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Investigation of visual long-term potentiation and visual recognition memory in older adults:

Developing a protocol to identify an early marker of Alzheimer's disease

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A thesis submitted in partial fulfilment of the requirements for the degree of Doctorate of Clinical Psychology, University of Auckland, 2012

Abstract

This research aimed to investigate recognition memory and electrophysiological functioning of healthy older adults in order to establish a procedure that could potentially be developed and tested in the future for utility as an early AD marker. This project was comprised of two parts: a recognition memory study and an electrophysiological study that used electroencephalography. The rationale underlying the recognition memory study was guided by two bodies of research. The first relates to findings that AD neuropathology develops first in perirhinal and entorhinal cortices, prior to the hippocampus. The second body of research relates to a model of recognition memory, which implicates a key role of the hippocampus in recollection and the involvement of perirhinal cortex in familiarity-based recognition. Together these two bodies of research suggest that assessing familiarity and recollection recognition, which are reliant on distinct medial temporal lobe regions that are differentially impacted early in the course of AD, may provide a sensitive memory test able to detect the earlier changes associated with AD. Research examining recognition memory in AD and MCI has produced conflicting findings. This study aimed to test and further develop the learning parameters for two recognition memory tasks. Participants were tested on two versions of recognition memory tasks: a replication of the task used by Westerberg et al.'s (2006) and an experimental task, in which the learning procedure was modified with the aim of reducing recollection learning. Both included a yes-no task (recollection) and a forced choice task (familiarity). The results indicated that the performance of healthy older adults on the tasks of recognition memory was reduced on the experimental procedure relative to the replication task. This suggests that opportunities for learning material were reduced by conditions of the experimental task as hypothesised. This study also found that older adults performed equally on the tests of the experimental procedure,

suggesting that the tests show an equal level of difficulty. These tests may, thus, be useful for further research with patient groups as interpreting a difference in performance on the yes-no and forced-choice tasks will not be confounded by differential difficulty of the two tasks.

The EEG study measured induction of long-term potentiation (LTP), a molecular mechanism thought to underlie memory formation in older adults. This study used a protocol that has successfully induced an LTP-like effect in young adults through the repeated brief presentation of a simple visual stimulus (tetanic stimulation). The results suggest that LTP may be induced and maintained over 30 minutes in healthy older adults. When examining possible relationship between visual LTP activity and memory performance, a significant correlation was found between the magnitudes of late LTP and forced-choice recognition memory scores (familiarity) on the experimental test procedure.

The findings of this research, thus, provide a foundation to guide further research in explicating the potential role of LTP in older adults as a marker of subtle neuropathological change related to early AD or MCI. The study findings indicate that the recognition protocol, on which the experimental task is based, may offer greater sensitivity in detecting early or transitional changes in individuals with AD and MCI. The current study, hence, provides a platform for further longitudinal research which can clarify the contribution of LTP as a biomarker of early cognitive change and provide opportunities for convergence with existing biomarkers from neuroimaging and biochemical paradigms.

Acknowledgements

I would like to express my deep gratitude to all participants who generously volunteered their time and made great efforts in performing this study. I sincerely thank them for making this study possible.

I owe a great debt to my supervisors, Dr Lynette Tippett and Associate Professor Ian Kirk, for their ongoing assistance and guidance. Their comprehensive knowledge, extensive experience, constructive criticism, passion and unswerving belief in the meaning of this work enabled fulfilment of this thesis.

I am greatly indebted to my mother, Vera, and son, Sasha, for their patience at times I had to devote myself to the thesis. I thank them for their unconditional love, acceptance, understanding and compassion. They provide stimulating and supportive environment enabling me to focus on what is meaningful to me.

I am grateful for the emotional and intellectual support to my dearest friend, Anna Clarkson, whose encouragement, wisdom, and consolation at times of need were necessary to sustain me throughout this work.

I would like to acknowledge all researchers who conducted studies I have used to develop and write my thesis. Their work, dedication, and knowledge were critical in conceptualisation of this thesis.

With special thanks to all others who have inspired, guided and encouraged me in some way throughout this journey, Chris Thompson, Gjurgjica Badzakova, Andrew Bakach, Nadejda, Nika and Leosha Koulikovi.

To all, my deepest gratitude.

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Abbreviations

AD	Alzheimer's disease
Ag/AgCl	Silver/Silver chloride
AMPA	α-amino-3-hydroxy-5-Methyl-4-isoxazolepropinate
ANOVA	Analysis of variance
AP	Amyloid plaques
APP	Amyloid precursor protein
BDNF	Brain-derived neurotrophic factor
Ca^{2+}	Calcium
CLS	Complementary learning systems
Cm	Centimetres
cpd	Cycles-per-degree
CT	Computerized tomography
Cz	Common vertex
DNMS	Delayed non-matching-to-sample task
EEG	Electroencephalography
EPSP	Excitatory post-synaptic potential
FA	False alarm
FAT	False alarm rate
fMRI	Functional magnetic resonance imaging
H:	Hit
HR:	Hit rate
Hz	Hertz
kΩ	Kilo ohm

LTP	Long term potentiation
µV	Microvolt
M	Mean
Mg^{2+}	Magnesium
MCI	Mild cognitive impairment
MMSE	Mini-Mental State Examination
MRI	Magnetic resonance imaging
Ms	Millisecond
MTL	Medial temporal lobe
Na^{+}	Sodium
NFT	Neurofribrillary tangles
NMDA	N-Methyl-D-aspartate receptor
p(c)	Percent Correct
R/K	Remember/Know
ROC	Receiver operating characteristics
SD	Standard deviation
SDT	Signal detection theory
SPSS	Statistical packages for the social sciences
STP	Short term potentiation
SVGA	Super video graphics array

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Overview

Alzheimer's disease (AD) is a worldwide public health concern of the highest priority. It is one of the most complex and perplexing neurodegenerative diseases with no current means of cure. AD is also the most common form of dementia afflicting millions of older adults (Aronson, Ooi, Geva, Masur, Blau, & Frishman, 1991; Lobo et al., 2000; Tognoni et al., 2005; Wimo, Winblad, Aguero-Torres, & von Strauss, 2003). The impact of AD on society and on the lives of affected individuals and their families is formidable. AD significantly impairs the quality of life of individuals and their family members, engenders numerous psychosocial problems, hastens death, and contributes to socio-economic burden (Aronson et al., 1991; Baldereschi et al., 1999; Ewbank, 1999; Katzman et al., 1994; Richter & Richter, 2004).

