactions Resting Relative Alpha Power – IFB

Resting Relative Alpha Power		Partial Eta²	p-value
Interaction (Condition x Group)	Wilks λ .98, F(2,61) 0.55	0.02	p>0.10
Main Effect – Condition (Closed, Open)	Wilks λ .38, F(1,61) 98.10	0.62	**p≤0.0005**
Main Effect Group (Young, High, Low)	**λ** F(2,61) 9.69	0.24	**p≤0.0005**

Note: High = high performing old. Low = low performing old. Closed = resting with eyes closed. Open = resting with eyes open.

Table 5:2 Main Effects and Interactions Resting Relative Alpha Power for PZ.

Relative Alpha Power		Partial Eta²	p-value
Interaction (Condition x Group)	Wilks λ .97, F(2,61) 1.06	0 .03	p >0.01
Main Effect – Condition (Closed, Open)	Wilks λ .45, F(1,61) 75.90	0.28	**p≤0.0005**
Main Effect Group (Young, High, Low)	F(2,61) 12.00	0.28	**p≤0.0005**

Note: High = high performing old. Low = low performing old. Closed = resting with eyes closed. Open = resting with eyes open.

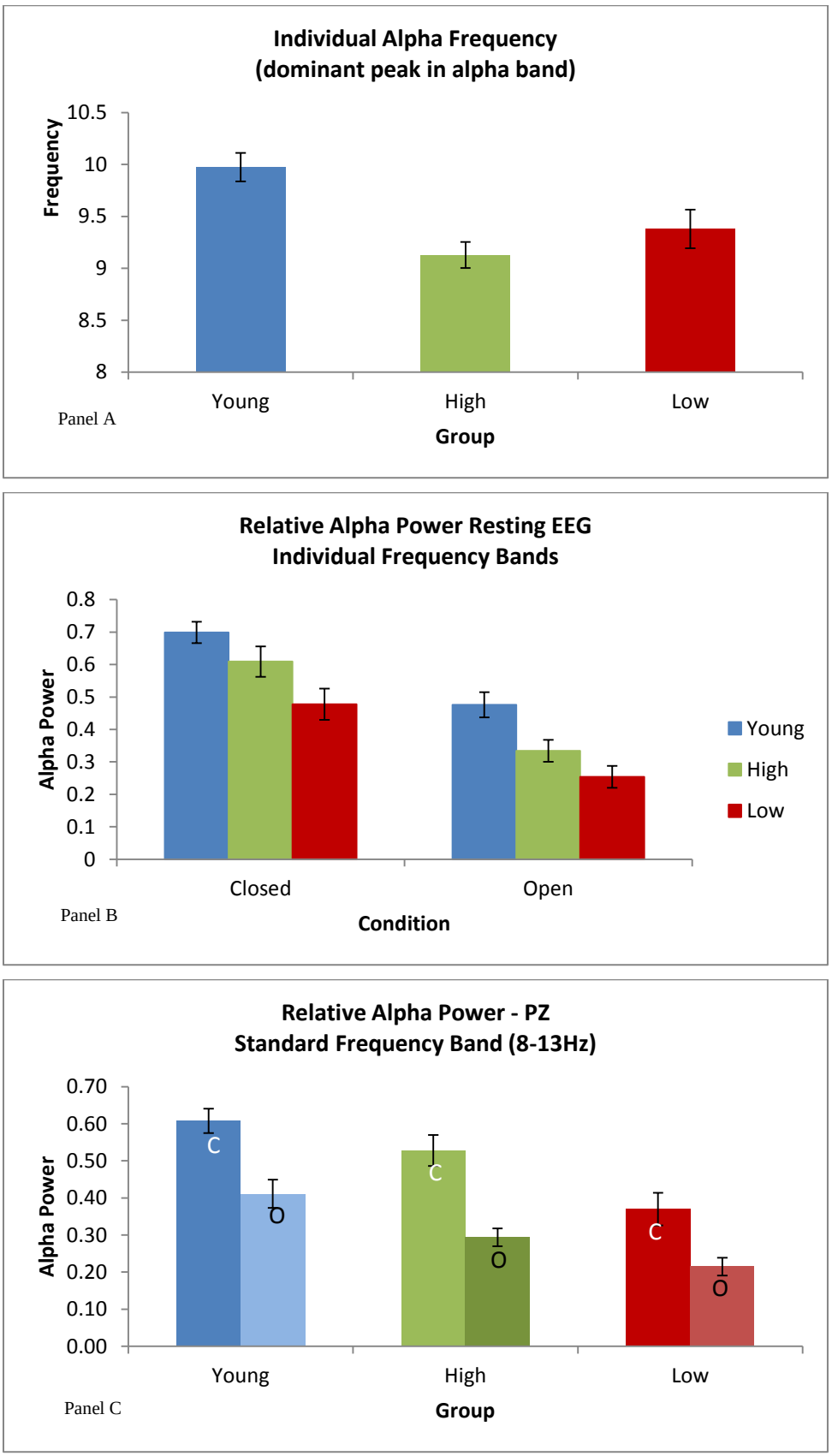

Figure 5:4 Means for Individual Alpha Frequency and Relative Alpha Power

Note: Panel A = Mean Individual Alpha Frequency averaged over Eyes Closed and Eyes Open conditions. Panel B = Mean relative alpha power calculated using individual frequency bands. Panel C =Mean relative alpha power for PZ using standard frequency bands. Closed = resting with eyes closed. Open = resting with eyes open. C= Resting Eyes Closed, O = Resting Eyes Open. High = high performing old. Low = low performing old. See Figure 5.2 for scalp location of electrode PZ. Error bars show one standard error.

5.3.2.3 Relative Alpha Power– Task – Individual Frequency Band

There was a reduction in relative alpha power, calculated during the encode phase of the Learn memory task using individual frequency bands, across the three groups for all conditions (L-Cue, X-Cue, L-Word and X-Word). Young displayed the highest alpha power and Low performers the lowest (Table 5:3). A mixed model ANOVA with three levels of Group (Young, High, Low) and two levels of Condition (L, X) was conducted separately for Cue and Word measures. For the Cue measure there was a main effect of Group, no main effect of Condition, and no significant interaction (Table 5:4). Post-hoc tests showed that the Young differed significantly from Low ($p \leq 0.0005$) and High performers ($p \leq 0.05$) who did not differ significantly from each other ($p > 0.10$). For the Word measure there was a main effect of Group, but no main effect of Condition and no significant interaction (Table 5:5). Post-hoc tests showed that the Young differed significantly from the Low ($p \leq 0.005$), but not from the High performers ($p > 0.10$). High and Low performers did not differ from each other ($p > 0.10$).

Table 5:3 Means and Standard Deviations for Task Relative Alpha Power.

Relative Alpha Power - Task	Young (n=18)	High (n= 20)	Low (n=18)
L-Cue-relative alpha power	0.34(0.11)	0.27(.12)	0.21(0.08)
X-Cue- relative alpha power	0.35(0.11)	0.27(.10)	0.22(0.09)
L-Word- relative alpha power	.031(0.11)	0.26(.10)	0.20(0.09)
X-Word- relative alpha power	0.32(0.10)	0.27(.10)	0.21(0.08)

Note: Standard deviations in parenthesis. High = high performing old. Low = low performing old. L-Cue = 1400ms when the letter 'L' appears on screen plus ISI1, X-Cue = 1400ms when the letter 'X' appears on screen plus ISI1.L-Word = 1500ms when word to be learned appears on screen. X-Word = 1500ms when word to be read appears on screen.

Table 5:4 Main Effects and Interactions Task Relative Alpha Power for Cue

Relative Alpha Power Task – Individual Frequency Bands		Partial Eta²	p-value
Interaction (Condition x Group)	Wilks λ .94, F(2,54) 1.79	0.06	p >0.10
Main Effect – Condition (L, X)	Wilks λ .99, F(1,54) 0.44	0.01	p>0.10
Main Effect Group (Young, High, Low)	F(2,54) 7.06	0.21	**p≤0.005**

Note: High = high performing old. Low = low performing old. L condition = 1400ms when the letter 'L' appears on screen plus ISI1, X condition = 1400ms when the letter 'X' appears on screen plus ISI1.

Table 5:5 Main Effects and Interactions Task Relative Alpha Power for Word

Relative Alpha Power Task – Individual Frequency Bands		Partial Eta²	p-value
Interaction (Condition x Group)	Wilks λ .1, F(2,54) 0.10	0.00	p >0.10
Main Effect – Condition (L, X)	Wilks λ .94, F(1,54) 3.32	0.06	*p =.07*
Main Effect Group (Young, High, Low)	F(2,54) 5.84	0.18	**p≤0.005**

Note: High = high performing old. Low = low performing old. L condition = 1500ms when word to be learned appears on screen. X condition = 1500ms when word to be read appears on screen.

5.3.3 Alpha Reactivity

5.3.3.1 Resting Alpha Reactivity – Individual Frequency Bands

There was a systematic reduction in alpha reactivity calculated using subject specific individual frequency bands across the three groups (Figure 5:5). Young demonstrated the greatest suppression of alpha from Eyes Closed to Eyes Open and Low performers the least. There was a significant difference in alpha reactivity for the three groups [F (2,59)=4.30, p≤0.05]. The effect size was medium (.12). Post-hoc comparisons indicated that mean alpha reactivity for Young was significantly different from Low (p≤0.05) but not from High performers (p>0.10). The Low and High performers did not differ significantly from each other (p>0.10).

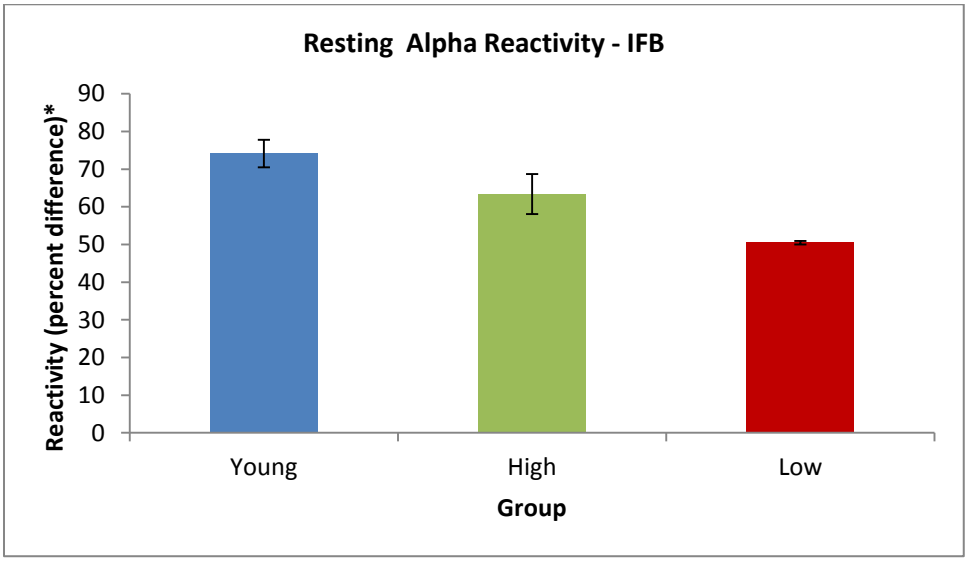

Figure 5:5 Mean Resting Alpha Reactivity using Individual Frequency Bands.

*Note: High = high performing old. Low = low performing old. Error bars show one standard error. *Difference in power between closed & open expressed as a percentage of closed power.*

5.3.3.2 Resting Alpha Reactivity for PZ using Standard Frequency Bands.

There was a significant main effect [F (2,59)=4.82, p≤0.05] and alpha reactivity showed a reduction across the three groups. Post-hoc comparisons showed that Low performers (M=36.01, SD=31.22) demonstrated significantly less alpha suppression to visual stimulation than Young (M=61.14, SD=20.0, p≤0.05) and the High performers (M=57.61, SD=29.18, p≤ 0.05). Alpha reactivity for Young and High performers was not significantly different (p>0.10).

5.3.3.3 Task Alpha Reactivity Individual Frequency Band.

For task alpha reactivity (Figure 5:6) averaged across conditions there was a statistically significant main effect of Group (Kruskal-Wallis H (2,54)=7.163, p≤0.05). Post-hoc tests (Mann-Whitney U) revealed that this was due to the fact that Low performers demonstrated significantly less alpha suppression to Task than Young

(p≤0.01). High performers did not differ significantly from Low performers (p>0.10) or Young (p=.09)

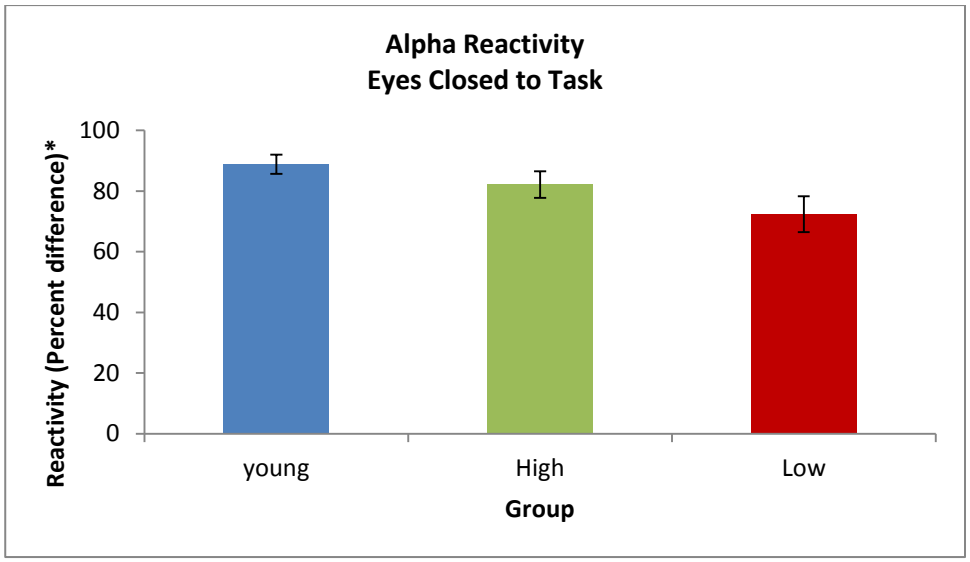

Figure 5:6 Mean Task Alpha Reactivity

*Note: Task alpha reactivity is averaged across conditions; L-Cue, X-Cue, L-Word, X-Word – Eyes Closed to Task. High = high performing old. Low = low performing old. Error bars show one standard error. *Difference in power between closed & task expressed as a percentage of closed power.*

Correlational Analysis

Spearman's rank order correlation coefficient was used to explore the relationship between alpha measures, and key neuropsychological test scores that measure memory and executive function (Table 5:6), for Young and Old participants separately. Correlations between alpha measures and neuropsychological tests are reported in Table 5:7 for the old adults and Table 5:8 for the Young. All neuropsychological tests are described in detail in Chapter 2. Correlations between alpha measures and RT latency and variability measures on the CRTsr task are reported in Table 5:9 for the old adults and Table 5:10 for the young adults. The CRTsr task is described in detail in Chapter 2.

Table 5:6 Measures - correlational analysis

Alpha Measures	Neuropsychological Measures
Resting IAF	Memory Self-Rate
Relative Alpha Power	Recall Memory (LM1 & LM2, WMS-III)
** Resting (Closed, Open) - IFB*	Recognition Memory (Learn Task, d-prime L & X)
** Resting (Closed, Open) SFB - PZ*	Working Memory (Digit Span, WMS-III)
** Task (L-, X- Cue &L-, X-Word)*	Executive function (Fluency & Stroop)
Alpha Reactivity	
Resting – IFB – closed to open	
Resting – SFB – PZ – closed to open	
Task - IFB – closed to task	

Note. IAF =individual alpha frequency. IFB = individual frequency band. SFB = standard frequency band. Memory self-rate – 5-point Likert self-rate score. LM = Logical Memory. LM1 = immediate recall standardised score. LM2 = delayed recall, standardised score, digit span (WMS-III, Wechsler, 1998). Fluency = number of animals named in 60 seconds. Stroop (t-score; Golden & Freshwater, 2002). IAF = individual alpha frequency, IFB = individual frequency band. SFB = standard frequency band. PZ – see Figure 5:2 for scalp location. L-Cue = 1400ms when the letter 'L' appears on screen plus ISI1, X-Cue = 1400ms when the letter 'X' appears on screen plus ISI1, L-Word = 1500ms when word to be learned appears on screen. X-Word = 1500ms when word to be read appears on screen.

5.3.4 Individual Alpha Frequency - Correlations

Resting IAF was not correlated with any of the neuropsychological tests in the Old adults. In the Young better immediate story recall (Logical Memory 1) was related significantly to higher resting peak alpha frequency. There were no other significant correlations (see Table 5:7 and Table 5:8). Resting IAF was not correlated with either the cognitive or the motor RT in either the Old or the Young. Although resting IAF was not significantly correlated with any of the variability measures in the Old it was negatively correlated significantly with all variability measures in the Young (see Table 5:9 and Table 5:10)

5.3.5 Relative Alpha Power - Correlations

5.3.5.1 Resting Relative Alpha Power using Individual Frequency Bands

In the Old adults, relative alpha power calculated using individual frequency bands, was significantly correlated with memory self-rate score in the Eyes Open condition. Higher self-ratings of memory were associated with greater alpha power. There were no other significant correlations with the neuropsychological tests (see Table 5:7 and Table 5:8). In the Old adults, lower relative alpha power in the Eyes Open condition was significantly correlated with greater variability (ISD, CV) for the cognitive element of the response. In the Old adults relative alpha power in the Eyes Open condition was also significantly negatively correlated with RT for the motor element of the task, with longer RTs associated with lower alpha power. There were no other significant correlations with the RT latency or variability measures (see Table 5:9 and Table 5:10).

5.3.5.2 Resting Relative Alpha Power (PZ) using Standard Frequency Bands

Higher relative alpha power in the Old adults at PZ in the Eyes Closed condition was significantly correlated with better immediate and better delayed story recall. There were no other significant correlations with neuropsychological measures (see Table 5:7 and Table 5:8). Lower relative alpha power at PZ was correlated with greater variability, as measured by both the CV and the ISD, for the cognitive element of the response during the Eyes Open condition. There were no other significant correlations with the RT latency or variability measures (see Table 5:9 and Table 5:10).

5.3.5.3 Task Relative Alpha Power using Individual Frequency Bands

In the Old adults relative alpha power, recorded during the encode phase of the memory recognition task (Learn task), was significantly correlated with the

memory self-rate measure in all four conditions of the task (L-Cue, X-Cue, L-Word, X-Word). Higher self-ratings of memory were associated with greater alpha power. For the Young there were borderline significant correlations between digit span and relative alpha power for the X-Cue (p=0.051) and the X-Word (p=0.058) conditions (see Table 5:7 and Table 5:8). In the Young greater relative alpha power during task was associated with greater variability, as measured by the CV, for the cognitive element of the task for the X-Cue condition in the Young. There were no other significant correlations with the RT latency or variability measures (see Table 5:9 and Table 5:10).

5.3.6 Alpha Reactivity - Correlations

5.3.6.1 Resting Alpha Reactivity using Individual Frequency Bands

Resting alpha reactivity, measured using individual frequency bands, was significantly related to memory self-rate scores, with greater alpha suppression to visual stimulation associated with higher self-rating of memory. In the Young there was a strong negative correlation between resting alpha reactivity, measured using individual frequency bands, and fluency, with greater alpha suppression to visual stimulation associated with a lower number of animals named in the fluency task. There were no other significant correlations (see Table 5:7 and Table 5:8). There were no significant correlations between alpha reactivity, measured using individual frequency bands, and any of the RT latency and variability measures (see Table 5:9 and Table 5:10).

5.3.6.2 Resting Alpha Reactivity Standard Frequency Bands

Resting alpha reactivity, recorded at PZ using standard frequency bands, was significantly correlated with delayed recall (Logical memory 2) in the Old adults, with greater alpha suppression associated with higher delayed story recall scores. There were no other significant correlations although in the Young the correlation between resting alpha reactivity at PZ and fluency approached significance (p=0.053), with greater alpha suppression to visual stimulation associated with lower number of animals named in the fluency task (see Table 5:7 and Table 5:8). Resting alpha reactivity at PZ was positively correlated with RT latency for the motor element of the response (see Table 5:9 and Table 5:10).There were no other significant correlations between alpha reactivity measured using standard frequency bands and any of the RT latency and variability measures (see Table 5:9 and Table 5:10).

5.3.6.3 Task Alpha Reactivity Individual Frequency Bands

Alpha reactivity measured from Eyes Closed to Task using individual frequency was not significantly correlated with any of the memory or executive measures in either the Young or the Old adults (see Table 5:7 and Table 5:8). There were no significant correlations between alpha reactivity measured from Eyes Closed to Task and any of the RT latency and variability measures (see Table 5:9 and Table 5:10).

Table 5:7 Correlations Old Adults

Measures	Spearman's rho	**Memory Self-Rate**	**Immediate Recall**	**Delayed Recall**	**Learn Word Recognition**	**Read Word Recognition**	**Digit Span**	**Fluency**	**Stroop**
Resting Measures (n)		43	43	43	39	39	43	43	43
IAF Resting	r	.141	-.007	-.096	-.135	.014	.008	-.054	-.098
	p-value 2-tailed	.366	.964	.541	.413	.934	.957	.729	.534
Relative Alpha Power IFB Eyes Closed	r	.273	.246	.236	-.030	-.056	.228	-.023	.065
	p-value 2-tailed	.076	.112	.128	.858	.736	.142	.883	.681
Relative Alpha Power IFB Eyes Open	r	**.340***	.150	.039	-.044	-.049	.209	-.029	.101
	p-value 2-tailed	**.026**	.335	.804	.791	.766	.179	.853	.519
Relative Alpha Power SFB (PZ) Eyes Closed	r	.245	**.362***	**.382***	.026	-.099	.114	.016	.097
	p-value 2-tailed	.113	**.017**	**.012**	.877	.549	.466	.920	.536
Relative Alpha Power SFB (PZ) Eyes Open	r	.138	.271	.198	.001	.039	.139	-.079	.209
	p-value 2-tailed	.378	.079	.204	.994	.812	.373	.614	.178
Alpha Reactivity IFB Closed to Open	r	**.344***	.183	.206	-.087	-.064	.267	.042	-.027
	p-value 2-tailed	**.024**	.240	.185	.599	.699	.083	.789	.865
Alpha Reactivity SFB (PZ) Closed to Open	r	.272	.281	**.355***	.116	-.074	.225	.138	-.021
	p-value 2-tailed	.077	.068	**.020**	.483	.653	.147	.378	.894
Task Measures (n)		**38**	38	38	38	38	38	38	38
Relative Alpha Power IFB X-Cue	r	**.396***	.250	.121	-.056	-.050	.100	-.253	-.096
	p-value 2-tailed	**.014**	.129	.469	.736	.764	.551	.125	.567
Relative Alpha Power IFB L-Cue	r	**.337***	.246	.112	-.143	-.154	.127	-.263	-.123
	p-value 2-tailed	**.039**	.137	.502	.391	.356	.448	.111	.461
Relative Alpha Power IFB X-Word	r	**.337***	.235	.115	-.160	-.143	.082	-.231	-.063
	p-value 2-tailed	**.039**	.155	.494	.338	.393	.623	.163	.705
Relative Alpha Power IFB L-Word	r	**.352***	.296	.183	-.184	-.177	.168	-.243	-.060
	p-value 2-tailed	**.030**	.071	.271	.269	.289	.315	.142	.722
Alpha Reactivity IFB Closed to Task	r	.113	.044	.176	.043	-.051	.165	-.073	.177
	p-value 2-tailed	.500	.791	.291	.800	.762	.324	.663	.287

Note: IAF = individual alpha frequency, IFB= individual frequency band. SFB = standard frequency band. Memory self-rate – 5-point Likert. Immediate recall (WMS-III, standardised scores). Delayed recall (WMS-III, standardised scores). Learn Recognition Task (D-prime scores). Digit Span (WMS-III). Fluency = number of animals named in 60 seconds. Stroop (t-score, Golden & Freshwater, 2002).

Table 5:8 Correlations Young Adults

Measures	Spearman's rho	**Memory Self-Rate**	**Immediate Recall**	**Delayed Recall**	**Learn Word Recognition**	**Read Word Recognition**	**Digit Span**	**Fluency**	**Stroop**
Resting Measures (n)		21	21	21	18	18	21	21	19
IAF Resting	r	.151	.493*	.227	.105	.099	-.181	.325	-.002
	p-value 2-tailed	.514	.023	.322	.678	.695	.431	.150	.993
Relative Alpha Power IFB Eyes Closed	r	-.159	-.361	-.338	.220	.190	.172	-.263	.074
	p-value 2-tailed	.492	.108	.135	.380	.450	.455	.250	.763
Relative Alpha Power IFB Eyes Open	r	.000	-.095	-.176	.223	.299	.357	.234	-.074
	p-value 2-tailed	1.000	.681	.446	.373	.227	.112	.307	.763
Relative Alpha Power SFB (PZ) Eyes Closed	r	-.161	-.106	-.090	.335	.281	.125	-.141	-.277
	p-value 2-tailed	.486	.646	.698	.175	.259	.589	.543	.251
Relative Alpha Power SFB (PZ) Eyes Open	r	-.044	-.163	-.194	.153	.216	.328	.057	-.140
	p-value 2-tailed	.849	.479	.399	.545	.390	.146	.807	.567
Alpha Reactivity IFB Closed to Open	r	.054	-.238	-.051	.021	-.137	.063	-.610**	.308
	p-value 2-tailed	.817	.299	.825	.935	.587	.787	.003	.200
Alpha Reactivity SFB (PZ) Closed to Open	r	.082	.044	.176	-.281	-.384	-.022	-.428	.024
	p-value 2-tailed	.722	.849	.446	.259	.116	.924	.053	.923
Task Measures (n)		18	18	18	18	18	18	18	18
Relative Alpha Power IFB – X-Cue	r	.035	-.333	-.214	.184	.105	.466	-.042	-.023
	p-value 2-tailed	.889	.176	.393	.465	.677	.051	.867	.928
Relative Alpha Power IFB L-Cue	r	-.009	-.320	-.233	.155	.088	.442	-.033	-.040
	p-value 2-tailed	.971	.196	.352	.539	.729	.066	.896	.873
Relative Alpha Power IFB X-Word	r	.038	-.307	-.229	.260	.158	.455	-.029	.019
	p-value 2-tailed	.881	.215	.361	.297	.531	.058	.909	.941
Relative Alpha Power IFB L-Word	r	.114	-.420	-.225	.244	.078	.282	-.003	-.070
	p-value 2-tailed	.652	.082	.370	.330	.757	.257	.990	.784
Reactivity IFB Task	r	.051	-.223	-.192	.108	.207	.228	-.203	-.017
	p-value 2-tailed	.840	.373	.445	.668	.411	.363	.420	.948

Note: IAF = individual alpha frequency, IFB= individual frequency band. SFB = standard frequency band. Memory self-rate – 5-point Likert. Immediate recall (WMS-III, standardised scores). Delayed recall (WMS-III, standardised scores). Learn Recognition Task (D-prime scores). Digit Span (WMS-III). Fluency = number of animals named in 60 seconds. Stroop (t-score Golden & Freshwater, 2002).

Table 5:9 Correlations Old Adults

Measures	Spearman's rho	CRT Cognitive RT	CRT Cognitive ISD	CRT Cognitive CV	CRT Motor RT	CRT Motor ISD	CRT Motor CV
Resting Measures (n)		39	39	39	39	39	39
IAF	r	.034	.214	.227	.130	.200	.208
Resting	p-value 2-tailed	.840	.190	.165	.430	.222	.203
Relative Alpha Power	r	.043	-.148	-.205	-.082	-.168	-.166
IFB Eyes Closed	p-value 2-tailed	.793	.368	.211	.618	.308	.312
Relative Alpha Power	r	-.170	-.365*	-.387*	-.331*	-.254	-.171
IFB Eyes Open	p-value 2-tailed	.301	.022	.015	.040	.119	.297
Relative Alpha Power	r	.096	-.194	-.283	-.042	-.217	-.248
SFB (PZ) Eyes Closed	p-value 2-tailed	.560	.237	.081	.798	.184	.128
Relative Alpha Power	r	-.083	-.312	-.332*	-.205	-.193	-.136
SFB (PZ) Eyes Open	p-value 2-tailed	.617	.053	.039	.210	.240	.410
Alpha Reactivity	r	.100	-.081	-.140	.017	-.122	-.139
IFB Closed to Open	p-value 2-tailed	.544	.622	.395	.916	.459	.400
Alpha Reactivity	r	.070	-.133	-.208	-.065	-.222	-.216
SFB (PZ) Closed to Open	p-value 2-tailed	.671	.420	.204	.696	.173	.186
Task Measures (n)		34	34	34	34	34	34
Relative Alpha Power	r	-.030	-.218	-.245	-.295	-.066	.125
IFB X-Cue	p-value 2-tailed	.864	.216	.163	.090	.713	.482
Relative Alpha Power	r	-.041	-.164	-.212	-.224	.001	.158
IFB L-Cue	p-value 2-tailed	.816	.353	.229	.204	.995	.373
Relative Alpha Power	r	-.024	-.222	-.258	-.293	-.089	.083
IFB:X-Word	p-value 2-tailed	.894	.207	.140	.093	.616	.641
Relative Alpha Power	r	-.043	-.148	-.202	-.275	-.094	.099
IFB L-Word	p-value 2-tailed	.808	.402	.252	.116	.596	.579
Reactivity	r	.085	-.042	-.041	-.043	-.126	-.110
IFB Task	p-value 2-tailed	.633	.813	.816	.809	.479	.537

Note: IAF = individual alpha frequency, IFB= individual frequency band. SFB = standard frequency band. CRT=Choice Reaction Time Task split response.. RT=reaction time latency, ISD = individual standard deviation. CV= coefficient of variation.

Table 5:10 Correlations Young Adults

Measures	Spearman's rho	CRT Cognitive RT	CRT Cognitive ISD	CRT Cognitive CV	CRT Motor RT	CRT Motor ISD	CRT Motor CV
Resting Measures (n)		18	18	18	18	18	18
I**AF**	r	.258	-.625**	-.798**	-.356	-.611**	-.579*
Resting	p-value 2-tailed	.301	.006	.000	.147	.007	.012
Relative Alpha Power	r	.005	.123	.150	.311	.354	.263
IFB Eyes Closed	p-value 2-tailed	.984	.627	.553	.210	.150	.291
Relative Alpha Power	r	.071	.164	.170	-.018	.040	.185
IFB Eyes Open	p-value 2-tailed	.779	.515	.499	.945	.874	.463
Relative Alpha Power	r	-.075	.022	.117	.106	.286	.350
SFB (PZ) Eyes Closed	p-value 2-tailed	.766	.932	.645	.675	.250	.155
Relative Alpha Power	r	.183	.282	.230	-.069	.086	.257
SFB (PZ) Eyes Open	p-value 2-tailed	.468	.257	.358	.785	.735	.303
Alpha Reactivity	r	-.168	-.036	.069	.313	.255	.055
IFB: Closed to Open	p-value 2-tailed	.505	.887	.785	.206	.307	.829
Alpha Reactivity	r	-.280	.011	.191	.511*	.313	.015
SFB (PZ) Closed to Open	p-value 2-tailed	.261	.964	.448	.030	.206	.951
Task Measures (n)		18	18	18	18	18	18
Relative Alpha Power	r	-.154	.296	.472*	-.253	-.053	.251
IFB X-Cue	p-value 2-tailed	.542	.233	.048	.311	.836	.316
Relative Alpha Power	r	.018	.232	.302	-.304	-.127	.187
IFB L-Cue	p-value 2-tailed	.945	.354	.223	.219	.616	.458
Relative Alpha Power	r	-.152	.218	.395	-.271	-.079	.228
IFB X-Word	p-value 2-tailed	.548	.385	.104	.276	.754	.363
Relative Alpha Power	r	.046	.304	.309	-.311	-.104	.191
IFB L-Word	p-value 2-tailed	.855	.219	.213	.210	.681	.448
Reactivity	r	-.046	.032	.044	.296	.344	.261
IFB Task	p-value 2-tailed	.855	.900	.861	.233	.163	.295

Note: IAF = individual alpha frequency, IFB= individual frequency band. SFB = standard frequency band. CRT=Choice Reaction Time Task split response.. RT=reaction time latency, ISD = individual standard deviation. CV= coefficient of variation.

5.4 DISCUSSION

This chapter assessed the ability of alpha frequency, relative alpha power, and alpha reactivity, all non-invasive measures of neuronal physiological function, to distinguish between age and cognitive performance groups, and to ascertain their relationship to established neuropsychological indices of cognitive performance. The key finding is that although alpha frequency and resting relative alpha power (individual frequency and standard frequency bands) distinguished groups on the basis of age, only the relative alpha power measures and alpha reactivity using standard frequency bands were sensitive enough to distinguish High performers from Low performers. Using a standard frequency band (8-13Hz) and a single electrode (PZ) for all participants is considerably less labour intensive than identifying each participant's site of maximal alpha power, peak alpha frequency, and individual frequency band. The results reported in this chapter suggest that adopting the standard frequency band approach may not only be, less labour intensive and more practical, but also has the same sensitivity as the individualised method and, in the case of alpha reactivity, greater sensitivity to cognitive performance. Of course it has to be acknowledged that this study treated alpha as a single band and so it is possible that the value of individualized bands becomes more evident when alpha sub-bands are employed.

Within adult populations a clear linear relationship has been reported between alpha peak frequency and age, such that the expected peak frequency for a 70 year old is 8.24 Hz (Köpruner et al., 1984). The mean peak alpha frequency for older participants in this study was, relatively speaking, considerably higher than this at ~9.25Hz, despite an average age of ~70 years. It is difficult to tell whether this difference has any real significance or whether it is an artefact of the lack of measurement standardization across studies. It is also possible that it simply reflects the considerable inter-individual variability in alpha frequency that exists even between age-matched controls (Klimesch et al., 1990; Köpruner et al., 1984). Nonetheless, as predicted, alpha peak frequency had the ability to differentiate groups on the basis of age. In contrast, this measure was not sensitive enough to distinguish the older adults on the basis of their cognitive performance. Based on the literature, a relationship between alpha frequency and measures of memory performance were predicted. However, his prediction did not hold for the older adults, but did hold in the Young for immediate recall on the logical memory test of Wechsler Memory Scale (Wechsler, 1998). It has been argued that alpha peak frequency reflects speed of processing in the thalamo-cortical networks (Klimesch, 1997; Steriade et al., 1990). However, no significant correlations between alpha frequency and speed of processing, as measured by RT latency on the Choice Reaction Time split response

task (CRTsr) were found in this study. With respect to the old participants, the findings reported here do not appear to support proposals that individual alpha frequency represent an index of memory ability or processing speed (Klimesch, 1997; Klimesch et al., 1990). However, it is interesting to note that strong negative correlations were found in the Young between alpha peak frequency and measures of intra-individual variability, which are thought to reflect neural integrity. It is unlikely that discrepant findings across studies will be resolved until standardized measurements for alpha peak frequency are agreed upon but it would seem that age effects are robust across different measurement approaches. Further exploration of the relationship between intra-individual variability and alpha peak frequency is warranted.

The age-effects for resting relative alpha power measures reported in this study are in line with general expectations of decreasing alpha power with increasing age. Young participants had significantly higher resting alpha power than both of the older adult groups and this significant difference held regardless of whether individual frequency bands or standard frequency bands were used. Higher alpha power was also significantly correlated with more consistent cognitive RTs on the CRTsr task in the older adults when calculated using individual or standard frequency bands. The reader will recall from Chapter 3 that cognitive RT variability measures distinguished age groups and cognitive performance groups. Interestingly both relative alpha power measures reported here were also able to distinguish groups on the basis of cognitive performance. A recent study has shown that EEG power markers discriminate among different sub-groups of MCI patients (Moretti et al., 2009) but as far as this author is aware, this is the first study to show that resting relative alpha power can discriminate sub-groups of normal healthy adults, who have been categorized on the basis of their memory performance relative to an estimate of their pre-morbid IQ. None of the resting relative alpha power measures were significantly associated with any of the neuropsychological measures in the Young. However, in the old adults, at rest with eyes closed, higher relative alpha power, calculated using standard frequency bands, was significantly correlated with better immediate and delayed story recall. Relative alpha power was also assessed during the encode phase of the Learn memory task. Chapter 2 reported significant differences between all three groups for recognition accuracy scores with the Young having the highest scores and the Low performers the worst. Relative alpha power recorded during the encoding phase of the task while participants viewed the stimuli (L-Cue, X-Cue, L-Word, X-Word), was strongest in the Young and weakest in the Low performers in all conditions. This difference was significant between the Young and both old groups during the cue and between the Young and the Low performers during the word. While relative alpha power measures

recorded during encoding did not distinguish the groups on the basis of cognitive performance, these measures were significantly correlated with memory self-rating scores in the old adults.

Decreased alpha reactivity is observed in later life (Duffy et al., 1984) and is associated with poorer memory performance and poorer executive function (Klimesch, 1999; van der Hiele, Vein, Kramer et al., 2007). The key finding is that alpha reactivity, measured at a single posterior electrode (PZ) using standard frequency band, was sensitive enough to distinguish the older adults on the basis of their cognitive performance. Greater alpha suppression was also significantly correlated with better delayed recall on the logical memory element of the Wechsler Memory Scale (Wechsler, 1998) in old adults. In the Young there was a significant correlation with a measure of executive function (category fluency). There were no clear age effects for the alpha reactivity measures recorded using individual or standard bands, at rest or during task, because alpha power for the High performers was never significantly different from the Young. In contrast, the Low performers always demonstrated significantly less alpha suppression than the Young.

The EEG parameters in this study were chosen not only because of their known sensitivity to age and memory performance but also because they are easy to obtain, non-invasive, and relatively inexpensive. The alpha power measures used in here not only satisfy criteria for population screening biomarkers, but also had the power to distinguish Low performers from High performers and were correlated with measures of memory in older adults. Relative alpha power recorded over parietal scalp electrodes at rest with eyes closed may have particular potential. AD and aMCI (amnestic Mild Cognitive Impairment) individuals demonstrate reduced alpha power and decreased alpha reactivity when compared to age-matched controls, as did our Low performers when compared to our High performers. AD and aMCI individuals demonstrate reduced cerebral glucose metabolism in the parietal and other regions of the brain (Pietrini, Alexander, Furey, Hampel, & Guazzelli, 2000), consistent with the site of diminished alpha power in the Low performers. It is possible that poorer memory performance and associated decreases in alpha power measures in the asymptomatic Low performers reflect underlying changes in the cholinergic system, making alpha power measures a potential surrogate marker of memory decline. The notion that EEG slowing observed in AD is thought to reflect a cholinergic deficit is supported by pharmacological studies (Agnoli, Martucci, Manna, Conti, & Fioravanti, 1983; Alhainen & Riekkinen, 1993; Jeong, 2004; Neufeld et al., 1994). Alpha and other spectral changes are observed in demented patients when treated with cholinesterase inhibitors, including tacrine (Almkvist et al., 2001), rivastigmine (Brassen & Adler, 2003; Fogelson et al., 2003) and donepezil (Balkan et al., 2003;

Kogan et al., 2001). Interestingly, sedative drugs, which cause different degrees of amnesia (alkylphenol, benzodiazepines or barbiturates), have the common effect of suppressing the alpha rhythm (Feshchenko, Veselis, & Reinsel, 1997). Given the considerable overlap observed at the boundary of normal and pathological decline, it is possible that the alpha activity observed in the Low performers may actually reflect the neurophysiology of individuals on the threshold of pathological decline. However, it is important to remember that participants classified as Low performers in this study still scored within the normal range on memory tests and so it is also possible that successful cognitive ageing, and associated alpha activity, is reflected in the High performers who, although showing decline in memory performance relative to Young controls, demonstrate significantly better performance than the Low performers whose performance, and associated alpha activity could well reflect usual decline.

This thesis marries neuropsychological and electrophysiological methodologies with a view to explicating differential decline in non-diseased populations. To this end this study has identified sub-groups representative of different cognitive profiles and has used electrophysiological measures to ascertain whether neurophysiological differences support these classifications. Chapter 2 argued that the data from neuropsychological testing support the proposal that the classification method adopted in this study identified sub-groups with cognitive profiles that differ specifically in terms of episodic memory. This chapter reports that these sub-groups also differ significantly from each other on neurophysiological measures (relative alpha power and alpha reactivity) with known sensitivity to ageing, memory performance, and disease induced decline.