AD has a distinctive clinical presentation, initially demonstrated by memory deficits with further decline in multiple domains of cognitive functioning and eventual loss of ability to self-care (Almkvist, 1996). Currently, clinical and research settings lack an operational tool which can detect AD in the preclinical stage. There is, thus, a compelling urgency in the need to develop an early marker of AD (Blennow, 2010; Blennow, de Leon, & Zetterberg, 2006; Forlenza, Diniz, & Gattaz, 2010). This would provide a tool that could identify a valuable window of time in which therapeutic interventions might potentially arrest and prevent progression of AD pathology before neural damage reaches an irreversible stage (Aisen et al., 2011; Blennow, 2010). A number of clinical trials have been, and continue to be, launched testing the efficacy of drugs

aiming to delay the progression of the disease. When effective pharmacological compounds become available in the future, the ability to detect AD in its very earliest stage will be crucial (Aisen et al., 2011; Blennow, 2010; Rafii & Aisen, 2009; Tuszynski et al., 2005).

Additionally, identification of an early marker of AD will be of value to individuals with diagnosis of mild cognitive impairment (MCI). MCI is recognized as a syndrome of cognitive decline, commonly involving memory deficits, to a greater extent than expected for an individual's age and educational level. Unlike AD patients, individuals with MCI possess intact ability to perform activities of daily living (Petersen & Bennett, 2005; Petersen et al., 2009; Winblad et al., 2004). MCI is considered to be a preclinical stage of AD for many individuals, due to its high conversion rate to dementia and its shared clinical and neuropathological appearance with AD (Petersen & Bennett, 2005; Petersen et al., 2009; Winblad et al., 2004). Nonetheless, not all individuals with MCI diagnosis progress to AD, with a significant proportion remaining stable (Petersen & Bennett, 2005; Petersen et al., 2009; Winblad et al., 2004).

Identification of an early AD marker has the potential to differentiate between progressive and static conditions underlying MCI in individual cases. This will both alleviate anxiety in patients and their families regarding prognosis of their future cognitive functioning and well-being and provide an opportunity for early intervention (Austrom & Lu, 2009; Joosten-Weyn Banningh, Vernooij-Dassen, Rikkert, & Teunisse, 2008; Lu & Haase, 2009). Potential benefits and

opportunities associated with development of an early marker of AD provided the motivation for development of the research aims of this thesis.

The main aim of this research was to develop a protocol that has the potential to identify an early marker of AD. The research described in this thesis involves the first phase of the protocol development, investigating mnemonic and electrophysiological functioning of healthy older adults on tasks which are mediated by neural areas where AD neuropathology originates. In later phases of the research, performance of healthy older adults will be compared to AD and MCI individuals

The present study consisted of two components: cognitive and electrophysiological measurements. First, the performance of healthy older adults on recognition memory tests was examined. Second, long-term potentiation, a physiological mechanism which underlies memory formation, was examined using electroencephalography (EEG). Finally, the results attained from cognitive and electrophysiological paradigms were correlated to assess whether there is a relationship between the two types of variables that could be used to underpin the development of a protocol sensitive to the early stages of AD.

This thesis is comprised of 5 chapters. The first three chapters present a comprehensive review of the research that guided the development of the current study. Chapter 1 focuses on a broad overview of the literature on Alzheimer's disease and mild cognitive impairment. Chapter 2 critically evaluates research assessing the validity of a neuro-anatomical model of recognition

memory, which plays an instrumental role in the design of this research. This chapter also provides an account of the rationale for the development of the neuropsychological component of the current study. This is followed by Chapter 3, which outlines a molecular mechanism of memory formation, LTP, and explores studies that allow detection of LTP in humans via non-invasive electroencelographic means. The rationale for the development of electrophysiological component of the research in this thesis is also explained in the final introductory chapter.

Chapter 4 describes the recognition memory study, defining hypotheses, the methodology, results and discussion, while Chapter 5 delineates the electrophysiological study, presenting hypotheses, the methodology, results and discussion. This chapter also integrates the results of the neuropsychological and electrophysiological studies, and discusses implications, the strengths and limitations of the current research.

CHAPTER 1

Alzheimer's disease &

Mild Cognitive Impairment

This chapter presents a broad overview of research on Alzheimer's disease and mild cognitive impairment, providing data on prevalence, neuropathology, and clinical features. This chapter also describes stages of neuropathological progression of AD. The hierarchical progression of AD pathology provides a key part of the rationale for the approach taken in the present research.

Alzheimer's disease

Alzheimer's disease is a neurodegenerative disorder of insidious onset and slowly progressing course (Khachaturian, 1985). It mainly affects the older population and accounts for the preponderance of dementia cases (Lee et al., 2002; Tognoni et al., 2005). The prevalence of AD is below 1% in people aged 60-64 years, but exponentially increases with age, afflicting approximately 10% of individuals older than 65 and 30% of people over the age of 80 (Aronson et al., 1991; Ebly, Parhad, Hogan, & Fung, 1994; Lee et al., 2002; Lobo et al., 2000; Tognoni et al., 2005).

AD is marked by progressive and irreversible decline of cognitive functioning, advancing by stages (Richter & Richter, 2004). In the earliest stage, the cardinal symptom of AD is memory disturbance, specifically characterized by difficulty in the acquisition and retention of new information (Almkvist, 1996; Carlesimo & Oscar-Berman, 1992; Herlitz, Hill, Fratiglioni, & Backman, 1995; Kasai, Meguro, Hashimoto, Ishizaki, Yamadori, & Mori, 2006; Locasio, Growdon, & Corkin, 1995; Rickert, Duke, Putzke, Marson, & Graham, 1998).

Over time, mental functions and activities of daily living progressively deteriorate, impairments of judgement, deficits in language and visuospatial skills emerge and personality changes appear (Almkvist, 1996; Herlitz et al., 1995; Richter & Richter, 2004; Schultz, Tredici, & Braak, 2004). At later stages, individuals lose reasoning abilities, the capacity to self-care and may present with severe psychiatric symptoms including hallucinations and delusions as well as behavioural difficulties of aggression and violence (Richter & Richter, 2004). At this stage, they may become mute, incontinent, and bedridden and develop coexisting medical illnesses, from which they usually die (Richter & Richter, 2004).

The rate of cognitive deterioration varies individually as does the survival time from the onset of symptoms to the end of life, ranging from 2 to 15 years (Richter & Richter, 2004). A number of studies have estimated the average survival rate of AD to be five years from presentation of clinical symptoms (Helmer, Joly, Letenneur, Commenges, & Dartigues, 2001; Wolfson et al., 2001).

Aetiology of AD

Causes of AD are still largely undetermined (Richter, 2004; Schultz et al., 2004). An emerging body of research suggests that AD is best understood as a complex disorder in which genetic and environmental factors play contributing roles (Richter, 2004; Schultz et al., 2004). Besides aging, which presents the most palpable risk factor, several tentative aetiological associations have been proposed, including genetic predisposition, low educational and occupational attainment and exposure to toxins (Gatz et al., 2006; Letenneur, Gilleron, Commenges, Helmer, Orgogozo, & Dartigues, 1999; Mayeux, 2003; Mortimer, Snowdon, & Markesbery, 2003; Schmand et al., 1997; Scwartz et al., 2000; Tyas, Manfreda, Strain, & Montgomery, 2001; Zhang et al., 1990). To date, research has failed to conclusively establish causative factors of this profoundly debilitating illness.

Pathogenesis of AD

In contrast to the limited understanding of the aetiology of AD, its pathogenesis is well defined. Deterioration of cognitive functioning appears to result from gradual neuronal loss across most brain regions (Braak, Braak, & Mandelkow, 1994). Processes that instigate neuronal degradation are associated with development of amyloid plaques (AP) and neurofribrillary tangles (NFT) (Braak et al., 1994; Khachaturian, 1985). Abnormal density and distribution of AP and NFT comprise essential criteria for establishing a definite diagnosis of AD at post-mortem (Goedert, 1993; Hyman, 1998; Hyman & Trojanowski, 1997). These pathological features are products of abnormal metabolism and folding of neuronal proteins which are normally involved in vital

processes in the central nervous system (Glenner & Wong, 1984; Iqbal et al., 2005).

Amyloid plaques are comprised of dense extracellular fibrils, which are generated through structural disintegration of amyloid precursor proteins via proteolysis (Glenner & Wong, 1984). Amyloid precursor protein is an integral membrane glycoprotein, shown to participate in a number of activities in the nervous system, including cell adhesion, signal transduction, synapse formation and neuronal growth (Glenner & Wong, 1984; Klier, Cole, Stalleup, & Schubert, 1990; Nishimoto, Okamoto, Matsuura, Takahashi, Murayama, & Ogata, 1993; Saitoh et al., 1989; Schubert, Jin, Saitoh, & Cole, 1989; Strooper & Annaert, 2000).

Neurofibrillary tangles are composed of collections of helical filaments inside the nerve cells (Goedert, 1993; Grundke-Iqbal, Iqbal, Quinlan, Tung, Zaidi, & Wisniewski, 1986; Grundke-Iqbal, Iqbal, Tung, Quinlan, Wisniewski, & Binder, 1986; Iqbal et al., 1998). Production of paired filaments is caused by hyperphosphorylation of intracellular protein tau (Goedert, 1993; Goedert, Spillantini, Cairns, & Crowther, 1992; Iqbal et al., 1998; Iqbal, Grundke-Iqbal, Smith, George, Tung, & Zaidi, 1989; Lee, Balin, Otvos, & Trojanowski, 1991). In non-phosphorylated active form, tau normally ensures assembly and stability of microtubules, which are responsible for transporting substances between neuronal cellular compartments (Binder, Frankfurter, & Rebhun, 1985; Drechsel, Hyman, Cobb, & Kirschner, 1992; Weingarten, Lockwood, Hwo, & Kirschner, 1975). Damage of neurons by AP and NFT and subsequent disruption of activities facilitated by tau and amyloid proteins lead to a cascade of events that eventually results in neuronal death (Alonso, Zaidi, Grundke-Iqbal, & Iqbal, 1994; Goedert, 1993; Hyman & Gomez-Isla, 1994; Iqbal et al., 1986; Iqbal et al., 1998; Iqbal et al., 2005; Lindwall & Cole, 1984).

Stages of Neuropathological Progression

Braak and associates, who examined brains of healthy older adults and individuals presenting at different stages of AD, noted a distinct pattern of progression of AP and NFT through cortical areas, which led to their description of stages of neuropathological progression in AD (Braak & Braak, 1991; Braak & Braak, 1994; Braak & Braak, 1997a; Braak & Braak, 1997b; Braak, Braak, & Bohl, 1993).

Accumulation of amyloid plaques is demonstrated to occur in three stages (Braak & Braak, 1997b). They first appear in the perirhinal and entorhinal areas (Stage A), then spread into the hippocampal formation (Stage B), and eventually reach all cortical areas, including primary fields of the neocortex (Stage C) (Braak & Braak, 1997b, refer to Figure 1 to view neuroanatomy of medial temporal lobe).