Chapter 6 AN ERP STUDY OF EPISODIC MEMORY RETRIEVAL

6.1 INTRODUCTION

This thesis marries neuropsychological and electrophysiological methodologies with a view to explicating differential decline in the non-diseased population and seeks neurocognitive and electrophysiological markers that index cognitive decline. The overall approach taken is to capture cognitive variability through the identification of sub-groups with different cognitive profiles and then use electroencephalography (EEG) to ascertain whether neurophysiological differences support these classifications. The pattern of significant differences on neuropsychological tests presented in Chapter 2 support the suggestion that the classification approach adopted in this study identified sub-groups with cognitive profiles that differed specifically in terms of episodic memory function. This chapter and the next examine event-related potentials (ERPs) recorded during an experimental episodic memory task designed to assess word recognition memory (Learn task). Significant age and cognitive performance effects were reported in Chapter 2 for recognition performance accuracy on this task, which comprises an encoding and a recognition phase. This chapter examines ERPs recorded while participants made these recognition judgments.

There is strong evidence from cognitive, neuropsychological, and neuroimaging studies that recognition memory reflects two distinct memory types, or neurocognitive processes, often referred to as recollection and familiarity (Rugg & Curran, 2007; Yonelinas, 2002). Although some researchers support single processing accounts of recognition (Donaldson, 1996; Dunn, 2004), most contemporary researchers ascribe to some kind of dual-process model (Rugg & Curran, 2007). Over the last 30 years several dual-processing models of memory recognition have been proposed (for a comprehensive review see; Yonelinas, 2002). Although the models differ in critical ways and can make conflicting predictions, some core assumptions about familiarity and recollection are similar across models (Yonelinas, 2002). For example, familiarity is thought to be fast acting, relatively automatic, and does not provide qualitative information about the study episode. In contrast, recollection is considered a slower, more effortful process that gives rise to consciously accessible information about the occurrence of the test item in the study episode together with associated contextual details (Friedman et al., 2010; Rugg & Curran, 2007). Recognition can be operationally defined as the judgment that a stimulus has been previously encountered, recollection defined as recognition accompanied by accurate source memory, and familiarity defined as information that supports recognition in the absence of recollection (Rugg & Curran, 2007). It should be noted that although the fractionation

of recognition memory into recollection and familiarity is widely accepted, the nature of the latter is disputed (for discussion and opposing views see Friedman et al., 2010; Paller et al., 2007; Rugg & Curran, 2007). Essentially the debate surrounds the degree to which familiarity and implicit memory (priming) are linked or distinct, with some researchers arguing that familiarity occurs in isolation and others that experiments conflate the two. Opposing views of familiarity need not be mutually exclusive and the definition of familiarity given above allows for the possibility that familiarity is multiply determined and that dissociations between familiarity and implicit memory might occur under some conditions but not others (Rugg & Curran, 2007).

Chapter 1 outlined the view that failures in episodic memory observed in elderly populations, in the absence of identifiable pathology, are due to impairments in controlled processes mediated by the frontal cortex and associated connections (Buckner, 2004). On this view, less successful recapitulation of study episodes is a consequence of a deficit in frontal systems that limits strategic processing at both encoding and retrieval (Wolk et al., 2009). This is consistent with reports of age-associated impairments in recollection and relative sparing of familiarity, when familiarity is considered an automatic process and recollection is considered a controlled process mediated by frontal and medial temporal connectivity (Wolk et al., 2009). Although incomplete and theoretically controversial, (for discussion see Paller et al., 2007) this view is supported by findings that have associated familiarity with medial temporal lobe (MTL) structures and recollection with both MTL structures and frontal lobe structures (Davidson & Glisky, 2002; Rugg & Yonelinas, 2003; Yonelinas, 2002). Alternative studies propose a direct association between MTL dysfunction and memory performance irrespective of frontal processing (Van Petten, 2004). Interestingly, some neuroimaging studies of episodic memory have shown increases in frontal activity in older adults when compared with young adults during completion of episodic memory tasks (for review see; Grady, 2008). When considered in conjunction with the notion that impairment of cognitive control underlies age-related memory failure, these increases could be regarded as paradoxical and have alternatively been proposed as reflecting either inefficient or compensatory mechanisms (Cabeza, 2002; Grady et al., 1995; Morcom, Li, & Rugg, 2007).

Some of the strongest support for distinct processes underlying recognition has come from ERP studies that use recognition memory paradigms in which participants decide whether test items were presented during the study phase of a task or not (for review see; Rugg & Curran, 2007). Familiarity and recollection are thought to be reflected in differences between the waveforms associated with correctly recognized old items, also referred to as Hits, and correctly rejected new items, also referred to as correct rejections (CRs). Thirty years has passed since the observation that ERPs

elicited by old items are more positive going than those elicited by correctly classified new items (Sanquist, Rohrbaugh, Syndulko, & Lindsley, 1980; Warren, 1980). An early (300-500ms), mid-frontal, negative ERP effect (FN400[7] old/new effect), and a later (400-800ms), parietal, positive ERP effect (late posterior component; LPC old/new effect) are thought to be linked to familiarity-driven recognition and the recollection of specific information respectively (Rugg & Curran, 2007; Wolk et al., 2009). Support for this view comes from studies that show that the LPC old/new effect is influenced by retrieval of contextual details and depth of encoding (Curran, 2004; Donaldson & Rugg, 1999; Duzel, Yonelinas, Mangun, Heinze, & Tulving, 1997; Woodruff, Hayama, & Rugg, 2006) and modulation of the FN400 old/new effect by items correctly identified in the absence of contextual details (Curran, 2004; Duzel et al., 1997), non-studied items that are conceptually or perceptually related to studied items (Curran, 2000; Curran & Cleary, 2003), and items studied in a shallow manner (Rugg, 1998). A third ERP modulation has also been reported that tends to be maximal over frontal sites, can last one second or longer, and can begin as early as 600ms post stimulus (Allan, Robb, & Rugg, 2000). This sustained slow wave, is thought to reflect post retrieval monitoring (Allan et al., 2000; Curran, Schacter, Johnson, & Spinks, 2001) or may represent an index of retrieval effort, or additional retrieval attempts when initial representations are impoverished (Ally & Budson, 2007; Ally et al., 2008).

Considerable behavioural and neuroimaging data from young adult samples support a functional, temporal, and neural distinction between familiarity and recollection (Eichenbaum, Yonelinas, & Ranganath, 2007; Friedman & Johnson, 2000; Rugg & Curran, 2007; Rugg & Yonelinas, 2003). Although lifespan data are relatively scarce they suggest that the development of episodic memory follows an inverted U-shaped function across the lifespan (De Chastelaine et al., 2009; Park et al., 2002). The relative contributions of familiarity and recollection to this trajectory is not yet clear, but it is thought that familiarity based processing is maintained across the lifespan while recollection declines with increasing age (Hay & Jacoby, 1999; Jennings & Jacoby, 1997; Prull, Dawes, Martin, Rosenberg, & Light, 2006). It has been argued that memory performance in young adults relies on genuine explicit memory traces with some contributions from feelings of familiarity, whereas automatically activated feelings of familiarity dominate the performance of older adults resulting in poorer recall accuracy when compared to young adults. Research exploring the impact of ageing on the ERP modulations that putatively reflect

[7] The relationship between the FN400 and the N400 is currently unclear. The 'F' was added by Tim Curran (2004) because it is more frontally distributed than the centro-parietal N400 recorded to semantic incongruity. Old/new effects have also been associated with the centro-parietal N400. All old/new effects in the 300-500ms range are considered potentially relevant to the FN400.

familiarity and recollection is sparse. In addition, only one or two studies have taken account of memory performance variability within ageing populations by examining the possibility that sub-groups with different memory profiles may exhibit different patterns of neural activity.

Findings from the ERP familiarity/recollection ageing literature to date are equivocal. While several studies have reported intact ERP correlates of familiarity in ageing (Morcom & Rugg, 2004; Nessler, Johnson, Bersick, & Friedman, 2008; Trott, Friedman, Ritter, Fabiani, & Snodgrass, 1999), evidence of impairment is emerging (Duarte, Ranganath, Trujillo, & Knight, 2006; Wegesin, Friedman, Varughese, & Stern, 2002). Data from a recent study assessing age-related changes in episodic memory retrieval suggest that although behavioural performance changes do not manifest until after the age of 65, changes in putative ERP correlates were already present by middle age (Guillaume et al., 2009). The study reports that ERP correlates of recollection and post-retrieval monitoring are affected first and show a linear decline with age while the ERP correlate of familiarity remain stable until the age of 65 (Guillaume et al., 2009). Late Positive Component (LPC) old/new effects have been reported in old adults relative to young controls in studies that examine responses associated with accurate contextual retrieval (Li, Morcom, & Rugg, 2004; Mark & Rugg, 1998; Trott et al., 1999; Wegesin et al., 2002). However, reductions in the LPC old/new effect in old relative to young have been reported in studies that tap into simple item recognition (Fjell, Walhovd, & Reinvang, 2005; Rugg, Mark, Gilchrist, & Roberts, 1997; Swick & Knight, 1997; Walhovd et al., 2006). The late sustained effect has only been examined in the context of source retrieval and findings have been mixed (Li, Huxhold et al., 2004; Mark & Rugg, 1998; Trott et al., 1999; Wegesin et al., 2002). In all likelihood, findings across studies vary as a consequence of factors related to the nature of the tasks and the stimuli employed, heterogeneity of participant characteristics and variance in cognitive ability. Recently a few studies have attempted to unpick ambiguity by examining ERP correlates of familiarity and recollection in sub-groups of high and low performing older adults. A study conducted by Duart and colleagues (2006) that shows different patterns of event-related neural activity in high performing old, low performing old, and young controls, reported intact recollection but impaired familiarity in high performing old and impairment in both processes in low performing old. Another recent study that classified participants on performance showed the absence or attenuation of both the FN400 old/new effect and the LPC old/new effect in old adults relative to young adults and an enhanced late sustained effect in poor performing old adults (Wolk et al., 2009).

This chapter aims to extend the literature on episodic memory in cognitive ageing by interrogating the impact of age and cognitive performance on the ERP

modulations of recognition memory in the Young controls, High performers, and Low performers described in Chapter 2. The main purpose is to examine whether the ERP modulations thought to reflect familiarity (FN400 old/new effect), recollection (LPC old/new effect), and post retrieval monitoring (late effect; LE) are affected by age and cognitive performance. Predictions are difficult given the dearth of age-related literature and the equivocal nature of findings to date. Nonetheless, the largest ERP old/new effects are predicted in the Young. Given the nature of the task used in this study (simple item recognition), attenuation of the LPC old/new effect in both of the old groups relative to the Young is predicted. Enhanced late sustained positivity is predicted in the Low performers relative to the Young. Given the reported relationship between ERP correlates of recognition memory and depth of encoding, a subsidiary analysis will be conducted to establish whether instructions given when words were encoded (Learn, Read) differentially affect ERP modulations associated with familiarity and recollection when these words are presented again at test. The ERP correlate of recollection is predicted to be attenuated for Read words relative to Learn words but no difference is predicted for the ERP correlate of familiarity.

6.2 METHOD

6.2.1 Participants

Participants were recruited through public and college advertising and from the Robertson Participant Panel (see Chapter 2 for full details). Forty-eight older adults aged between 65 and 80 and twenty-two Young controls aged between 18 and 30 years satisfied the eligibility criteria. Four older adults failed to attend for Session 2 due to ill health (n=2), personal problems (n=1) and voluntary withdrawal (n=1). In addition, one older adult disclosed taking CNS medication after testing was complete and one young adult drank a substantial amount of alcohol in the 24 hours preceding Session 2 and so both were excluded. Data for forty-three (18 male) older adults (M=69.95, SD ± 3.70) and twenty-one young (9 males) controls (M=21.28, SD ± 2.97) were analysed. The older participants were assigned to sub-groups based on their memory performance relative to an estimate of their pre-morbid IQ. Participants were defined as Low performers if they scored more than one standard deviation below their NART (National Adult Reading Test) estimated pre-morbid IQ on the Wechsler Memory Scale logical memory delayed recall test (for a full description of the classification procedure see Chapter 2 section2.2.2). Classifying participants in this way yielded; a) 25 High performers (10 male, M=70.28, SD ± 3.39 and b) 18 Low performers (8 male; M=69.48 ± 4.14).

6.2.2 Procedure

6.2.2.1 Testing Protocol

Testing was conducted between September 2008 and May 2009. Participants were assessed in two ~2 hour sessions that took place approximately one week apart. During Session 1 participants completed the mini mental state exam, a memory self-rating scale, the Hospital Anxiety and Depression Scale, the National Adult Reading Test, animal naming, the Stroop task, and sub-sets of the Wechsler Memory Scale (Logical Memory 1 and 2, Face Recognition 1 and 2, Visual Reproduction 1 and 2 and Digit span). In addition, during Session 1 participants were taught how to perform the Choice Reaction Time split response task (CRTsr) and the Sustained Attention to Response Task fixed version SART$_{fixed}$. During Session 2 the electrical activity in participant's brains was recorded while participants rested (6 minutes) and while they performed three computerized experimental tasks: the Learn memory task, the CRTsr task, and the SART$_{fixed}$. The Learn task had an encoding and a delayed recognition phase which each took approximately 8.5 minutes to complete. Participants completed the CRTsr (self-paced) and the SART$_{fixed}$ (~5 minutes) during the interval between the

encoding and recognition phases of the Learn task. All materials and experimental tasks are described in detail in Chapter 2. ERP analysis of data collected during Session 2 while participants completed the recognition phase of the Learn task is presented in this chapter (See Figure 6:1).

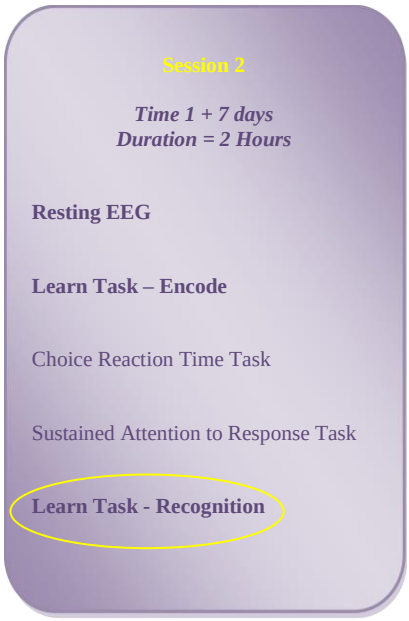

Figure 6:1 Event Related Potential (ERP) analysis of the recognition phase of the Learn task.

6.2.2.2 Fitting Participants with Cap and Electrodes

During Session 2 participants were seated in a comfortable chair ~65 cm from a computer screen in a dimly lit EEG testing room. The circumference of the participant's head was measured just above the eyebrows and over the inion at the back of the head. This circumference was used to guide selection of appropriate cap size. The distance from the nasion to the inion was then measured and divided by two to determine the proper location of the Vertex electrode (CZ). The mastoid electrodes were then attached to the participant. The cap was carefully placed on the participant's head in such a way as to ensure that the midline of the cap lined up with the nose and the vertex electrode was in the correct location. The chin strap was then fitted to ensure that the cap remained in a secure position. After each electrode holder was filled with gel the remaining electrodes were attached. The electrodes were then plugged into the A/D box. Using the Actiview software the trace for each electrode was examined to check for impedance. Once any problems with poor connections were rectified testing began. Participants were made aware of artefact related problems induced by blinks, other facial movements, head, and neck movements and other twitches. They were asked to keep such movements to a minimum.

6.2.3 Materials

6.2.3.1 Task

Learn Memory Task (Cued Encoding & Delayed Recognition)

All materials and experimental tasks, including the Learn task, are described in detail in Chapter 2. For ease of reference, the recognition phase of the Learn task is described here. ERP analysis of the recognition phase of the Learn task is reported in this chapter and ERP analysis of the encoding phase is reported in Chapter 7.

In general, the free recall design of standardised tests of memory, such as the Wechsler Memory Scale, precludes them from event-related potential (ERP) analysis because the memory process under investigation needs to be time-locked to some particular event. ERPs are useful in memory research, not in the least, because their high temporal resolution makes them suited to addressing questions about the temporal aspects of brain activity associated with memory processes but also because they represent covert measures of processing in the absence of overt responding facilitating the investigation of brain activity to different stimuli, such as cues, where no discriminative response is required (Rugg, 1995). Variants on a single paradigm have generally been used in ERP research to examine memory encoding. The paradigm typically comprises a study phase and a test phase. A series of items, for example words, are presented during the encoding phase during which EEG epochs time-locked to the presentation of the stimulus are recorded and stored. Subsequently the memory for these items is tested for example in an 'old/new' recognition task. The Learn task used in this study was based on a task employed by Hogan *et al* (2006) that aimed to assess the relationship between electrophysiological and information processing variability and memory decrements associated with normal age-related decline and with Alzheimer's disease. However, initial pilot participants in this study found this task almost impossible to complete. To avoid floor effects, adaptations informed by other studies (Johnson & Rugg, 2006; Rugg, Cox, Doyle, & Wells, 1995; Van Strien, Verkoeijen, Van der Meer, & Franken, 2007) were made to the task. Specifically, the discrimination element of the task was removed, the size of the 'X' cue was altered so as to be consistent with the 'L' cue, and stimulus timings were altered.

Delayed Recognition

In the recognition phase of this task participants were asked to discriminate between new words and old words by pressing the 'green' button for old words and the 'red' button for new words on the RB530 Response Box illustrated in Chapter 2. Old words were words that they encountered in the encode phase of the task regardless of whether those words were preceded by an 'L' (Learn Words) or an 'X' (Read

Words). For each trial an inter-stimulus interval (ISI, 100ms), a Target (500ms), a second ISI (ISI2, 2444), and a third ISI (ISI3, 200ms) were presented sequentially. In total 126 trials that comprised 6 buffers, 40 Learn Words, 40 Read Words and 40 new words were presented to all participants in the same order over a period of ~ 8.5 minutes. Responses were not collected during ISI3. Four conditions of interest were identified within the recognition phase of the task; 1) Hits (words correctly identified as old irrespective of whether they had been preceded by an L (Learn) or an X (Read) during the encoding phase of the task), 2) Correct Rejections (CRs, words correctly identified as new), 3) words participants were instructed to learn (Learn Words) during the encoding phase irrespective of accuracy of response in the recognition phase (40 trials), and 4) words participants were instructed to read (Read Words) during the encoding phase irrespective of accuracy of response during the recognition phase (40 trials). Due to the low number of Read Words correctly identified as old it was not possible to conduct comparative analysis for Learn Word Hits and Read Word Hits.

6.2.4 Data Analysis and Processing

Data were analysed with BESA Version 5.2 (Brain Electronic Source Analysis www.besa.de) software. After acquisition, data were average referenced and filtered (low pass 0.1Hz, 6db slope, high pass 40Hz, zero phase). The data for each participant were manually inspected and trials with excessive EMG (electromyogram, muscle activity) or noise transients were removed, bad channels were interpolated and horizontal and vertical EOG (electrooculograph, eye movement) artefacts were corrected by means of an automated (BESA) eye movement correction procedure. Buffer trials were excluded from analysis.

6.3 RESULTS

6.3.1 Analysis Strategy

ERP averages were calculated for each participant for correctly identified old words (HITs) and correctly rejected new words (CRs). In addition, ERP averages were calculated for old words participants were instructed to learn during the encode phase, irrespective of response accuracy (Learn Words), and old words participants were instructed to read during the encode phase, irrespective of response accuracy (Read Words). An epoch of -100 to 1500ms was used to calculate the HIT, CR, Learn Word, and Read Word ERPs. Grand averages were then calculated for each of the three groups (Young, High, Low) for each of the four dependent variables (HIT, CR, Learn Word, Read Word). Analysis was constrained to two components putatively associated with ERP modulations of familiarity and recollection: the Frontal negativity FN400 and the late positive component (LPC). In addition, a late effect (LE), which might possibly reflect post retrieval monitoring was also analysed. The selection of appropriate time-windows and electrodes for statistical analysis was guided by previous research (e.g. Guillaume et al., 2009; Nessler et al., 2008; Wolk et al., 2009) and visual inspection of the waveforms. A minimum of 16 trials were required for inclusion in ERP averages for each condition of interest. The number of participants, mean, minimum, and maximum number of trials entering each of the averages are detailed in Table 6:1.

Table 6:1 Mean, minimum, and maximum of trials contributing to ERP averages.

	Old/New Analysis		Learn/Read Analysis (L/X)	
	CR	Hit	Learn	Read
Young n=18	34 (25-40)	48 (32-66)	39 (35-40)	39 (35-40)
High n=19	31 (24-38)	37 (18-57)	36 (24-40)	36 (26-40)
Low n=16	29 (18-37)	38 (20-58)	36 (28-40)	35 (26-40)

Note: Hit = correctly identified old words; CR = Correct Rejection, correctly rejected new words; Learn = old words participants were instructed to learn during the encoding phase irrespective of response accuracy (these words were preceded by an 'L' at encoding;, Read = old words participants were instructed to read during the encoding phase irrespective of response accuracy (these words were preceded by an 'X' at encoding).

6.3.2 Analysis of Old/New Effects

ERP waveforms associated with Hit (Old) responses and CRs (New) and responses were quantified over two consecutive latency periods: 300-500ms and 500-800ms at frontal and centro-parietal sites. Analyses were conducted separately at frontal sites and centro-parietal sites. The FN400 and LPC waveforms were tested in the frontal region with 3x2x5 mixed between within subjects ANOVAs. The factors were Group (Young, High, Low), Response Type (Old, New), and Electrode (F3, F1, FZ, F2, F4). The same two components (FN400, LPC) were tested at centro-parietal

sites with 3x2x2x3 mixed between within subjects ANOVAs. The LE was quantified in three intervals (800-1000ms, 1000-1200ms, 1200-1500ms) and tested at parietal sites with a 3x2x2x3 mixed between within subjects ANOVA. The factors were Group (Young, High, Low), Response Type (Old, New), Hemisphere (Left hemisphere; LH, Right Hemisphere; RH), and Electrode (three electrodes at homologous locations over each hemisphere see Table 6:2). Only interactions involving Group, Response Type, or Hemisphere were of interest. Main effects or interactions that did not involve these factors, as well as non-significant results will not be discussed unless of theoretical interest. The epochs chosen for testing are shown in Table 6:2. The data at each electrode site were averaged across the appropriate epoch and the area under the waveform (vs the μV baseline) during this epoch was calculated for each of the relevant electrodes in each of the conditions. These measures were then used as the dependent variable.

General Description of components of interest for Hits and Correct Rejections

Figure 6:2 shows data from a selection of scalp electrodes that outline the response waveform morphologies for Hits and Correct Rejections that were observed in the Young, High performers, and Low performers. Shading is used to identify the epochs chosen to test the components of interest (FN400, LPC, LE). Looking first to the FN400: a negativity was evident in frontal regions in the Young that was strongly attenuated in both of the older groups. No old/new effects appear evident on visual inspection of this negativity, which is over by about 400ms. In contrast, old/new differences can be seen in the Young at centro-parietal electrodes during the 300-500ms epoch traditionally associated with the FN400. No old/new differences are evident in either of the older groups. This pattern continued in the 500-800ms epoch traditionally associated with the LPC. Old/new differences appear in Young but are not present in either of the older groups. The positivity appears attenuated in the older adults relative to the Young. Moving forward on the scalp during the same epoch, the positivity in the Young reduces to the same level as the older adults through central electrodes and by the time frontal electrodes are reached it appears attenuated in the Young relative to the older adults. With regard to old/new differences, no clear pattern is evident on visual inspection during the 500-800ms epoch at frontal electrodes. Finally, for the remainder of the epoch (1500ms), a striking sustained positivity is evident in a cluster of occipito-parietal electrodes in the right hemisphere in the Low performers but not the High performers or the Young.

300-500ms

In the epoch traditionally associated with the FN400 old/new effect, there were no significant main effects or interactions at the frontal electrodes analysed ($p>0.10$). Although using windows that span several hundred milliseconds is common in the ERP literature (Rugg, 1995), there is a possibility that several distinct effects get averaged together and a danger that important memory-related effects get missed (Wegesin et al., 2002). Visual inspection of the ERP waveform revealed that the negativity of interest was over by ~400ms and so the analysis was repeated using a narrower epoch (300-400ms). This analysis confirmed that the group effect that was evident on visual inspection was statistically significant [$F(50,2)=5.45$, $p\leq0.01$]. Post-hoc tests revealed that this was due to greater negativity in the Young when compared with the High ($p\leq0.05$) and the Low performing older adults ($p\leq0.01$). There was no old/new effect ($p\geq0.10$) and no Group x Response Type interaction ($p\geq0.10$). At centro-parietal electrodes there was a main effect of Group [$F(50,2)=8.74$, $p\leq0.001$], post-hoc tests revealed that the component was significantly larger in the Young when compared with both older groups ($p\leq0.005$), who did not differ significantly from each other ($p>0.10$). There was no main effect of Response Type (Old, New). However, there was a significant Group x Response Type interaction [$F(50,2)=3.46$, $p\leq0.05$; see Figure 6:2]. Contrasts revealed an old/new effect only in the Young arising from significantly greater processing of Hits relative to CRs ($F=4.40$, $p\leq0.05$). There was no differential processing in either of the old groups ($p>0.10$).

500-800ms

In the temporal window usually associated with the LPC there were no significant main effects or interactions at frontal electrodes ($p>0.1$). For centro-parietal electrodes there was a main effect of Group [$F(50,2)=3.20$, $p\leq0.05$], which was driven by a significant attenuation of the component in both older groups ($p\leq0.05$) relative to the Young. There was no main effect of Response Type ($p>0.1$) but there was a significant Group x Response Type interaction [$F(50, 2)=5.05$, $p\leq0.01$]. Contrasts revealed a significant old/new effect in the Young where Hits were significantly more positive-going than CRs ($p\leq0.05$). There was no significant differential processing evident in either of the old groups ($p>0.10$).

800-1000ms

There were no significant main effects or interactions.

1000-1200ms

There were no significant main effects or interactions.

1200-1500

There was a main effect of Group [$F(50,2)=3.32$, $p \leq 0.05$] for this LE and post-hoc tests revealed that this was due to significantly greater processing in the Low performers relative to the Young ($p \leq 0.05$).

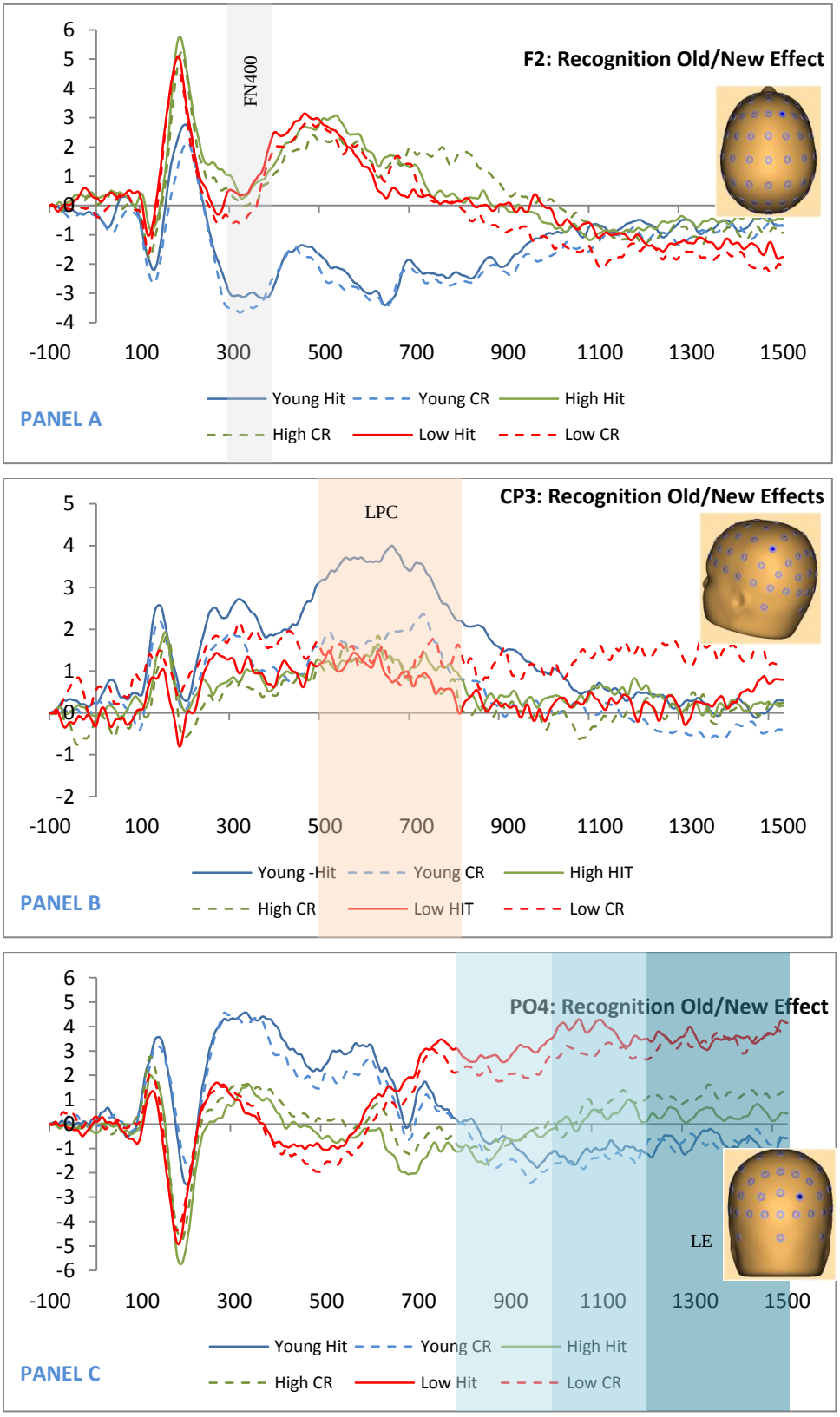

Figure 6:2 Hits and Correct Rejections for the FN400, LPC, and LE.

Note: FN400 illustrated at F2, the LPC (late positive component) illustrated at CP3, and the LE (late effect) illustrated at PO4. Hit = correctly identified old words. CR= correct rejections (correctly identified new words). High = high performing old. Low = low performing old. Results for the LE at 800-1000 and 1000-1200ms were not significant.

Table 6:2 Main effects & interactions for the FN400 (Familiarity) & the LPC (Recognition).

Component	Time (ms)	Electrodes	Main Group	Main Response	Main Hemisphere	Group x Response	Group x Hemisphere
			Old/New Effect (Hits/CRs)				
FN400 frontal	300-400	F3, F1, FZ, F2, F4	**	ns	N/A	ns	N/A
FN400 centro-parietal	300-500	CP3, CP1, P3 CP4, CP2, P4	***	ns	ns	*	ns
LPC frontal	500-800	F3, F1, FZ, F2, F4	ns	ns	N/A	ns	N/A
LPC centro-parietal	500-800	CP3, CP1,P3 CP4,CP2,P4	*	ns	ns	**	ns
LE	1200-1500	P1, P3, PO3 P2, P4, PO4	*	ns	ns	ns	ns
Component	**Time (ms)**	**Electrodes**	**Main Group**	**Main Encode**	**Main Hemisphere**	**Group x Encode**	**Group x Hemisphere**
			Encode Effect (Learn/Read)				
FN400 frontal	300-400	F3, F1, FZ, F2, F4	**	ns	N/A	ns	N/A
FN400 centro-parietal	300-500	CP3, CP1, P3 CP4, CP2, P4	****	*	ns	ns	ns
LPC frontal	500-800	F3, F1, FZ, F2, F4	ns	p=0.055	N/A	ns	N/A
LPC centro-parietal	500-800	CP3, CP1,P3 CP4,CP2,P4	*	***	ns	**	ns
LE	1200-1500	P1, P3, PO3 P2, P4, PO4	ns	ns	ns	*	ns

*Note: FN400 is also known as the frontal episodic memory effect (EM). Late Positive Component (LPC) is also known as the parietal episodic memory effect. *p ≤0.05, **p≤0.01, ***p≤0.001, **** p≤0.0005, ns = not significant. Type (Old, New), See Chapter 5 for scalp location of electrodes.*

6.3.3 Analysis of Learn/Read (L/X) Effects

ERP waveforms associated with Learn Word and Read Word encode types irrespective of response accuracy were also quantified using the same latency periods and electrodes in order to explore the effects, if any, of the Learn/Read (L, X) instruction given during the encoding phase of the task. ERP waveforms associated with Learn Words and Read Words irrespective of response accuracy were quantified over two consecutive latency periods; 300-500ms and 500-800ms. Analysis was conducted separately at selective frontal and centro-parietal sites. The FN400 and LPC waveforms were tested in the frontal region with 3x2x5 mixed between within subjects ANOVAs. The factors were Group (Young, High, Low), Encode Type (Learn, Read; L, X) and Electrode (F3, F1, FZ, F2, F4). The same two components (FN400, LPC) were tested at centro-parietal sites with 3x2x2x3 mixed between within subjects ANOVAs. The LE was quantified in three intervals (800-1000ms, 1000-1200ms, 1200-1500ms) and tested at parietal sites with a 3x2x2x3 mixed between within subjects ANOVA. The factors were Group (Young, High, Low), Encode Type (Learn Word, Read Word; L, X), Hemisphere (Left Hemisphere; LH, Right Hemisphere) and Electrode (three electrodes at homologous locations over each hemisphere see Table 6:2). Only interactions involving Group, Encode Type, or Hemisphere were of interest. Main effects or interactions that did not involve these factors, as well as non-significant results will not be discussed unless of theoretical interest. The time-windows chosen for testing are shown in Table 6:2. The data at each electrode site were averaged across the appropriate epoch and the area under the waveform (vs the μV baseline) during this epoch was calculated for each of the relevant electrodes in each of the conditions. These measures were then used as the dependent variable.

General Description of Learn/Read (L, X) effects.

Figure 6:3 shows data from a selection of electrodes that outline the waveform morphologies for Learn and Read words in all three groups (Young, High, Low). Shading is used to identify the epochs chosen to test the components of interest (FN400, LPC, LE). The morphology of the waveforms for the Learn Words and Read Words broadly follow the same pattern as for Hits and CRs described above. Significant main effects and interactions are summarised in Table 6:2. Differential processing of Learn Words and Read Words is evident on visual inspection of the waveform in the Young but not in the older adults at centro-parietal and parietal sites during the 500-800ms epoch. Visual inspection also reveals different patterns of word processing in the three groups towards the end of the analysis window.

300-500ms

Guided by visual inspection (Handy, 2005) at frontal electrodes, a 300-400ms epoch was employed. There was a main effect of Group [F (50,2)=4.65, p ≤0.01]. Post-hoc tests revealed that this was due to greater amplitudes in the Young relative to the Low performers (p≤0.05), the difference between Young and High performers approached significance (p=0.06) but the High and Low performers did not differ significantly from each other (p≥0.10). There was no main effect of Encode Type or Encode Type by Group interaction at frontal electrodes. During the 300-500ms temporal window at centro-parietal electrodes there was a strong main effect of Group [F (50,)=11.04, p ≤0.0001]. Post-hoc tests indicated that this was due to significantly greater amplitudes in the Young relative to the High (p≤0.001) and the Low performers (p ≤0.0001). There was also a main effect of Encode Type [F (50,1)=11.04, p ≤0.05], which was due to greater processing of Learn Words relative to Read Words in all three groups.

500-800ms

In the 500-800ms temporal window at frontal electrodes only a main effect of Encode Type (Learn, Read; L, X) approached significance [F (50,1)=3.85, p =0.055]. This borderline effect was driven by greater processing of Learn Words relative to the Read Word in all three groups (Figure 6:3). For the centro-parietal electrodes in this 500-800ms temporal window there was a main effect of Group [F (50,2)=3.89, p≤0.05]. Post-hoc tests revealed that this was due to greater amplitudes in the Young group compared with the older groups. This difference was significant in the Low performers (p≤0.05) and borderline in the High performers (p=0.06). There was a main effect of Encode Type [F (50,1)=13.32, p≤0.001] and a Group x Encode Type interaction [F (50,2)=5.03, p≤0.01] which was driven by greater processing of Learn Words relative to Read Words in the Young (p≤0.01) and the High performers (p≤0.01), but not in the Low performers (p>0.10, see Figure 6:3).

800-1000ms

There were no significant main effects or interactions (p>0.10).

1000-1200ms

There were no significant main effects or interactions (p>0.10).

1200-1500ms

There was a Group x Encode Type interaction [F (50,2)=3.14, p≤0.05], which was driven by significantly greater processing of Read Words relative to Learn Words in the Low performers (p≤0.05). Differential word processing was not evident in the Young or the High performers (p>0.10). There were no other main effects or interactions.

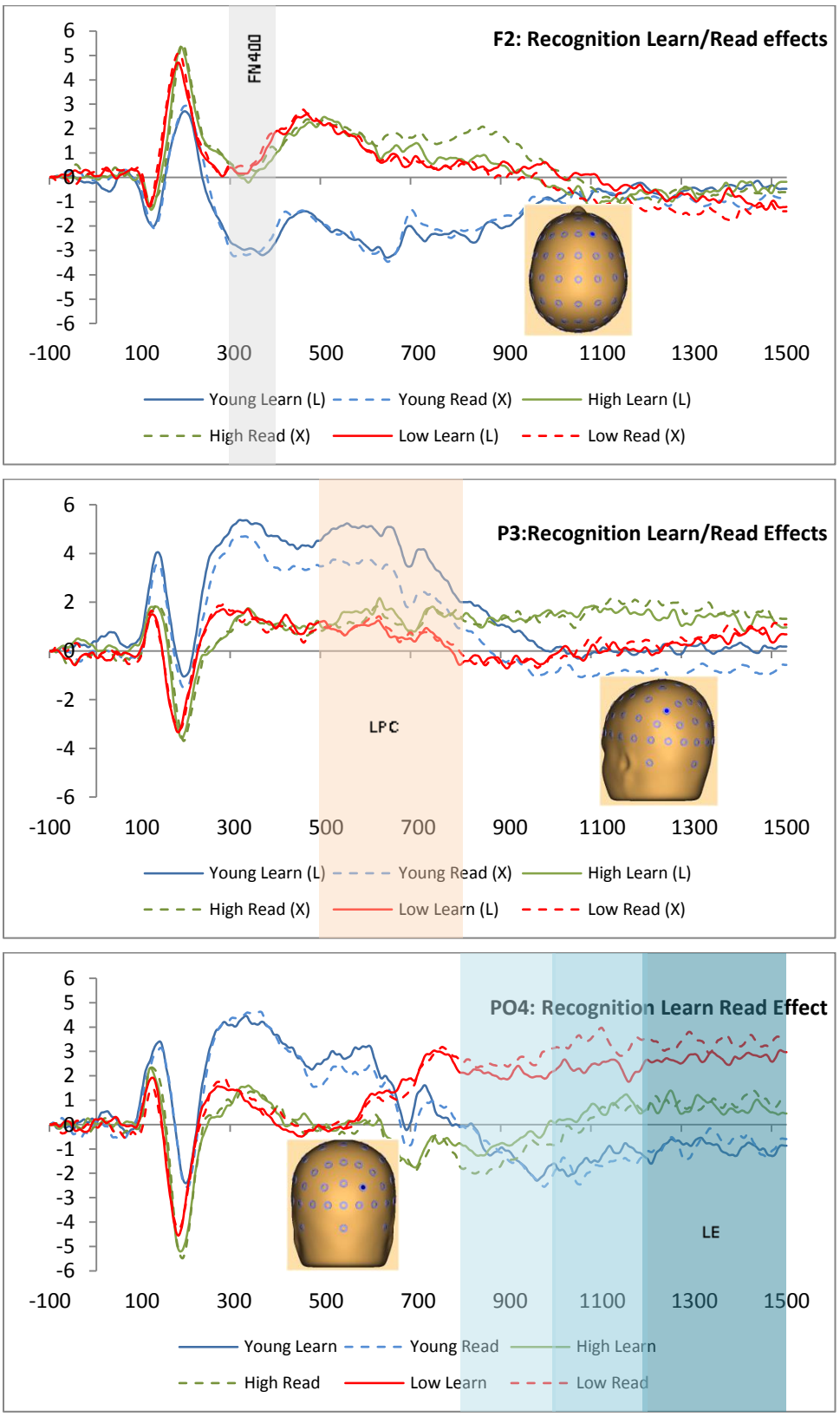

Figure 6:3 Learn (L) and Read (X) words for the FN400, LPS, and LE.

Note: FN400 illustrated at F2, the LPC (late positive component) illustrated at P3, and the LE (late effect) illustrated at PO4. High = high performing old. Low = low performing old.

6.4 Discussion

The main purpose of this chapter was to examine whether the ERP modulations thought to reflect familiarity (FN400 old/new effect), recollection (LPC old/new effect), and post-retrieval monitoring (late effect; LE), are affected by age and cognitive performance. The key finding is that significant old/new effects were only evident in the Young for the putative ERP correlates of recollection and familiarity. Of additional interest is the finding that the Low performers demonstrated a different pattern of event-related neural activity than the High performers and the Young controls when ERP waveforms were analysed according to the type of encoding irrespective of response accuracy. Specifically, when the High performers and the Young were engaging in greater processing of Learn Words relative to Read Words in the period associated with the LPC old/new effect, the Low performers failed to discriminate. In addition, the Low performers engaged in greater processing of the Read words relative to the Learn Words between 1200ms and 1500ms when the other two groups were not engaging in differential processing. The findings suggest that both familiarity and recollection processes are affected by age. Furthermore, taking account of cognitive performance facilitates understanding of memory recognition and its putative ERP correlates.

Relatively little attention has been paid to the FN400 old/new effect in the ERP ageing literature and findings are equivocal, but extensive behavioural research suggests that familiarity based processing is maintained across the lifespan (Hay & Jacoby, 1999; Jennings & Jacoby, 1997; Prull et al., 2006). Of interest, in this study, is the Group by Response (old/new) interaction that revealed a significant early familiarity ERP old/new effect in the Young but not in the older adults. This result can be interpreted as meaning that the ERP modulation of familiarity is not maintained in senescence. However, given the extensive behavioural literature that supports sparing of familiarity, it is also possible that that the FN400 old/new effect does not index familiarity in the elderly and different ERP modulations underlie familiarity in older adults relative to young adults (Wolk et al., 2009). While there is considerable neuroimaging data from young adults correlating FN400 old/new effect with familiarity (Eichenbaum et al., 2007; Friedman & Johnson, 2000; Rugg & Curran, 2007; Rugg & Yonelinas, 2003), as already mentioned, the ageing literature is sparse and equivocal. In all likelihood, the mixed findings are a consequence of task differences and participant heterogeneity. Interestingly, recent ERP studies that have taken account of individual differences in memory performance report diminished or absent FN400 old/new effects (Duarte et al., 2006; Wolk et al., 2009). The absence of this effect has been reported as specific to words but not pictures (Ally et al., 2008)

but other studies have found the reverse (e.g. Li, Morcom et al., 2004). Consistency of tasks across studies together with the identification of performance based participant sub-groups may help to tease apart these ambiguous findings. In this study the FN400 component itself was significantly more positive in the older adults when compared with the Young. In a recent study aimed at characterizing age-related changes in the ERP correlates of memory recognition, Guillaume and colleagues (2009) reported more positive waveforms in adults over the age of 50. Other studies have also reported a positive shift in older adults (Morcom & Rugg, 2004; Nessler et al., 2008; Trott et al., 1999). It is possible that the increased positivity observed here reflects cerebral reorganization such as changes in generator orientation (Mark & Rugg, 1998).

The LPC component was also significantly attenuated in the older adults relative to the Young at occipito-parietal electrodes. Again, of particular interest, is the Group by Response Type interaction, which revealed no significant differential processing in the older adults but a significant old/new effect in the Young. Again, it is important to remember the equivocal nature of age-related findings with regard to the LPC old/new effect (recollection). While some studies have reported intact ERP old/new effects in older adults (Li, Morcom et al., 2004; Mark & Rugg, 1998) others, like the present study, have found diminished or absent ERP recollection effects in older adults (Rugg et al., 1997; Swick & Knight, 1997). Conflicting findings may be a consequence of a number of factors that vary across studies including; participant heterogeneity, task type, task difficulty, stimulus type, and study-test interval. Many of the studies that demonstrate intact LPC old/new effects in older adults use source memory tasks (Li, Morcom et al., 2004; Mark & Rugg, 1998; Trott, Friedman, Ritter, & Fabiani, 1997), that require the retrieval of associative details which has, in turn, been linked to the amplitude of the LPC (Donaldson & Rugg, 1998; Wilding & Rugg, 1997). In item memory tasks, such as the one employed in this study, older adults are less likely to recruit resources to the encoding and retrieval of associative details than they would if completing a task that explicitly requires this (e.g. source memory task) (Wolk et al., 2009). Furthermore, source memory studies use a select sample of 'Hits' in their analysis that are specifically associated with recollection, making it more likely that LPC old/new effects will be present, regardless of age, because the component indexes retrieval of contextual detail (Wolk et al., 2009). In contrast, correct responses on item memory tasks represent a mixture of recollection and familiarity. Studies, like this one, that use item memory recognition tasks have mostly found diminished LPC old/new effects (Wolk et al., 2009). Studies that show spared old/new recollection effects tend to use incidental encoding tasks that require semantic elaboration (Li, Morcom et al., 2004; Mark & Rugg, 1998) or present words in a context (e.g. a sentence) which naturally enhances semantic elaboration (Trott et al.,

1997). Studies that report markedly diminished recollection effects (e.g. Wolk et al., 2009) tend to use intentional encoding tasks, wherein participants are simply asked to try to remember words for a later test. There is a good deal of literature supporting the idea that older adults perform more poorly than younger adults on intentional rather than incidental encoding tasks due to failure to spontaneously engage in appropriate encoding strategies (Glisky, Rubin, & Davidson, 2001; Naveh-Benjamin, Brav, & Levy, 2007). The weaker memory traces in older participants in this study could be due to differences between old and Young participants in memory strategies (Wolk et al., 2009)

Several ERP studies have shown that the LPC old/new effect increases with level of processing (Paller, 1992, 1995; Rugg, Allan, & Birch, 2000; Rugg et al., 1998). The influence of level of processing on the FN400 old/new effects are less reliable but have been shown to be unaffected when conditions are randomized within blocks (Rugg et al., 1998), but when conditions are manipulated between blocks the FN400 old/new effect is evident after deep but not shallow processing (Rugg et al., 2000). In this study, when participant responses to old words were analysed on the basis of instructions given at encoding, irrespective of response accuracy, an interesting pattern emerged for the ERP modulations associated with recognition memory. At centro-parietal electrodes there was a strong main effect of Encode Type for the FN400 old/new effect (familiarity) which was due to greater processing of the Learn Words relative to the Read Words in all three groups. Interestingly, at the same electrode sites in the period associated with the LPC old/new effect (recollection) there was a Group by Encode Type interaction which was driven by significantly greater processing of Learn Words relative to Read Words in the Young and High performers but not in the Low performers. These results suggest that, when response accuracy is taken out of the equation, Low performers fail to distinguish between words that they were instructed to Learn and words that they were instructed to Read, thus engaging in qualitatively different neural processing of words at test than High performers and Young controls.

A late right frontal old/new effect thought to reflect post retrieval monitoring processes has frequently been reported (Nessler, Mecklinger, & Penney, 2001; Ranganath & Paller, 2000). Again findings from ageing studies are mixed, with reports of either a diminished (Ally et al., 2008; Li, Morcom et al., 2004; Trott et al., 1999; Wegesin et al., 2002) or a preserved effect in older adults. The only study that has used an item memory task to assess this late sustained old/new effect reported an augmentation of the effect in poor performing old adults relative to high performers and young controls (Wolk et al., 2009). The study reported here failed to find any late sustained frontal activity in any of the three groups but a striking late sustained

positivity was evident in a cluster of occipito-parietal electrodes in the right hemisphere in the Low performers that was diminished or absent in the High performers and the Young. In addition, there was a Group by Encode Type interaction, irrespective of response accuracy, reflecting significantly greater processing of Read Words relative to Learn Words in the Low performers that was not evident in the Young or High performers. Neuroimaging studies of ageing have reported that older adults can recruit different neural networks than young controls during the same memory task (Cabeza et al., 1997) and this differential processing can be interpreted as either compensatory or inefficient. It is difficult to tell whether the late increased recruitment and differential processing demonstrated by the Low performers in this study represents compensation or inefficiency. When poorer performers demonstrate increased activation it can be can be considered as a reflection of inefficient processing (Colcombe, Kramer, Erickson, & Scalf, 2005). However, in light of the lack of differentiation of words in the Low performers for the LPC (recollection) component, it is possible that the Low performers were engaging in some kind of compensatory post-retrieval monitoring that is not necessary in High performers (Zarahn, Rakitin, Abela, Flynn, & Stern, 2007) or enaging in a last attempt at retrieval before the next trial. The results reported here support the view that age-related memory changes and underlying neural correlates may be more precisely characterised by examining effects in high and low performing elderly individuals who might have different underlying patterns of neural activity (Cabeza, Anderson, Locantore, & McIntosh, 2002). This is one of a handful of studies that has examined ERP correlates of recognition memory based on performance in older adults and the only one, as far as the author is aware, to do so with participants classified based on cognitive asymmetry between memory performance and an estimate of pre-morbid IQ.

Chapter 7 AN ERP STUDY OF EPISODIC ENCODING

7.1 INTRODUCTION

Age-related decline in episodic memory performance is well documented; nonetheless it remains unclear whether these deficits are a consequence of encoding or retrieval failures, or a combination of both (Friedman et al., 2007; Park & Gutchess, 2005; Perfect, Williams, & Anderton-Brown, 1995; Rugg & Morcom, 2005). Research is emerging that suggests that the two processes may be differentially affected and that encoding deficiencies may exert a larger influence (Friedman et al., 2007). Chapter 6 reported some interesting significant differences and interactions that emerged from exploratory analyses of components associated with recognition memory, on the basis of the instruction cue given at encoding (Learn/Read; L/X), irrespective of response accuracy. During the recognition phase of the task, in the epoch traditionally associated with ERP modulations of familiarity (300-500ms), Young, High performers, and Low performers, all generated greater neural activity for words that they were instructed to learn (Learn Words), relative to words that they were instructed to read at encoding (Read Words), irrespective of whether they correctly identified these words as old or not. In the epoch traditionally associated with ERP modulations of recollection (500-800ms), the Young and High performers continue to make this distinction but the Low performers do not. Interestingly, between 1200 and 1500ms post stimulus, the Low performers generate more positive neural activity for Read Words relative to Learn Words. At this late stage in the epoch no differential processing is evident in either the Young or the High performers. The reader may recall from Chapter 2 that the Young had the best recognition accuracy scores and the Low performers the poorest for both Learn Words and Read Words. All three groups differed significantly from each other and all three groups performed above chance for Learn Words. The Young also performed above chance for the Read Words. In contrast, the High performers responded poorly but not randomly for the Read Words while the Low performers' response to the Read Words could be described as random or below chance. Perhaps most interesting is the fact that all three groups seemed to benefit from the cue to Learn despite different levels of performance across groups. When taken together this pattern of behavioural and neurophysiological findings warrant further investigation. If differences in neural activity at encoding modulate memory performance at recognition then two possibilities pertain: a) older adults could display similar neural processing to the Young but with High performers demonstrating minimal functional decay relative to the Low performers, or alternatively b) better recognition memory in the High performers may be

underpinned by successful recruitment and amplification of control processes in order to compensate for age-related sensory decline. This chapter reports detailed exploratory analysis of the ERP activity recorded during the encoding phase of the Learn task with specific focus on the effects of age, cognitive performance, and encode type.

7.2 METHOD

7.2.1 Participants

Participants were recruited through public and college advertising and from the Robertson Participant Panel (see Chapter 2 for full details). Forty-eight older adults aged between 65 and 80 and twenty-two Young controls aged between 18 and 30 years satisfied the eligibility criteria. Four older adults failed to attend for Session 2 due to ill health (n=2), personal problems (n=1) and voluntary withdrawal (n=1). In addition, one older adult disclosed taking CNS medication after testing was complete and one young adult drank a substantial amount of alcohol in the 24 hours preceding Session 2 and so both were excluded. Data for forty-three (18 male) older adults (M=69.95, SD ± 3.70) and twenty-one young (9 males) controls (M=21.28, SD ± 2.97) were analysed. The older participants were assigned to sub-groups based on their memory performance relative to an estimate of their pre-morbid IQ. Participants were defined as Low performers if they scored more than one standard deviation below their NART (National Adult Reading Test) estimated pre-morbid IQ on the Wechsler Memory Scale logical memory delayed recall test (for a full description of the classification procedure see Chapter 2 section 2.2.2). Classifying participants in this way yielded; a) 25 High performers (10 male, M=70.28, SD ± 3.39 and b) 18 Low performers (8 male; M=69.48 ± 4.14).

7.2.2 Procedure

7.2.2.1 Testing Protocol

Testing was conducted between September 2008 and May 2009. Participants were assessed in two ~2 hour sessions that took place approximately one week apart. During Session 1 participants completed the mini mental state exam, a memory self-rating scale, the Hospital Anxiety and Depression Scale, the National Adult Reading Test, animal naming, the Stroop task, and sub-sets of the Wechsler Memory Scale (Logical Memory 1 and 2, Face Recognition 1 and 2, Visual Reproduction 1 and 2 and Digit span). In addition, during Session 1 participants were taught how to perform the Choice Reaction Time split response task (CRTsr) and the Sustained Attention to Response Task fixed version SART$_{fixed}$. During Session 2 the electrical activity in participant's brains was recorded while participants rested (6 minutes) and while they performed three computerized experimental tasks: the Learn memory task, the CRTsr task, and the SART$_{fixed}$. The Learn task had an encoding and a delayed recognition phase which each took approximately 8.5 minutes to complete. Participants completed the CRTsr (self-paced) and the SART$_{fixed}$ (~5 minutes) during the interval between the

encoding and recognition phases of the Learn task. All materials and experimental tasks are described in detail in Chapter 2. ERP analysis of data collected during Session 2 while participants completed the encode phase of the Learn task is presented in this chapter (see Figure 7:1).

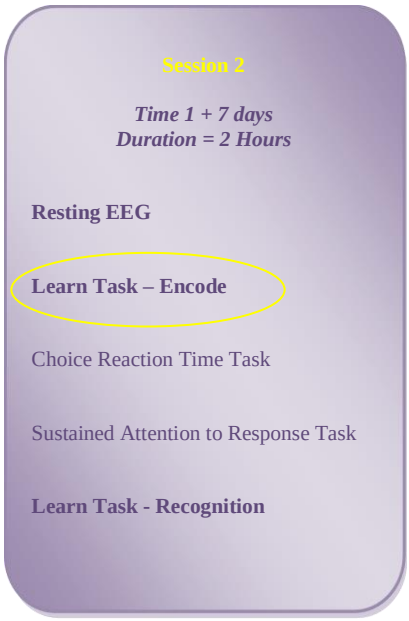

Figure 7:1 Event Related Potential (ERP) analysis of the recognition phase of the Learn task.

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7.2.2.2 Fitting Participants with Cap and Electrodes

During Session 2 participants were seated in a comfortable chair ~65 cm from a computer screen in a dimly lit EEG testing room. The circumference of the participant's head was measured just above the eyebrows and over the inion at the back of the head. This circumference was used to guide selection of appropriate cap size. The distance from the nasion to the inion was then measured and divided by two to determine the proper location of the Vertex electrode (CZ). The mastoid electrodes were then attached to the participant. The cap was carefully placed on the participant's head in such a way as to ensure that the midline of the cap lined up with the nose and the vertex electrode was in the correct location. The chin strap was then fitted to ensure that the cap remained in a secure position. After each electrode holder was filled with gel the remaining electrodes were attached. The electrodes were then plugged into the A/D box. Using the Actiview software the trace for each electrode was examined to check for impedance. Once any problems with poor connections were rectified testing began. Participants were made aware of artefact related problems induced by blinks, other facial movements, head, and neck movements and other twitches. They were asked to keep such movements to a minimum.

7.2.3 Materials

7.2.3.1 Task

Cued Encoding

All materials and experimental tasks, including the Learn task are described in detail in Chapter 2. For ease of reference the encode phase of the Learn task is illustrated in Figure 7:2. Four conditions of interest, each with 60 trials, were identified within the encode phase of the task; L-Cue (defined as the L-Cue + L-ISI1 = 1400ms), X-Cue (defined as X-Cue + X-ISI1 = 1400ms), L-Word =1500ms and X-Word = 1500ms.

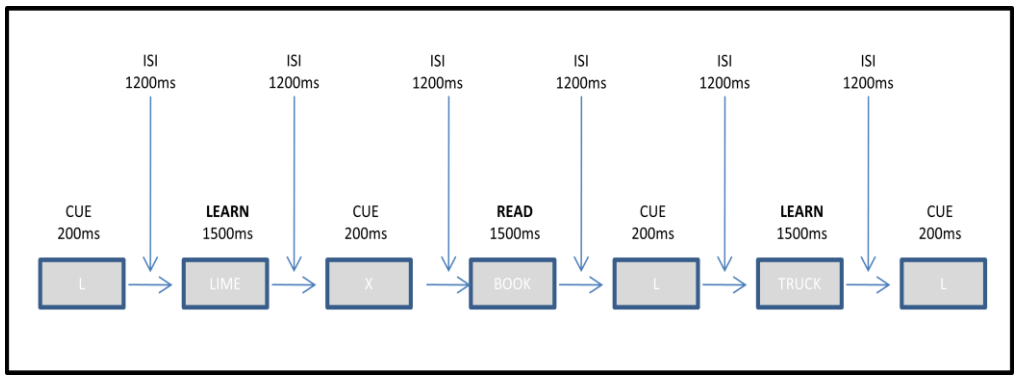


Figure 7:2 Learn Task Sequence – Encode Phase.

Note Participants were instructed to Learn words that followed the letter L & to Read words that followed the letter X.

7.2.4 Data Analysis and Processing

Data were analysed with BESA Version 5.2 (Brain Electronic Source Analysis www.besa.de) software. After acquisition data were average referenced and filtered (low pass 0.1Hz, 6db slope, high pass 40Hz, zero phase). The data for each participant were manually inspected and trials with excessive EMG or noise transients were removed, bad channels were interpolated and horizontal and vertical EOG artefacts were corrected by means of an automated (BESA) eye movement correction procedure. Baseline was defined as -100 to 0ms epoch. Buffer trials were excluded from analysis. Scalp topographic voltage maps presented below represent interpolated voltage distributions derived from 64-scalp measurements. These interpolated potential maps are displayed on a 3D reconstruction of a rendered scalp surface as implemented in the BESA (Version 5.2) multi-modal neuroimaging analysis software package. The analysis strategy and results for the encode phase of the Learn task will be presented in two sections; (1.Cue Analysis, and 2.Word Analysis).

7.3 RESULTS

7.3.1 Analysis Strategy

The componentry of the ERPs over occipito-parietal, central, and frontal regions were investigated following the strategy described in Wylie et al. (2003). In summary this involved calculating ERP averages for each participant for the X-Cue, L-Cue, X-Word, and L-Word. An epoch of -100 to 1400ms was used to calculate the Cue ERPs and -100 to 1500ms to calculate the Word ERPs. Grand averages were then calculated for each of the three groups (Young, High, Low) for each of the four dependent variables (L-Cue, X-Cue, L-Word, X-Word). The data were then collapsed across the X and L conditions to produce two composite waveforms: one for the Cue and one for the Word. The componentry of each of these composite waveforms were visually inspected and broadly defined. Using broadly-defined component peaks limits the number of statistical tests and represents a very conservative approach to the analysis of high density ERP data (for further discussion please consult Wylie et al., 2003). Seven components of interest were identified for the Cue conditions and eleven for the Word conditions. Scalp topographic voltage maps for Cue components and Word components are illustrated Figure 7:3 and Figure 7:8 respectively. The composite waveforms were used to guide the selection of appropriate epochs and electrodes for the statistical analysis of each of the identified components for both of the Cue conditions and both of the Word conditions for each of the three groups (see Table 7:1). The average number of accepted trials was: Young = 225 (94%, 200 to 240), High = 210 (88%, 158 to 240), and Low = 222 (92%, 179 to 240).

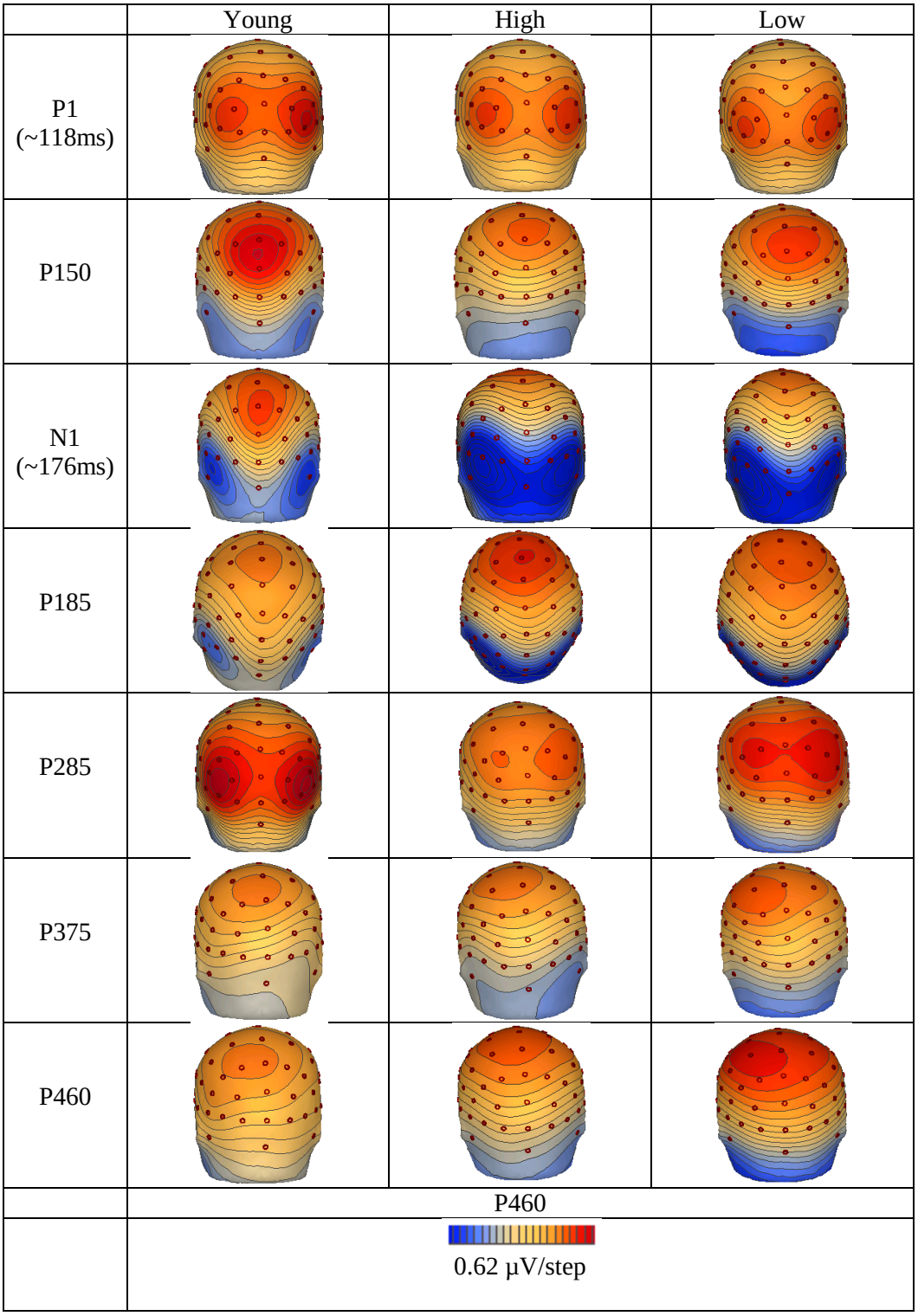


Figure 7:3 Cue: Topographic voltage mapping of spline interpolated potential distributions.

Note: Topographic voltage mapping of spline interpolated potential distribution plotted at each of the seven components of interest collapsed across the L-Cue and X-Cue conditions for each of the three groups. High = high performing old. Low = low performing old.

7.3.2 Cue Analysis

Three parietal (P1, N1, P285) components were tested with 3x2x2x3 mixed between within subjects ANOVAs. The factors were Group (Young, High, Low), Hemisphere (Right, Left), Cue (L, X), and Electrode (three electrodes at homologous locations over each hemisphere see (Table 7:1). Central and frontal components (P150, P185, P375, P460) were tested with 3x2 mixed between within ANOVAs. The factors were Group (Young, High, Low), and Cue (L, X). Only interactions involving Group, Cue, or Hemisphere were of interest. Main effects or interactions that did not involve these factors, as well as non-significant results will not be discussed unless of theoretical interest. The epochs chosen for testing are shown in Table 7:1. The data at each electrode site were averaged across the appropriate epoch and the area under the waveform (vs the μV baseline) during this epoch was calculated for each of the relevant electrodes in each of the conditions. These measures were then used as the dependent variable.

General Description of Cue – ERP Componentry

Eigure 7:4 shows data from a selection of scalp electrodes that outline the composite Cue waveform morphologies (collapsed across L and X conditions) that were observed in the Young, High, and Low performers. Looking over occipito-parietal sites typical P1 (~118ms) and N1 (~176ms) VEPs (visual evoked potentials) were evident. These obligatory components are generally associated with sensory processing and the early decoding of stimulus properties. Different Cue processing patterns were evident across groups in these early components. Cue differentiation was evident at P1with both the Young and, to a lesser extent, the Low performers showing enhanced processing of X-Cues relative to L-Cues whereas the High performers showed enhanced X-Cue processing relative to L-Cue processing at N1. Three $\overline{P2}$ components with distinct spatial and topographic characteristics were evident at central-parietal (P150), fronto-central (P185), and parietal (P285) regions. All three groups showed enhanced X-Cue processing relative to L-Cue processing at P150 with the Young demonstrating larger Cue amplitudes than both of the older groups. At this point the High performers demonstrate early frontal engagement with a larger P185 over frontal scalp. Moving to posterior regions no Cue differentiation is evident at the bilateral P285 where the amplitude is greater in the Young relative to both of the older groups. Bilateral $\overline{P2}$ components have been considered a marker of top down control over task relevant stimuli. Over central regions the P385 component is more markedly distinguishable from the more frontal P460 component in the Young but both components are largest in the High performers who also demonstrated enhanced X-Cue processing at the frontal P485 component.

Table 7:1 Main effects and interactions (ANOVA) for Encode Phase - Cue Components

Component	Group	Time (ms)	Electrodes	Main Effect Group	Main Effect Cue	Main Effect Hemisphere	Group x Cue	Group x Hemisphere
				CUE				
P1 parietal-occipital	Young High Low	122+/- 5 116+/- 5 115+/- 5	P6, P8, PO8 P5,P7, PO7	ns	***	***	.063	*
N1 parietal-occipital	Young High Low	173 +/- 5 180+/- 5 175+/- 5	P8, P10, PO8 P7, P9, PO&	ns	ns	*	**	ns
P2 Components								
P150 central-parietal	Young High Low	154+/- 10 148+/- 10 145+/- 10	CPZ, PZ, POZ, P1,P2	**	**	N/A	ns	N/A
P185 fronto-central	Young High Low	190+/- 5 184+/- 5 181+/- 5	FZ, FCZ, CZ FC1, FC2	**	ns	N/A	.07	N/A
P285 parietal	Young High Low	278+/- 10 290+/- 10 285+/- 10	P6,P8,PO8 P5,P7,PO7	***	ns	*.053	Ns	ns
P3 Components								
P375 central	Young High Low	368+/- 5 378+/- 5 378+/- 5	CZ, C1, C2, CPZ	*	ns	N/A	ns	N/A
P460 fronto-Central	Young High Low	454+/- 5 466+/- 5 454+/- 5	FZ, F1, F2, FCZ, FC1, FC2	**	ns	N/A	*	N/A

*Note: *p ≤0.05, **p≤0.01, ***p≤0.001, **** p≤0.0005, ns = not significant. High = high performing old. Low = low performing old. Group (Young, High, Low). Cue (L, X). Hemisphere (Right, Left). See Chapter 5 for scalp location of electrodes.*

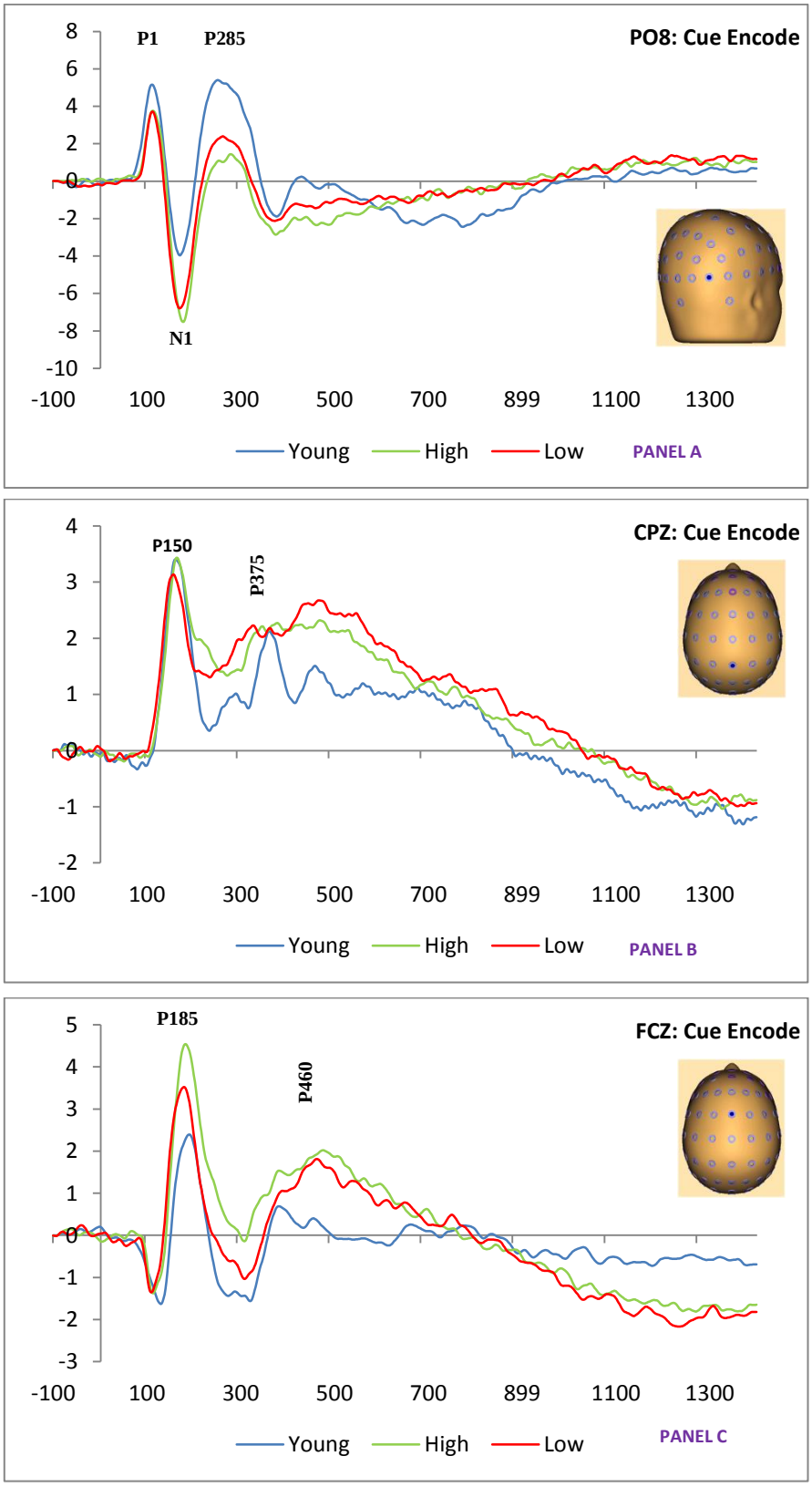


Figure 7:4 Composite Cue waveforms (collapsed across L-Cue and X-Cue conditions).

Note: Data from 3 electrodes are shown. Panel A shows data from an electrode over a parietal site (PO8), Panel B over a central-parietal site (CPZ) and Panel C over a fronto-central site (FCZ). In all cases the data have been collapsed across conditions in order to assess the componentry of the waveforms without reference to the dependent variables. The seven components of interest are labelled and the scalp location of the electrodes are marked with a blue dot. High = high performing old. Low = low performing old.

P1: Cue – Encode Phase

For the P1 component (see Figure 7:5) measured over a +/- 5ms epoch centred on the peak latency there was a strong main effect of Cue [F (53,1)=13.33, p≤ 0.001], a main effect of Hemisphere [F (53,1)=12.07, p≤0 .001], and a Hemisphere x Group Interaction [F (53,2)=3.32, p≤0 .05]. Contrasts revealed asymmetry in the expression of the P1 component only in the Young group where the component was significantly larger in the RH than the LH (F=12.58, p≤0.05). There was also a marginal Cue x Group interaction [F (53,1)=2.89, p≤0 .06). Contrasts revealed that X-Cue amplitudes were significantly larger than L-Cue amplitudes for the Young (F=13.16, p≤0.005) and the Low performers (F=5.49, p≤ 0.05) but not for the High performers (p>0.10).

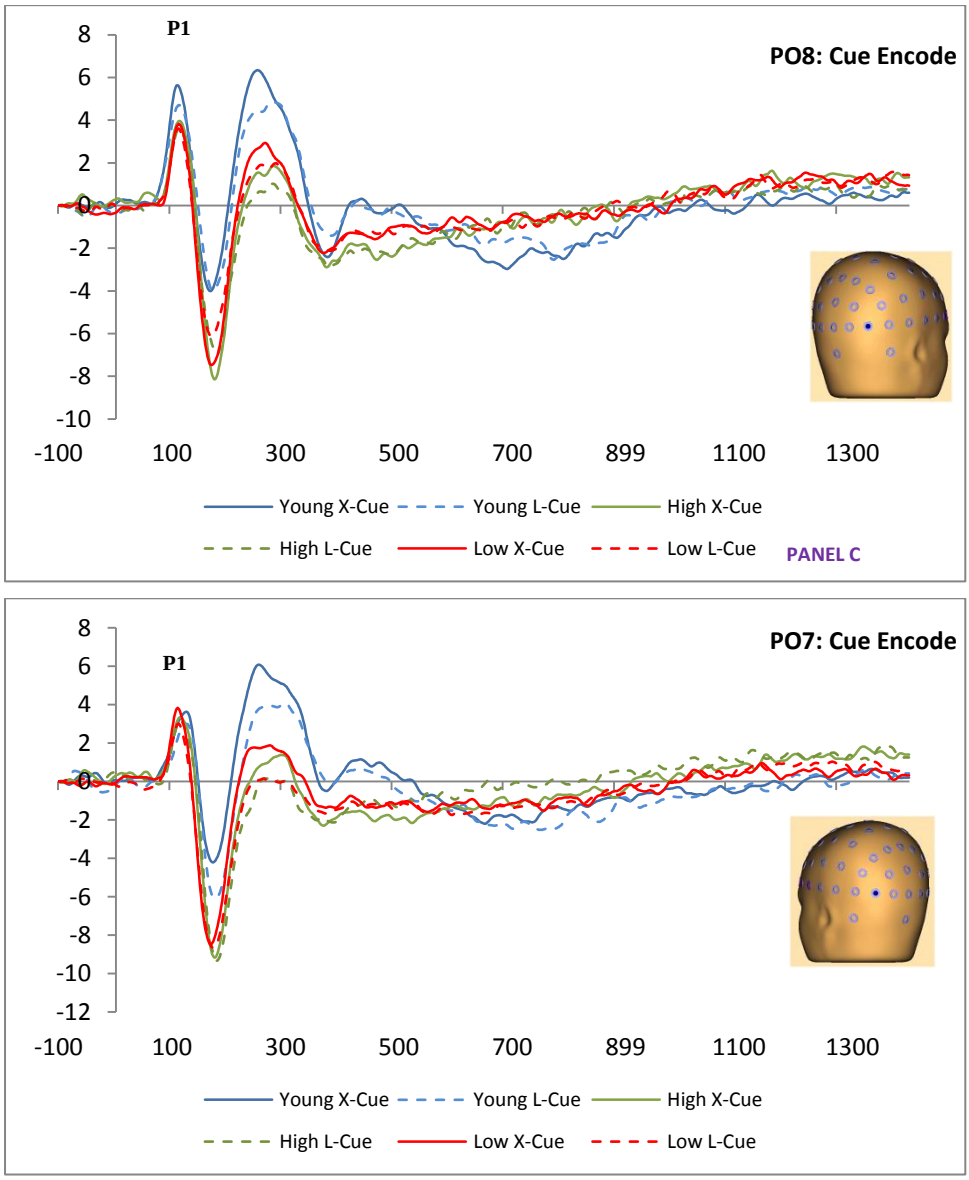


Figure 7:5 The P1 effect illustrated at two homologous bilateral posterior sites (PO8, PO7).

Note: Cue differentiation is not evident in the High performers. There is asymmetry in the expression of the component in the Young group. High = high performing old. Low = low performing old.

N1: Cue – Encode Phase

For the N1 (see Figure 7:6) component measured over a +/- 5ms epoch centred on the peak latency there was a Cue by Group interaction [F (53,2)=4.83, p≤0 .01] which was driven by significantly larger X-Cue processing than L-Cue processing in the High performers (F, 9.40, p≤ 0.01). There was also a main effect of hemisphere [F (53,1)=4.23, p≤0.05], where the N1 component was larger in the LH than the RH.

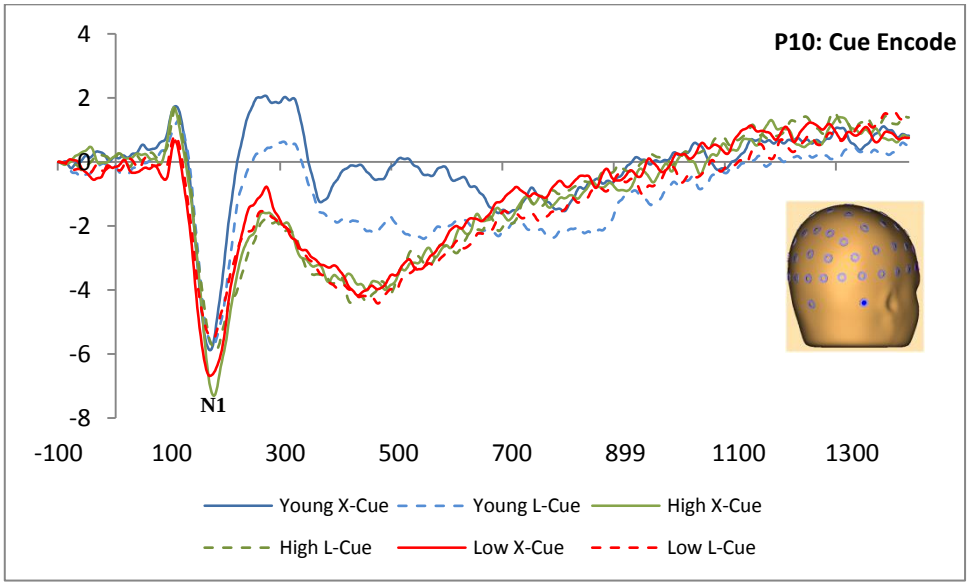


Figure 7:6 The N1 component illustrated at a posterior site (P10).

Note: There is significantly enhanced Cue differentiation in the High performers. High = high performing old. Low = low performing old.

P150: Cue – Encode Phase

For the P150 component measured over a +/- 10ms epoch centred on the peak latency the X-Cue was significantly larger than the L-Cue in all three groups [F (53,1)=7.63, p≤0 .01]. There was a main effect of Group [F (53,2)=4.75, p ≤0 .01] and post-hoc tests revealed that the P150 was significantly larger in the Young than it was in the High performers (p≤0 .01). There was no Group by Cue interaction.

P185: Cue – Encode Phase

For the P185 component (Figure 7:4) measured over a +/- 5ms epoch centred on the peak latency there was a main effect of Group [F (53,2)=6.65, p≤0.005] and post-hoc tests revealed that this fronto-central component was significantly larger in the High performers than it was in the Young (p≤0.01). A Group by Cue interaction fell short of significance (p=0.07).

P285: Cue – Encode Phase

There was a strong main effect of group [F (53, 2)=11.11, p≤0.0005] for the P285 component (see Figure 7:4), which was measured over a +/- 10ms epoch centred on the peak latency. Post-hoc tests revealed that the component was significantly larger in the Young than it was in the High (p≤0.001) and the Low performers (p≤0.01) who did not differ from each other.

There was also a borderline effect of hemisphere [F (53,1)=3.90, p=0.053] with the component more strongly expressed in the RH than in the LH.

P375: Cue – Encode Phase

For the central P385 component, which was measured over a +/- 5ms epoch centred on the peak latency, there was a main effect of Group [F (53,2)=3.87 p≤0.05] which was driven by significantly larger Cue processing in the High performers when compared with the Young (p≤0.05).