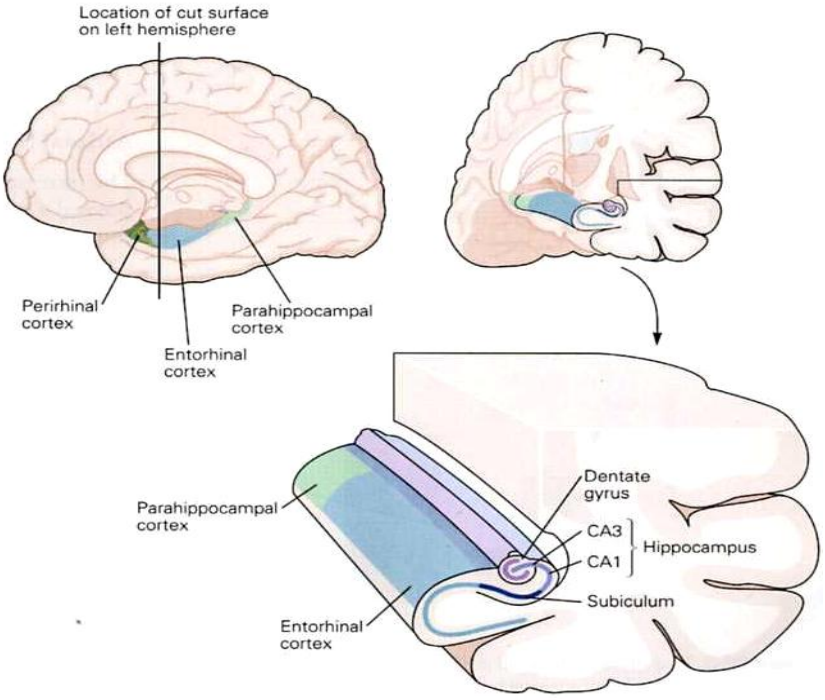


Figure 1. The medial temporal system; hippocampal system = layers CA1-3, subicular complex and dentate gyrus, parahippocampal system = perirhinal, entorhinal and parahippocampal cortices (Kandel, Schwartz, & Jessel, 2000, p.1232).

Aggregation of neurofibrillary tangles has been differentiated into six stages (Braak & Braak, 1991; Braak & Braak, 1994; Braak & Braak, 1997a, 1997b; Braak et al., 1993). Initially, NFT affect the transentorhinal area and perirhinal cortex (Stage I), gradually progressing into the entorhinal region (Stage II) (Braak & Braak, 1991; Braak & Braak, 1994; Braak & Braak, 1997a, 1997b; Braak et al., 1993; Galton et al., 2001; Gomez-Isla, Price, McKeel, Morris, Growdon, & Hyman, 1996; Van Hoesen, Hyman, & Damasio, 1991). They then advance to the hippocampal formation proper (Stage III) with later infiltration of all temporal and basal neocortex (Stage IV). The pathological process of NFT further extends to adjoining higher-order multimodal association areas and finally damages primary areas, disabling sensory and motor areas (Stage

VI) (Braak & Braak, 1991; Braak & Braak, 1994; Braak & Braak, 1997a, 1997b; Braak et al., 1993).

Diagnosis of AD

Clinical diagnosis of probable AD follows evidence of a progressive deterioration of cognitive functioning within at least two cognitive domains, one of which should be memory, and exclusion of other possible causes of this deterioration (American Psychiatric Association, DSM 4th edition-Revised, 2000). Changes in other cognitive domains may include deficits in language, visuospatial skills, and executive functioning. Importantly, the extent of cognitive impairment should be significant enough to adversely affect the activities of daily living of an older person and other aspects of his/her life, such as occupational and social activities (American Psychiatric Association, DSM 4th edition-Revised, 2000). A profile of cognitive functioning is established through neuropsychological assessment, which is essential to inform diagnostic decision and document the progression of clinical symptoms over the course of the illness (Almkvist & Winblad, 1999; Blennow et al., 2006; Knopman et al., 2001; Taylor & Monsch, 2004). It should be noted that new diagnostical criteria are currently under revision.

Mild Cognitive Impairment

In clinical practice numerous older adults present with negative changes in cognitive functioning despite relatively intact abilities in their execution of daily activities (Bennett et al., 2002; Petersen et al., 2009; Petersen, Smith, Waring, Ivnik, Tangalos, & Kokmen, 1999; Visser, 2004; Wahlund, Pihlstrand, & Jonhagen, 2003). In such circumstances, individuals are diagnosed with

mild cognitive impairment (MCI) which implies impairment in cognitive functioning with intact or minimally impaired capacity to participate in daily affairs and engage in social, occupational, and personal spheres of life (Bennett et al., 2002; Petersen et al., 2009; Visser, 2004; Wahlund et al., 2003; Winblad et al., 2004). The most common presentation of MCI is amnestic MCI, comprising a sole deficit in memory function. This type has been a main focus of research and represents interest to the current study (Petersen et al., 2009; Wahlund et al., 2003; Winblad et al., 2004).

Prevalence and Conversion Rate

Estimates of the prevalence of MCI in older adults range from 3% to 20% (Busse, Bischkopf, Riedel-Heller, & Angermeyer, 2003; Das et al., 2007; Ganguli, Dodge, Shen, & DeKosky, 2004; Hanninen, Hallikainen, Tuomainen, Vanhanen, & Soininen, 2002; Kumar et al., 2005; Larrieu et al., 2002; Lee et al., 2009; Lopez et al., 2003; Ravaglia et al., 2008; Ritchie, Artero, & Touchon, 2001; Tognoni et al., 2005). Higher figures are documented in studies in which the MCI sample includes wider age spans, inclusion of different types of MCI and selection of participants from clinical settings (Fisk, Merry, & Rockwood, 2003; Ganguli et al., 2004; Lee et al., 2009; Ravaglia et al., 2008). Estimated rates of progression from MCI to AD are 10-15% per year, compared to only 1-2% in older adults without an MCI diagnosis (Busse et al., 2003; Farias, Mungas, Reed, Harvey, & DeCarli, 2009; Jack et al., 1999; Larrieu et al., 2002; Petersen, 2001; Ravaglia et al., 2008). The risk of conversion is shown to increase with time (Ganguli et al., 2004). Follow-up investigations indicate that between 50-70% of MCI individuals will develop AD over a period of 5-10 years (Ganguli et al., 2004; Hansson, Zetterberg, Buchhave, Londos, Blennow, & Minthon, 2006; Ishikawa, Ikeda, Matsumoto, Shigenobu, Brayne, & Tanabe, 2006;

Jack et al., 1999; Mitchell, Arnold, Dawson, Nestor, & Hodges, 2009; Ritchie et al., 2001; Wahlund et al., 2003).