P460: Cue – Encode Phase

For the frontal P460 (Figure 7:7), which was measured over a over a +/- 5ms epoch centred on the peak latency, there was a Group by Cue interaction (F (53,2)=3.75 p≤0.05) that picked up on greater processing of the X-Cue relative to the L-Cue in High performers (p≤0.05). The main effect of Group [F (53,2)=6.04 p≤0.005] was due to a significantly smaller P460 component in the Young when compared with the High (p≤0.05) and Low performers (p≤0.01).

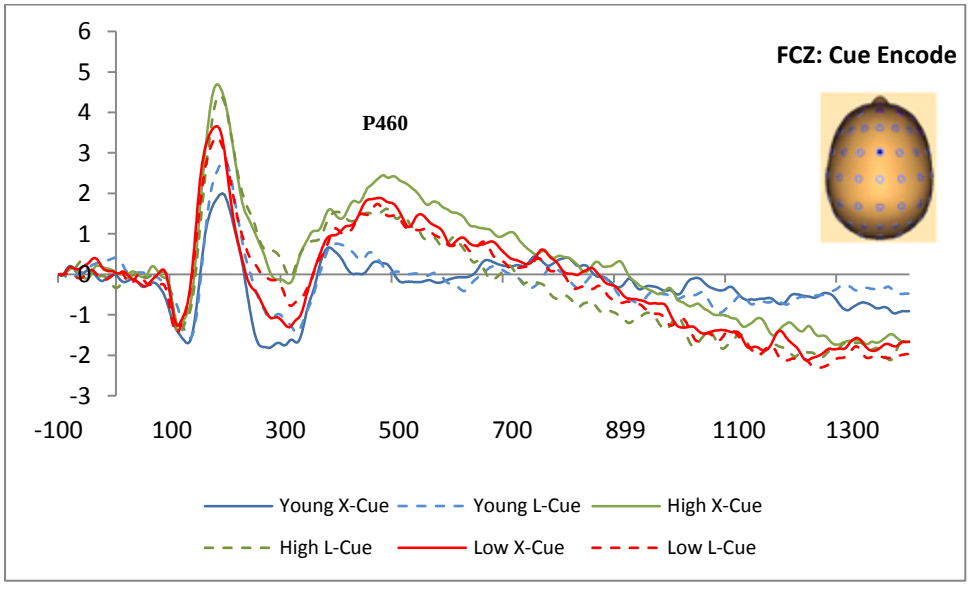


Figure 7:7 The P460 component at a frontal site (FCZ).

Note: There is enhanced X-Cue processing in this frontal component only in the High performers. High = high performing old. Low = low performing old.

7.3.3 Word Analysis

Five parietal (P1, N1, P250, P300, and P400) components were tested with 3x2x2x3 mixed between within subjects ANOVAs. The P300 and P400 were strong in the Young but attenuated or absent in both of the older groups. Two central components (P300 central, P400 central), which were enhanced in the older adults relative to the Young and appeared to be related temporally to the parietal P300 and P400, were also tested at central sites. The factors were Group (Young, High, Low), Hemisphere (Right, Left), Cue (L, X), and Electrode (three electrodes at homologous locations over each hemisphere see (Table 7:2). The remaining central and frontal components (P155, P185, P266, Late Positive) were tested with 3X2 mixed between within ANOVAs. The factors were Group (Young, High, Low), and Cue (L, X). Only interactions involving Group, Cue, or Hemisphere were of interest. Main effects or interactions that did not involve these factors, as well as non-significant results will not be discussed unless of theoretical interest. The epochs chosen for testing are shown in Table 7:2. The data at each electrode site were averaged across the appropriate epoch and the area under the waveform (vs the μV baseline) during this epoch was calculated for each of the relevant electrodes in each of the conditions. These measures were then used as the dependent variable.

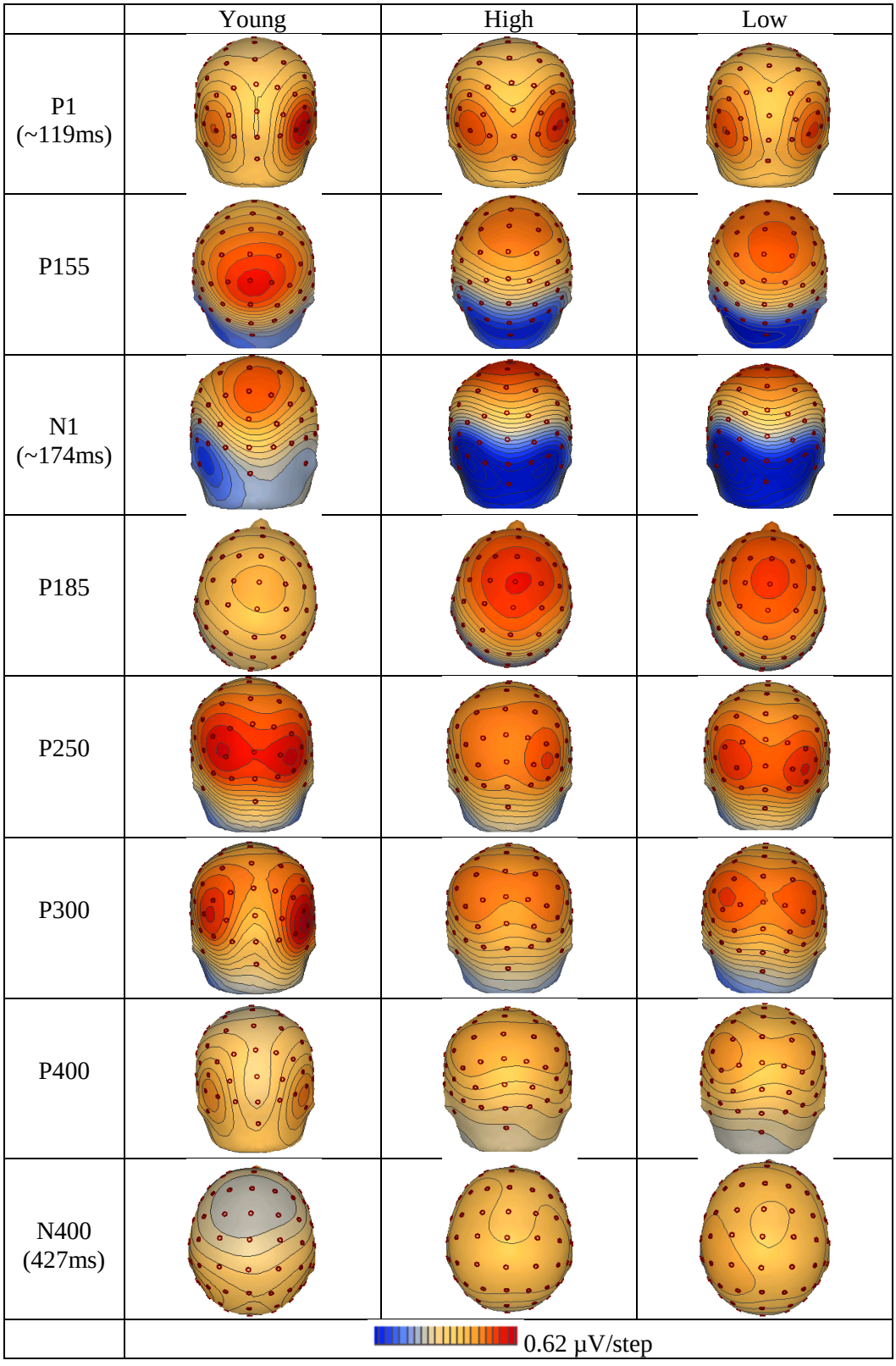


Figure 7:8 Word: Topographic voltage mapping of spline interpolated potential distributions

Note: Word: Topographic voltage mapping of spline interpolated potential distributions the components of interest collapsed across the L-Word and X-Word conditions for each of the three groups (Young, High = high performing old. Low = low performing olds).

General Description of Word – Encode Phase– ERP Componentry

Figure 7:9 shows data from a selection of scalp electrodes that outline the Word waveform morphologies (collapsed across L and X conditions) that were observed in the Young, High performers, and Low performers. Over occipito-parietal sites typical P1 (~119ms) and N1 (~174ms) VEPs were evident during Word processing. In the Young the P1 component was significantly larger in the RH. In contrast, the N1 component was more strongly expressed in the LH in all three groups. Word differentiation is first evident at N1 and then at the more central P155 component with largest amplitudes observed for L-Words, in all groups, for both components. Moving to more frontal regions the enhancement of the L-Word relative to the X-Word is still evident at P185 but this component is significantly enhanced in both of the older groups relative to the Young. Moving to posterior regions no differences or interactions are evident at the widely distributed parietal $\overline{P2}$ component, which peaks at ~ 250ms in all three groups. In the Young, this component is immediately followed by another positive parietal component at ~300ms (P300) that has a distinct bilateral distribution and shows a significant RH bias. In contrast, in the older adults this P300 component is more diffuse and has a more anterior distribution. Another positive parietal bilateral component, which peaks at ~400ms, is then evident in the Young. Again, in the older adults this P400 is more anterior and more diffuse. Looking towards frontal regions an N400 component is significantly enhanced in the Young relative to the Low performers. Following on from this language-related component is a somewhat sustained positivity (Late Positive) that is evident at central sites in all three groups. Word differentiation is obvious in all groups at this component but follows a different time course for each group with word differentiation completed by ~680ms and 725ms in the Young and Low performers respectively. In contrast, the High performers continue to differentiate between L-words and X-words until ~940ms post-stimulus.

Table 7:2 Main Effects and Interactions for Word during Encode Phase of Learn Task

Component	Group	Time (ms)	Electrodes	Main Effect Group	Main Effect Word	Main Effect Hemi	Group x Word	Group x Hemi
				WORD				
P1 parietal-occipital	Young High Low	119+/-10 121+/-10 118+/-10	P6, P8, PO8 P5,P7, PO7	ns	ns	***	ns	.06
P155 central-parietal	Young High Low	157+/-10 160+/-10 152+/-10	CPZ, PZ, P1,P2	ns	**	N/A	ns	N/A
N1 parietal-occipital	Young High Low	169+/-5 180+/-5 172+/-5	P8, P10, PO8 P7, P9, PO7	.06	***	***	ns	ns
P185 fronto-central	Young High Low	198+/-5 182+/-5 174+/-5	FZ, FCZ, FC1, FC2	**	*	N/A	ns	N/A
P250 Parietal-occipital	Young High Low	250+/-5 247+/-5 247+/-5	P08, PO4, O2, PO7, P03,O1	ns	ns	ns	ns	ns
P300	Young High Low	302+/-10 310+/-10 310+/-10	P6,P8,PO8, P5,P7,PO7 P2, P4, CP4, P1, P3, CP3	****	ns	*	ns	****
P400	Young High Low	404+/-10 390+/-10 390+/-10	PO8,P8,P10 PO7,P7,P9 P4, CP2, CP4 P3, CP1, CP3	****	ns	ns	****	ns
N400	Young High Low	427+/- 50 427+/- 50 427+/- 50	F1, F2, FZ, FC1, FC2, FCZ, C1, C2, CZ	*	ns	N/A	ns	N/A
Late Positive	Young High Low	725+/-275 725+/-275 725+/-275	CPZ, CP1, CP2 PZ	ns	****	N/A	ns	N/A

*Note: *p ≤0.05, **p≤0.01, ***p≤0.001, **** p≤0.0005, ns = not significant. High = high performing old. Low = low performing old. Group (Young, High, Low). Word (L, X). Hemi = hemisphere (Right, Left). See Chapter 5 for scalp location of electrode.*

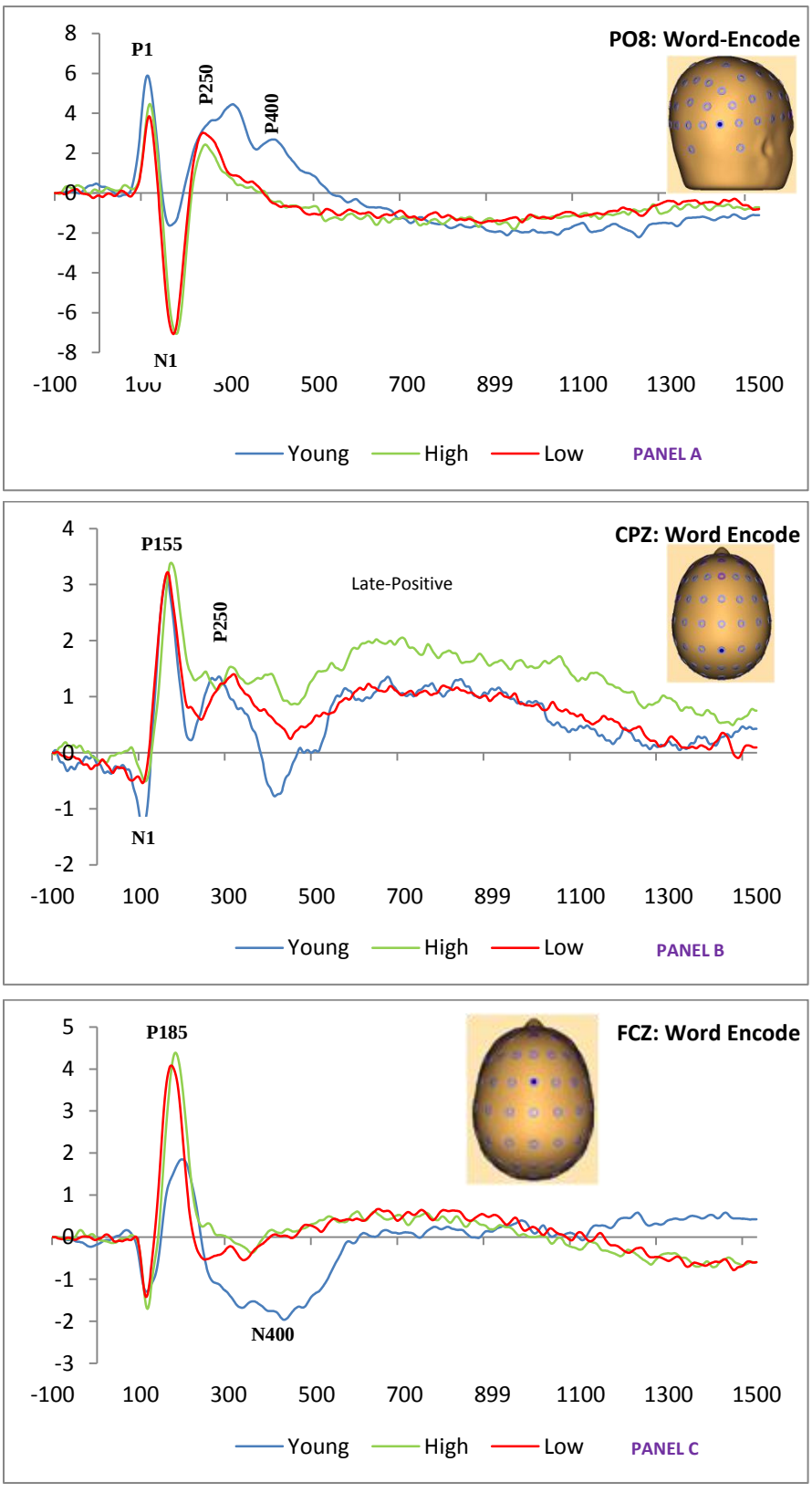


Figure 7:9 ERP data collapsed across Word conditions (L-Word, X-Word).

Note: Data from 3 electrodes are shown. Panel A shows data from and electrode over a parietal site (PO8), Panel B over a central-parietal site (CPZ) and Panel C over a fronto-central site (FCZ). In all cases the data have been collapsed across conditions in order to assess the componentry of the waveforms without reference to the dependent variables. The components of interest are labelled and electrodes are marked with a blue dot. High = high performing old. Low = low performing old.

P1: Word Encode Phase

For the P1 component (Figure 7:9) measured over a +/- 10ms epoch centred on the peak latency there was a strong main effect of Hemisphere [F (53,1)=11.71, p≤ 0.001], and a borderline Hemisphere by Group Interaction [F (53,2)=2.87, p≤0.06]. Contrasts revealed asymmetry in the expression of the P1 component only in the Young group where the component was significantly larger in the RH than the LH (F= 10.69, p≤0.005).

N1: Word – Encode Phase

For the N1 component (Figure 7:10) measured over a +/- 5ms epoch centred on the peak latency there was a strong main effect of Word [F (53,1)=11.84, p≤ 0.001] driven by larger amplitudes for the L-Word when compared to the X-Word in all groups, and a main effect of Hemisphere [F (53,1)=15.49, p≤0.0005] where the component was more strongly expressed in the LH than in the RH.

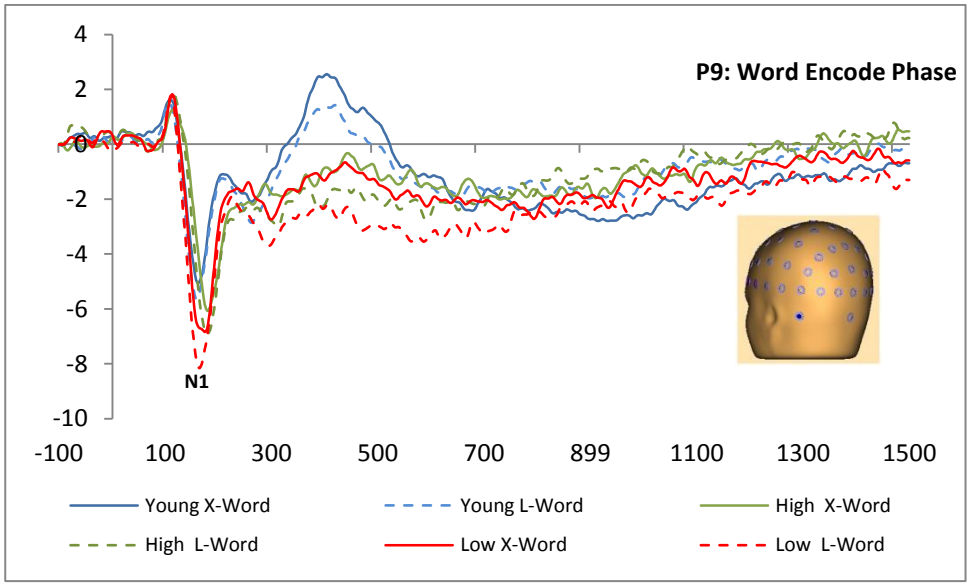


Figure 7:10 The N1 component over posterior sites.

Note: The graph shows the waveform for the two Word types (L, X) for the three Groups (Young, High performers, Low performers) from a parietal electrode site (P9). The topographic voltage maps that represent the peak latency of the component collapsed across conditions for each group illustrate the Left Hemisphere bias and the enhancement of the component in the two older groups relative to the Young although this group difference did not reach significance (p=0.06).

P155: Word - Encode Phase

For the P155 (Figure 7:11) component measured over a +/- 5ms epoch centred on the peak latency the L-Word was significantly larger than the X-Word [F (53,1]=6.58, p≤0 .01].

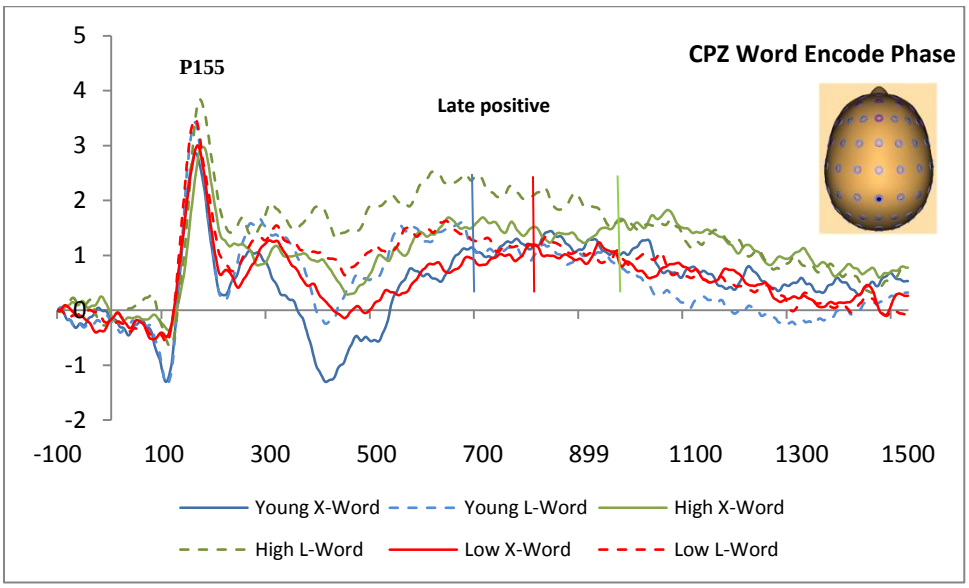


Figure 7:11 P155 & Late Positive Word effects illustrated at a central parietal region (CPZ).

Note: There is an enhancement of the P155 component in the L condition for all three Groups. The vertical lines mark the point at which the divergence between L Words and X Words ends for each of the Groups (Young= 682ms, High performers = 938ms and Low performers = 724ms).

P185: Word - Encode Phase

For the P185 (Figure 7:12) component measured over a +/- 5ms epoch centred on the peak latency the L-Word was significantly larger than the X-Word [F (53,1 =4.8, $p \leq 0.05$]. There was a main effect of Group [F (53,2=6.83, $p \leq 0.005$] and post-hoc tests revealed that the amplitude of the P185 component was significantly smaller in the Young than it was in the High ($p \leq 0.01$) and the Low performers ($p \leq 0.05$) who did not differ significantly from each other ($p > 0.10$).

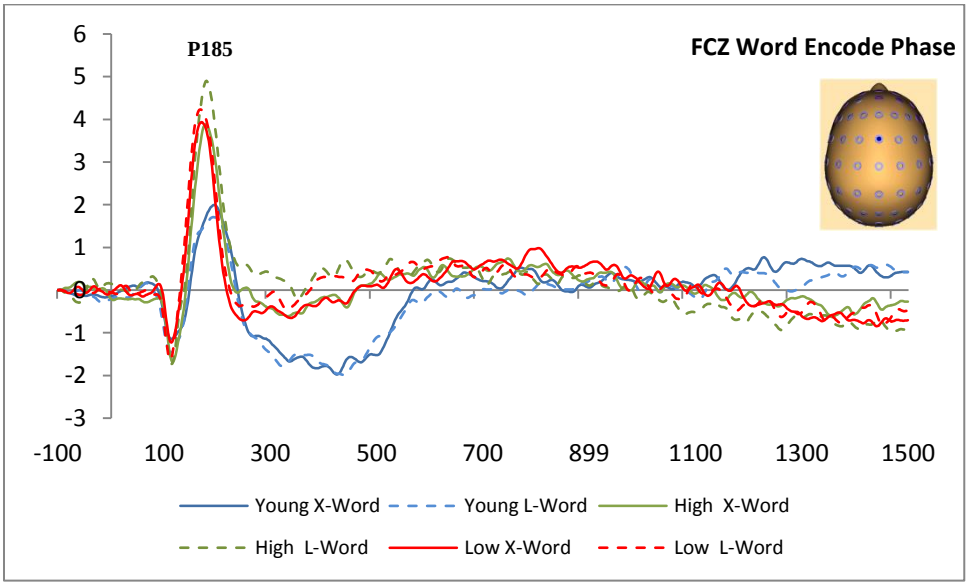


Figure 7:12 The P185 effect over fronto-central region.

Note: the component is significantly attenuated in the Young group when compared with the two older groups. High = high performing old. Low = low performing old.

P250 Word - Encode Phase

There were no main effects and no significant differences for the P250 component (Figure 7:9).

P300 Word - Encode Phase

The P300 component (Figure 7:13) was measured over a +/- 10ms epoch at different electrode locations for the Young and the Old groups (Figure 7:13). There was a strong main effect of Group [F (53,2 =10.29, $p \leq 0.0005$] driven by significant enhancement of the component in the Young when compared with the High ($p \leq 0.0005$) and the Low ($p \leq 0.005$) performing older adults. There was a Hemisphere by Group interaction [F (53, 1 = 9.55, $p \leq 0.0005$] and a main effect of Hemisphere [F (53,1)=5.38, $p \leq 0.05$]. Contrasts revealed asymmetry in the expression of the P300 component only in the Young group where the component was significantly larger in the RH than in the LH (F=13.80, $p \leq 0.005$) There was no significant difference in expression of the component between hemispheres in either of the older groups ($p > 0.10$).

P400 Word - Encode Phase

The P400 component was measured over a +/- 10ms epoch at different electrode locations for the Young and the Old groups (Figure 7:14). There was a main effect of Group [F (53,2)=15.55, $p \leq 0.0005$], driven by significant attenuation of the component in both of the older groups when compared with the Young ($p \leq 0.0005$). There was a Word by Group interaction [F (53,1)=9.82, $p \leq 0.0005$] and contrasts revealed that this was driven by significantly greater processing of the X-Word compared to the L-Word in the Young (F=7.19, $p \leq 0.05$) and significantly greater processing of the L-Word relative to the X-Word in both the High (F=6.74, $p \leq 0.05$ and the Low (F=6.31, $p \leq 0.05$) performers.

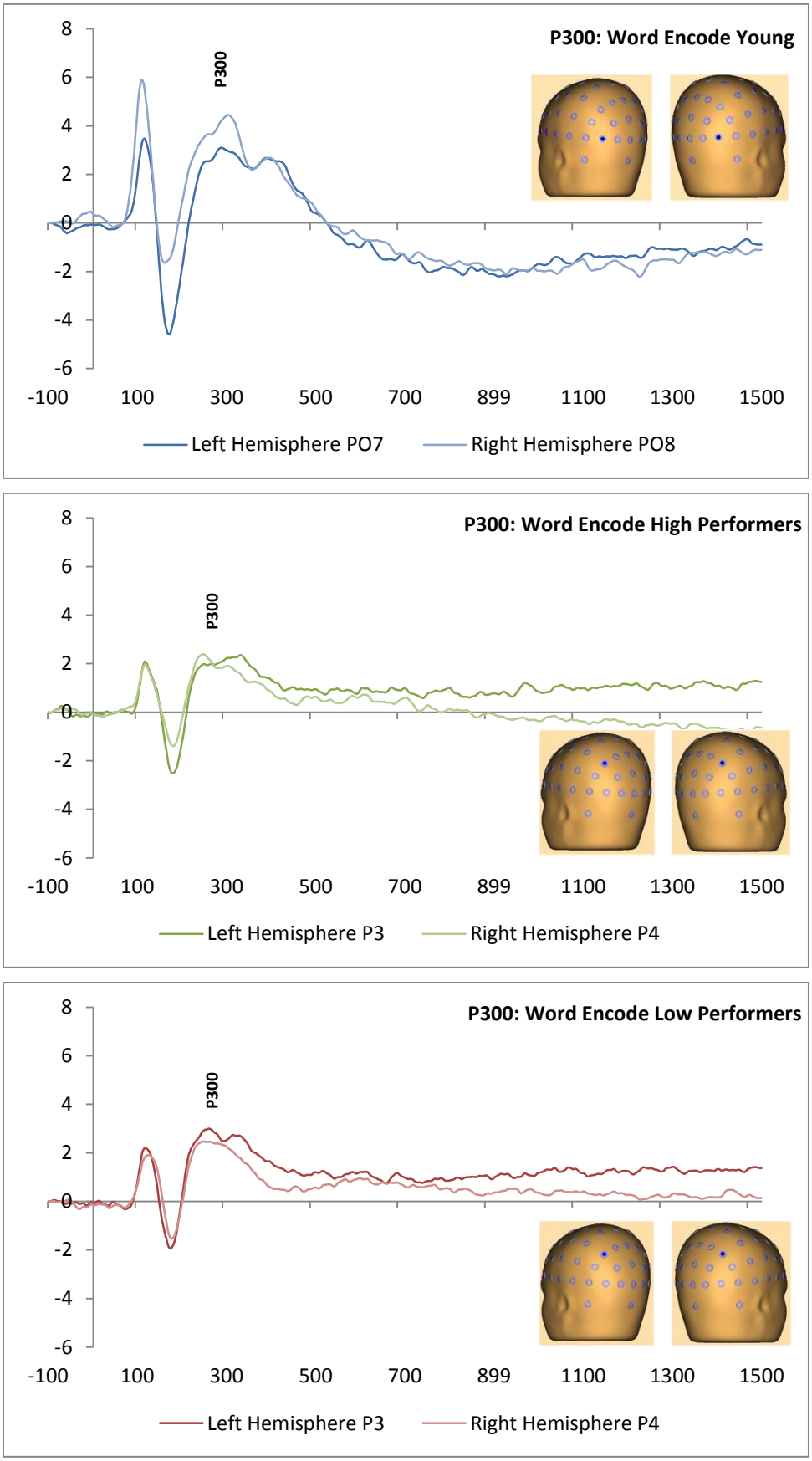


Figure 7:13 The P300 component

Note: The P300 is illustrated at two representative homologous sites in the Young (PO7/PO8) and two representative homologous sites in the Old (P3/P4). Note attenuation of the component in older adults and significant enhancement of the component in the Right Hemisphere in the Young. High = high performing old. Low = low performing old.

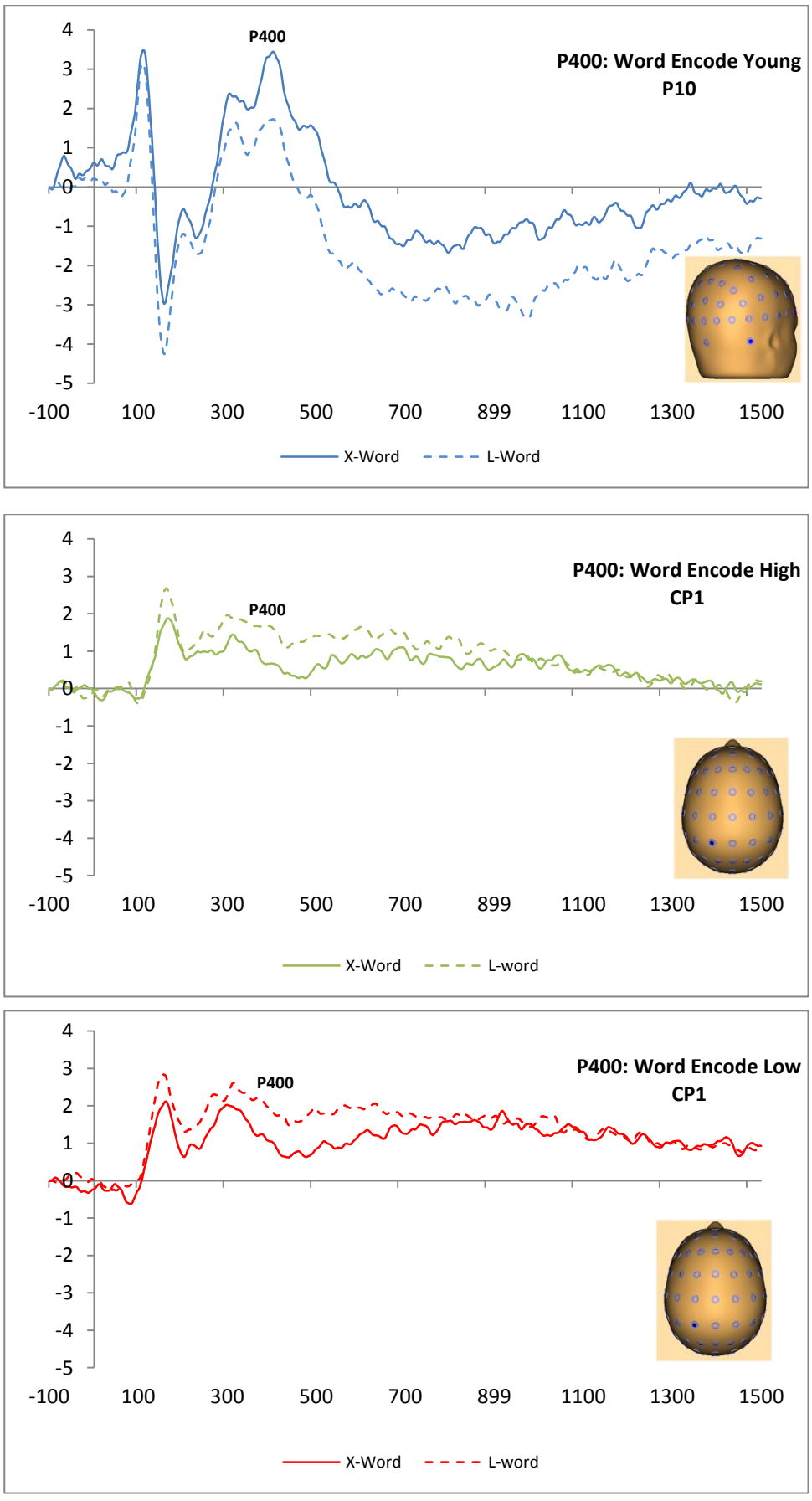


Figure 7:14 The P400 component illustrated in the Young (P10) & the Old (CP1).

Note attenuation of the component in the older adults relative to the Young. Also note significantly greater processing of the X-Word relative to the L-Word in the Young. In contrast, in both of the older groups note significantly greater processing of the L-Word relative to the X-Word. High = high performing old. Low = low performing old.

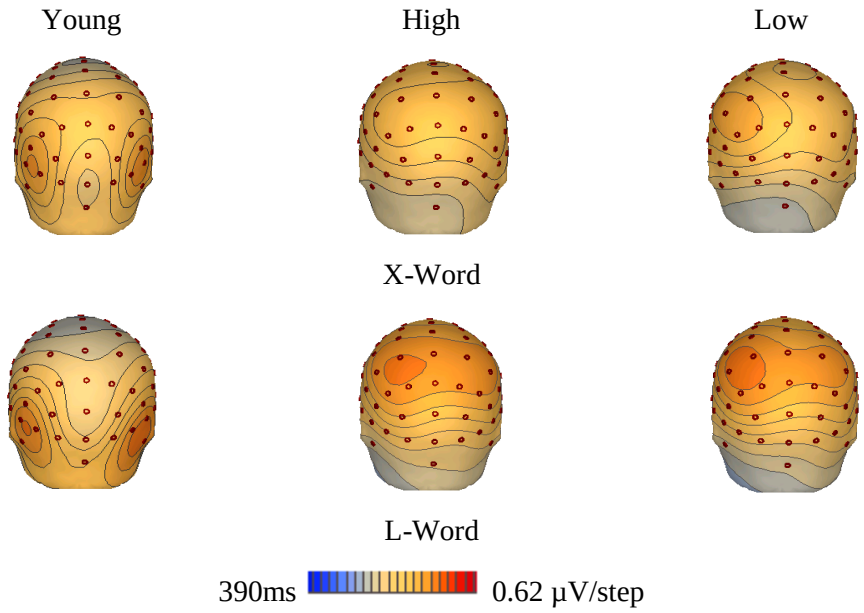


Figure 7:15 Word P400

Note: Figure shows topographic voltage mapping of spline interpolated potential distributions plotted at ~400ms. The component is shown separately for L-Words and X-Words for each of the three groups High = high performing old. Low = low performing old Note hemisphere asymmetry and greater processing of the L-Word in the two older groups.

N400: Word - Encode Phase

The N400 component (Figure 7:9) was measured over a 427 +/- 50ms epoch. There was a main effect of Group [F (53,2)=3.63, p ≤0 .05] that was driven by greater Word processing in the Young than in the Low performers (p≤0.05).

Late Positivity Word Encode Phase

An analysis of a +/-275ms epoch centred on 725ms revealed a main effect of Word [F (53,1)=223.59, p≤ 0.0005) that was driven by greater processing of the L-Word in all groups (Figure 7:11). Visual inspection of the waveform showed that the L, X differentiation extended for a longer period in the High performers relative to both the Young and the Low performers. This L, X differentiation was explored with subsidiary point-wise analyses. Figure 7:16 shows point-by-point t-tests at the electrode (CPZ) where differentiation was extended in the High performers.

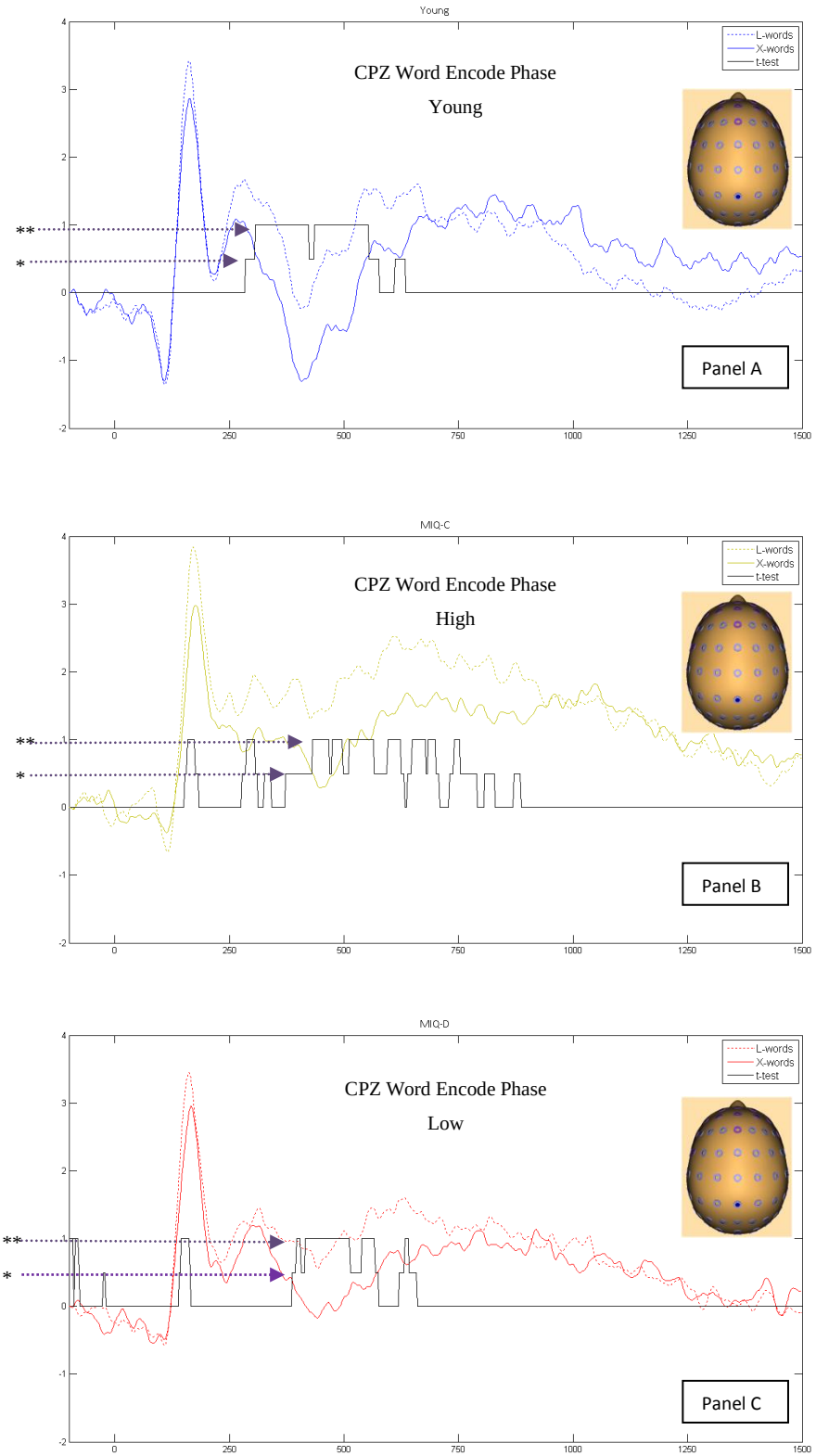


Figure 7:16 Point by point t-tests evaluating differences between L-Words and X-Words

*Note: Figure shows point by point t-tests for Young (a), High performers (b), and Low performers (c) at electrode CPZ the site, where on visual inspection of the waveform, the group differences in the time course of L, X differentiation was most apparent. The horizontal black line shows the significance level of point-by-point t-tests (0 = non-significant, 1=p≤0.01, 0.5=p≤0.05). *= p≤0.05, ** = p≤0.01*

7.3.4 Analysis Summary

Cue Analysis

The Young show early cue differentiation at P1 and P150 with significantly larger X-Cue amplitudes relative to L-Cue amplitudes. There was a strong RH bias in the expression of the P1 component that was absent in the older groups. Early age effects are also evident with the Young showing greater P150 and P285 cue amplitudes relative to both of the older groups. Cue differentiation in the Young is spatially restricted to centro-parietal and occipito-parietal regions and seems to be completed early, by 285ms. The Low performers display a similar, but smaller, cue discrimination pattern to the Young at P1 and P150. As already mentioned, the P285 is attenuated in the Low performers compared with the Young but the subsequent P375 does not differ from that observed in the Young. Finally, although some later frontal engagement to cue information is evident in the Low performers it does not discriminate cue types. In contrast, the High performers, who overall show a more distributed pattern of scalp effects than the Young and the Low performers, do not differentiate the cues at P1 but do discriminate, later and in a reduced fashion, at P150 and at N1. While the N1 component was largest in the LH for all groups an interesting Cue by Group interaction was driven by enhanced X-Cue processing in the RH only in the High performers. The High performers also engaged in significantly greater cue processing than the Young in fronto-central regions at ~185ms and at central regions at ~375ms. There is also enhanced frontal engagement (P460) in the High and Low performers relative to the Young. However, at this point only the High performers discriminate cues with greater processing of the X-Cue relative to the L-Cue.

Word Analysis

Word differentiation first occurs at P155 over central-parietal scalp regions when all three groups engage in greater processing of Learn Words relative to Read Words. This pattern of word discrimination continues in all three groups for the N1 component, which is left lateralised in all three groups. Word discrimination continues through to the P185 at fronto-central regions in all groups. The P185 is significantly enhanced in both of the older groups relative to the Young. In contrast, the P300 component is significantly enhanced in the Young relative to both of the older groups who display a more anterior and diffuse component. The Young also demonstrate a RH bias that is absent in the older groups. The P400 component is expressed at more anterior scalp sites in the older adults when compared with the Young. A Word by Group interaction is driven by greater processing of the X-Word relative to the L-Word in the Young and the reverse pattern in the older adults. Late sustained

differential Word processing also occurs over different time courses for each of the three groups.

7.4 DISCUSSION

This chapter reports detailed exploratory analysis of the ERP activity recorded during the encoding phase of the Learn task in order to examine the effects of age, cognitive performance, and encode type. The Learn task is described in detail in Chapter 2 and Figure 7:1 presents a schematic of the task sequence. The key findings are that during cue presentation the High performers demonstrate a pattern of neural activity, which that is qualitatively different from that observed in the Young and which could be described as compensatory. In contrast, the Low performers engage in a similar, but attenuated pattern, as the Young, which could be described as inefficient processing. During Word encoding, attenuation, anteriorisation, and bilaterality, is evident in the older adults relative to the Young. In addition, there is also evidence of some late sustained, possibly, compensatory processing in the High performers. Analysis of the Cue and Word epochs are discussed separately and in turn below.

Cue Analysis

In summary (for detailed summary see section 7.3.4) both Young and High performers differentiate the cue information albeit in different ways: the Young via early perceptual processing and the High performers via somewhat diminished perceptual processing that is supported by early frontal engagement and later P3 like activity over the central and frontal regions. By contrast the Low performers show generally reduced perceptual processing, only differentiating cues at P1 and P150, and not thereafter, without the same compensatory recruitment of frontal regions observed in the High performers.

There is evidence of age differences in the amplitude of ERP components thought to index early sensory processing (P1, N1). However, the findings are mixed and compounded by task differences and participant performance levels (De Sanctis et al., 2008), with most studies reporting enhancement (e.g. Falkenstein et al., 2006; Kolev et al., 2006) but other studies reporting attenuation of VEPs (Visual Evoked Potentials) (Czigler & Balazs, 2005). Early sensory components can be modulated by task requirements and possibly arousal (De Sanctis et al., 2008; Falkenstein et al., 2006), and by task parameters and attention (Dockree et al., 2005; Foxe, McCourt, & Javitt, 2003). In a passive, task free study, designed to assess whether age-effects on early VEPs represented genuine age-differences in sensory processing, de Sanctis and colleagues (2008) found enhanced N1 amplitudes in healthy elderly relative to young controls but no differences in the P1. They concluded that the N1 enhancement was indicative of age-related differences in sensory processing. However, they also reported age differences in asymmetry with the old adults displaying significantly more bilateral processing which they interpreted as early compensatory processing. In

this study no significant age differences in amplitude were evident for the early P1 or the N1 components but the slightly later P150 and P285 show attenuation in the older adults relative to the Young. However, Group by Cue and Hemisphere by Cue interactions, coupled with significant age effects in later and more frontal components, suggest a complex picture. While the absence of age effects in the amplitude of early VEPs could be taken to mean comparable early sensory processing across age groups, the older adult's failure to discriminate cues at P1 could be viewed as sensory-perceptual decline. However, it is probably misleading to interpret component effects in isolation, particularly given the patterns of neural activity and dissociations observed across the cue epoch. A better understanding might be obtained by examining the overall pattern of neural activity observed over of the course of the cue epoch.

The ability to process and integrate advance information in order to bias processing is crucial to the facilitation of goal-directed behaviour (Corbetta & Shulman, 2002). It has been shown that information provided by advance cues affects brain activity (Lorist, 2008). Specifically, cues elicit a more pronounced P2 component, which is considered a reliable index of top-down control over selection of relevant information (Kenemans, Kok, & Smulders, 1993; Luck & Hillyard, 1994; Wijers, Mulder, Okita, Mulder, & Scheffers, 1989). In the context of this study the L-Cues (Learn) and X-Cues (Read) carry relevant task information to facilitate preparation for the upcoming word. The Young appear to be using this information to deploy increased perceptual processing to this cue information at the parietal P2 component labelled P285 in this study. Throughout the epoch cue differentiation always takes the form of greater processing of X-Cues relative to L-Cues, which could possibly be interpreted as inhibitory processing in service of the goal to learn only words that follow the L-Cue. It seems that discriminatory cue processing is already complete less than 300ms post stimulus in the Young. In contrast, the High performers show a more distributed pattern of neural activity, demonstrate later cue differentiation, and amplified frontal engagement, which fits well with a compensatory view that their relatively successful performance is mediated through large-scale recruitment of relevant neural circuitries that compensate for earlier failures to discriminate during sensory processing at P1 and reduced engagement of filtering mechanisms associated with the identification of relevant information at P285 relative to the Young. Paradoxically, the Low performers more closely resemble the Young and their pattern of neural activity might best be described as inefficient given their lack of compensatory engagement in response to early sensory and filtering failures. Although there does seem to be evidence of some late compensatory frontal recruitment in the Low performers it fails to discriminate between cues. When de

Sanctis and colleagues (2009) examined executive function in high and low performing elderly they found a similar pattern, of what they described as compensatory and inefficient neural activity, in the high and low performers respectively. The interpretation of the cue processing given here assumes that the very early cue discrimination observed in the Young reflects low level perceptual sensitivity to parameter variations in the 'L' and the 'X' stimuli and that later cue effects are related to higher-order cognitive processes. The P1 component is sensitive to variations in stimulus parameters and to state of arousal (Vogel & Luck, 2000). ERP data also suggest that a P150 priming effect reflects low level feature processing (Petit, Midgley, Holcomb, & Grainger, 2006). Very few ERP studies have explored single letter processing, so it is impossible to tell whether the significant difference between the X-Cues and L-Cues observed is of a magnitude and direction consistent with feature level processing of orthographic differences between the letters 'L' and 'X'.[8]

Word Analysis

In summary, (for detailed summary see section 7.3.4) there were little or no differences in the way that the groups processed the early sensory components and filtering mechanisms (P1, N1, P155, P250). Word differentiation is evident in all three groups in components that can be considered mesogenous (P155, N1, P185), with enhanced processing of L-Words relative to X-Words. The older adults demonstrate early enhanced frontal engagement relative to the Young (P185). Patterns of processing begin to diverge once the more endogenous, cognitive components come into play. Of particular note is the anteriorisation of the P300 and P400 components in the older adults relative to the Young. For the P300 there is also an interesting Hemisphere by Group interaction that is driven by a RH bias in the Young that is absent in the older adults. Early Word differentiation took the form of greater processing of the L-word relative to the X-Word. For the P400 there is an unusual Word by Group interaction where the Young switch to enhanced processing of the X-Word relative to the L-Word while the older adults persist with the already established differentiation pattern. The N400 language component is significantly attenuated in the Low performers relative to the Young. At central sites Word differentiation is also evident in a late sustained positivity that occurs in all three groups. This is worthy of note because of the different time course of Word differentiation observed across the three groups.

[8] Aside from letter shape the cue stimuli were identical with regard to orthographic features including case, font size, orientation, and luminance. Of course, the letters differed in in terms of their names, semantic associations, the frequency with which they are regularly encountered, and their meaning within the context of the task (L=Learn; X=Read).

P300 amplitude is related to the processing resources demanded by a particular task (Donchin, Kramer, & Wickens, 1986) and is sensitive to the probability of a stimulus subjectively judged as relevant (Squires, Wickens, Squires, & Donchin, 1976). P300 latency is thought to reflect stimulus evaluation or categorisation time (Donchin, 1979). With regard to functional significance it has been proposed that the P300 reflects controlled processing (Rósler, 1983) or the updating of context in working memory when stimulus input engages attention and working memory (Donchin, 1981). The amplitude of a P300 elicited by an item is related to its subsequent memorability and response accuracy is higher for shorter latencies (Coles, Gratton, Bashore, Eriksen, & Donchin, 1985). Task relevant items are expected to produce large P300s, however, the magnitude of this memory effect is contingent on the mnemonic or rehearsal strategies employed by participants (Karis, Fabiani, & Donchin, 1984). Although the P300 has been linked to memory it has been argued that it is more sensitive to the amount of attentional resources engaged during a task (Gonsalvez & Polich, 2002; Wickens, Kramer, Vanasse, & Donchin, 1983). Based on the foregoing, the anteriorisation, attenuation, longer latency, and reduced lateralisation observed in the P300 of the older adults relative to the Young could reflect age-related slowing of categorisation time (longer latency), and reduced engagement of attentional and or memory processes in the service of task goals (amplitude attenuation). The hemispheric asymmetry reduction and anteriorisation may reflect dedifferentiation and/or have a compensatory function in light of earlier slowing and reduced engagement (Cabeza, 2002). However, it must be acknowledged that strategic differences across participants, and even possibly within-subjects across trials, within the task, exert confounding influences that cannot be measured within this study.

The N400 is one of the most studied language components, some N400 activity is elicited by any content word but this component is usually researched in terms of its sensitivity to deviant aspects of an eliciting stimulus such as meaning, for example congruity versus incongruity in sentence endings (Coles & Rugg, 2002). The component usually peaks around 400ms over temporal parietal regions, but a more frontal component for concrete words than abstract words has been reported (Sawaab, Baynes, & Knight, 2002; Zhang, Guo, Ding, & Wang, 2006). The N400 has alternately been proposed as reflecting either, the retrieval of the lexical or semantic information associated with a word (Kutas & Hillyard, 1984), or the integration of word semantics into the broader semantic context (Brown, Champagne, Fortune, & Sherr, 1993). Both views can be accommodated by an approach recently suggested by Dien and colleagues (2010) who argue for the existence of multiple N400 components, some of which correspond to lexical access and others to semantic

integration. For example, they suggest that two components contribute to the prototypical N400 component: a N400 (pz): which reflects some version of the lexical access view, and a P400 (cz), which reflects some aspect of semantic integration. They argue that the P400 is specific to the expectation for a specific event to occur at a specific time and so is sensitive to sequential probabilities when viewed as a context into which the stimulus can be integrated (e.g. integrating words into the context of a sentence). It is important to remember that because research tends to examine difference waves with very specific stimuli it is difficult to know the extent of the relationship between two effects (Kutas, 1997). On Dien and colleague's view attenuated processing of the N400 component in the Low performers relative to the Young could possibly reflect lexical access difficulties that are not present in the High performers who engage in similar processing to the Young. With regard to the P400 attenuation and anteriorisation of the component observed in both of the older adults could reflect reduced engagement of semantic integration processes. Speculation is difficult in the absence of information regarding the mnemonic strategy adopted by participants in this study. What is very clear and interesting is that all three groups are engaging in qualitatively different processing of the Words at this point (see Figure 7:14, Figure 7:15). The older adults persist with enhanced processing of L-Words relative to X-Words, possibly in service of the goal of committing the L-Words to memory. In contrast, the Young devote considerable additional neural resources to processing the X-Words, perhaps in the service of inhibiting learning of the X-Word, which they were instructed only to read. It could be that the pattern of differential Word processing observed in the Young underlies their enhanced recognition performance accuracy in some way. It is difficult to tell whether the N400 and P400 effects observed in this study relate to effects reported in other studies that use different tasks and test different conditions. The components observed at ~400ms in this study may not even index the same processes as those engaged in other studies but whatever the case the pattern of interactions reported suggest that Young and old adults are engaging neural processes in qualitatively different ways.

The amplitude of positive slow waves in the 300ms to 1000ms time frame have been associated with phasic memory operations (Mecklinger & Pfeifer, 1996). In addition, to the P300, other late positive components in this time range have been shown to be predictive of the memorability of a stimulus. Late positivity's have also been associated with the recruitment of attention networks for the activation and maintenance of task goals and have been found to predict performance on a sustained attention task (Dockree et al., 2005; Dockree et al., 2004; O'Connell et al., 2009). In memory research encoding is frequently measured through subtraction of the ERPs elicited by study items that are subsequently forgotten from those that are

subsequently remembered. This method yields the subsequent memory effect (SME), which usually has a positive polarity that onsets ~400ms and lasts about 600ms (Friedman et al., 2007). This positivity can have a number of forms including a sustained frontally maximum wave, an even distribution over the midline, or a posterior maximum (Rugg, 1995). However, it is important to note that the analysis conducted here looks at the effect of Encode Type (Learn, Read) given during encoding, across age and cognitive performance groups, irrespective of subsequent response accuracy. Nonetheless, within this timeframe, over central sites, Word differentiation is evident, with all three groups engaging in significantly greater processing of the L-Words relative to the X-Words. The time course of this discriminatory processing is different for each of the three groups. Differential Word processing is completed by ~680ms in the Young and 725ms in the Low performers. However, the High performers sustain discrimination until ~940ms. It is possible that the temporal extension of the differential processing in High performers reflects increased and/or compensatory neural recruitment of memory and/or attentional resources in the service of task goals to compensate for earlier processing attenuations. Although there is some evidence of extended differential processing, the Low performers fail to sustain this activity and speculatively this failure underlies their relatively poorer performance, although it should be noted that all words were analysed irrespective of response accuracy.

This chapter investigated the ERP activity recorded during the encoding phase of the Learn task with specific focus on the effects of age, cognitive performance, and Encode Type. In the introduction to this chapter two possibilities pertaining to differences in neural activity were proposed: older adults could either a) display similar neural processing to the Young but with High performers demonstrating minimal functional decay relative to the Low performers, or b) better recognition memory in the High performers might be underpinned by successful recruitment and amplification of control processes in order to compensate for age-related sensory decline. The results reported here suggest that the pattern of neural activity is best described by possibility b), particularly during the cue epoch and the latter part of the encode epoch, but it should be noted that both Low and High performers demonstrated similar patterns of activity in the earlier part of the encode epoch. The distinct patterns of neural activity observed support the view that that age-related memory changes and underlying neural correlates may be more precisely characterised by examining effects in high and low performing elderly individuals who might have different underlying patterns of neural activity (Cabeza et al., 2002).

Chapter 8 **GENERAL DISCUSSION**

"Whereas aging is associated with the passage of time,

it should not be confused with it."

- Naftali Raz

8.1 SUMMARY

- Significant age-differences for measures of memory, executive function, and processing speed but High and Low performers only differ significantly on measures of memory.
- Significant age differences in accuracy, RT latency and variability on the CRTsr. Accuracy and RT latency on the CRTsr task distinguish High and Low performers but only cognitive variability (ISD) distinguishes High and Low performers.
- Significant age differences in alpha frequency and resting relative alpha power. Relative alpha power and alpha reactivity distinguish High and Low performers.
- Only the Young show significant old/new effects for the ERP correlates of recollection and familiarity in the recognition phase of the Learn task. Low performers demonstrate a different pattern of event-related neural activity than the High performers and the Young controls when type of encoding is considered.
- Qualitatively different pattern of neural activity is evident in High performers when compared with theYoung while encoding cues. Low performers have similar but attenuated pattern to the Young. Anteriorisation and bilaterality in older adults relative to Young when encoding words. Late sustained processing in High performers.

8.2 CONCLUSIONS

The aim of this thesis was to identify neurocognitive and electrophysiological indices of cognitive performance in ageing. Cognitive decline has emerged as one of the greatest health threats of senescence (Bishop et al., 2010). It represents the single biggest obstacle to the social and economic integration of older people and is associated with increased health care costs (Albert, Glied, Andrews, Stern, & Mayeux, 2002), increased neuropsychiatric symptoms, increased disability (Lyketsos et al., 2002), and increased risk for progression to dementia (Edland, Rocca, Petersen, Cha, & Kokmen, 2002). In addition, increased individual differences in cognitive profiles in the elderly can make it difficult to distinguish between age-related deficits and those that represent pre-clinical Alzheimer's disease (AD). Combining neuropsychological testing with neuroimaging has been proposed as one of the best means of exploring the overlap observed at the boundaries of normal and pathological decline (Dubois & Albert, 2004). The overall approach taken in this thesis was to capture cognitive variability through the identification of sub-groups with different cognitive profiles and then to ascertain whether neurocognitive and electrophysiological differences support these classifications. The association of IQ and education level with differential susceptibility to age-related and disease-induced memory change, highlights the need to benchmark an older adult's memory function to his or her global intellectual ability or cognitive reserve (CR). In order to classify participants in a meaningful way, that could possibly tap change for an individual relative to their younger self, older participants in this study were sub-divided on the basis of their performance on a memory task relative to an estimate of their pre-morbid IQ. Older participants with asymmetric cognitive profiles were classified as Low performers and older participants with symmetric profiles were classified as High performers. A group of young adults were employed as controls to facilitate the exploration of age effects. The pattern of cognitive differences that emerged from neuropsychological assessment of the three groups, suggests that classifying participants in this way facilitated a meaningful exploration of cognitive decline in ageing and investigation of indices of such decline.

The pattern of age-effects, together with the interesting dissociation between measures of episodic memory and measures of executive function and attention, reported in Chapter 2, suggests that while older adults show declines in memory and executive and attention domains relative to the Young controls, the difference between the High and Low performers is specific to the episodic memory domain. A distinction is frequently drawn in the literature between the cognitive decline associated with attention and executive function and that associated with declarative memory

(Buckner, 2004). Glisky and colleagues (1995) propose a two-factor model of cognitive decline based on this distinction, with parallel functional disruptions observed in frontal-striatal systems, and medial temporal and associated cortical networks. The pattern of differences reported here add to the literature accumulating in support of this kind of multiple factor model that suggest that multiple cascades arising from distinct processes result in distinct cognitive outcomes (Andrews-Hanna et al., 2007). The identification of sub-groups within this study revealed subtle differences that were masked when the older adults were treated as a homogenous group. This highlights the importance of acknowledging different cognitive profiles and the need to move away from young /old comparisons that focus only on average tendencies within groups.

It is important to underscore that all of the older adults performed within the normal range for their age. Low performers were only classified as such based on asymmetry between their memory performance and an estimate of their IQ. Behavioural theories of cognitive ageing generally agree that with age, the ability to perform mental tasks is constrained by diminished mental resources. However, it has been argued that even if age-related decline in mechanisms affecting cognition was uniform across systems and individuals the behavioural manifestations of this decline would differ across individuals as a consequence of differences in levels of cognitive resource (Baltes & Lindenberger, 1997). Evidence suggests that individuals with high levels of education also possess high levels of cognitive resource (Baltes & Lindenberger, 1997). The related but distinct concept of cognitive reserve (CR) proposes that individual differences in cognitive processes or neural networks underlying task performance allow some people to cope better with brain changes incurred as a consequences of ageing (Stern, 2009). Education and pre-morbid IQ have been proposed as useful proxy measures for CR. Assessing individuals relative to age-norms without regard to individual levels of CR may miss early subtle changes in cognitive function and result in an inaccurate assessment of ageing. Chapter 2 argued that by benchmarking participant's performance to their IQ this study tapped into subtle memory changes and may represent an approach that can more accurately assess age-related decline and so adds to the ageing literature in important ways. Of course other approaches (e.g. median split based on task performance) that consider performance heterogeneity within the elderly are valid and informative, but the approach used here has an advantage in that participants can be classified independent of the study sample and so may have utility as a screening tool for research, and potentially, in clinical settings. Establishing why the older participants differ from each other in this way is not possible due to the influence of multiple dynamic variables across the lifespan but it is possible that the High performers represent a

group of successful agers and the Low performers reflect usual ageing. Alternatively, it is possible that the High performers reflect usual ageing and the Low performers represent a group on the threshold of pathological decline even though their performance is within the statistically normal range. Another possibility is that classifying participants in this way tapped into long-standing and possibly innocuous group differences.

Chapter 3 examined whether intra-individual variability in reaction time (RT), a putative index of neural integrity and possible marker of emerging cognitive impairment, could distinguish participant groups on the basis of age and cognitive performance. While RT latency and intra-individual variability measures, both had the ability to distinguish groups on the basis of age, only the cognitive RT intra-individual variability measures discriminated on the basis of cognitive performance as well although this fell just short of significance when processing speed was controlled for. Further research is warranted because specificity of the cognitive performance finding to the decision element of the response means that it is possible that it reflects differences in the integrity of neural processes or availability of neural or cognitive resources rather than a decline in general sensory functioning or motor slowing. If, as has been suggested, intra-individual variability represents a marker of prefrontal pathology (Stuss et al., 2003) then it is possible that the Low performers may represent a group on the cusp of pathological decline, although further research is needed. Intra-individual variability has been viewed as a disorder of control (Stuss & Binns, 2008) and an index of the efficiency with which executive control processes are instantiated in the brain (Bellgrove et al., 2004). Although it seems paradoxical, that this putative index of executive control can distinguish groups that differ from each other on episodic measures, but not on measures that index frontal function, the finding fits well with the view that failures in episodic memory observed in healthy elderly populations, are due to impairments in control processes mediated by the frontal cortex and associated connections (Buckner, 2004). Degraded white matter tracts and ensuing disconnectivity in associative pathways are thought to underpin intra-individual variability. Frontal-striatal systems show particular vulnerability to age-related white matter degradation and disconnectivity and this change is thought to result, not only in reduced executive function, but also non-pathological memory deficits. On this view the Low performers' relatively poorer memory performance may be a consequence of inefficient executive control processes, which in turn may be a consequence of degraded white matter tracts, and reduced connectivity relative to the High performers.

The main purpose of the next three chapters was to establish whether electrophysiological measures support the sub-group classifications and to seek

possible markers of cognitive performance. Chapter 5 not only reported that relative alpha power had the ability to distinguish groups on the basis of age and cognitive performance but higher power was also significantly correlated with better recall and more consistent performance. While a recent study showed that EEG power markers discriminate among different sub-groups of MCI (Mild Cognitive Impairment) patients (O'Connell et al., 2009) this, as far as the author is aware, is the first to show that resting relative alpha power can discriminate sub-groups of healthy adults who have been categorised on the basis of their memory performance relative to their IQ.

Chapters 6 and 7 examined event-related potential activity during the encoding and recognition phases of an episodic memory task. Although age-related decline in episodic memory performance is well documented, it remains unclear whether these deficits are a consequence of encoding or retrieval failures, or a combination of both (Friedman et al., 2007; Park & Gutchess, 2005; Perfect et al., 1995; Rugg & Morcom, 2005). The pattern of significant differences and interactions reported in Chapters 5 and 6 suggest a complex pattern wherein neural processing of recollection and familiarity old/new effects during recognition is influenced by age but neural processing during recognition and encoding, when examined irrespective of response accuracy on the basis of Encode Type (Learn/Read: L/X), is influenced by both age and cognitive performance. The age effects reported for recognition suggest that the ERP modulations of familiarity and recollection are not maintained in senescence. Alternatively, it is possible that due to cerebral reorganisation that the FN400 no longer indexes familiarity in later life. The absence of the recollection effect could be due to a failure to engage encoding strategies and so could be task specific. At specific points during encoding and recognition the neural activity observed in the High performers was qualitatively different to the Low performers such that it was suggested that they engaged compensatory processing while the Low performers, with the exception of some post-retrieval monitoring at recognition, engaged in neural activity that could be described as similar but less efficient than that observed in the Young.

As with intra-individual variability discussed above, these findings also fit well with the view that failures in episodic memory observed in healthy elderly populations, are due to impairments in control processes mediated by the frontal cortex and associated connections (Buckner, 2004). The pattern of effects and interactions observed may reflect differences in the integrity of neural processes or availability of neural or cognitive resources. It is possible that age-related sensory decline and slowing necessitate recruitment of later frontal control processes, in a compensatory fashion, in order to boost performance in the service of goal-directed behaviour. So while both High and Low performers demonstrate diminished

perceptual processing only the High performers seem to compensate for this through the recruitment of frontal regions. There is evidence that Low performers attempt to engage frontal regions but recruitment falls short of that observed in the High performers. It is possible that this is a consequence of inefficient executive control processes, which in turn, may be a consequence of degraded white matter tracts, and reduced connectivity relative to the High performers. It is interesting to note that when the Low performers engage in what could be described as compensatory post-retrieval monitoring at recognition it occurs at parietal and occipito-parietal scalp sites. Processing resource views suggest that while self-initiated processes require conscious effort and reflect declines in frontal lobe efficiency, they also respond to environmental support, which may explain why even the Low performers benefitted from the cue to Learn. When taken together with neuropsychological, experimental and variability measures the electrophysiological analyses suggest that EEG and ERP measures may have the capacity to indentify subtle functional changes associated with normal ageing or those that precede the structural or metabolic deficits of disease. Overall the findings support the view that age-related memory changes and underlying neural correlates may be more precisely characterised by examining effects in high and low performing elderly individuals who might have different cognitive profiles and different underlying patterns of neural activity.

8.3 RESEARCH ISSUES

This section highlights a number of important issues worth keeping in mind when reading and interpreting cognitive ageing research. By necessity most theories of cognitive ageing have emerged from cross-sectional research which measures an inter-individual effect and so reflects age-difference in cognitive performance, in contrast, longitudinal research measures age-related change which is an intra-individual effect (Sliwinski, 1999). Any interpretation of the literature and the findings reported here should consider that stable differences between birth cohorts may confound cross-sectional age differences while longitudinal observations may contain selective attrition and practice effects (MacDonald et al., 2009). Examining average age-related differences and changes using cross-sectional or longitudinal designs assumes the stability of the examined behaviour over time or similar trajectories of change (Hultsch & MacDonald, 2004). Furthermore, within cognitive ageing research inter-individual variability is frequently taken as a valid proxy for intra-individual variability. However, such an approach presupposes variation equivalence and homogeneity of change without testing whether these assumptions are met (for discussion see Lindenberger & von Oertzen, 2006).

Although most cognitive research focuses on mean differences, the value and accuracy of cognitive performance assessment based on single occasion measurement is questionable when it is likely that any score at any given time comprises stable components, transient components, and measurement error (Bunce et al., 2004; Nesselroade, 1991). While this approach can provide useful information when intra-individual variability in performance is small, However, with increasing levels of intra-individual variability only calculating mean performance from a single measurement occasion may result in erroneous inference and oversimplification of behaviour patterns (MacDonald et al., 2009). Thus a repeated assessment approach may facilitate more accurate analysis of cognitive performance and avoid confounding stable and variable components particularly when measuring constructs with a relatively large range of intra-individual variability (Hultsch & MacDonald, 2004; Stuss et al., 1994). In addition, given the dynamic nature of age-related cognitive change, any theory of cognitive ageing must also consider the relationship between intra-individual variability and intra-individual change given the possible influence that hypothesised changing parameters in intra-individual variability distributions might have on the measurement of intra-individual change (Baltes et al., 1999; Hultsch & MacDonald, 2004).

Age-related differences in the neural correlates of task performance can be difficult to interpret in the present state of knowledge. It is possible that age-related

differences provide evidence that cognitive performance is supported by functionally and neurally distinct operations in young and old groups or alternatively that the neural correlates of functionally equivalent cognitive operations differ in both groups (Rugg & Morcom, 2005). These interpretations reflect two theoretically distinct perspectives with the former implying that age-related performance changes are associated with and may result from a shift to a less efficient cognitive strategy and the latter implies that age-related changes in cognitive performance are a consequence of age-related decline in the efficiency of a common cognitive operation (Rugg & Morcom, 2005).

The comparability of measures of brain activity across the lifespan is often an inherent assumption when age-related differences in neuroimaging measures are reported. While this is not as problematic for direct electrophysiological measures as it might be for hemodynamic measures it should still be acknowledged that, for example, it is as yet unclear whether age-related differences in morphology and scalp distribution of ERP waveforms have functional significance or simply reflect age-correlated changes in brain morphology (Rugg & Morcom, 2005). Where possible this study has tried to focus on age-by-condition interactions rather than main effects in order to minimise this influence.

8.4 FUTURE DIRECTIONS

The findings presented here offer real promise and endless possibilities for future research aimed at unpicking differential cognitive decline and the identification of markers of that decline. The first step following on from this study would, of course, be to replicate these findings and to address and shortcomings in task and study design. For example, it would be important to reassess the Learn task with a view to finding a way to examine the subsequent memory effects by Encode Type. This analysis was not possible in this study due to the low number of Read Words correctly identified. Further exploration of intra-individual variability is warranted, specifically in a way that facilitates the exploration of differences between cognitive and motor responding across tasks of increasing complexity. It would also be interesting to examine the impact of cognitive performance on event-related responding in other types of memory task as well as tasks that tap other domains such as executive function or attention. Examining other cognitive profiles and different cognitive asymmetries would also add to the ageing literature.

Appendix A

1. Demographics

Date: ____/____/____

Date of Birth: ____/____/____

Study Location: *TCIN* ☐ *NUIG* ☐

Sex: *Male* ☐ *Female* ☐

Dominant hand: *Right* ☐ *Left* ☐

No. of years in formal education _____

Occupation _____

Former Occupation _____

Native Language: _____

Living independently in the community

Yes ☐ *No* ☐

2. Personal Medical History

Do you have a history of any of the following:

epilepsy ☐ *head injury* ☐ *stroke* ☐
heart attack ☐ *hypertension* ☐ *diabetes* ☐
syncopal episode ☐ *psychiatric illness* ☐
depression requiring treatment ☐
anxiety requiring treatment ☐

Do you currently have any medical condition, disease or disorder? *Yes* ☐ *No* ☐

If yes specify general type: (e.g. heart condition)

If specifics are known tick appropriate box.

Neurological

MS ☐ TIA ☐ parkinson's ☐
peripheral neuropathy ☐ supranuclear palsy ☐

Cardiovascular

mycocardial infarction ☐ ischaemic disease ☐ atrial fibrillation ☐
orthostatic hypotension ☐ pacemaker ☐

Endocrine

thyroidism : hypo - ☐ hyper- ☐

Respiratory

Asthma ☐ COPD ☐

Other

ADHD ☐ Dyslexia ☐

_____

Do you have any allergies? *Yes* ☐ *No* ☐

*Specify*_____

3. Family Medical History

Is there a family history of any of the following?

epilepsy ☐ *dementia* ☐ *psychiatric illness* ☐

4. Current Medication

Are you currently taking any medication?

heart ☐ *sleeping* ☐ *BP* ☐
diabetes ☐ depression ☐ anxiety ☐
asprin ☐ psychotropic ☐ oral steroids ☐

Specify drug/s:

Dose:

Frequency:

5. Other

Alcohol Use

never ☐ *previous drinker* ☐ *year ceased* _____

daily ☐ 2-4 times per week ☐ 1-3 times per month ☐

no of units per week _____

binge 5+
never ☐
daily ☐
2-4 times per week ☐
1-3 per month ☐

Recreational Drugs

Recreational drug use yes ☐ no ☐

Smoking

smoker ☐ *no. a day*_____*years* _____

ex-smoker ☐ yr ceased _____ non-smoker ☐

Vision

normal ☐ *normal with glasses* ☐ *impaired* ☐

details _____

Are you sensitive to flickering stimuli or visually demanding screens? Yes ☐ No ☐

Hearing

normal ☐ *normal with aid* ☐ *impaired* ☐

details_____

How did you hear about research?

_____

Appendix B

Letter of Consent:
For the attention of Research Participants

An investigation of Cognitive Function in Older Adults

Research Team: Sabina Brennan (PhD student), Dr. Paul Dockree and Prof. Ian Robertson

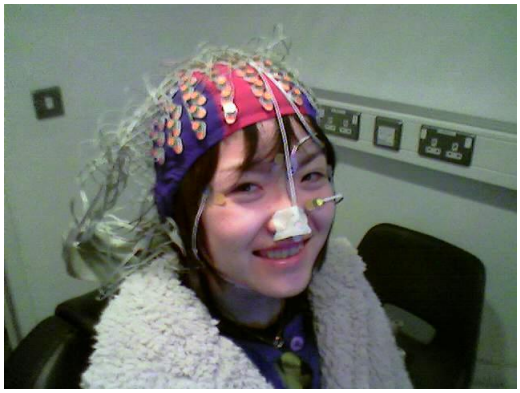
What is the project?

We would like to invite you to participate in a study which is looking at how the ageing process changes the way the brain attends to information in the world. The study involves two sessions, one week apart:

SESSION 1: You will be asked to complete a series of pen and paper tests and some simple computerized tests that measure your mood, attention, memory, language and reaction time. These are all standard tests of mental function that are used regularly with younger and older people. These tests will take approx 90 minutes to complete.

SESSION 2: In the second session you will be asked to perform simple computerized tests of attention and memory during which you will be asked to identify particular target items on a computer screen or memorize certain words. While you are performing these tasks we will measure electrical changes in your brain using the electroencephalogram (EEG):

The recording of EEG involves a special cap (as below)



Conductive gel is used to form a link between small electrodes and your scalp. The experience is very comfortable, but it does mean that you will have water soluble gel in your hair at the end of the experiment. This gel washes out easily and you can wash it out quickly in a specially fitted sink in the Institute of Neuroscience. **(Shampoo, conditioner, towels, hairdryer are provided)**

There are no risks associated with any of the procedures in neurologically healthy individuals; however, if you meet any of the following criteria you should not participate in this experiment:

- Personal or family history of epilepsy
- Personal history of neurological or psychiatric illness or brain injury

Any costs associated with your travel to Trinity College Institute of Neuroscience for this research will be covered by the project.

What are my rights if I join the study?

Participation in the study is entirely voluntary and if you agree to participate you have the following rights:

1. The information from this study will be kept strictly confidential and will not be made available to any other people.

2. We will aim to publish our results in scientific journals but any information we have will be completely anonymous and presented as a group.

3. As participation is completely voluntary, you are free to withdraw from the study at any time. You are also free to withdraw your data at the conclusion of your participation should you so wish.

4. Under the Freedom of Information Act you can have access to any information we store about you, if requested.

I, the undersigned, give my informed consent to participate in the "*An investigation of Cognitive Function in Older Adults" study* conducted by the Trinity College Institute of Neuroscience, Trinity College Dublin.

Full Name: _____

Signed _____

Date _____

Paul Dockree & Sabina Brennan
Research Investigators
Department of Psychology & Institute of Neuroscience
Trinity College Dublin
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Appendix C

Memory Self-Rate Scale

DATE:_____ ID NO:

How would you rate your memory overall?

Excellent	Good	Neither Good Nor Bad	Not so Bad	Very Bad
5	4	3	2	1

Circle the Response that you feel is most appropriate.

Score:

Appendix D

Neuropsychological Testing- GSK-TCIN

Standard Operating Procedure

Preparation

1. Schedule appointment, send appointment letter and book testing room
2. Advise reception that a participant is expected, give name, participant name and your phone/ext number.
3. Replenish water jug
4. Place the participant record form and background questionnaire on the clip board
5. Place consent form, expense form, debrief sheet and petty cash in testing room
6. Make sure that all of the necessary test forms have been placed in the correct order for administration (see appendix for list). Note each form with the participants unique ID.
7. Please ensure that all of the required props are in the prop box. (see appendix for list).

At the Door

Greet the participant in reception – make them feel welcome, explain that testing will take up to two hours and invite them to use the bathroom. As you enter the lift say ***we are going to the third floor*** as you press the button. (This is to let the participant know what floor we are on as it is a question on the MMSE).

In the Room

Turn off mobile phones

1. Enquire whether participant remembered to bring the **consent** form. If they did check that it has been signed and file. If they didn't ask them to read the consent and if they are happy to proceed ask them to sign the form.
2. Check whether there has been a change in **meds** or health since telephone interview. If there has note the background questionnaire.
3. If participants completed telephone screening prior to July 2008. Record highest level of education attained.
4. Check whether participant has consumed **alcohol** with the past 24 hours
5. Tell the participant that they will be required to complete a number of pen and paper tasks and two computerised tasks. Do not describe the tasks as easy.
6. Tell the participant that you will use a Dictaphone to record their responses to some of the tasks. Reassure the participant that the recording you make will not be made available to anyone else and will simply be used to ensure accuracy when scoring the tests.
7. Prior to testing ensure that eyeglasses, if needed, are being worn. If the individual has poor hearing, allow time to adjust a hearing aid or speak more loudly toward his/her better ear. Regardless of the participant's hearing acuity, you should **speak very clearly** and more **slowly** than you might in ordinary conversation. In general keep

your vocabulary simple, using short sentences or questions that contain a single idea. Then pause and wait for a reply or response.

Testing

1. Mini Mental State Examination (MMSE)

- Because questions may be difficult for some individuals, do not describe the questions as "silly" or "easy". Similarly it is not a good idea to say "These are routine questions that I have to ask everybody". This might make the individual feel anxious or embarrassed if he/she is unable to answer some of the questions correctly.

- Furthermore, if the participant answers incorrectly, do not correct the response or convey any concern (e.g. by your facial expression). If the individual asks whether an answer was correct, say something like; ***That was pretty close.*** Try to be supportive and encouraging without being condescending but **do not provide** any clues or hints to the correct answer.

- For each item, record the individual's response in the space provided on the form. Place a 'tick' or 1 if the individual's response was correct, or a X or 0 if the response was incorrect. If the individual is anxious, it may be helpful to periodically say; ***You are doing fine.*** If the individual refuses to answer one or more of the questions, score the item(s) as a zero. However you should note on the form why the individual refused.

Begin by asking ***May I ask you some questions about your memory?***

1. Orientation to time:

1. ***What is the year?***
2. ***What is the season?***
3. ***What is the month of the year?***
4. ***What is the day of the week?***
5. ***What is the date?***

2. Orientation to place:

1. ***What is the name of this country?***
2. ***What is the name of this county?***
3. ***What is the name of this city?***
4. ***What is this place? (eg Trinity College, Lloyd building)***
5. ***What floor are we on?***

3. Registration:

Listen carefully. I am going to say three words. You say them back after I stop. Ready? Here they are… APPLE, PENNY, TABLE. Pause for 1 second after each of the three words. ***Now repeat those words back to me.***

4. Attention and Calculation:

Now I'd like you to subtract 7 from 100. Then keep subtracting 7 from each answer until I tell you to stop. What is 100 minus 7? After the respondent gives you an answer, say ***Keep going*** (as needed) until he/she has given you a total of five answers.

If the participant is clearly unable to perform the Serial 7s or refuses to do so, then he/she can be asked to spell the word WORLD first forward (correct any misspelling) and then backward. ***Spell WORLD for me.*** Correct any misspelling. ***Now spell WORLD backwards.*** .

5. Recall:

Ask the participant ***what were those three words I asked you to remember?*** Do not prompt the participant or provide any clues or hints.

6. Naming:

Show the participant a pencil from the prop box and ask; ***what is this?*** Then repeat the same question while pointing to a watch. If a pen, pencil and/or watch are not available, other common objects can be substituted (e.g. eyeglasses, chair, keys).

7. Repetition:

Now I am going to ask you to repeat what I say. Ready? NO IFS, ANDS OR BUTS. Now you say that. Be sure to articulate clearly so that all the "s" endings are audible.

8. Comprehension:

Listen carefully because I am going to ask you to do something. Take this paper in your right hand, fold it in half and put it on the floor. If the individual is disabled or physically positioned in such a way that he/she cannot place the paper on the floor, instruct him/her to place the paper on a table. You can the blank sheet of paper from the prop box.

9. Reading:

Please read this and do what it says. Then show the individual the page with the words CLOSE YOUR EYES that you keep stored in your prop box.