Pathology

The pattern of memory impairment of MCI individuals closely resembles that of clinically diagnosed AD with significant deficits in learning and retaining new information (Gavrilova, Fedorova, Roshchina, & Korovaitseva, 2008, Greenaway, Lacritz, Binegar, Weiner, Lipton, & Cullum, 2006; Perri, Carlesimo, Serra, Caltagirone, & the Early Diagnosis Group, 2005; Perri, Serra, Carlesimo, Caltagirone, & the Early Diagnosis Group, 2007; Ritter, Despres, Monsch, & Manning, 2006).

Neuroimaging and autopsy studies indicate that neuropathology of MCI commonly includes prominent features of AD neuropathology, particularly an abundance of amyloid plaques and neurofibrillary tangles and atrophy of medial temporal lobe structures, including the hippocampus, entorhinal and perirhinal cortices (Apostolova et al., 2006; Bell-McGinty et al., 2005; DeToledo-Morrell et al., 2004; Devanand et al., 2007; Dickerson et al., 2001; Du et al., 2001; Du et al., 2004; Jack et al., 2000; Jicha et al., 2006; Juottonen et al., 1998; Mufson, Chen, Cochran, Beckett, Bennett, & Kordower, 1999; Muth, Schonmeyer, Matura, Haenschel, Schroder, & Pantel, 2010; Pennanen et al., 2004; Petersen et al., 2006; Saito & Murayama, 2007; Schneider, Arvanitakis, Leurgans, & Bennett, 2009; Stoub et al., 2005). The findings from diverse areas of research, hence, indicate that MCI syndrome frequently forms a preclinical stage of AD (Bennett et al., 2002; Petersen et al., 2009; Winblad et al., 2004).

Heterogeneity of MCI

Not all MCI individuals, however, evolve to develop clinical AD. Indeed a considerable proportion of patients who experience problems associated with a diagnosis of MCI remain stable (Apostolova et al., 2006; Gavrilova et al., 2008; Jack et al., 2000; Larrieu et al., 2002). Numerous research endeavours have found that 30% of MCI sufferers do not show any further cognitive deterioration after prolonged follow-up periods varying between two and ten years, which is incongruent with the typical clinical course of AD (Fisk et al., 2003; Ganguli et al., 2004; Hansson et al., 2006; Mitchell et al., 2009; Ravaglia et al., 2008; Ritchie et al., 2001; Wahlund et al., 2003).

Research suggests that MCI is not a unitary disease, but rather a heterogeneous concept, incorporating evolving and stable states (Winblad et al., 2004). No diagnostic parameters are currently available that reliably differentiate progressive MCI from stable MCI (Visser, 2004). Development of a sensitive prognostic tool/s that enables clinicians to predict the cognitive outcome of individuals with MCI has been a major focus of recent research endeavours. Additionally, such an instrument/s might potentially serve as an early marker of AD, which would allow implementation of curative and preventive therapies at the earliest stage of disease manifestation before neuropathological damage reaches irreversible levels (Diaz-Arrastia & Baskin, 2004; Welsh-Bohmer, Hulette, Schmechel, Burke, & Saunders, 2001).

A number of possible clinical markers have recently emerged in the research arena with potential to predict the trajectory of MCI and detect AD in its preclinical stage. They include positive testing for apolipoprotein E4 gene, presence of high levels of protein tau in cerebrospinal fluid and atrophy of entorhinal and hippocampal regions (Andreasen et al., 1999; Dickerson et al., 2001; Hansson et al., 2006; Jack et al., 2000; Stoub et al., 2005; Tang & Kumar, 2008). Evidence of histopathological substances in the form of amyloid-β 42, total tau and phosphorylated tau in the cerebrospinal fluid currently constitute the leading diagnostic biomarkers of AD (Holtzman, 2011). A series of studies found that individuals with AD show a significant reduction in amyloid-β 42 and increase in total tau and phosphorylated tau in cerebrospinal fluid compared to healthy older adults (Holtzman, 2011; Mattsson, Zetterberg, & Blennow, 2010). Research also implicated decreased levels of amyloid-β 42 and increased concentration of total tau and phosphorylated tau in patients with MCI who later converted into AD (Holtzman, 2011; Mattsson, Zetterberg, & Blennow, 2010). A longitudinal research project, using structural neuroimaging techniques, revealed that MCI individuals who progress to AD are best differentiated from non-converters on the basis of the entorhinal cortex volume and some regions (subiculum and CA1 subfield) of the hippocampal volume (Apostolova et al., 2006; Dickerson et al., 2001). The volumes of these structures are also found to reliably differentiate AD patients from healthy older adults (Du et al., 2004). Although these tools provide a promising foundation for potential development of early markers for AD, currently they lack sufficient specificity and sensitivity to be reliable and valid diagnostic measures. For example, it has been found that healthy older adults can possess similar neuropathological characteristics to those detected in AD and MCI (Holtzman, 2011). Some biochemical markers, such as amyloid-β 42 and tau levels, don't correlate with AD severity and can be observed in other

neurodegenerative diseases (i.e., tau concentration) (Holtzman, 2011). Importantly, most research on biomarkers use between-group design, which are likely bound to series confounding factors inherent in individual differences' presentation. The above limitations, therefore, greatly limit specificity and sensitivity of currently identified biomarkers. Further, they are based on the detection of structural and metabolic deficits that are evident at later stages of disease progression, so by the time individuals are diagnosed with MCI the neural damage might become too severe and extensive for potential therapeutic damage to induce desired effect (Mattsson et al., 2010; Tang & Kumar, 2008).

The focus of the current research was to design a protocol that may lead to identification of an early marker of AD with potential to add value to currently identified biomarkers. The approach utilised involved convergence of two methodologies. The first method was based on evidence from autopsy studies revealing hierarchial progression of AD neuropathology and on evidence from studies supporting a neuro-anatomical model of recognition memory, which identifies differential roles of perirhinal cortex and hippocampus in recognition memory (see Chapter Two). The first method led to development of recognition memory study, which assessed dual processes of recognition memory in older adults. The second method involved measuring long-term potentiation (LTP) in older adults, a molecular mechanism underlying the formation of memory, using an experimental protocol developed by the Research Centre for Cognitive Neuroscience at the University of Auckland. Recent studies have discovered significant disruption of LTP by neuropathological mechanisms involved in AD pathogenesis (see Chapter Three).