10: Writing:

Give the participant the lined sheet and a pen or pencil. ***Please write a sentence***. If he/she does not respond, say ***Write about the weather.***

11. Drawing:

Place the sheet with the design in front of the participant, along with a pencil. Show them the design and say. ***Please copy this design.***

****

2. Memory Self-Rating Scale

Hand the participant the Memory Self-Rating Scale and a pen and say; ***please read this and circle the response that you feel is most appropriate.***

****

3. Hospital Anxiety and Depression Scale (HADS)

Hand the participant the HAD Scale and a pen and say; ***Please read this and place a firm tick in the box opposite the reply which comes closest to how you have been feeling in the past week. 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. Tick only one box in each section.***

****

4. National Adult Reading Test (NART)

(The NART is usually presented as a list of words on a single page – however Dr Robert Coen of St James's hospital advises that when working with elderly populations that each word be presented in large print on a separate page. For continuity words will be presented in the same way for young and older participants)

Place the flip book containing the NART word pages in front of the participant and say;

I want you to read the word on each page slowly. After each word please wait until I say 'next' before turning the page to read the next word. I must warn you that there are many words that you probably won't recognise, in fact most people don't know them, so just have a guess at these. *I will use this Dictaphone to record your responses.* ***OK? Go ahead.*** When the participant reaches the end of the word book say ***thank-you*** and remove the book.

****

5. Animal Names/Animal Fluency

This next test will be timed. *I will use a stopwatch and this Dictaphone to record your responses.* ***I want you to name as many different kinds of animals as you can in 60 seconds. OK? You can start now.*** Do NOT interrupt the respondent. If the respondent is saying the names more quickly than you can write them down in full, use abbreviations or tally. It's a good idea to use the Dictaphone so that you can double check the score. ONLY if the respondent asks for clarification, explain that animals include birds, insects, fish etc. If the respondent gets stuck, say ***can you think if any more?*** When the 60 seconds have elapsed say; ***Stop. Thank - you.***

****

6. Wide Range Achievement Test (WRAT3)

Hand the WRAT 3 blue card to the participant. ***Look at each of these words carefully*** (point). ***Read the words across the page so I can hear you. When you finish the first line go to the next line and so on.*** Discontinue after the individual has missed 10 consecutive words. Allow 10 seconds for the individual to respond. If the individual is in the middle of a response allow him/her to continue. If there is no response after 10 seconds move on to the next by simply saying: ***Try the next one please.*** After the first error the individual should be asked to repeat the word which was missed. If the word is said correctly, score as correct. No other help should be given. Other than the first error per list, the individual should not be asked to repeat a word unless the examiner is unable to hear the word clearly. When this occurs, say: ***I could not hear you clearly. Please say the word again just as you did the first time.*** Discontinue the list after 10 consecutive errors. If the individual does not pronounce at least 5 words correctly, the examiner should have the individual read the 15 letters in the letter reading section **after** completion of the word reading section. There is a note on the test card that refers to the 5/10 rule. This refers to the administration of the Letter Reading section if there are less than 5 correct formal reading responses and the subtest is discontinued after 10 consecutive errors. Scoring should be strict but also take into consideration any problems which could be attributed to dialect or articulation difficulties.

****

7. STROOP Colour and Word Test Adult Version

The participant is given a booklet containing all three pages, but views only one page at a time. The booklet is placed directly in front of the subject on a flat surface. The

participant may be allowed to rotate the book up to 45 degrees to either the right or the left; the participant is not allowed to rotate the booklet to a greater degree nor to lift the booklet off the flat surface. The Colour-Word page must be done in the same fashion as the Colour page: if the Colour page was completed unrotated, then the colour-word page must be unrotated. None of the pages may be covered in any way.

Instructions for the word page.

After the participant has been given the test booklet, the following instructions are read:

This is a test of how fast you can read the words on this page. After I say begin, you are to read down the columns starting with the first one (point to the left-most column) until you complete it (run hand down the left-most column) ***and then continue without stopping down the remaining columns in order*** (run your hand down the second column, then the third, fourth and fifth columns)***. If you finish all the columns before I say "STOP", then return to the first column and begin again*** (point to the first column). ***Remember do not stop reading until I tell you to "STOP" and read out loud as quickly as you can. If you make a mistake, I will say "No" to you. Correct your error and continue without stopping. Are there any questions?"*** Instructions may be repeated or paraphrased as often as necessary so that the subject understands what is to be done. Then continue: ***Ready? … Then begin.*** As the subject says the first response (whether right or wrong), start timing. After 45 seconds say: ***STOP. Circle the item you are on. If you finished the entire page and began again put a 1 by your circle. Then turn to the next page.***

Instructions for the Colour page.

The instructions for the colour page are identical, except the first sentence reads:

This is a test of how fast you can name the colours on this page. If the participant generally understands the instructions for the Word page, the remaining instructions can be given briefly: ***You will complete this page just as you did the previous page, starting with the first column. Remember to name the colours out loud as quickly as you can.*** If the subject has had any trouble following the instructions, they should be repeated in their entirety. As with the first page, the subject should be allowed 45seconds.

Instructions for the Colour-Word page.

At the beginning of the colour word page, the following instructions should be used:

This word page is like the page you just finished. I want you to name the colour ink the words are printed in, ignoring the word that is printed for each item. For

example (point to the first item of the first column), ***this is the first item: what would you say?*** If the subject is correct, go on with the instructions. If incorrect, say: ***No. That is the word that is spelled there. I want you to name the colour of the ink the word is printed in. Now,*** (pointing to the same item) ***what would the response be to this item?*** If correct, proceed; if incorrect repeat above as many times as necessary until the subject understands or it becomes clear that it is impossible to go on. Continue with the statement:

Good. You will do this page just like the others, starting with the first column (pointing) ***and then going on to as many columns as you can. Remember if you make a mistake, just correct it and go on. Are there any questions?"*** (As with the other two pages, the instructions can be repeated or paraphrased as often as necessary.) ***Then begin.*** (Time for 45 seconds, then say:) ***Stop. Circle the item you are on."***

****

Now might be a good time to ask the participant if they would like a short break or whether they would like to use the bathroom.

The next two tasks are computer based. Because some participants may not be familiar with computer based activities do not describe the tasks as 'simple' or 'easy'. This might make the individual feel anxious or embarrassed if he/she has difficulty mastering the task or response box. Explain that everybody will be given a chance to practice before beginning the first task, say; ***we will use this computer for the next task.*** *Show the participant the computer.* ***You will use this device to complete the task. Please use the index finger of your dominant hand to make all responses.*** Hand the response box to the participant and ensure that they hold it correctly and face the computer directly.

8. Choice Reaction Time CRT

We will begin with a practice session so that you can get used to the task and the response device. Point to each button in turn and explain what each one is for. ***A fixation cross will appear on screen throughout which I would like you to focus on during the task.*** Start the practice version of the CRT task. ***Please read the instructions on screen and tell me in your own words what you have been instructed to do.*** If the participant has not understood correctly repeat the instructions until they do for e.g. say; ***hold this key down*** (point to the appropriate key) ***until the word appears on screen then press this key*** (point to the appropriate key) ***if 'YES' appears***

or press this key (point to the appropriate key) ***if 'NO' appears.*** Tell the participant; ***you must press the keys quite firmly, the 'YES' and 'NO' words will disappear as soon as you make your response – if they don't this means that you did not depress the key fully – if this happens simply press the key again more firmly. Remember you must return to this key*** (point to the appropriate key) ***once you have made your selection. Are you ready to begin a practice session?*** Watch the participant as they complete the practice session. If you and they are happy with their performance you can proceed to the task. If you or they are unhappy with their performance of the task allow the participant to practice again. Once you are both happy you can proceed to the task. Open the Neuropsychological version of the CRT. ***Do you have any questions? The task will take about 5 minutes. Are you ready to complete the task?*** When the task is finished thank the participant and ask them if they need a break before moving on to the next computer task.

****

9. Sustained Attention Response Task Fixed SART$_{fixed}$.

In this task, numbers between 1 and 9 will appear on screen one at a time. They will appear in a fixed order, so you will see a repeating pattern of 1, 2, 3, 4, 5, 6, 7, 8, 9, 1, 2, 3… and so on. The numbers will appear above a fixation cross, which I would like you to focus on during the task. All you have to do is to press this key (point to the appropriate key) ***every time you see a number <u>except</u> for number 3. When the number 3 appears, you should not press the key, just don't do anything and wait for the next number to appear.***

Now, each number appears for a short amount of time and is followed by a blank screen, which also only stays for a short amount of time before the next number appears. Because the numbers appear in a predictable order it is tempting to make a response before the number actually appears on screen but it is important that you wait until the next number appears before you press the key.
Is that ok? Have you any questions? There is no practice session for this task. Are you happy to begin?

****

LOGICAL MEMORY 1

**Note time and ensure that Logical Memory II is administered 25-35 minutes later.*

I will use a Dictaphone to record your responses.

Follow instructions in the WMSIII manual.

****

FACES 1

**Note time and ensure that Faces II is administered 25-35 minutes later.*

Follow instructions in the WMSIII manual.

****

VISUAL REPRODUCTION 1

**Note time and ensure that Visual Reproduction II is administered 25-35 minutes later.*

Follow instructions in the WMSIII manual.

****

DIGIT SPAN

Follow instructions in the WMSIII manual.

Make sure that between 25-35 minutes have elapsed since completing Logical Memory I. before beginning Logical Memory II. There may be time for a short break.

LOGICAL MEMORY 2

****

I will use a Dictaphone to record your responses.

Follow instructions in the WMSIII manual.

****

Make sure that between 25-35 minutes have elapsed since completing Faces I. before beginning Faces II. There may be time for a short break.

FACES 2

Follow instructions in the WMSIII manual.

****

Make sure that between 25-35 minutes have elapsed since completing visual Reproduction I. before beginning Visual Reproduction II. There may be time for a short break.

VISUAL REPRODUCTION 2

Follow instructions in the WMSIII manual.

****

At the end of the session thank the participant and verify that they are happy to return for Session 2. Answer any questions that they may have about the EEG sessions. Remind them of their appointment date and ask them to refrain from drinking coffee in the preceding hour and alcohol in the preceding 24 hours. Ask them also to refrain from using hair products and to keep jewellery to a minimum. Double check that they do not have a pacemaker. If they decide not to complete Session 2 debrief them, pay them for one session, reimburse any expenses and have them sign the expense form.

Standard Operating Appendix

TEST ORDER

1. MMSE
2. Memory
3. HADS
4. NART *
5. Fluency *
6. WRAT*
7. STROOP
8. CRT
9. SART
10. Logical memory I *
11. Faces I
12. Visual Repro I
13. Digit Span
14. Logical Memory II *
15. Faces II
16. Visual Repro II

Documentation & Stimuli

1. Blank consent in case participant forgot theirs
2. Expense form and envelope with petty cash in case participant decides to withdraw after Session 1.
3. Participant record form
4. Background questionnaire
5. MMSE – Record sheet, lined sheet, design sheet (pencil, watch, paper for folding, Close Your Eyes page)
6. Memory Self-Rating – Record sheet.
7. HADS – Record sheet
8. NART – Record Sheet (Dictaphone, word flip book)
9. Fluency – Record sheet (stopwatch)
10. WRAT3 – blue Word Card
11. STROOP – Stimulus booklet (stopwatch)
12. CRT – computer, response box, usb memory stick.
13. SART – computer, response box, presentation dongle, usb memory stick.
14. Logical Memory I – Record Booklet, Stimulus book I, Dictaphone
15. Faces I – Record Book, Stimulus Book I
16. Visual Reproduction I – Record Booklet, Visual Reproduction Response Booklet, Stimulus Book I, Pencil, Rubber.
17. Digit Span – Record Booklet, Stimulus Book I
18. Logical Memory II – Record Booklet – Stimulus Book II
19. Faces II – Record Booklet – Stimulus Book II
20. Visual Reproduction II – Record booklet, Visual Reproduction booklet, Stimulus Book II, Pencil, Rubber.

Prop Box

1. Two Clipboards and two pens
2. Pencil
3. Watch
4. Paper for folding
5. CLOSE YOUR EYES page
6. Dictaphone
7. Stopwatch
8. NART word Book
9. WRAT3 Word Card
10. STROOP copy for researcher
11. 2 pencils with rubbers
12. WMSIII – Flip book 1
13. WMSIII – Flip book 2

Appendix E

Standard Operating Procedures

EEG

At The Door

"*Thank you so much for coming.* (Please make general chit chat and make the participant feel welcome.) ***I know that I have asked you already but I need to double check that you don't have a pacemaker. You will be in the EEG chair for 1.5 to 2 hours so would you like me to show you where the bathroom is before we begin."***

1. Participant is met in the lobby of the Lloyd building and brought down to the EEG room.
2. IMPORTANT: Don't forget to check again (since you already mentioned it in the letter) that the **PARTICIPANT DOES NOT HAVE A PACEMAKER**. This is necessary for them to safely pass through the security door into the vicinity of the MRI machine.
3. Ask the participant if they would like to use the bathroom as they will be in the testing room for the best part of two hours.

In The Room

(Please make general chit chat about the room show them where they will be sitting and where you will be sitting etc.)

"Can I just double check with you whether there has been any change to your health or your prescribed medications since we last spoke. Have you consumed coffee with the last hour or alcohol within the last 24 hours.

1. Check whether there has been any change to meds or health since last visit
2. Check whether the participant has consumed coffee within the last hour
3. Check whether the participant has consumed alcohol within the last 24hours
4. Participants should be told that they can stop any time they like. Particularly for frail patients, sitting in the chair for so long may become too much after a while and it is important that they do not feel obliged or trapped.
5. Explain to the participant that they will be asked to complete some computer tasks while we measure their brain activity. Reassure them that the procedure is pain free, that there are no known risks and that we will not be doing anything to them.

"Before we begin I just want to reassure you that the procedure is pain free and there are no known risks. We will be measuring your brain activity but we will not be doing anything to you. Participation is entirely voluntary and so you are free to stop at any time. If you feel that you need a break please let me know"

(Continue to check how the participant is feeling throughout the tasks, particularly with older participants.)

Fitting Participants with Cap and Electrodes

Measure Head

"First of all I am going to measure your head to establish which cap will be most comfortable for you.

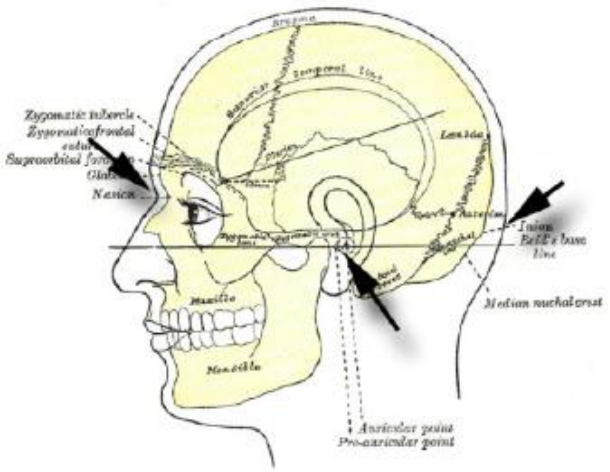

Figure -1 a) Nasion, b) inion, c) Left preauricular point (LPA) and right preauricular point RPA, Vertex (intersection of lines between nasion/inion and LPA/RPA known as CZ.

Using the soft measuring tape measure the circumference of the participant's head just above the eyebrows and over the inion at the back of the head. Use this circumference size as a guide in choosing cap size.

Measure the distance from nasion to inion and divide by two to determine the proper location of the Vertex electrode (CZ). Remember this measurement.

Fix the mastoid electrodes before putting on the cap (see wall chart for hang down numbering). *"I am going to place a small electrode behind each of your ears."*

Apply the mastoid electrodes behind each ear:

- Using the syringe, place a small amount of gel onto the electrode of the hang-down. This should not completely fill the space/hole.
- Peel off the top of the sticker
- Place the electrode behind the ear **on the line from the nose to the ear**. (Make sure to move as much hair out of the way as possible.)

If the participant has long hair advise them to let their hair down and distribute it evenly around the back and the sides of the head.

Applying the Cap

"I am now going to place the cap on your head. **(the cap can be shown to the participant first).** ***I need to make sure that the midline of the cap lines up with your nose and follows a straight line. I then need to check that the line from ear to ear meets at the same point. Final I need to pull the label out. Does the hat feel***

comfortable? Ok so now I am going to attach chin straps to the cap and fasten them under your chin. Are you comfortable?

Standing behind the participant, place the frontal electrode holders on the participant's head and stretch the cap back over the head. Pull the label out so that it is visible. Reach under the participant's chin and fix the chin strap. Ask the participant if the strap is comfortable - offer to place tissue under the chin strap for comfort.

After putting on the cap, measure to be sure that the vertex electrode (CZ) is where it should be.

Open the ear slit in the left side of the head cap and find the LPA. Place the zero point of the measuring tape at LPA. Stretch the tape over the head as close to the vertex electrode as possible while trying to avoid placing the tape over the electrode holders. Note that if one side of the tape goes over the electrode holders and the other side of the tape goes next to electrode holders, the measurement of the halfway point will be inaccurate. Open the right ear split in the cap and find the measurement at RPA. Divide this distance by two to determine the correct position of the vertex from left to right.

Ensure that the cap is not rotated. Standing behind (or in front of) participant, visualize a line following the centre hole in each of the midline electrode holders from vertex toward front of the head. If this line does not line up with the nose, then rotate the cap to line up the midline electrodes with the nose.
Repeat the above steps to make ensure vertex is at half-way point between nasion/inion and LPA/RPA and cap is not rotated.

Applying Gel

When the cap is fitted correctly the gel can be applied. The cap cannot be moved on the head after the gel has been applied as this may cause the gel in 2 or more electrodes to meet, causing bridging.

"Now I am going to apply gel to form a link between the small electrodes and your scalp. I am using a plastic syringe - there is no needle attached. You may feel the syringe move about a little as I move the hair out of the way **(adjust this statement for balding men).** ***This should be painless but let me know if it is uncomfortable for you in anyway."***

Place the tip of the syringe into one of the electrode holders, being careful to touch the scalp and lift the syringe away from the head as you press the plunger. If you hold the tip at the scalp and do not pick up while pressing the plunger, the gel will spread across the scalp rather than forming a conductive column from the scalp to the top of the electrode holder. As your first site choose a position where the hair seems to be fullest. IMPORTANT - do not abrade the scalp, as with other systems, as this will only increase the risk of breaking skin, which can result in infection.

Ask the participant whether they feel the gel at the scalp. If the participant does not feel the cold sensation of the gel at the scalp, then use the tip of the syringe to part their hair (touch the scalp with the tip and rock gently back and forth once or twice) and then inject a small amount of gel. Ask the participant again if they feel the gel. If so then proceed to the next step. If not then try another location where the hair is less full. Repeat this until the participant reports feeling the cold sensation of the gel on the

scalp. Use this self report technique any time you doubt that the gel is making contact with the scalp. Fill the remaining electrode holders with gel.

Try not to overfill a hole. It is better at this stage to have too little gel than too much as bridging is a danger.

Applying Electrodes

"Now I am going to attach the electrodes. This should be pain free but let me know if it is uncomfortable for you."

When each hole has been filled with gel, the electrodes may be applied.
There are two bunches of electrodes for the hat grouped by even and odd numbers. Even numbers go on the right side of the hat and odd numbers go on the left.
Insert the active electrodes into the head cap. Drape the ribbon cable containing the electrodes around your neck and over your shoulders. Observe that pin 1 and channel 1 are on the side of the ribbon cable with the red line. Take a group of four electrodes at one or the other end of the cable in one hand, being careful to control the others so that they do not hit the participant in the eye. After applying each electrode set, drape the ribbon cable over the participants shoulder.

Applying Hang Downs

Now prepare the skin for the hang-downs by wiping with an alcohol wipe.

"Do you have any allergy to alcohol? Do you mind if I wipe your skin with a medical alcohol wipe?"

Places to wipe:

- behind each ear
- At the outer corner of each eye (end of eyebrow)
- Above and below the left eye
- Tip of nose

Apply a small amount of gel to the electrode pellet. Remove the paper backing and place the electrode where you want it. Note that when you position the electrode, you will be looking at the label side. Remember that the electrode contact is at about the junction of the lead wire with the plastic housing rather than directly under the label. After applying each flat-type electrode drape the lead over the participant's shoulder.
"Finally I am going to attach some electrodes to your face. It is easy for these electrodes to slip off so I use a small piece of surgical tape to keep them in place. Is the tape uncomfortable or obscuring your vision in any way?"

Follow the note on the wall to place each hang down on participant's face – if necessary use small pieces of surgical tape to secure hang downs.

CAUTION WHEN HANDLING ELECTRODES!

Cap electrodes are very delicate and expensive. A major danger is pulling the wire out of the electrode so no undue strain should be put on individual electrode wires. Particular care should be taken of the first electrode on each string (with the red wire). These two electrodes are at risk of having the weight of the other electrodes dragging on them.

Attaching electrodes to the A/D box.

Plug the electrodes that are attached to the participant into the A/D box. The ribbon cables with the 68-pin D connectors are labelled A1-32, B1-32 . Plug these connectors into the A/D box first, taking care that the connector is oriented so that the label is legible to you if you are standing facing the front of the A/D box. ** Take care to plug connectors in the correct orientation to avoid costly damage to connectors on the cable or on the A/D box.

Individual leads with key-shaped connectors should be plugged in at the EXG1-8 on the top panel of the A/D box in such a way that the labels match.

Verify that the blue CM in Range LED comes on.

Check Electrode Offset/Check for poor connections

"It will now take me a few minutes to check the readings from the electrodes on my computer. You can relax while I do this."

Start ActiView, press the start button on the screen so that you see a trace for each electrode. Select the Electrode Offset tab at the top of the screen. This will indicate if each electrode is reading scalp electrical activity. If any electrode's red bar is higher than 25, this indicates that it has a poor connection and it may be without gel or obstructed by hair. The best practice in this case is to remove the electrode, put the syringe back in the hole, wiggle it around to move hair and apply a little more gel. Plug the electrode in again and this should fix the problem. It is a good idea to ask the participant to move while viewing the offsets to ensure a good stable connection.

"The signal from this electrode is not very clear so I am just going to take it out, reapply the gel and then reconnect it."

You are now ready to start the experiment.

RECORDING AND RUNNING TASKS

Brief Participant

"The quality of the data we record can be affected by things like speech, movement and eye blinks. Sometimes when we make mistakes it is natural to say something like 'oops' or 'oh no' – it would be great if you could resist the temptation to speak while we are recording a task. It would also be really helpful if you can be as still as possible throughout the tasks. Keeping both feet flat on the ground is also good. Obviously it is natural to blink but sometimes we can blink at the same time that we press the response button and this causes problems for us. So if possible it would be great if you could keep blinking to a minimum. Excessive eye movement can also contaminate our recordings. To minimise this kind of movement most of the tasks have a fixation cross on the screen. Try to keep your eyes fixed on this cross when you are completing the tasks. You don't have to 'stare' at the cross just focus on it rather than allowing your eyes to wander around the computer screen."

If possible show the participant the ActiView screen while asking them to blink or move so that they can see what happens to the recording when they do.

Eyes closed/Eyes open

"The first thing that we need to do is get a baseline reading. To do this we will record the activity in your brain for three minutes while you have your eyes closed and for three minutes while you have your eyes open. Before we begin each recording we have to set up a file on the computer just outside this room. When I am ready to begin recording I will tell you to close your eyes. You can simply relax with your eyes closed. I will tell you when three minutes has passed. When I am ready to make the next recording I will tell you to look at the fixation cross on the screen. Again I will tell you when three minutes has passed."

Turn on the monitor and allow the participant to read the on screen instructions.

When ready to begin recording:

1. Turn on Biosemi and select the 'Start File' button to make a file for the participant in which all parts of the experiment will be saved.
2. Name it Eyesclosed_participantID_your initials – save in Sabina's documents
3. Tell the participant that you are about to begin recording
4. Press stop watch and start recording
5. After 3 minutes – press pause, and tell the participant that they can open their eyes.
6. Press Stop
7. Select Start File – name file Eyesopen_participant ID_your initials
8. Remind the participant to stay still and look at fixation
9. Tell the participant that you are about to begin recording
10. Start stop watch and start recording
11. After 3 minutes stop recording and tell the participant to relax.

Practice

The participant should be somewhat familiar with using the response box for computer tasks having completed the CRT and SART during session one. If needs be refresh the participants memory about how to use the response box.

Learn Task

The next screen will go through the instructions for the task – Can you read the instructions on screen and tell me in your own words what you have to do. Ensure that the participant has correctly understood what is required. Before you begin the task I need to set up a file on the computer outside the room. When you reach the screen that says please do not proceed until instructed to do so I will leave the room to set up the file. When I am ready to begin recording I will knock on the door. This will be your signal to press the start button and begin the task. I will be just outside the door while you do the task. When you reach the end of the task please call to me through the door."

1. Open the E run file for Encode
2. Put in the participant's ID and session number
3. Explain to the participant that you are now going to run the task. Go through the general instructions. Explain that you will now be recording the task on the EEG.
4. Ask the participant to read the instructions for task one and tell you in their own words what they have to do.
5. Once the participant is ready to begin leave the room.
6. Select the 'Start File' button to make a file for the participant
7. Name it Encode_participantID_your initials – save in Sabina's documents
8. Tell the participant that you are about to begin recording
9. Start recording
10. When the participant calls through the door – stop recording and thank them.

CRT

"You will be familiar with this next task as you completed it the last day that you were here. Can you read the instructions on screen and tell me in your own words what you have to do. When you reach the screen that says please do not proceed until instructed to do so I will leave the room to set up the file. Do not press the start button yet. When I am ready to begin recording I will knock on the door. This will be your signal to press the start button and begin the task. When you reach the end of the task you can call to me through the door."

1. Open the E run file for CRT
2. Put in the participant's ID and session number.
3. Ask the participant to read the instructions for the task and tell you in their own words what they have to do.
4. Once the participant is ready to begin leave the room.
5. Select the 'Start File' button to make a file for the participant
6. Name it CRT_participantID_your initials – save in Sabina's documents
7. Tell the participant that you are about to begin recording
8. Start recording
9. When the participant calls through the door – stop recording and thank them.

SART

"You will be familiar with this next task as you completed it the last day that you were here. Can you read the instructions on screen and tell me in your own words what you have to do. When you reach the screen that says please do not proceed until instructed to do so I will leave the room to set up the file. Do not press the start button yet. When I am ready to begin recording I will knock on the door. This will be your signal to press the start button and begin the task. When you reach the end of the task you can call to me through the door."

1. Open the presentation file for SART
2. Make sure that the file path is correct for the current participant

3. Ask the participant to read the instructions for task one and tell you in their own words what they have to do.
4. Once the participant is ready to begin leave the room.
5. Select the 'Start File' button to make a file for the participant
6. Name it SART_participantID_your initials – save in Sabina's documents
7. Tell the participant that you are about to begin recording
8. Start recording
9. When the participant calls through the door – stop recording and thank them.

RECOGNITION

"Can you read the instructions on screen and tell me in your own words what you have to do. When you reach the screen that says please do not proceed until instructed to do so I will leave the room to set up the file. Do not press the start button yet. When I am ready to begin recording I will knock on the door. This will be your signal to press the start button and begin the task. When you reach the end of the task you can call to me through the door."

1. Open the E run file for RECOG
2. Put in the participant's ID and session number.
3. Ask the participant to read the instructions for the task and tell you in their own words what they have to do.
4. Once the participant is ready to begin leave the room.
5. Select the 'Start File' button to make a file for the participant
6. Name it RECOG_participantID_your initials – save in Sabina's documents
7. Tell the participant that you are about to begin recording
8. Start recording
9. When the participant calls through the door – stop recording and thank them

MAINTAINGING EEG EQUIPMENT AND ROOM

<u>Procedure For Electrode Cleaning</u>

1. Hold the electrodes under tepid (not hot) running water or swish them around in clear water to remove gel. We DO NOT use soap or any other substance on the electrodes. DO NOT soak electrodes.

Run your thumbs around the outside of the electrode (each individual electrode) under running water, making sure that this area which has been in the gel is now free of gel.

2. Towel dry /pat dry and hang to dry further.

Electrodes are damaged by the light in the EEG room so must be covered by a towel when left to hang.

Electrodes are also damaged by metal and MUST NOT come in contact with metal. Please pay special attention to this point as metal is all around.

NOTE: The plug ends of the electrodes must not come in contact with water. Pay special attention when you are cleaning the electrodes and hanging them around your neck that the wet end in not in contact with the dry end (plug end).
For this reason, electrodes are best worn like a scarf with the end to be washed hanging in front of you and the plug end hanging at your back.

3. So AFTER you gently clean the electrodes, hand-wash the cap. Use the force of the water (shower head not tap) to clean the gunk out of the holes on the cap, but do handle the cap gently and DON'T STRETCH IT. It is also important to clean all gel off the material of the cap as this degrades the fibres of the cap.

Cap MUST be checked after washing to ensure that all holes are free from gel. This is done by shaking out the cap vigorously and holding it up to the light to look through each hole. If a blockage or a bubble is apparent in any hole, blow on this hole. If the blockage is water, blowing will burst it but if it is gel it will not bust and the cap must be cleaned again, paying special attention to the blocked holes. Blockages will lead to poor recordings the next time the cap is used so dirty caps waste time for both experimenters and participants! When the cap is completely free of blockages and there is no gel left on the material. Pat the cap dry and hang well away from the electrodes.

Batteries

Batteries must not be left to charge overnight.

Towels

There are a number of towels for use in the EEG room. These should be monitored and washed (at home or at a laundry facility) when the number of clean towels is running low.

Computers

All electronic devices must be switched off before leaving the EEG room. This includes battery chargers, computers, monitors, and of course, lights.

Adrian, E. D., & Matthews, B. H. (1934). The interpretation of potential waves in the cortex. *J Physiol, 81*(4), 440-471.

Agnoli, A., Martucci, N., Manna, V., Conti, L., & Fioravanti, M. (1983). Effect of cholinergic and anticholinergic drugs on short-term memory in Alzheimer's dementia: a neuropsychological and computerized electroencephalographic study. *Clin Neuropharmacol, 6*(4), 311-323.

Albert, M. (1997). The aging brain: normal and abnormal memory. *Philos. Trans. R. Soc. Lond. B Biol. Sci, 352*, 1703-1709.

Albert, S. M., Glied, S., Andrews, H., Stern, Y., & Mayeux, R. (2002). Primary care expenditures before the onset of Alzheimer's disease. *Neurology, 59*(4), 573-578.

Alhainen, K., & Riekkinen, P. J., Sr. (1993). Discrimination of Alzheimer patients responding to cholinesterase inhibitor therapy. *Acta Neurol Scand Suppl, 149*, 16-21.

Allaire, J. C., & Marsiske, M. (2005). Intraindividual variability may not always indicate vulnerability in elders' cognitive performance. *Psychology and Aging, 20*, 390-401.

Allan, K., Robb, W. G., & Rugg, M. D. (2000). The effect of encoding manipulations on neural correlates of episodic retrieval. *Neuropsychologia, 38*(8), 1188-1205.

Allison, T., McCarthy, G., Nobre, A., Puce, A., & Belger, A. (1994). Human extrastriate visual cortex and the perception of faces, words, numbers, and colors. *Cereb Cortex, 4*(5), 544-554.

Alloway, C., Ogilvie, R., & Shapiro, C. (1997). The alpha attenuation test: assessing excessive daytime sleepiness in narcolepsy–cataplexy, . *American Sleep Disorders and Sleep Research Society, 20*.

Ally, B. A., & Budson, A. E. (2007). The worth of pictures: using high density event-related potentials to understand the memorial power of pictures and the dynamics of recognition memory. *Neuroimage, 35*(1), 378-395.

Ally, B. A., Waring, J. D., Beth, E. H., McKeever, J. D., Milberg, W. P., & Budson, A. E. (2008). Aging memory for pictures: using high-density event-related potentials to understand the effect of aging on the picture superiority effect. *Neuropsychologia, 46*(2), 679-689.

Almkvist, O., Jelic, V., Amberla, K., Hellstrom-Lindahl, E., Meurling, L., & Nordberg, A. (2001). Responder characteristics to a single oral dose of cholinesterase inhibitor: a double-blind placebo-controlled study with tacrine in Alzheimer patients. *Dement Geriatr Cogn Disord, 12*(1), 22-32.

Anand, A., Li, Y., Wang, Y., Wu, J., Gao, S., Bukhari, L., et al. (2005). Activity and connectivity of brain mood regulating circuit in depression: a functional magnetic resonance study. *Biol Psychiatry, 57*(10), 1079-1088.

Ancelin, M., & Ritchie, K. (2005). Lifelong endocrine fluctuations and related cognitive disorders *Current Pharmaceutical Design 11*(32).

Andersen, P., & Andersson, S. A. (1968). *Physiological basis of the alpha rhythm*. New York: Century-Crofts.

Andrews-Hanna, J., Snyder, A., Vincent, J., Lustig, C., Head, D., Raichle, M., et al. (2007). Disruption of Large Scale Brain Systems in Advanced Aging. *Neuron, 56*, 924-935.

Angelakis, E., Lubar, J. F., Stathopoulou, S., & Kounios, J. (2004). Peak alpha frequency: an electroencephalographic measure of cognitive preparedness. *Clin Neurophysiol, 115*(4), 887-897.

Anson, O., & Paran, E. (2005). Hypertension and cognitive functioning among elderly: an overview. *American Journal of Therapeutics, , 12* (4).

Anstey, K. J. (1999). Sensorimotor variables and forced expiratory volume as correlates of speed, accuracy and variability in reaction time performance in late adulthood. *Aging, Neuropsychology, and Cognition,, 6*, 84-95.

Anstey, K. J., Dear, K., Christensen, H., & Jorm, A. F. (2005). Biomarkers, health, lifestyle, and demographic variables as correlates of reaction time performance in early, middle, and late adulthood. *Q J Exp Psychol A, 58*(1), 5-21.

Anstey, K. J., Mack, H. A., Christensen, H., Li, S. C., Reglade-Meslin, C., Maller, J., et al. (2007). Corpus callosum size, reaction time speed and variability in mild cognitive disorders and in a normative sample. *Neuropsychologia, 45*(8), 1911-1920.

Atkinson, R. C., & Shiffrin, R. M. (1968). Human memory: a proposed Asystem and its control processes. In K. Spence (Ed.), *The psychology of learning and motivation.* (Vol. 2). New York: Academic Press.

Auld, D. S., Kornecook, T. J., Bastianetto, S., & Quirion, R. (2002). Alzheimer's disease and the basal forebrain cholinergic system: relations to beta-amyloid peptides, cognition, and treatment strategies. *Prog Neurobiol, 68*(3), 209-245.

Babiloni, C., Binetti, G., Cassetta, Cerboneschi, D., Dal Forno, G., Del Percio, C., et al. (2004). Mapping distributed sources of cortical rhythms in mild Alzheimers disease. A multi-centric EEG study,. *NeuroImage, 22*, 57-67.

Babiloni, C., Cassetta, E., Dal Forno, G., Del Percio, C., Ferreri, F., Ferri, R., et al. (2006). Donepezil effects on sources of cortical rhythms in mild Alzheimer's disease: Responders vs. Non-Responders. *Neuroimage, 31*(4), 1650-1665.

Babiloni, C., Frisoni, G., Steriade, M., Bresciani, L., Binetti, G., Del Percio, C., et al. (2006). Frontal white matter volume and delta EEG sources negatively correlate in awake subjects with mild cognitive impairment and Alzheimer's disease. *Clin Neurophysiol, 117*(5), 1113-1129.

Backman, L., Small, B. J., & Wahlin, A. (2001). Aging and Memory: Cognitive and biological proceses. In J. E. Birren & K. W. Schaie (Eds.), *Handbook of the psychology of aging*. New York: Academic Press.

Baddeley, A. D. (1986a). *Working Memory*. Oxford: Clarendon Press.

Baddeley, A. D., Logie, R., Bressi, S., Della Salla, S., & Spinnler, H. (1986). Dementia and working memory. *Quarterly Journal of Experimental Psychology: Human Experimental Psychology, 38(a)*, 603-618.

Balkan, S., Yaras, N., Mihci, E., Dora, B., Agar, A., & Yargicoglu, P. (2003). Effect of donepezil on EEG spectral analysis in Alzheimer's disease. *Acta Neurol Belg, 103*(3), 164-169.

Balota, D. A., Dolan, P. O., & Duchek, J. M. (2000). *Memory changes in healthy older adults*. New York: Oxford University Press.

Baltes, P. B., & Graf, P. (1996). Psychological aspects of aging: Facts and frontiers. In D. Magnusson, B. Winblad, T. Greitz, L. Terenius & T. Hokfelt (Eds.), *The lifespan development of individuals: behavioural*

neurobiological, and psychological perspectives. Cambridge: Cabridge University PRess.

Baltes, P. B., & Lindenberger, U. (1997). Emergence of a powerful connection between sensory and cognitive functions across the adult life span: A new window to the study of cognitive aging? *Psychology and Aging, 12*(1), 12-21.

Baltes, P. B., Staudinger, U. M., & Lindenberger, U. (1999). Lifespan psychology: theory and application to intellectual functioning. *Annu Rev Psychol, 50*, 471-507.

Band, G. P., Ridderinkhof, K. R., & Segalowitz, S. (2002). Explaining neurocognitive aging: is one factor enough? *Brain Cogn, 49*(3), 259-267.

Barry, R. J., Clarke, A. R., Johnstone, S. J., Magee, C. A., & Rushby, J. A. (2007). EEG differences between eyes-closed and eyes-open resting conditions. *Clin Neurophysiol, 118*(12), 2765-2773.

Basar, E., Basar-Eroglu, C., Karakas, S., & Schurmann, M. (2001). Gamma, alpha, delta, and theta oscillations govern cognitive processes. *Int J Psychophysiol, 39*(2-3), 241-248.

Basar, E., Schurmann, M., Basar-Eroglu, C., & Karakas, S. (1997). Alpha oscillations in brain functioning: an integrative theory. *International Journal of Psychophysiology, 26*(5-29).

Basar, E., Yordanova, J., Kolev, V., & Basar-Eroglu, C. (1997). Is the alpha rhythm a control parameter for brain responses? *Biol Cybern, 76*(6), 471-480.

Bellgrove, M. A., Hester, R., & Garavan, H. (2004). The functional neuroanatomical correlates of response variability: Evidence from a response inhibition task. *Neurpsychologia, 42*(14), 1910-1916.

Ben-Simon, E., Podlipsky, I., Arieli, A., Zhdanov, A., & Hendler, T. (2008). Never resting brain: simultaneous representation of two alpha related processes in humans. *PLoS One, 3*(12), e3984.

Besthorn, C., Zerfass, R., Geiger-Kabisch, C., Sattel, H., Daniel, S., Schreiter-Gasser, U., et al. (1997). Discrimination of Alzheimer's disease and normal aging by EEG data. *Electroencephalogr. Clin. Neurophysiol., 103*, 241-248.

Birren, J. R., & Schaie, K. H. (Eds.). (1990). *Aging and Attentional Processes*. San Diego: Academic Press.

Bishop, N. A., Lu, T., & Yankner, B. A. (2010). Neural mechanisms of ageing and cognitive decline. *Nature, 464*(7288), 529-535.

Brassen, S., & Adler, G. (2003). Short-term effects of acetylcholinesterase inhibitor treatment on EEG and memory performance in Alzheimer patients: an open, controlled trial. *Pharmacopsychiatry, 36*(6), 304-308.

Brenner, R. P., Ulrich, R. F., Spiker, D. G., Sclabassi, R. J., Reynolds, C. F., 3rd, Marin, R. S., et al. (1986). Computerized EEG spectral analysis in elderly normal, demented and depressed subjects. *Electroencephalogr Clin Neurophysiol, 64*(6), 483-492.

Breslau, J., Starr, A., Sicotte, N., Higa, J., & Buchsbaum, M. S. (1989). Topographic EEG changes with normal aging and SDAT. . *Electroencephalogr Clin Neurophysiol*(72).

Brown, B. A., Champagne, A. E., Fortune, H. T., & Sherr, R. (1993). Nature of the 20Na 2646-keV level and the stellar reaction rate for 19Ne(p, gamma)20Na. *Phys Rev C Nucl Phys, 48*(3), 1456-1459.

Bruhn, P., & Parsons, O. A. (1977). Reaction time variability in epileptic and brain-damaged patients. *Cortex, 13*(4), 373-384.

Brunia, C. H. (1999). Neural aspects of anticipatory behavior. *Acta Psychol (Amst), 101*(2-3), 213-242.

Buckner, R. (2004). Memory and Executive Function in Aging and AD: Multiple Factors that Cause Decline and Reserve Factors that Compensate. *Neuron, 44*, 195-208.

Buckner, R. L., Head, D., & Lustig, C. (2005). Brain Changes in Aging: A Lfespan Perspective. In E. Bialystock & F. I. Craik (Eds.), *Lifespan Cognition*. Oxford: Oxford University Press.

Buckner, R. L., Sepulcre, J., Talukdar, T., Krienen, F. M., Liu, H., Hedden, T., et al. (2009). Cortical hubs revealed by intrinsic functional connectivity: mapping, assessment of stability, and relation to Alzheimer's disease. *J Neurosci, 29*(6), 1860-1873.

Buckner, R. L., & Vincent, J. L. (2007). Unrest at rest: default activity and spontaneous network correlations. *Neuroimage, 37*(4), 1091-1096; discussion 1097-1099.

Bunce, D., Anstey, K. J., Christensen, H., Dear, K., Wen, W., & Sachdev, P. (2007). White matter hyperintensities and within-person variability in community-dwelling adults aged 60-64 years. *Neuropsychologia, 45*(9), 2009-2015.

Bunce, D., MacDonald, S. W., & Hultsch, D. F. (2004). Inconsistency in serial choice decision and motor reaction times dissociate in younger and older adults. *Brain Cogn, 56*(3), 320-327.

Bunce, D. J., Warr, P. B., & Cochrane, T. (1993). Blocks in choice responding as a function of age and physical fitness. *Psychol Aging, 8*(1), 26-33.

Burke, D. (1997). Language, aging, and inhibitory deficits: Evaluation of a theory. *Journal of gerontology: Psychological sciences, 52B*, 254-264.

Burke, S., & Barnes, C. (2006). Neural plasticity in the ageing brain. *Nat Rev Neurosci, 7*(1), 30-40.

Burton, C. L., Hultsch, D. F., Strauss, E., & Hunter, M. A. (2002). Intraindividual variability in physical and emotional functioning: comparison of adults with traumatic brain injuries and healthy adults. *Clin Neuropsychol, 16*(3), 264-279.

Burton, C. L., Strauss, E., Hultsch, D. F., Moll, A., & Hunter, M. A. (2006). Intraindividual variability as a marker of neurological dysfunction: a comparison of Alzheimer's disease and Parkinson's disease. *J Clin Exp Neuropsychol, 28*(1), 67-83.

Cabeza, R. (2002). Hemispheric asymmetry reduction in older adults: the HAROLD model. *Psychol Aging, 17*(1), 85-100.

Cabeza, R., Anderson, N. D., Locantore, J. K., & McIntosh, A. R. (2002). Aging gracefully: compensatory brain activity in high-performing older adults. *Neuroimage, 17*(3), 1394-1402.

Cabeza, R., Grady, C. L., Nyberg, L., McIntosh, A. R., Tulving, E., Kapur, S., et al. (1997). Age-related differences in neural activity during memory encoding and retrieval: a positron emission tomography study. *J Neurosci, 17*(1), 391-400.

Charlton, R. A., Barrick, T. R., Markus, H. S., & Morris, R. G. The relationship between episodic long-term memory and white matter integrity in normal aging. *Neuropsychologia, 48*(1), 114-122.

Charlton, R. A., Barrick, T. R., McIntyre, D. J., Shen, Y., O'Sullivan, M., Howe, F. A., et al. (2006). White matter damage on diffusion tensor

imaging correlates with age-related cognitive decline. *Neurology, 66*(2), 217-222.

Chiaramonti, R., Muscas, G., Paganini, M., Müller, T., Fallgatter, A., Versari, A., et al. (1997). Correlations of topographical EEG features with clinical severity in mild and moderate dementia of Alzheimer type. *Neuropsychobiology, 36*(3), 153-158.

Christensen, H. (2001). What cognitive changes can be expected with normal aging? *Australian and New Zealand Journal of Psychiatry, 35:* , 768-775.

Christensen, H., Dear, K. B., Anstey, K. J., Parslow, R. A., Sachdev, P., & Jorm, A. F. (2005). Within-occasion intraindividual variability and preclinical diagnostic status: is intraindividual variability an indicator of mild cognitive impairment? *Neuropsychology, 19*(3), 309-317.

Clark, C. R., Veltmeyer, M. D., Hamilton, R. J., Simms, E., Paul, R., Hermens, D., et al. (2004). Spontaneous alpha peak frequency predicts working memory performance across the age span. *International journal of psychophysiology, 53*, 1-9.

Coben, L. A., Danziger, W. L., & Berg, L. (1983). Frequency analysis of the resting awake EEG in mild senile dementia of Alzheimer type. *Electroencephalogr Clin Neurophysiol, 55*(4), 372-380.

Cohen, J. (1988). *Statistical power analysis for the behavioural sciences*. Hilsdale NJ: Erlbaum

Colcombe, S. J., Kramer, A. F., Erickson, K. I., & Scalf, P. (2005). The implications of cortical recruitment and brain morphology for individual differences in inhibitory function in aging humans. *Psychol Aging, 20*(3), 363-375.

Coles, M. G., Gratton, G., Bashore, T. R., Eriksen, C. W., & Donchin, E. (1985). A psychophysiological investigation of the continuous flow model of human information processing. *J Exp Psychol Hum Percept Perform, 11*(5), 529-553.

Coles, M. G. H., & Rugg, M. D. (2002). Event-related potentials: an introduction. In D. S. Ruchkin & M. G. H. Coles (Eds.), *Electrophysiology of mind event related brain potentials and cognition*. Oxford: Oxford University Press.

Coltheart, M. (1981). The MRC Psycholinguistic Database. *Quarterly Journal of Experimental Psychology, 33A*, 497-505.

Corbetta, M., & Shulman, G. L. (2002). Control of goal-directed and stimulus-driven attention in the brain. *Nat Rev Neurosci, 3*(3), 201-215.

Craik, F., & Bialystok, E. (2006). Cognition through the lifespan mechanisms of change. *Trends in Cognitive Sciences, 10*(3).

Craik, F., & Byrd, M. (1982). *Aging and cognitive deficits: The role of attentional resources.* . New York: Plenium Press.

Craik, F., & McDowd, J. (1987). Age differences in recall and recognition. *Journal of Experimental Psychology Learning Memory and Cognition, 13*, 474-479.

Craik, F. I. (1994). Memory Changes in normal aging. *Current Directions in Psychological Science, 3*, 155-158.

Craik, F. I. (2008). Memory changes in normal and pathological aging. *Can J Psychiatry, 53*(6), 343-345.

Craik, F. I., & Jennings, J. m. (1992). Human Memory. In F. I. Craik & T. A. Salthouse (Eds.), *Handbook of the psychology of aging.* Hillsdale NJ: Erblaum.

Crowley, K. E., & Colrain, I. M. (2004). A review of the evidence for P2 being an independent component process: age, sleep and modality. *Clin Neurophysiol, 115*(4), 732-744.

Curran, T. (2000). Brain potentials of recollection and familiarity. *Mem Cognit, 28*(6), 923-938.

Curran, T. (2004). Effects of attention and confidence on the hypothesized ERP correlates of recollection and familiarity. *Neuropsychologia, 42*(8), 1088-1106.

Curran, T., & Cleary, A. M. (2003). Using ERPs to dissociate recollection from familiarity in picture recognition. *Brain Res Cogn Brain Res, 15*(2), 191-205.

Curran, T., Schacter, D. L., Johnson, M. K., & Spinks, R. (2001). Brain potentials reflect behavioral differences in true and false recognition. *J Cogn Neurosci, 13*(2), 201-216.

Czigler, I., & Balazs, L. (2005). Age-related effects of novel visual stimuli in a letter-matching task: an event-related potential study. *Biol Psychol, 69*(2), 229-242.

D'Esposito, M., Zarahn, E., Aguirre, G. K., & Rypma, B. (1999). The effect of normal aging on the coupling of neural activity to the bold hemodynamic response. *Neuroimage, 10*(1), 6-14.

Dal Forno, G., & Kawas, C. (1995). Cognitive problems in the elderly. *Current Opinion in Neurology, 8*, 256-261.

Davidson, P. S., & Glisky, E. L. (2002). Neuropsychological correlates of recollection and familiarity in normal aging. *Cogn Affect Behav Neurosci, 2*(2), 174-186.

Davidson, R., Jackson, D., & Larson, C. (2000). Human Encephalography. In J. T. Cacioppo, L. G. Tassinary & G. G. Bernston (Eds.), *Handbook of psychophysiology*. Cabridge: Cambridge University Press.

Davies, P., & Maloney, A. J. (1976). Selective loss of central cholinergic neurons in Alzheimer's disease. *Lancet, 2*(8000), 1403.

De Chastelaine, M., Friedman, D., Cycowicz, Y. M., & Horton, C. (2009). Effects of multiple study-test repetition on the neural correlates of recognition memory: ERPs dissociate remembering and knowing. *Psychophysiology, 46*(1), 86-99.

De Luca, M., Beckmann, C. F., De Stefano, N., Matthews, P. M., & Smith, S. M. (2006). fMRI resting state networks define distinct modes of long-distance interactions in the human brain. *Neuroimage, 29*(4), 1359-1367.

De Sanctis, P., Gomez-Ramirez, M., Sehatpour, P., Wylie, G. R., & Foxe, J. J. (2009). Preserved executive function in high-performing elderly is driven by large-scale recruitment of prefrontal cortical mechanisms. *Hum Brain Mapp, 30*(12), 4198-4214.

De Sanctis, P., Katz, R., Wylie, G. R., Sehatpour, P., Alexopoulos, G. S., & Foxe, J. J. (2008). Enhanced and bilateralized visual sensory processing in the ventral stream may be a feature of normal aging. *Neurobiol Aging, 29*(10), 1576-1586.

Deary, I. J. (2001). Human intelligence differences: a recent history. *Trends Cogn Sci, 5*(3), 127-130.

Deary, I. J., & Der, G. . (2005). Reaction time, age and cognitive ability:Longitudinal findings from age 16 to 63 years in representative population samples. *Aging, Neuropsychology, and Cognition,, 12*, 187-215.

Deary, I. J., Johnson, W., & Starr, J. M. (2010). Are processing speed tasks biomarkers of cognitive aging? *Psychol Aging, 25*(1), 219-228.

Der, G., & Deary, I. J. (2006). Age and sex differences in reaction time in adulthood: results from the United Kingdom Health and Lifestyle Survey. *Psychol Aging, 21*(1), 62-73.

Deutschl, G., & Eisen, A. (1999). *Recommendations for the practice of clinical neurophysiology.* (Vol. Supplement 52). Amsterdam: Elsevier.

Dien, J., Michelson, C. A., & Franklin, M. S. (2010). Separating the visual sentence N400 effect from the P400 sequential expectancy effect: cognitive and neuroanatomical implications. *Brain Res, 1355*, 126-140.

Dierks, T., Ihl, R., Frolich, L., & Maurer, K. (1993). Dementia of the Alzheimer type: effects on the spontaneous EEG described by dipole sources,. *Psychiatry REs, 50*, 151-162.

Dixon, R. A., Garrett, D. D., Lentz, T. L., MacDonald, S. W., Strauss, E., & Hultsch, D. F. (2007). Neurocognitive markers of cognitive impairment: exploring the roles of speed and inconsistency. *Neuropsychology, 21*(3), 381-399.

Dochin, E., & Coles, M. G. H. (1988). Is the P300 component a manifestation of context updating? *Behavioural and Brain Sciences, 11*, 355 - 372.

Dockree, P. M., Bellgrove, M., O'Keeffe, F., Moloney, P., Aimola, L., Carton, S., et al. (2006). Sustained attention in traumatic brain injury (TBI) and healthy controls: enhanced sensitivity with dual-task load. *Exp Brain Res, 168*(1-2), 218-229.

Dockree, P. M., Kelly, S. P., Foxe, J. J., Reilly, R. B., & Robertson, I. H. (2007). Optimal sustained attention is regulated by the spectral content of background EEG activity: Greater ongoing tonic alpha (~10Hz) power supports successful phasic goal activation. *European Journal of Neuroscience, 25*, 900-907.

Dockree, P. M., Kelly, S. P., Robertson, I. H., Reilly, R. B., & Foxe, J. J. (2005). Neurophysiological markers of alert responding during goal-directed behavior: A high-density electrical mapping study. *NeuroImage, 27*(3), 587-601.

Dockree, P. M., Kelly, S. P., Roche, R. A. P., Hogan, M. J., Reilly, R. B., & Robertson, I. (2004). Behavioural and physiological impairments of sustained attention after traumatic brain injury. *Cognitive Brain Research, 20*, 403-414.

Donaldson, D. I., & Rugg, M. D. (1998). Recognition memory for new associations: electrophysiological evidence for the role of recollection. *Neuropsychologia, 36*(5), 377-395.

Donaldson, D. I., & Rugg, M. D. (1999). Event-related potential studies of associative recognition and recall: electrophysiological evidence for context dependent retrieval processes. *Brain Res Cogn Brain Res, 8*(1), 1-16.

Donaldson, W. (1996). The role of decision processes in remembering and knowing. *Mem Cognit, 24*(4), 523-533.

Donchin, E. (1979). Event-related potentials: A tool in the study of human information processing. In H. Begleiter (Ed.), *Evoked potentials and behaviour* (pp. 13-75). New York: Plenium.

Donchin, E. (1981). Presidential address, 1980. Surprise!...Surprise? *Psychophysiology, 18*(5), 493-513.

Donchin, E., Kramer, E., & Wickens, C. D. (1986). Applications of event related potentials to problems in engineering psychology. . In M. G. H. Coles, E. Dochin & W. Porges (Eds.), *Psychophysiology, systems, processes and applications* (pp. 702-718). New York: Guilford.

Donchin, E., Ritter, W., & McCallum, C. (1978). Cognitive psychophysiology: the endogenous components of the ERP. In P. Callaway, P. Tueting & S. H. Koslow (Eds.), *Brain event-related potentials in man* (pp. 349 - 411). New York: Academic.

Donders, F. C. (1868). On the speed of mental processes. *Acta Psychologica, 30*, 412-431.

Duarte, A., Ranganath, C., Trujillo, C., & Knight, R. T. (2006). Intact recollection memory in high-performing older adults: ERP and behavioral evidence. *J Cogn Neurosci, 18*(1), 33-47.

Dubois, B., & Albert, M. L. (2004). Amnestic MCI or prodromal Alzheimer's disease? *Lancet Neurol, 3*(4), 246-248.

Duffy, F. H., Albert, M. S., McAnulty, G., & Garvey, A. J. (1984). Age-related differences in brain electrical activity of healthy subjects. *Ann. Neurol, 16*, 430-438.

Dunn, J. C. (2004). Remember-know: a matter of confidence. *Psychol Rev, 111*(2), 524-542.

Duzel, E., Yonelinas, A. P., Mangun, G. R., Heinze, H. J., & Tulving, E. (1997). Event-related brain potential correlates of two states of conscious awareness in memory. *Proc Natl Acad Sci U S A, 94*(11), 5973-5978.

Edland, S. D., Rocca, W. A., Petersen, R. C., Cha, R. H., & Kokmen, E. (2002). Dementia and Alzheimer disease incidence rates do not vary by sex in Rochester, Minn. *Arch Neurol, 59*(10), 1589-1593.

Eichenbaum, H., Yonelinas, A. P., & Ranganath, C. (2007). The medial temporal lobe and recognition memory. *Annu Rev Neurosci, 30*, 123-152.

Elias, M. F., Beiser, A., Wolf, P. A., Au, R., White, R. F., & D'Agostino, R. B. (2000). The preclinical phase of alzheimer disease: A 22-year prospective study of the Framingham Cohort. *Arch Neurol, 57*(6), 808-813.

Esposito, F., Bertolino, A., Scarabino, T., Latorre, V., Blasi, G., Popolizio, T., et al. (2006). Independent component model of the default-mode brain function: Assessing the impact of active thinking. *Brain Res Bull, 70*(4-6), 263-269.

Fabiani, M., Gratton, G., & Coles, M. G. H. (2000). Event Related Potentials Methods, Theory, and Applications. In J. T. Cacioppo, L. G. Tassinary & G. G. Bernston (Eds.), *Handbook of Psychophysiology*. Cambridge: Cambridge University Press.

Falkenstein, M., Yordanova, J., & Kolev, V. (2006). Effects of aging on slowing of motor-response generation. *Int J Psychophysiol, 59*(1), 22-29.

Ferri, C. P., Prince, M., Brayne, C., Brodaty, H., Fratiglioni, L., Ganguli, M., et al. (2005). Global prevalence of dementia: a Delphi consensus study. *The Lancet, 366*(9503), 2112-2117.

Feshchenko, V. A., Veselis, R. A., & Reinsel, R. A. (1997). Comparison of the EEG effects of midazolam, thiopental, and propofol: the role of underlying oscillatory systems. *Neuropsychobiology, 35*(4), 211-220.

Fjell, A. M., Walhovd, K. B., & Reinvang, I. (2005). Age-differences in verbal recognition memory revealed by ERP. *Clin EEG Neurosci, 36*(3), 176-187.

Fogelson, N., Kogan, E., Korczyn, A. D., Giladi, N., Shabtai, H., & Neufeld, M. Y. (2003). Effects of rivastigmine on the quantitative EEG in demented Parkinsonian patients. *Acta Neurol Scand, 107*(4), 252-255.

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res, 12*(3), 189-198.

Foxe, J. J., McCourt, M. E., & Javitt, D. C. (2003). Right hemisphere control of visuospatial attention: line-bisection judgments evaluated with high-density electrical mapping and source analysis. *Neuroimage, 19*(3), 710-726.

Francis, W. N., & Kucera, H. (1982). Frequency Analysis of English usage. In. Boston Houghton Miflin Co.

Fransson, P. (2006). How default is the default mode of brain function? Further evidence from intrinsic BOLD signal fluctuations. *Neuropsychologia, 44*(14), 2836-2845.

Friedman, D. (2003). Cognition and aging: a highly selective overview of event-related potential (ERP) data. *J Clin Exp Neuropsychol, 25*(5), 702-720.

Friedman, D., de Chastelaine, M., Nessler, D., & Malcolm, B. (2010). Changes in familiarity and recollection across the lifespan: an ERP perspective. *Brain Res, 1310*, 124-141.

Friedman, D., & Johnson, R., Jr. (2000). Event-related potential (ERP) studies of memory encoding and retrieval: a selective review. *Microsc Res Tech, 51*(1), 6-28.

Friedman, D., Nessler, D., & Johnson, R., Jr. (2007). Memory encoding and retrieval in the aging brain. *Clin EEG Neurosci, 38*(1), 2-7.

Fromholt, P., Mortensen, D. B., Torpdahl, P., Bender, L., Larsen, P., & Rubin, D. C. (2003). Life-narrative and word-cued autobiographical memories in centenarians: comparisons with 80-year-old control, depressed, and dementia groups. *Memory, 11*(1), 81-88.

Gabrieli, J. (1996). *Memory systems analyses of mnemonic disorders in aging and age-related diseases*. Paper presented at the Proc. Natl. Acad. Sci. USA.

Galambos, R. (1992). A comparison of certain gamma band (40Hz) brain rhythms in cat and man. In E. Basar & T. Bullock (Eds.), *Induced rhythms in the brain* (pp. 201-216). Boston: Birkhauser.

Gallagher, M. (1997). Animal models of memory impairment. *Philos Trans R Soc Lond B Biol Sci, 352*(1362), 1711-1717.

Garrett, H. E. (1946). A developmental theory of intelligence. *Am Psychol, 1*(9), 372-378.

Gevins, A. S., Morgan, N. H., Bressler, S. L., Doyle, J. C., & Cutillo, B. A. (1986). Improved event-related potential estimation using statistical pattern classification. *Electroencephalogr Clin Neurophysiol, 64*(2), 177-186.

Glatt, S. J., Chayavichitsilp, P., Depp, C., Schork, N. J., & Jeste, D. V. (2007). Successful aging: from phenotype to genotype. *Biol Psychiatry, 62*(4), 282-293.

Glisky, E. L., Polster, M. R., & Routhieaux, B. C. (1995). Double dissociations between item and source memory. *Neuropsychology, 9*, 229-235.

Glisky, E. L., Rubin, S. R., & Davidson, P. S. (2001). Source memory in older adults: an encoding or retrieval problem? *J Exp Psychol Learn Mem Cogn, 27*(5), 1131-1146.

Gloor, P. (1969). Hans Berger Uber das Electrenephalogramm des menschen. Translated and reprinted - Hans Berger on the electroencephalogram of man. . In *Electroencephalography and Clinical Neurophysiology* (Vol. Supp 28). Amsterdam: Elsevier.

Goh, J. O. (2011). Functional Dedifferentiation and Altered Connectivity in Older Adults: Neural Accounts of Cognitive Aging. *Aging Dis, 2*(1), 30-48.

Golden, C. J., & Freshwater, S. M. (2002). *Stroop color and Word Test. A manual for clinical and experimental users*: Stoelting.

Gonsalvez, C. L., & Polich, J. (2002). P300 amplitude is determined by target-to-target interval. *Psychophysiology, 39*(3), 388-396.

Gordon, E. B., & Sim, M. (1967). The E.E.G. in presenile dementia. *J Neurol Neurosurg Psychiatry, 30*(3), 285-291.

Gorus, E., De Raedt, R., Lambert, M., Lemper, J. C., & Mets, T. (2008). Reaction times and performance variability in normal aging, mild cognitive impairment, and Alzheimer's disease. *J Geriatr Psychiatry Neurol, 21*(3), 204-218.

Gorus, E., De Raedt, R., & Mets, T. (2006). Diversity, dispersion and inconsistency of reaction time measures: effects of age and task complexity. *Aging Clin Exp Res, 18*(5), 407-417.

Grady, C. L. (2008). Cognitive neuroscience of aging. *Ann N Y Acad Sci, 1124*, 127-144.

Grady, C. L., McIntosh, A. R., Horwitz, B., Maisog, J. M., Ungerleider, L. G., Mentis, M. J., et al. (1995). Age-related reductions in human recognition memory due to impaired encoding. *Science, 269*(5221), 218-221.

Grady, C. L., Protzner, A. B., Kovacevic, N., Strother, S. C., Afshin-Pour, B., Wojtowicz, M., et al. (2010). A multivariate analysis of age-related differences in default mode and task-positive networks across multiple cognitive domains. *Cereb Cortex, 20*(6), 1432-1447.

Greenwood, P. M. (2000). The frontal aging hypothesis evaluated. *J Int Neuropsychol Soc, 6*(6), 705-726.

Gregoire, J., & Van der Linden, M. (1997). Effects of age on forward and backward digit spans. *Aging Neuropsychol cognition, 4*, 140-149.

Group. (1998). *The Ronald and Nancy Reagan Research Institute of the Alzheimer's Association and the National Institute on Aging. Consensus report of the working group on Molecular and biochemical Markers of Alzheimers disease* o. Document Number)

Guillaume, C., Clochon, P., Denise, P., Rauchs, G., Guillery-Girard, B., Eustache, F., et al. (2009). Early age-related changes in episodic memory retrieval as revealed by event-related potentials. *Neuroreport, 20*(2), 191-196.

Gunning, -. D. F. M., Head, D., McQuain, J., Acker, J. D., & Raz, N. (1998). Differential aging of the human striatum: A prospective MR imaging study. *American Journal of Neuroradiology, 19*, 1501-1507.

Gusnard, D. A., & Raichle, M. E. (2001). Searching for a baseline: functional imaging and the resting human brain. *Nat Rev Neurosci, 2*(10), 685-694.

Guttmann, C. R., Jolesz, F. A., Kikinis, R., Killiany, R. J., Moss, M. B., Sandor, T., et al. (1998). White matter changes with normal aging. *Neurology, 50*(4), 972-978.

Hale, S., Myerson, J., Smith, G. A., & Poon, L. W. (1988). Age, variability, and speed: between-subjects diversity. *Psychol Aging, 3*(4), 407-410.

Hampson, M., Driesen, N. R., Skudlarski, P., Gore, J. C., & Constable, R. T. (2006). Brain connectivity related to working memory performance. *J Neurosci, 26*(51), 13338-13343.

Handy, C. (2005). Basic Principles of ERP Quantification. In T. C. Handy (Ed.), *Event Related Potentials a methods handbook*. Massachusetts: MIT Press.

Happe, F. G., Winner, E., & Brownell, H. (1998). The getting of wisdom: theory of mind in old age. *Dev Psychol, 34*(2), 358-362.

Hartley, A. A. (1993). *Attention*. Hove: Emblaum.

Hasher, L., Goldstein, D., & May, C. (2005). *It's about time: Circadian rhythms, memory and aging*. Kansas: Erblaum.

Hasher, L., & Zacks, R. T. (1988). *Working memory, comprehension, and aging: A review and a new view*. San Diego: Academic Press.

Hay, J. F., & Jacoby, L. L. (1999). Separating habit and recollection in young and older adults: effects of elaborative processing and distinctiveness. *Psychol Aging, 14*(1), 122-134.

Head, D., Buchner, R., Shimony, J., Williams, L., Akbudak, E., Conturo, T., et al. (2004). Differential vulnerability of anterior white matter in nondemented aging with minimal accleration in dementia of the Alzheimer's type: evidence from diffusion tensor imaging. *Cereb. Cortex, 14*, 410-423.

Head, H. (1926). *Aphasia and kindred disorders of speech. .* Cambridge: Cambridge University Press.

Hedden, T., & Gabrieli, J. D. (2004). Insights into the ageing mind: a view from cognitive neuroscience. *Nat Rev Neurosci, 5*(2), 87-96.

Herrmann, C. S., Grigutsch, M., & Busch, N. A. (2005). EEG Oscillations and Wavelet Analysis. In T. C. Handy (Ed.), *Event Related Potentials A Methods Handbook*. Massachusetts: MIT Press.

Hilborn, J. V., Strauss, E., Hultsch, D. F., & Hunter, M. A. (2008). Intraindividual variability across cognitive domains: Investigation of dispersion levels and performance profiles in older adults.

Hockey, G. R. J. (1983). *Stress and fatigue in human performance*. New York: Wiley.

Hofland, B. F., Willis, S. L., & Baltes, P. G. (1981). Fluid intelligence performance in the elderly: intraindividual variability and conditions of assessment. *Journal of educational psychology., 73*, 573-586.

Hogan, M. J., Carolan, L., Roche, R. A., Dockree, P. M., Kaiser, J., Bunting, B. P., et al. (2006). Electrophysiological and information processing variability predicts memory decrements associated with normal age-related cognitive decline and Alzheimer's disease (AD). *Brain Res, 1119*(1), 215-226.

Hogan, M. J., Swanick, G. R. J., Kaiser, J., Rowan, M., & Lawlor, B. (2003). Memory-related EEG power and coherence reductions in Mild Alzheimer's Disease. *Internation journal of Psychophysiology, 49*, 147 - 163.

Horn, J. L. (Ed.). (1986). *Intellectual stability concepts*. Hillsdale: Erblaum.

Horn, J. L., & Cattell, R. B. (1967). Age differences in fluid and crystallized intelligence. *Acta Psychol (Amst), 26*(2), 107-129.

Horne, J. A., & Ostberg, O. (1976). A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. *Int J Chronobiol, 4*(2), 97-110.

Howieson, D. B., Loring, D. W., & Hannay, H. J. (2004). Neurobehavioural variables and diagnostic issues. In M. D. Lezak, D. B. Howieson & D. W. Loring (Eds.), *Neuropsychological Assessment*. Oxford: Oxford University Press.

Huang, C., Wahlund, L., Dierks, T., Julin, P., Winblad, B., & Jelic, V. (2000). Discrimination of Alzheimer's disease and mild cognitive impairment by equivalent EEG sources: a cross-sectional and longitudinal study,. *Clinical Neurophysiology, 111*, 1961-1967.

Hubbard, O., Sundae, D., & Goldensohn, E. (1976). The EEG in centenarians, Electroencephalograph. *Clinical Neurophysiology, 40*, 407-417.

Hultsch, D. F., & Dixon, R. A. (1990). Learning and memory in aging. In J. E. Birren & K. W. Schaie (Eds.), *Handbook of the psychology of aging*. San Diego: Academic Press.

Hultsch, D. F., Hertzog, C., Dixon, R. A., & Small, B. J. (1998). *Memory Change in the Aged*. Cambridge: Cambridge University Press.

Hultsch, D. F., Hertzog, C., Small, B. J., McDonald-Miszczak, L., & Dixon, R. A. (1992). Short-term longitudinal change in cognitive performance in later life. *Psychol Aging, 7*(4), 571-584.

Hultsch, D. F., Hunter, M. A., MacDonald, S. W. S., & Strauss, E. (2005). *Inconsistency in response time as an indicator of cognitive aging.* New York: Oxford University Press.

Hultsch, D. F., MacDonald, S. W., & Dixon, R. A. (2002). Variability in reaction time performance of younger and older adults. *J Gerontol B Psychol Sci Soc Sci, 57*(2), P101-115.

Hultsch, D. F., MacDonald, S. W., Hunter, M. A., Levy-Bencheton, J., & Strauss, E. (2000a). Intraindividual variability in cognitive performance in older adults: comparison of adults with mild dementia, adults with arthritis, and healthy adults. *Neuropsychology, 14*(4), 588-598.

Hultsch, D. F., & MacDonald, S. W. S. (2004). *Intraindividual variability in performance as a theoretical window onto cognitive aging.* New York: Oxford University Press.

Hultsch, D. F., MacDonald, S. W. S., Hunter, M. A., Levy-Bencheton, J., & Strauss, E. (2000b). Intraindividual variability in cognitive performance in older adults: comparison of adults with mild dementia, adults with arthritis, and healthy adults. *Neuropsychology, 14*(4), 588-598.

Hultsch, D. F., MacDonald, S. W. S., Hunter, M. A., Levy-Bencheton, J., & Strauss, E. (2000c). Intraindividual variability in cognitive performance in older adults: Comparison of adults with mild dementia, adults with arthritis, and healthy adults. *Neuropsychology, 14*(4), 588-598.

Huppert, F. A., & Brayne, C. (1994). *What is the relationship between dementia and normal aging*. Cabridge: Camridge University Press.

Hurks, P. P., Adam, J. J., Hendriksen, J. G., Vles, J. S., Feron, F. J., Kalff, A. C., et al. (2005). Controlled visuomotor preparation deficits in attention-deficit/hyperactivity disorder. *Neuropsychology, 19*(1), 66-76.

Ince, P. (2001). Pathological correlates of late onset dementia in a multi-centre community based population in England and Wales. *Lancet,* (357), 169.

Jackson, C. E., & Snyder, P. J. (2008). Electroencephalography and event-related potentials as biomarkers of mild cognitive impairment and mild Alzheimer's disease. *Alzheimer's and Dementia, 4*(1, Supplement 1), S137-S143.

Jacobson, M. W., McEvoy, L. K., Dale, A., & Fennema-Notestine, C. (2009). Cognitive phenotypes, brain morphometry and the detection of cognitive decline in preclinical AD. *Behav Neurol, 21*(1), 29-37.

Jelic V, Shigeta M, Julin P, Almkvist O, Winblad B, & LO., W. (1996). Quantitative Electroencephalography power and coherence in Alzheimer's disease and mild cognitive impairment. *Dementia, 7*, 314-323.

Jennings, J. M., & Jacoby, L. L. (1997). An opposition procedure for detecting age-related deficits in recollection: telling effects of repetition. *Psychol Aging, 12*(2), 352-361.

Jensen, A. R. (1992). THe importance of intraindividual variation in reaction time. *Personality and Individual Differences, 13*, 869-881.

Jeong, J. (2004). EEG dynamics in patients with Alzheimer's disease. *Clin Neurophysiol, 115*(7), 1490-1505.

Jevas, S., & Yan, J. H. (2001). The effect of aging on cognitive function: a preliminary quantitative review. *Research Quarterly for Exercise and Sport, 72*.

Jiang, Z. Y. (2005). Study on EEG power and coherence in patients with mild cognitive impairment during working memory task. *J Zhejiang Univ Sci B, 6*(12), 1213-1219.

Johnson, J. D., & Rugg, M. D. (2006). Electrophysiological correlates of retrieval processing: effects of consistent versus inconsistent retrieval demands. *J Cogn Neurosci, 18*(9), 1531-1544.

Johnson, K. A., Kelly, S. P., Bellgrove, M. A., Barry, E., Cox, M., Gill, M., et al. (2007). Response variability in Attention Deficit Hyperactivity Disorder: evidence for neuropsychological heterogeneity. *Neuropsychologia, 45*, 630-638.

Juhasz, C., Kamondi, A., & Szirmai, I. (1997). Spectral EEG analysis following hemispheric stroke: evidences of transhemispheric diaschisis. *Acta Neurol Scand, 96*(6), 397-400.

Karis, D., Fabiani, M., & Donchin, E. (1984). P300 and memory: Individual differences in the rostoroff effect. *Cognitive Psychology, 16*, 177-216.

Kates, W. R., Krauss, B. R., AbdulSabur, N., Colgan, D., Antshel, K., Higgins, A. M., et al. (2007). The neural correlates of non-spatial working memory in velocardiofacial syndrome (22q11.2 deletion syndrome). *Neuropsychologia, 45*(12), 2863-2873.

Keller, J. N. (2006). Age-related neuropathology, cognitive decline, and Alzheimer's disease. . *Ageing Research Reviews,, 5* 1-13.

Kelly, S. P., Gomez-Ramirez, M., & Foxe, J. J. (2008). Spatial attention modulates initial afferent activity in human primary visual cortex. *Cereb Cortex, 18*(11), 2629-2636.

Kenemans, J. L., Kok, A., & Smulders, F. T. (1993). Event-related potentials to conjunctions of spatial frequency and orientation as a function of

stimulus parameters and response requirements. *Electroencephalogr Clin Neurophysiol, 88*(1), 51-63.

Kennedy, D. P., Redcay, E., & Courchesne, E. (2006). Failing to deactivate: resting functional abnormalities in autism. *Proc Natl Acad Sci U S A, 103*(21), 8275-8280.

Kim, D., Lipsitz, L., Ferrucci, L., Varadhan, R., Guralnik, J., Carlson, M., et al. (2006). Association between reduced heart rate variability (HRV) and cognitive impairment in older disabled women in the community: Women's Health and Aging Study I. . *Journal of American Geriatric Society,, 54* (11).

Klimesch, W. (1996). Memory processes, brain oscillations and EEG synchronization, . *Int. J. Psychophysiol., 24*, 61-100.

Klimesch, W. (1997). EEG-alpha rhythms and memory processes. *Int J Psychophysiol, 26*(1-3), 319-340.

Klimesch, W. (1999). EEG alpha and theta oscillations reflect cognitive and memory performance a review and analysis. . *Brain Research Reviews*(29), 169-195.

Klimesch, W., Doppelmayr, M., Russegger, H., & Pachinger, T. (1996). Theta band power in the human scalp EEG and the encoding of new information, . *NeuroReport, 7*, 1235-1240.

Klimesch, W., Doppelmayr, M., Schimke, H., & Pachinger, T. (1996). Alpha frequency, reaction time and the speed of processing information. *Journal Clin. Neurophysiol.*(13), 511-518.

Klimesch, W., Pfurtscheller, G., & Schimke, H. (1993). Electroencephalogr.ERD—attentional and cognitive processes in the upper and lower alpha band,. *Clin. Neurophysiol., 87*, 133.

Klimesch, W., Sauseng, P., & Hanslmayr, S. (2007). EEG alpha oscillations: the inhibition-timing hypothesis. *Brain Res Rev, 53*(1), 63-88.

Klimesch, W., Schimke, H., Ladurner, G., & Pfurtscheller, G. (1990). Alpha frequency and memory performance,. *J. Psychophysiol., 4*, 381-390.

Klimesch, W., Schimke, H., & Pfurtscheller, G. (1993). Alpha frequency, cognitive load and memory performance. *Brain Topogr, 5*(3), 241-251.

Kogan, E. A., Korczyn, A. D., Virchovsky, R. G., Klimovizky, S., Treves, T. A., & Neufeld, M. Y. (2001). EEG changes during long-term treatment with donepezil in Alzheimer's disease patients. *J Neural Transm, 108*(10), 1167-1173.

Kolev, V., Falkenstein, M., & Yordanova, J. (2006). Motor-response generation as a source of aging-related behavioural slowing in choice-reaction tasks. *Neurobiol Aging, 27*(11), 1719-1730.

Köpruner, V., Pfurtscheller, G., & Auer, L. (1984). Quantitative EEG in normals and in patients with cerebral ischemia, . In G. Pfurtscheller, E. Jonkman & F. Lopes de Silva (Eds.), *Brain Ischemia: Quantitative EEG and imaging techniques, Progress in Brain Research* (Vol. 62): Elsevier Science Publishers.

Kutas, M. (1997). Views on how the electrical activity that the brain generates reflects the functions of different language structures. *Psychophysiology, 34*(4), 383-398.

Kutas, M., & Hillyard, S. A. (1984). Brain potentials during reading reflect word expectancy and semantic association. *Nature, 307*(5947), 161-163.

La Voie, D., & Light, L. L. (1994). Adult age differences in repetition priming: a meta-analysis. *Psychol Aging, 9*(4), 539-553.

Larson, G. E., & Alderton, D. L. (1990). Reaction time variability and intelligence: A "worst performance analysis of individual differences. . *Intelligence, 14*, 309 - 325.

Letemendia, F., & Pampiglione, G. (1958). Clinical and electroencephalographic observations in Alzheimer's disease. *J Neurol Neurosurg Psychiatry, 21*(3), 167-172.

Li, J., Morcom, A. M., & Rugg, M. D. (2004). The effects of age on the neural correlates of successful episodic retrieval: an ERP study. *Cogn Affect Behav Neurosci, 4*(3), 279-293.

Li, S., Aggen, S. H., Nesselroade, J. R., & Baltes, P. B. (2001). Short-term fluctuations in elderly people's sensorimotor functioning predict text and spatial memory performance: The Macarthur Successful Aging Studies. *Gerontology, 47*(2), 100-116.

Li, S., Huxhold, O., & Schmiedek, F. (2004). Aging and attenuated processing robustness. *Gerontology, 50*, 28-34.

Li, S. C., Lindenberger, U., Hommel, B., Aschersleben, G., Prinz, W., & Baltes, P. B. (2004). Transformations in the couplings among intellectual abilities and constituent cognitive processes across the life span. *Psychol Sci, 15*(3), 155-163.

Li, S. C., & Sikstrom, S. (2002). Integrative neurocomputational perspectives on cognitive aging, neuromodulation, and representation. *Neurosci Biobehav Rev, 26*(7), 795-808.

Lindenberger, U., & Baltes, P. (1994). Sensory functioning and intelligence in old age: A strong connection. *Psychology and Aging, 9*(3), 339-355.

Lindenberger, U., & von Oertzen, T. (2006). *Variability in Cognitive Aging: From Taxonomy to Theory*. Oxford: Oxford University Press.

Lipton, R., Sliwinski, M., & Buschke, H. (1996). Cognitive decline in normal aging: removing the effects of preclinical dementia. *Neurology, 46*.

Lorist, M. M. (2008). Impact of top-down control during mental fatigue. *Brain Res, 1232*, 113-123.

Lowe, M. J., Phillips, M. D., Lurito, J. T., Mattson, D., Dzemidzic, M., & Mathews, V. P. (2002). Multiple sclerosis: low-frequency temporal blood oxygen level-dependent fluctuations indicate reduced functional connectivity initial results. *Radiology, 224*(1), 184-192.

Luck, S. (2005). An introduction to event-related potentials and their neural origins. In *An introduction to the event-related potential technique*. Massachusetts: MIT Press.

Luck, S., & Hillyard, S. (1994). Electrophysiological correlates of feature analysis during visual search. *Psychophysiology, 31*(3), 291-308.

Lustig, C., Snyder, A. Z., Bhakta, M., O'Brien, K. C., McAvoy, M., Raichle, M. E., et al. (2003). Functional deactivations: change with age and dementia of the Alzheimer type. *Proc Natl Acad Sci U S A, 100*(24), 14504-14509.

Luszcz. (2004). Whats it all about: Variation and Aging. *Gerontology, 50*(1).

Lyketsos, C. G., Lopez, O., Jones, B., Fitzpatrick, A. L., Breitner, J., & DeKosky, S. (2002). Prevalence of neuropsychiatric symptoms in dementia and mild cognitive impairment: results from the cardiovascular health study. *JAMA, 288*(12), 1475-1483.

MacDonald, S. W., Hultsch, D. F., & Dixon, R. A. (2003). Performance variability is related to change in cognition: evidence from the Victoria Longitudinal Study. *Psychol Aging, 18*(3), 510-523.