CHAPTER 2

Neuro-Anatomical Model of Recognition Memory

Aggleton and Brown (1999) proposed a neuro-anatomical model of recognition memory, which implicates differential involvement of hippocampus and perirhinal cortex in recognition memory processes. Based on evidence from animal and neuropsychological studies, Aggleton and Brown argue that the hippocampal network system is involved in recollective recognition memory while the perirhinal network system is involved in mediation of familiarity-based recognition (Aggleton & Brown, 1999; Aggleton & Brown, 2006; Brown, Warburton, & Aggleton, 2010). Given this proposition and findings demonstrating that AD neuropathology originates in perirhinal cortex before spreading further to the hippocampus, there is the possibility that studying recognition memory in AD and MCI may lead to identification of an early marker of AD. First, however, it is critically important to review research upon which this neuro-anatomical recognition memory model was developed and corroborated, to ensure its validity before applying it to the study of recognition memory in AD and MCI. This critical review is one of the main objectives of this chapter. Further aims of the chapter are to review existing literature on assessment of recognition memory performance in AD and MCI.

Recognition Memory

A single exposure to a stimulus, whether it is a person, event, or an object, is enough to induce neural changes for the information to be registered, processed and retrieved on its following encounter. This sensitivity is the result of an intricate mnemonic phenomenon known as recognition memory (Yonelinas, 2002). Numerous findings indicate that recognition memory reflects two distinct mnemonic processes: recollection and familiarity (Gardiner, 1988; Jacoby, 1991; Mandler, 1980; Tulving, 1985; Yonelinas, 1999, 2001, 2002; Yonelinas, Dobbins, Szymanski, Dhaliwal, & King, 1996; Yonelinas & Jacoby, 1996). Recollection refers to recognition of a stimulus in conjunction with recollection of its details and contextual environment accompanying an initial presentation of that stimulus, whereas familiarity refers to a feeling that an item has been experienced prior, however, is devoid of contextual details of that item (Gardiner, 1988; Jacoby, 1991; Mandler, 1980; Tulving, 1985; Yonelinas, 1999, 2001, 2002; Yonelinas et al., 1996; Yonelinas & Jacoby, 1996). This distinction can be illustrated by a common experience of recognizing a person as familiar yet being unable to recollect any qualitative information about that person, such as the name or the place that person has been met before.

Evidence for dual processes of recognition memory originated from cognitive research, which revealed that recollection and familiarity exhibit distinct functional characteristics. For instance, recollection has been found to be slower compared to familiarity-based recognition (Yonelinas & Jacoby, 1994, 1996). Additionally, several studies have documented a negative effect of divided attention during encoding and retrieval phases on recollection in contrast to familiarity which

shows minimal response to divided attention (Gardiner & Parkin, 1990; Gruppuso, Lindsay, & Kelley, 1997; Yonelinas, 2001). Conversely, performance accuracy of familiarity significantly declines with an increase in time between the presentation of items and their subsequent retrieval, while recollection remains intact (Hockley, 1992; Yonelinas & Levy, 2002).

Neuro-Anatomical Model of Recognition Memory

A number of neuro-anatomical models have been introduced to account for functional differentiation of retrieval processes of recognition memory (Yonelinas, 2002). The one that has received the most empirical support is the model proposed by Aggleton and Brown (1999), who posit that retrieval processes of recognition memory are reliant on interactive, but dissociable neural circuits. Based on evidence from animal and neuropsychological research, Aggleton and Brown suggest that the hippocampal network supports processes of recollection, while the perirhinal network subserves familiarity-based recognition, independently of the hippocampus proper (Aggleton & Brown, 1999; Aggleton, Nicol, Huston, & Fairbairn, 1988; Aggleton & Sahgal, 1993; Dusoir, Kapur, Byrnes, McKinstry, & Hoare, 1990; Markowitsch, 1982; Meunier, Bachevalier, Mishkin, & Murray, 1993; Suzuki, Zola-Morgan, Squire, & Amaral, 1993; Zola-Morgan, Squire, Clower, & Rempel, 1993). Specifically, information from the hippocampus is projected to the prefrontal cortex via the anterior thalamus, whereas information from the perirhinal cortex is projected to the prefrontal cortex via the dorso-medial thalamic nucleus (Aggleton & Brown, 1999; Aggleton & Brown, 2006).

Support for this model comes from diverse research, encompassing studies with varied populations, experimental designs, and methodological approaches. Understanding the role of the hippocampus and perirhinal cortex in mediating these dual processes is of particular relevance to the current thesis.

Animal Studies

Experiments with primates provided the first source of evidence for involvement of perirhinal cortex in familiarity-based recognition and further guided research in separating functions of medial temporal lobe (MTL) structures in recognition memory performance. To study recognition memory in monkeys Mishkin and Delacour (1975) designed a task, known as the delayed non-matching-to-sample task (DNMS), which examines an animal's ability to recognize the previously seen stimulus. The animal is first shown an object and after a time-delay is presented with a choice of two objects: the previously seen one and a novel object. The animal is required to select a novel object, which it learns to achieve through positive reinforcement training. It is hypothesized that the DNMS task can be solved by a familiarity- judgment alone. This test has been utilised extensively in studies with animals and has contributed invaluably to the knowledge of neurophysiology of recognition memory.

Monkeys with bilateral lesions confined to perirhinal cortex exhibit impaired performance on the DNMS task compared to a control-group (Meunier et al., 1993; Nemanic, Alvarado, & Bachevalier, 2004; Winters & Bussey, 2005). Additionally, lesions to perirhinal cortex had an

enduring effect on recognition memory performance with memory deficits shown to persist more than two years post-surgery (Suzuki et al., 1993; Zola-Morgan et al., 1993).

Experiments assessing selective involvement of the hippocampus and perirhinal cortex in recognition memory processes further corroborate these findings. Monkeys with conjoint lesions of the hippocampus and perirhinal cortex have greater deficits on the DNMS task than monkeys with lesions exclusively to the hippocampus proper (Alvarez, Zola-Morgan, & Squire, 1995; Zola-Morgan et al., 1993; Zola-Morgan, Squire, & Ramus, 1994; Zola-Morgan, Squire, Rempel, Clower, & Amaral, 1992). Moreover, performance on the DNMS task is significantly less impaired following hippocampal damage than after perirhinal resection (Alvarez et al., 1995; Zola-Morgan et al., 1992, 1993, 1994). Indeed, the greatest disruption to recognition memory performance is found following injury solely to the perirhinal cortex, compared to damage to any other single structure within MTL alone, or in combination (Meunier et al., 1993; Murray & Richmond, 2001).

Research examining the role of the hippocampus in familiarity judgments, however, has produced conflicting results. Murray and Mishkin (1998) documented spared recognition memory performance on the DNMS following bilateral hippocampal ablations. In contrast, experiments performed by Zola-Morgan and colleagues identified a marked deficit on the DNMS task after lesions bilaterally to the hippocampus (Alvarez et al., 1995; Zola, Squire, Teng, Stefanacci, Buffalo, & Clark, 2000). Similar results were reported in earlier research (Zola-Morgan & Squire, 1986). It should be noted, however, that in the study by Zola-Morgan and

Squire (1986), resection of the hippocampus also caused damage of perirhinal and entorhinal cortices, confounding the significance of the study results.

A number of possible explanations have been suggested to explicate these inconsistent findings. They include heterogeneity in the size of the neural lesions, the methods used to determine the extent of neuronal damage, delay intervals used to assess memory performance after the surgery, and differences in procedures used to induce neural lesions (Murray & Mishkin, 1998).

It has been established that the direct surgical removal of a structure inevitably damages adjacent regions. For instance, ablation of the hippocampus has been shown to transect some posterior perirhinal and entorhinal efferents projecting to thalamic structures, thus disrupting the function of perirhinal and entorhinal cortical fields (Murray & Mishkin, 1998). Therefore, recognition deficits following selective hippocampal ablation might be caused by combined damage of the hippocampus and perirhinal and entorhinal cortices (Murray & Mishkin, 1998). There is also variance in surgical procedures used to induce lesions to neural substrates. The type of surgery influences the severity and extent of damage to neural structures. Inconsistency in research results may, hence, in part be due to variations across studies in the efficacy of surgical procedures utilized to fully ablate activity of neural structures (Zola-Morgan et al., 1992). Debate also exists regarding variance in the sensitivity of techniques employed to measure the extent of neuronal injury (Murray & Mishkin, 1998).

There is further a discrepancy across studies in delay intervals between the surgery and the task performance (Murray & Mishkin, 1998; Zola & Squire, 2001). Administration of the memory task soon after the surgery can significantly confound performance, as time is required for cortical activity to adapt and recover following surgical interference (Murray & Mishkin, 1998). The factors that might have contributed to the inconsistency in the aforementioned research differ across studies. This impedes ability to infer definite conclusions regarding disparity in study results. Despite these limitations, overall findings from animal research suggest that the perirhinal cortex plays a crucial role in retrieval processes of familiarity-based recognition in monkeys.

Research with Amnesic Patients

Studies of recognition memory in amnesic patients following medial temporal lobe lesions provide additional support for the Aggleton and Brown (1999) model. This model predicts that patients with hippocampal damage are expected to show a selective impairment in recollection, whereas patients with selective damage to perirhinal regions are expected to display a sole deficit in familiarity-based recognition.

To differentiate the role of hippocampus and MTL structures in recognition memory, Yonelinas and colleagues studied two groups of patients: patients with hippocampal damage induced by hypoxia and patients with extensive damage to MTL regions, including the hippocampus and the surrounding perirhinal and entorhinal regions, produced by temporal lobectomy and hypoxia following extensive cardiac arrest (Yonelinas et al., 2002). The damage to MTL areas were

determined by structural magnetic resonance imaging (MRI) scans. Patients were administered a number of verbal recognition memory tests, using lists of words. Two approaches, analysis of remember/know (R/K) responding and receiver operating characteristics (ROC) of responding were employed to investigate the effect of neuropathology of different temporal lobe regions on recollection and familiarity. Both approaches are commonly used to study mechanisms of recognition memory and have been found to be valid and reliable measures of familiarity and recollection (Kelley & Wixted, 2001; Ochsner, 2000; Rotello, Macmillan, & Van Tassel, 2000; Yonelinas, 1994, 2001; Yonelinas et al., 1996).

In R/K procedures, participants are asked to say "remember" if they can recollect an item and associated information about the item and its features, or, to say "know" if the item seems familiar, but they cannot recollect any specific information about the item. "Remember" responses are hypothesized to assess recollection-based recognition, while "know" responses are posited to measure familiarity-based recognition (Jacoby, 1991; Tulving, 1985; Yonelinas & Jacoby, 1995). The receiver operating characteristic (ROC) is a graphical plot of sensitivity, in which hits are plotted against false alarms using a scale of recognition judgement for participants to indicate how confident they are that the item has been presented in a study list (Kelley & Wixted, 2001; Yonelinas, 1994, 1999). Greater numbers on this judgment scale reflect the activity of recollection while lower numbers account for familiarity-based processes. The analysis of R/K and ROC procedures is founded on signal detection theory, that is, assessing an individual's sensitivity to discriminate between old/studied items and new/unstudied items (Macmillan & Creelman, 2004).

Yonelinas et al. (2002) identified the following pattern of recognition memory performance: patients with the hippocampal damage showed a selective deficit in recollection while patients with widespread MTL damage exhibited impairment on dual processes, recollection and familiarity. The evidence from this research implicates the involvement of hippocampus in recollective processes and surrounding MTL in familiarity-based recognition processes.

The utility of the Aggleton and Brown (1999) model is also substantiated by the work of Vargha-Khadem and collaborators (Vargha-Khadem, Gadian, Watkins, Connelly, Van Paesschen, & Mishkin, 1997). The authors described three amnesic adults who sustained lesions to the hippocampus in early childhood. Comprehensive neuropsychological assessments revealed a vast discrepancy between performance involving different types of memory. The patients displayed pervasive deficits on tasks examining recall and recollection of recognition memory, despite preserved performance on tests assessing familiarity-based recognition. These results were among the first in the neuropsychological literature to associate the functional role of hippocampus with recollective processes of recognition memory (Vargha-Khadem et al., 1997; Baddeley, Vargha-Khadem, & Mishkin, 2001).