MacDonald, S. W., Li, S. C., & Backman, L. (2009). Neural underpinnings of within-person variability in cognitive functioning. *Psychol Aging, 24*(4), 792-808.

MacDonald, S. W., Nyberg, L., & Backman, L. (2006). Intra-individual variability in behaviour: links to brain structure, neurotransmission and neuronal activity. . *Trends in Neuroscience, 29*(8).

MacDonald, S. W., Nyberg, L., Sandblom, J., Fischer, H., & Backman, L. (2008). Increased Response-time Variability is Associated with Reduced Inferior Parietal Activation during Episodic Recognition in Aging. *J Cogn Neurosci*.

MacMillan, N. A., & Creelman, C. D. (2005). *Detection Theory: A User's Guide* (2 ed.). Mahwah, N.J: Lawrence Erlbaum Associates.

Madden, D. J. (2001). Speed and timing of behavioral processes. In J. E. Birren & K. W. Schaie (Eds.), *Handbook of the psychology of aging*. San Diego, CA: : Academic Press.

Madden, D. J., Bennett, I. J., & Song, A. W. (2009). Cerebral white matter integrity and cognitive aging: contributions from diffusion tensor imaging. *Neuropsychol Rev, 19*(4), 415-435.

Madden, D. J., Costello, M. C., Dennis, N. A., Davis, S. W., Shepler, A. M., Spaniol, J., et al. (2010). Adult age differences in functional connectivity during executive control. *Neuroimage, 52*(2), 643-657.

Manly, T., Davison, B., Heutink, J., Galloway, M., & Robertson, I. (2000). Not enough time or not enough attention? Speed error and self-maintained control in the sustained attention to response test (SART). *Clinical Neuropsychological Assessment, 3*, 167-177.

Manly, T., Owen, A. M., McAvenue, L., Datta, A., Lewis, G. H., Scott, S. K., et al. (2003). Enhancing the sensitivity of sustained attention task to frontal damage: Convergent clinical and functional imaging evidence. *Neurocase, 9*(4), 340 - 349.

Mark, R. E., & Rugg, M. D. (1998). Age effects on brain activity associated with episodic memory retrieval. An electrophysiological study. *Brain, 121 (Pt 5)*, 861-873.

Markand, O. N. (1990). Alpha rhythms. *J Clin Neurophysiol, 7*(2), 163-189.

Martin, & Hofer. (2004). Intraindividual variability Change & Aging: Conceptual and Analytical Issues. *Gerontology, 50*(1).

Maruff, P., Falleti, M. G., Collie, A., Darby, D., & McStephen, M. (2005). Fatigue-related impairment in the speed, accuracy and variability of psychomotor performance: comparison with blood alcohol levels. *J Sleep Res, 14*(1), 21-27.

Mc Dowd, J. M. (1997). Inhibition in attention and aging. *Journal of Gerontology: Psychological Sciences, 52B*(265-273.).

McClearn, G. E. (1997). Biomarkers of age and aging. *Exp Gerontology, 32*(1-2), 87-94.

McFall, R. M., & Treat, T. A. (1999). Quantifying the information value of clinical assessments with signal detection theory. *Annu. Rev. Psychol., 50*(215).

Mecklinger, A., & Pfeifer, E. (1996). Event-related potentials reveal topographical and temporal distinct neuronal activation patterns for spatial and object working memory. *Brain Res Cogn Brain Res, 4*(3), 211-224.

Mesulam, M. (2004). The cholinergic lesion of Alzheimer's disease: pivotal factor or side show? *Learn Mem, 11*(1), 43-49.

Moffat, S. (2005). Effects of testosterone on cognitive and brain aging in elderly men. *Annals of the New York Academy of Sciences 1055*, 80-92.

Montross, L. P., Depp, C., Daly, J., Reichstadt, J., Golshan, S., Moore, D., et al. (2006). Correlates of self-rated successful aging among community-dwelling older adults. *Am J Geriatr Psychiatry, 14*(1), 43-51.

Morcom, A. M., & Fletcher, P. C. (2007). Does the brain have a baseline? Why we should be resisting a rest. *Neuroimage, 37*(4), 1073-1082.

Morcom, A. M., Li, J., & Rugg, M. D. (2007). Age effects on the neural correlates of episodic retrieval: increased cortical recruitment with matched performance. *Cereb Cortex, 17*(11), 2491-2506.

Morcom, A. M., & Rugg, M. D. (2004). Effects of age on retrieval cue processing as revealed by ERPs. *Neuropsychologia, 42*(11), 1525-1542.

Moretti, D., Babilonia, C., Binettib, G., Cassettac, E., Dal Fornod, G., Ferrericd, F., et al. (2004). Individual analysis of EEG frequency and band power in mild Alzheimer's disease. *Clinical Neurophysiology, 115*, 299-308.

Moretti, D. V., Pievani, M., Geroldi, C., Binetti, G., Zanetti, O., Rossini, P. M., et al. (2009). EEG markers discriminate among different subgroup of patients with mild cognitive impairment. *Am J Alzheimers Dis Other Demen, 25*(1), 58-73.

Morse, C. K. (1993). Does variability increase with age? An archival study of cognitive measures. *Psychology and Aging, 8*, 156-164.

Murphy, K. J., West, R., Armilio, M. L., Craik, F. I., & Stuss, D. T. (2007). Word-list-learning performance in younger and older adults: intra-individual performance variability and false memory. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn, 14*(1), 70-94.

Murtha, S., Cismaru, R., Waechter, R., & Chertkow, H. (2002). Increased variability accompanies frontal lobe damage in dementia. *J Int Neuropsychol Soc, 8*(3), 360-372.

Naatanen, R., & Picton, T. (1987). The N1 wave of the human electric and magnetic response to sound: a review and an analysis of the component structure. *Psychophysiology, 24*(4), 375-425.

Naveh-Benjamin, M., Brav, T. K., & Levy, O. (2007). The associative memory deficit of older adults: the role of strategy utilisation. *Psychol Aging, 22*(1), 202-208.

Nelson, E. A., & Dannefer, D. (1992). Aged heterogeneity: fact or fiction? The fate of diversity in gerontological research. *Gerontologist, 32*(1), 17-23.

Nelson, H. E. (1982). *National Adult Reading Test.* . Windsor UK: : NFER-Nelson.

Nesselroade, J. (2004a). Intraindividual variability and short term change. *Gerontology, 50*(1).

Nesselroade, J., & Salthouse, T. (2004). Methodological and theoretical implications of intraindividual variability in perceptual-motor performance. *J Gerontol B Psychol Sci Soc Sci, 59*(2), P49-55.

Nesselroade, J. R. (1991). *The warp and woof of the developmental fabric.* Hillsdale: Erblaum.

Nesselroade, J. R. (2004b). Intraindividual Variability and Short-Term Change. *Gerontology, 50*(1), 44-47.

Nessler, D., Johnson, R., Jr., Bersick, M., & Friedman, D. (2008). Age-related ERP differences at retrieval persist despite age-invariant performance and left-frontal negativity during encoding. *Neurosci Lett, 432*(2), 151-156.

Nessler, D., Mecklinger, A., & Penney, T. B. (2001). Event related brain potentials and illusory memories: the effects of differential encoding. *Brain Res Cogn Brain Res, 10*(3), 283-301.

Neufeld, M. Y., Rabey, M. J., Parmet, Y., Sifris, P., Treves, T. A., & Korczyn, A. D. (1994). Effects of a single intravenous dose of scopolamine on the quantitative EEG in Alzheimer's disease patients and age-matched controls. *Electroencephalogr Clin Neurophysiol, 91*(6), 407-412.

Nilsson, L. G. (2003). Memory function in normal aging. *Acta Neurol Scand Suppl, 179*, 7-13.

Nilsson, L. G., Backman, L., & Erngrund, K. (1997). The Betula prospective cohort study; memory, health, and aging. *Aging Neuropsychol cognition, 4*, 1-32.

Nunez, P. L. (1981). *Electrical fields of the brain: The neurophysics of EEG.* New York: Oxford University Press.

Nunez, P. L. (1995). *Neocortical Dynamics abd Human EEG*. New York: Oxford University Press.

Nunez, P. L., Wingeier, B. M., & Silberstein, R. B. (2001). Spatial-temporal structures of human alpha rhythms: theory, microcurrent sources, multiscale measurements, and global binding of local networks. *Hum Brain Mapp, 13*(3), 125-164.

Nuwer, M. (1988). Quantitative EEG I: technique and problems of frequency analysis and topographic mapping. . *J Clin Neurophysiol, 5*, 1-43.

Nyberg, L., Maitland, S. B., Ronnlund, M., Backman, L., Dixon, R. A., Wahlin, A., et al. (2003). Selective adult age differences in an age-invariant multifactor model of declarative memory. *Psychol Aging, 18*(1), 149-160.

O'Connell, R. G., Dockree, P. M., Bellgrove, M. A., Turin, A., Ward, S., Foxe, J. J., et al. (2009). Two types of action error: electrophysiological evidence for separable inhibitory and sustained attention neural mechanisms producing error on go/no-go tasks. *J Cogn Neurosci, 21*(1), 93-104.

O'Sullivan, M., Jones, D., Summers, P., Morris, R., Williams, S., & Marcus, H., 2001 . 57 632-638. (2001). Evidence for cortical "disconnection" as a mechanism of age related cognitive decline. *Neurology, 57*, 632-638.

Ogilvie, R. D., A, S. L., Kuderian, R. H., T, M., & Rustenburg, J. (1991). Behavioural Event Related Potential, and EEg/FFT changes at sleep onset. *Psychophysiology, 28*, 54-64

Ong, A. D., & Allaire, J. C. (2005). Cardiovascular intraindividual variability in later life: the influence of social connectedness and positive emotions. *Psychol Aging, 20*(3), 476-485.

Otten, L. J., & Rugg, M. D. (2005). Interpreting event related potentials. In T. C. Handy (Ed.), *Event-Related Potentials a methods handbook.* (pp. 3-16). Massachusetts: MIT Press.

Paller, K. A. (1992). Brain potentials during memory retrieval provide neurophysiological support of the distinction between conscious recollection and priming. *Journal of cognitive neuroscience, 4*, 375-491.

Paller, K. A. (1995). Monitoring conscious recollection via the electrical activity of the brain. *Psychological science, 6*( ), 107-111.

Paller, K. A., Voss, J. L., & Boehm, S. G. (2007). Validating neural correlates of familiarity. *Trends Cogn Sci, 11*(6), 243-250.

Park, D. (1997). *Psychological issues related to competence: Cognitive aging and instrumental activities of daily living*. Mahwah, NJ: Erblaum.

Park, D. (1999). *Aging and the controlled and automatic processing of medical information and medical intentions.* Mahwah, NJ: Erblaum.

Park, D. (2000). The basic mechanisms accounting for age-related decline in cognitive function. In D. Park & N. Schwarz (Eds.), *Cognitive Aging A Primer*. New York: Psychology Press

Park, D. C., & Gutchess, A. H. (2005). Long-Term Memory and Aging: A cognitive Neuroscience Perspective. In R. Cabeza, L. Nyberg & D. Park (Eds.), *Cognitive Neuroscience of Aging*. Oxford: Oxford University Press.

Park, D. C., Lautenschlager, G., Hedden, T., Davidson, N. S., Smith, A. D., & Smith, P. K. (2002). Models of visuospatial and verbal memory across the adult life span. *Psychol Aging, 17*(2), 299-320.

Park, D. C., Polk, T. A., Park, R., Minear, M., Savage, A., & Smith, M. R. (2004). Aging reduces neural specialization in ventral visual cortex. *Proc Natl Acad Sci U S A, 101*(35), 13091-13095.

Parkin, A. J., & Lawrence, A. (1994). A dissociation in the relation between memory tasks and frontal lobe tests in the normal elderly. *Neuropsychologia, 32*, 1523-1532.

Passero, S., Rocchi, R., Vatti, G., Burgalassi, L., & Battistini, N. (1995). Quantitative EEG mapping, regional cerebral blood flow, and neuropsychological function in Alzheimer's disease. *Dementia, 6*(3), 148-156.

Perfect, T. J., Williams, R. B., & Anderton-Brown, C. (1995). Age differences in reported recollective experience are due to encoding effects, not response bias. *Memory, 3*(2), 169-186.

Peters, K. R., Graf, P., Hayden, S., & Feldman, H. (2005). Neuropsychological subgroups of cognitively-impaired-not-demented (CIND) individuals: delineation, reliability, and predictive validity. *J Clin Exp Neuropsychol, 27*(2), 164-188.

Petersen, R. (2004). Mild cognitive impairment as a diagnostic entity. *Journal of Internal Medicine 256*, 183-194.

Petit, J. P., Midgley, K. J., Holcomb, P. J., & Grainger, J. (2006). On the time course of letter perception: a masked priming ERP investigation. *Psychon Bull Rev, 13*(4), 674-681.

Petrides, M., & Milner, B. (1982). Deficits on subject ordered tasks after frontal- and temporal-lobe lesions in man *Neuropsychologia, 3*, 249-262.

Pfurtscheller, G. (1999). Event related sychronisation (ERS): an electrophysiological correlate of cortical areas at rest. *Electroencephalography and Clinical Neurophysiology, 110*, 1842-1857.

Pfurtscheller, G., & Lopes da Silva, F. H. (1999). Event-related EEG/MEG synchronization and desynchronization: basic principles. *Clin Neurophysiol, 110*(11), 1842-1857.

Picton, T. W., Bentin, S., Berg, P., Donchin, E., Hillyard, S. A., Johnson, R., Jr., et al. (2000). Guidelines for using human event-related potentials to study cognition: recording standards and publication criteria. *Psychophysiology, 37*(2), 127-152.

Pietrini, P., Alexander, G., Furey, M., Hampel, H., & Guazzelli, M. (2000). The neurometabolic landscape of cognitive decline: in vivo studies with

positron emission tomography in Alzheimer's disease. *Int J Psychophysiology, 37*, 87-98.

Pijnenburg, Y. A., v d Made, Y., van Cappellen van Walsum, A. M., Knol, D. L., Scheltens, P., & Stam, C. J. (2004). EEG synchronization likelihood in mild cognitive impairment and Alzheimer's disease during a working memory task. *Clin Neurophysiol, 115*(6), 1332-1339.

Plassman, B. L., Langa, K. M., Fisher, G. G., Heeringa, S. G., Weir, D. R., Ofstedal, M. B., et al. (2008). Prevalence of Cognitive Impairment without Dementia in the United States. *Annals of Internal Medicine, 148*(6), 427-W490.

Polich, J. (1997). EEG and ERP assessment of normal aging. *Electroencephalogr Clin Neurophysiol, 104*(3), 244-256.

Potts, G. F., & Tucker, D. M. (2001). Frontal evaluation and posterior representation in target detection. *Brain Res Cogn Brain Res, 11*(1), 147-156.

Princhep, L. S., John, E. R., H, F. S., Rausch, L., Fang, Z., Cancro, R., et al. (1994). Quantitative EEG correlates of cognitive deterioration in the elderly *Neurobiol Aging, 15*(1), 85-90.

Prull, M. W., Dawes, L. L., Martin, A. M., 3rd, Rosenberg, H. F., & Light, L. L. (2006). Recollection and familiarity in recognition memory: adult age differences and neuropsychological test correlates. *Psychol Aging, 21*(1), 107-118.

Rabbitt, P., Osman, P., Moore, B., & Stollery, B. (2001). There are stable individual differences in performance variability, both from moment to moment and from day to day. *Q J Exp Psychol A, 54*(4), 981-1003.

Raichle, M. E. (2006). Neuroscience. The brain's dark energy. *Science, 314*(5803), 1249-1250.

Raichle, M. E., MacLeod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., & Shulman, G. L. (2001). A default mode of brain function. *Proc Natl Acad Sci U S A, 98*(2), 676-682.

Ram, N., Rabbitt, P., Stollery, B., & Nesselroade, J. R. (2005). Cognitive performance inconsistency: intraindividual change and variability. *Psychol Aging, 20*(4), 623-633.

Ranganath, C., & Paller, K. A. (2000). Neural correlates of memory retrieval and evaluation. *Brain Res Cogn Brain Res, 9*(2), 209-222.

Rapp, P. R., & Gallagher, M. (1996). Preserved neuron number in the hippocampus of aged rats with spatial learning deficits. *Proc Natl Acad Sci U S A, 93*(18), 9926-9930.

Raz, N. (2000a). Aging of the brain and its impact on cognitive performance: integration of structural and functional findings. In F. I. Craik & T. A. Salthouse (Eds.), *The handbook of aging and cognition* (pp. 1-90). Mahwah NJ: Lawrence Erblaum Associates.

Raz, N. (2000b). *Aging of the brain and its impact on performance: Integration of structural and functional findings* (2nd ed.). Mahaw, NJ: Erblaum.

Raz, N., Lindenberger, U., Rodrigue, K. M., Kennedy, K. M., Head, D., Williamson, A., et al. (2005). Regional brain changes in aging healthy adults: general trends, individual differences and modifiers. *Cereb Cortex, 15*(11), 1676-1689.

Raz, N., & Rodrigue, K. M. (2006). Differential aging of the brain: patterns, cognitive correlates and modifiers. *Neurosci Biobehav Rev, 30*(6), 730-748.

Reuter-Lorenz, P. A. (2000). *Cognitive Neuroscience of the Aging Brain*. New York: Psychology Press.

Riis, J. L., Chong, H., McGinnnis, S., Tarbi, E., Sun, X., Holcomb, P. J., et al. (2009). Age-related changes in early novelty processing as measured by ERPs. *Biol Psychol, 82*(1), 33-44.

Ritchie, L. J., & Tuokko, H. (2010). Clinical decision trees for predicting conversion from Cognitive Impairment No Dementia (CIND) to dementia in a longitudinal population-based study. *Archives of Clinical Neuropsychology*(December 8).

Roberts, R. D., & Pallier, G. (2001). Individual differences in performance on elementary cognitive tasks (ECTs): lawful vs. problematic parameters. *J Gen Psycho, 128*, 279-314.

Robertson, I. H., Manly, T., Andrade, J., Baddeley, B. T., & Yiend, J. (1997). 'Oops!': Performance correlates of everyday attentional failures in traumatic brain injured and normal subjects. *Neuropsychologia, 35*(6), 747-758.

Rósler, F. (1983). Endogneous ERPs and cognition: Probes, prospects, and pitfalls in matching pieces of the mind-body problem. In A. W. K. Gaillard & W. Ritter (Eds.), *tutorials in event-related potential research: Endogenous components.* (pp. 9-35). Amsterdam: Elsevier.

Rossini, P. M., Rossi, S., Babiloni, C., & Polich, J. (2007). Clinical neurophysiology of aging brain: from normal aging to neurodegeneration. *Prog Neurobiol, 83*(6), 375-400.

Roubicek, J. (1977). The electroencephalogram in the middle-aged and the elderly. *J Am Geriatr Soc, 25*(4), 145-152.

Rowe, J., & Kahn, R. (1987). Usual and Successful Aging. *Science, 237*, 143-149.

Rubin, D. C. (1999). Frontal-striatal circuits in cognitive aging: Evidence for caudate involvement. Aging. *Neuropsychoogy and Cognition, 6*(241-259).

Rugg, M. D. (1995). *ERP studies of memory*. Oxford: Oxford University Press.

Rugg, M. D. (1998). An electrophysiological comparison of two indices of recollection *J of Memory and Language, 39*, 47-69.

Rugg, M. D., Allan, K., & Birch, C. S. (2000). Electrophysiological evidence for the modulation of retrieval orientation by depth of study processing. *J Cogn Neurosci, 12*(4), 664-678.

Rugg, M. D., Cox, C. J. C., Doyle, M. C., & Wells, T. (1995). Event-related potentials and the recollection of low and high frequency words. *Neuropsychologia, 33*(4), 471-484.

Rugg, M. D., & Curran, T. (2007). Event-related potentials and recognition memory. *Trends Cogn Sci, 11*(6), 251-257.

Rugg, M. D., Mark, R. E., Gilchrist, J., & Roberts, R. C. (1997). ERP repetition effects in indirect and direct tasks: effects of age and interitem lag. *Psychophysiology, 34*(5), 572-586.

Rugg, M. D., Mark, R. E., Walla, P., Schloerscheidt, A. M., Birch, C. S., & Allan, K. (1998). Dissociation of the neural correlates of implicit and explicit memory. *Nature, 392*(6676), 595-598.

Rugg, M. D., & Morcom, A. M. (2005). The relationship between brain activity, cognitive performance and aging: the case of memory. In R. Cabeza, L. Nyberg & D. Park (Eds.), *Cognitive Neuroscience of Aging Linking Cognitive and Cerebral Aging*. New York: Oxford University Press.

Rugg, M. D., & Yonelinas, A. P. (2003). Human recognition memory: a cognitive neuroscience perspective. *Trends Cogn Sci, 7*(7), 313-319.

Sakakura, K., Ishikawa, J., Okuno, M., Shimada, K., & Karia, K. (2007). Exaggerated ambulatory blood pressure variability is associated with cognitive dysfunction in the very elderly and quality of life in the younger elderly. *American Journal of Hypertension, 20*(7), 720-727.

Salat, D., Tuch, D., Greve, DN., van der Kouwe, A., Havelone, N., Zaleta, A., Rosen, B., et al. (2005). Age-related alterations in white matter microstructure measured by diffusion tensor imaging. *Neurobiol. Aging, 26*, 1215-1227.

Salthouse, T. A. (1985). *A cognitive theory of aging*. Berlin: Springer-Verlag.

Salthouse, T. A. (1991). *Theoretical Perspectives on cognitive aging*. Hilsdale New Jersey: Erblaum.

Salthouse, T. A. (1993). Speed mediation of adult age differences in cognition. *Developmental Psychology, 29*, 722-738.

Salthouse, T. A. (1996a). General and specific speed mediation of adult age differences in memory. *Journal of gerontology: Psychological Sciences, 51B*, 30-42.

Salthouse, T. A. (1996b). The processing speed theory of adult age differences in cognition. *Psychological Review, 103*, 403-428.

Salthouse, T. A., Atkinson, T. M., & Berish, D. E. (2003). Executive function as a potential mediator of age related cognitive decline in normal adults. *Journal of Experimental Psychology, 132*, 566-594.

Salthouse, T. A., & Ferrer-Caja, E. (2003). What needs to be explained to account for age-related effects on multiple cognitive variables? *Psychol Aging, 18*(1), 91-110.

Sanquist, T. F., Rohrbaugh, J. W., Syndulko, K., & Lindsley, D. B. (1980). Electrocortical signs of levels of processing: perceptual analysis and recognition memory. *Psychophysiology, 17*(6), 568-576.

Sarter, M., & Bruno, J. P. (1998a). Age-related changes in rodent cortical acetylcholine and cognition: main effects of age versus age as an intervening variable. *Brain Res Brain Res Rev, 27*(2), 143-156.

Sarter, M., & Bruno, J. P. (1998b). Cortical acetylcholine, reality distortion, schizophrenia, and Lewy Body Dementia: too much or too little cortical acetylcholine? *Brain Cogn, 38*(3), 297-316.

Sawaab, T. Y., Baynes, K., & Knight, R. T. (2002). Separable effects of priming an dimageability on word processing: an ERP study. *Brain ResearchCogn. Brain Research, 15*(1), 99-103.

Scarmeas, N., Albert, S. M., Manly, J. J., & Stern, Y. (2006). Education and rates of cognitive decline in incident Alzheimer's disease. *J Neurol Neurosurg Psychiatry, 77*(3), 308-316.

Schaie, K., Maitland, S., Willis, S., & Ntieri, R. (1998). Longitudinal invariance of adult psychometric ability factor structures across 7 years. *Psychology and Aging, 13*, 8-20.

Schaie, K. W. (1996). *Intellectual Development in Adulthood. The Seattle longitudinal study*. Cambridge: Cambrisge University Press.

Schmidt C, C. F., Cajochen C, Peigneux P. (2007). A time to think: circadian rhythms in human cognition. *Cogn Neuropsychol, 24*(7), 755-789.

Schonfield, D., & Robertson, B. A. (1966). Memory storage and aging. *Can J Psychol, 20*(2), 228-236.

Schurmann, M., & Basar, E. (2001). Functional aspects of alpha oscillations in the EEG. *Int J Psychophysiol, 39*(2-3), 151-158.

Schwartz, F., Carr, A. C., Munich, R. L., Glauber, S., Lesser, B., & Murray, J. (1989). Reaction time impairment in schizophrenia and affective illness: the role of attention. *Biol Psychiatry, 25*(5), 540-548.

Shallice, T., Marozocchi, G. M., Coser, S., Del Savio, M., Meuter, R. F., & Rumiati, R. I. (2002). Executive function profile of children with attention deficit hyperactivity disorder. *Developmental Neuropsychology, 21*(1), 43-71.

Shammi, P., Bosman, E., & Stuss, D. T. (1998). Aging and variability in performance. *Aging, Neuropsychology and Cognition, 5*(1), 1-13.

Shaw, J. C. (2003). *The brain's alpha rhythms and the mind*. Amsterdam: Elsevier Sciences.

Sheridan, P. H., Sato, S., Foster, N., & Bruno, G. (1988). Relation of EEG alpha background to parietal lobe function in Alzheimer's disease as measured by positron emission tomography and psychometry. *Neurology, 38*, 747-750.

Shimamura, A. P., & Jurica, P. J. (1994). Memory interference effects and aging: Findings from a test of frontal lobe function. *Neuropsychology, 8*, 408-412.

Shipley, B. A., Der, G., Taylor, M. D., & Deary, I. J. (2006). Cognition and all-cause mortality across the entire adult age range: health and lifestyle survey. *Psychosom Med, 68*(1), 17-24.

Sliwinski, M., & Buschke, H. . (1999). Cross-sectional and longitudinal relationships among age, cognition, and processing speed. *Psychology and Aging, 14*(1), 18-33.

Sliwinski, M., Lipton, R., Buschke, H., & Stewart, W. (1996). The effects of preclinical dementia on estimates of cognitive functioning in aging. *Journals of gerontology Psychological sciences J51B*, 217-225.

Sloane, P. D., Zimmerman, S., Suchindran, C., Reed, P., Wang, L., Boustani, M., et al. (2002). The public health impact of Alzheimer's disease, 2000-2050: potential implication of treatment advances. *Annu Rev Public Health, 23*, 213-231.

Small, B. J., Fratiglioni, L., Viitanen, M., Winblad, B., & Backman, L. (2000). The course of cognitive impairment in preclinical Alzheimer disease: three- and 6-year follow-up of a population-based sample. *Arch Neurol, 57*(6), 839-844.

Small, S. A. (2001). Age-related memory decline: current concepts and future directions. *Arch Neurol, 58*(3), 360-364.

Somsen, R. J., van't Klooster, B. J., van der Molen, M. W., van Leeuwen, H. M., & Licht, R. (1997). Growth spurts in brain maturation during middle childhood as indexed by EEG power spectra. *Biol Psychol, 44*(3), 187-209.

Sowell, E. R., Peterson, B. S., Thompson, P. M., Welcome, S. E., Henkenius, A. L., & Toga, A. W. (2003). Mapping cortical change across the human life span. *Nat Neurosci, 6*(3), 309-315.

Squire, L. R., & Zola-Morgan, S. (1991). The medial temporal lobe memory system. *Science, 253*(5026), 1380-1386.

Squires, K. C., Wickens, C., Squires, N. K., & Donchin, E. (1976). The effect of stimulus sequence on the waveform of the cortical event-related potential. *Science, 193*(4258), 1142-1146.

Starr, J. M., & Lonie, J. (2008). Estimated pre-morbid IQ effects on cognitive and functional outcomes in Alzheimer disease: a longitudinal study in a treated cohort. *BMC Psychiatry, 8*(27).

Steriade, M., Deschenes, M., Domich, L., & Mulle, C. (1985). Abolition of spindle oscillations in thalamic neurons disconnected from nucleus reticularis thalami. *J Neurophysiol, 54*(6), 1473-1497.

Steriade, M., Jones, E., & Llinas, R. (1990). *Thalamic occilations and signalling*. New York: Wiley.

Steriade, M., & Llinas, R. (1998). The functional states of the thalamus and the associated neuronal interplay. *Physiol. Rev., 68*, 649-742.

Stern, Y. (2002). What is cognitive reserve? Theory and research application of the reserve concept. *J Int Neuropsychol Soc, 8*(3), 448-460.

Stern, Y. (2009). Cognitive reserve. *Neuropsychologia, 47*(10), 2015-2028.

Stern, Y., Gurland, B., Tatemichi, T. K., Tang, M. X., Wilder, D., & Mayeux, R. (1994). Influence of education and occupation on the incidence of Alzheimer's disease. *JAMA, 271*(13), 1004-1010.

Stern, Y., Habeck, C., Moeller, J., Scarmeas, N., Anderson, K. E., Hilton, H. J., et al. (2005). Brain networks associated with cognitive reserve in healthy young and old adults. *Cereb Cortex, 15*(4), 394-402.

Strauss, E., MacDonald, S. W., Hunter, M., Moll, A., & Hultsch, D. F. (2002). Intraindividual variability in cognitive performance in three groups of older adults: cross-domain links to physical status and self-perceived affect and beliefs. *J Int Neuropsychol Soc, 8*(7), 893-906.

Stuss, D., & Binns, M. (2001). *Aging: Not an Escarpment, But Many Different Slopes.*

Stuss, D., Murphy, K., Binns, M., & Alexander, M. (2003). Staying on the job: The frontal lobes control individual performance variability. *Brain, 126*(11), 2363-2380.

Stuss, D. T., & Binns, M. A. (Eds.). (2008). *The patient as a moving target: the importance to rehabilitation of understanding variability* (2 ed.): Cambridge University Press.

Stuss, D. T., Pogue, J., Buckle, L., & Bondar, J. (1994). Characterization of stability of performance in patients with traumatic brain injury Variability and consistency on reaction time tests. *Neuropsychology,, 8*(3), 316-324.

Sullivan, E. V., & Pfefferbaum, A. (2006). Diffusion tensor imaging and aging. *Neurosci Biobehav Rev, 30*(6), 749-761.

Surwillo, W. (1961). Frequency of the alpha rhythm, reaction time and age. *Nature, 191*(823-824).

Surwillo, W. (1963). The relation of simple response time to brain-wave frequency and the effects of age,. *Electroencephalogr. Clin. Neurophysiol*, (15), 105-114.

Sutton, S., Braren, M., Zubin, J., & John, E. R. (1965). Evoked-potential correlates of stimulus uncertainty. *Science, 150*(700), 1187-1188.

Swick, D., & Knight, R. T. (1997). Event-related potentials differentiate the effects of aging on word and nonword repetition in explicit and implicit memory tasks. *J Exp Psychol Learn Mem Cogn, 23*(1), 123-142.

Tanaka, Y., Hanyu, H., Sakurai, H., Takasaki, M., & Abe, K. (2003). Atrophy of the substantia innominata on magnetic resonance imaging predicts response to donepezil treatment in Alzheimer's disease patients. *Dement Geriatr Cogn Disord, 16*(3), 119-125.

Thatcher, R. W., & John, E. R. (1977). *Functional Neuroscience, Foundations of cognitive Prcesses* (Vol. 1). Hillsdale NJ: Erblaum.

Tian, L., Jiang, T., Wang, Y., Zang, Y., He, Y., Liang, M., et al. (2006). Altered resting-state functional connectivity patterns of anterior

cingulate cortex in adolescents with attention deficit hyperactivity disorder. *Neurosci Lett, 400*(1-2), 39-43.

Tisserand, & Jolles. (2003). On the involvement of prefrontal networks in cognitive aging. *Cortex, 39*(4/5), 1107-1128.

Tombaugh, T. N., Kozak, J., & Rees, L. (1999). Normative Data stratified by age and education for two measures of verbal fluency: FAS and animal naming. *Archives of Clinical Neuropsychology, 14*, 167-177.

Torres, F., Faoro, A., Löwenson, R., & E. Johnson, E. (1983). The electroencephalogram of elderly subjects revisited,. *Electroencephalogr. Clin. Neurophysiol, 56*, 391-398.

Travis, F., & Wallace, R. K. (1999). Autonomic and EEG patterns during eyes-closed rest and transcendental meditation (TM) practice: the basis for a neural model of TM practice. *Conscious Cogn, 8*(3), 302-318.

Trott, C. T., Friedman, D., Ritter, W., & Fabiani, M. (1997). Item and source memory: differential age effects revealed by event-related potentials. *Neuroreport, 8*(15), 3373-3378.

Trott, C. T., Friedman, D., Ritter, W., Fabiani, M., & Snodgrass, J. G. (1999). Episodic priming and memory for temporal source: event-related potentials reveal age-related differences in prefrontal functioning. *Psychol Aging, 14*(3), 390-413.

Tulving, E. (1987). Multiple memory systems and consciousness. *Hum Neurobiol, 6*(2), 67-80.

Tulving, E. (1991). Concepts of human memory. In L. R. Squire (Ed.), *Organisation and locus of change.* New york: Oxford University Press.

Valentine, E. R. (1997). *Conceptual Issues in Psychology* (2nd ed.). London: Rutledge.

Van Boxtel, Buntinx, F., Houx, P., Metsemakers, J., Knottnerus, A., & Jolles, J. (1998). The relation between morbidity and cognitive performance in a normal aging population. *Journal of Gerontology, 53*, 147-154.

Van Boxtel, M., Van Beijsterveldt, C., Houx, P., Anteunis, L., Metsmakers, J., & Jolles, J. (2000). Mild hearing impairment can reduce verbal memory performance in a healthy adult population. *Journal of clinical and experimental neuropsychology, 22*, 147-154.

van der Hiele, K., Vein, A. A., Kramer, C., Reijntjes, R. H. A. M., van Buchem, M., Westendorp, R., et al. (2007). Memory activation enhances EEG abnormality in mild cognitive impairment. *Neurobiol Aging, 28*(1), 85-90.

van der Hiele, K., Vein, A. A., Reijntjes, R. H. A. M., Westendorp, R., Bollen, E. L. E. M., van Buchem, M., et al. (2007). EEG correlates in the spectrum of cognitive decline. *Clinical neurophysiology, 118*, 1931-1939.

Van Petten, C. (2004). Relationship between hippocampal volume and memory ability in healthy individuals across the lifespan: review and meta-analysis. . *Neuropsychologia, 42*(10), 1394 - 1413.

Van Strien, J. W., Verkoeijen, P. P., Van der Meer, N., & Franken, I. H. (2007). Electrophysiological correlates of word repetition spacing: ERP and induced band power old/new effects with massed and spaced repetitions. *Int J Psychophysiol, 66*(3), 205-214.

Vinogradov, S., Poole, J. H., Willis-Shore, J., Ober, B. A., & Shenaut, G. K. (1998). Slower and more variable reaction times in schizophrenia: what do they signify? *Schizophrenia Research, 32*(3), 183-190.

Vogel, E. K., & Luck, S. J. (2000). The visual N1 component as an index of a discrimination process. *Psychophysiology, 37*(2), 190-203.

Walhovd, K. B., & Fjell, A. M. (2007). White matter volume predicts reaction time instability. *Neuropsychologia, 45*(10), 2277-2284.

Walhovd, K. B., Fjell, A. M., Reinvang, I., Lundervold, A., Fischl, B., Quinn, B. T., et al. (2006). The functional and structural significance of the frontal shift in the old/new ERP effect. *Brain Res, 1081*(1), 156-170.

Wang, L., Zang, Y., He, Y., Liang, M., Zhang, X., Tian, L., et al. (2006). Changes in hippocampal connectivity in the early stages of Alzheimer's disease: evidence from resting state fMRI. *Neuroimage, 31*(2), 496-504.

Warren, L. R. (1980). Evoked potential correlates of recognition memory. *Biol Psychol, 11*(1), 21-35.

Wechsler, D. (1998). *WMS-III uk Administration and Scoring Manual (Third ed.)*: The Psychological corporation Limited.

Wegesin, D. J., Friedman, D., Varughese, N., & Stern, Y. (2002). Age-related changes in source memory retrieval: an ERP replication and extension. *Cognitive Brain Research, 13*(3), 323-338.

West, R. (2000). In defense of the frontal lobe hypothesis of cognitive aging. *J Int Neuropsychol Soc, 6*(6), 727-729; discussion 730.

West, R., Murphy, K. J., Armilio, M. L., Craik, F. I., & Stuss, D. T. (2002). Lapses of intention and performance variability reveal age-related increases in fluctuations of executive control. *Brain Cogn, 49*(3), 402-419.

West, R. L. (1996). An application of prefrontal cortex function theory to cognitive aging. *Psychol Bull, 120*(2), 272-292.

Westerberg, H., Hirvikoski, T., Forssberg, H., & Klingberg, T. (2004). Visuo-Spatial Working Memory Span: A Sensitive Measure of Cognitive Deficits in Children With ADHD. *Child Neuropsychology, 10*(3), 155 - 161.

Wickens, C., Kramer, A., Vanasse, L., & Donchin, E. (1983). Performance of concurrent tasks: a psychophysiological analysis of the reciprocity of information-processing resources. *Science, 221*(4615), 1080-1082.

Wijers, A. A., Mulder, G., Okita, T., Mulder, L. J., & Scheffers, M. K. (1989). Attention to color: an analysis of selection, controlled search, and motor activation, using event-related potentials. *Psychophysiology, 26*(1), 89-109.

Wilding, E. L., & Rugg, M. D. (1997). An event-related potential study of memory for words spoken aloud or heard. *Neuropsychologia, 35*(9), 1185-1195.

Wilkenson, G. S. (1993). *The Wide Range Achievment Test Administration Manual*: wide Range Inc.

Williams, B. R., Hultsch, D. F., Strauss, E. H., Hunter, M. A., & Tannock, R. (2005). Inconsistency in Reaction Time Across the Life Span. *Neuropsychology, 19*(q).

Winblad, B., Palmer, K., Kivipelto, M., Jelic, V., Fratiglioni, L., Wahlund, L. O., et al. (2004). Mild cognitive impairment – beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. *Journal of Internal Medicine 256*, 240-246.

Wingfield, A., & Stine-Morrow, E. A. I. (2000). Language and speech. . In F. I. Craik & T. A. Salthouse (Eds.), *The Handbook of Aging and Cognition* (pp. 359-416). New Jersey: Erblaum.

Wolk, D. A., Sen, N. M., Chong, H., Riis, J. L., McGinnis, S. M., Holcomb, P. J., et al. (2009). ERP correlates of item recognition memory: effects of age and performance. *Brain Res, 1250*, 218-231.

Wood, C. C. (1987). *Generators of event related potentials* (Vol. A textbook of clinical neurophysiology). New York: Wiley.

Woodruff, C. C., Hayama, H. R., & Rugg, M. D. (2006). Electrophysiological dissociation of the neural correlates of recollection and familiarity. *Brain Res, 1100*(1), 125-135.

Wylie, G. R., Javitt, D. C., & Foxe, J. J. (2003). Task switching: a high-density electrical mapping study. *Neuroimage, 20*(4), 2322-2342.

Ylikoski, R., Ylikoski, A., Keskivaara, P., Tilvis, R., Sulkava, R., & Erkinjuntti, T. (1999). Heterogeneity of cognitive profiles in aging: successful aging, normal aging, and individuals at risk for cognitive decline. *European Journal of Neurology, 6*, 645-652.

Yonelinas, A. P. (2002). The nature of recollection and familiarity. A review of 30 years of research. *Journal of Mmeory and Language, 46*, 441-517.

Yoon, C., May, C., & Hasher, L. (2000). *Aging, circadian arousal patterns, and cognition.* New York: Psychology Press.

Youngjohn, J. R., & Crook, T. H. (1993). Learning, forgetting, and retrieval of everyday material across the lifespan. *Journal of clinical experimental Neuropsychology, 15*, 447-460.

Zachs, R. T., & Hasher, L. (2005). Aging and Long-Term Memory: Deficits are not Inevitable. In E. Bialystock & F. I. Craik (Eds.), *Lifespan cognition Mechanisms of Change*. Oxford: Oxford University Press.

Zarahn, E., Rakitin, B., Abela, D., Flynn, J., & Stern, Y. (2007). Age-related changes in brain activation during a delayed item recognition task. *Neurobiol Aging, 28*(5), 784-798.

Zhang, Q., Guo, C. Y., Ding, J. H., & Wang, Z. Y. (2006). Concreteness effects in the processing of Chinese words. *Brain Lang, 96*(1), 59-68.

Zigmond, A. S., & Sims, A. C. (1983). The effect of the use of the International Classification of Diseases 9th revision: upon hospital in-patient diagnoses. *Br J Psychiatry, 142*, 409-413.