These findings were challenged, however, by Squire and colleagues who tested recognition memory in three individuals with adult-onset selective hippocampal damage (Manns & Squire, 1999; Reed & Squire, 1997). Their performance was impoverished on a series of recollection and familiarity tests despite the overlap in test measures used with those used in Vargha-Khadem

et al.'s study (1997) to assess recognition memory performance in developmental amnesic, Jon. Squire and colleagues argue that Jon has likely undergone functional and anatomical reorganization of cortical regions in early life, enabling surrounding rhinal cortices to compensate for hippocampal loss, thus accounting for his good performance on familiarity tasks.

Mayes, Holdstock, Isaac, Hunkin, and Roberts (2002), however, investigated recognition memory in patient Y.R., who has adult-onset hippocampal damage. Findings starkly illustrated Y.R.'s spared ability to perform tasks relying on familiarity function compared to her impaired ability to complete tasks that tap recollection aspects of recognition memory, independent of memory modality (visual/verbal), delay-intervals as long as 4 weeks, and task difficulty.

Y.R.'s bilateral hippocampal damage suffered in adulthood is similar to the patients described by Squire and colleagues, therefore her preserved familiarity-based recognition cannot be accounted for neural reorganisation early in life, which was postulated for Jon. Structural MRI revealed that relative to an age-and-gender matched control group, Y.R.'s hippocampal volume was reduced by 45% with no indication of volumeric reduction in other brain regions, including perirhinal and entorhinal cortices. Additionally, her hippocampal volume reduction was greater than at least two of the three patients studied by Squire and colleagues (1999) (L.J. 34% and P.H. 22%) and comparable to the hippocampal contraction (46%) of Jon (Vargha-Khadem et al., 1997). Hence, if sparing of familiarity-based recognition depends on the functional contribution of a residual hippocampus as hypothesised by Squire and collaborators (1999), then L.J.'s and P.H.'s performances would have been superior to Y.R. and Jon. Notably, the opposite was

observed. Furthermore, no evidence was found to suggest any discrepancy in structural make-up of residual hippocampus between the two cohorts of patients.

Other studies involving patients with adult-onset hippocampal lesions report marked deficits on recollection tasks, while displaying intact ability on tests assessing familiarity judgements, consistent with the performance of Y.R. and Jon (Aggleton et al., 2005; Barbeau, Felician, Joubert, Sontheimer, Ceccaldi, & Poncet, 2005; Bastin et al., 2004; Henke et al., 1999). These findings imply that the sparing of familiarity-based recognition following hippocampal damage is not restricted to cases with early onset of hippocampal damage.

Why the findings are so divergent across studies is unclear. The use of different tests and estimation methods offers a limited explanation, since a number of patients have been assessed by identical tests using the same methodological approach. Discrepancies could possibly relate to variations in patient characteristics, such as aetiology of hippocampal damage, extent of injury, existence of possible lesions outside the hippocampus, including rhinal cortices as well as thalamic and frontal areas, which are part of the circuitries thought to be involved in recollection and familiarity (Aggleton & Brown, 2006; Holdstock et al., 2002; Mayes et al., 2002). Those lesions might be left undetected by MRI techniques as at present the degree of cortical damage can only be reliably identified by histological examinations. On balance, the majority of neuropsychological studies implicate dissociable involvement of the hippocampus and medial temporal lobe structures in retrieval of recognition memory. Notably, however, patient-based research has seldom revealed instances of impaired familiarity and intact recollection to

corroborate the role of perirhinal cortex in familiarity, possibly because discrete lesions to perirhinal cortex are extremely rare.

Neuro-Imaging Studies

Several imaging studies using functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) have provided support for the role of hippocampal activity in recollection and perirhinal activity in familiarity. Eldridge, Knowlton, Furmanski, Bookheimer, and Engel (2000) examined neural activity using fMRI in healthy individuals using the remember/know paradigm while participants performed a verbal recognition memory test. Hippocampal activity was elevated during retrieval of successfully recognized words and remember responses ("recalling features of the item"), but not during unrecognized items or know responses ("unable to recall details of the item"). These results provide evidence supporting the functional specialization of the hippocampus in recollection processes of recognition memory.

In attempts to explore neural activity underlying recognition memory, Davachi, Mitchell and Wagner (2003) generated compelling evidence corroborating the neural dichotomy underlying dual processes of recognition memory using an associative memory test. During the study phase, participants were presented with a list of words and with each word presentation they were asked to either imagine a scene associated with that word ("imagine" task) or pronounce the word backwards ("read" task). In the retrieval trial which took place a day later, participants were shown a list of words and instructed to make "new/old" judgments. If words were recognised as

"old", participants had to indicate which task ("imagine/read") they were asked to perform when studying the word. Results indicated that hippocampal activity increased during correct identifications of words together with the tasks accompanying their learning ("imagine/read"). No hippocampal activity was evident in cases of incorrectly recognised items. Activation of perirhinal cortex was registered during correct detections of words only, without recollection of the associated tasks. Furthermore, hippocampal activity during the encoding phase predicted correct recognition of words and the accompanying tasks, while perirhinal activity predicted correct identification of words only. These findings indicate the importance of hippocampal activity in recollective mechanisms (a representation of an item and its contextual material) of recognition memory and the significance of perirhinal activity in familiarity-based recognition (a sense of a general experience of a prior encounter with an item).

Engagement of the perirhinal cortex in familiarity tasks was also observed during other fMRI studies (Henson, Hornberger, & Rugg, 2005; Ranganath, Yonelinas, Cohen, Dy, Tom, & D'Esposito, 2004), although a number of studies with similar methodological approaches failed to identify perirhinal activation with familiarity (Henson, 2005; Yonelinas, Hopfinger, Buonocore, Kroll, & Baynes, 2001). These studies, however, reported activation of parahippocampal areas during performance on familiarity tasks, which might have included entorhinal and periririrhinal cortices (Yonelinas, Otten, Shaw, & Rugg, 2005).

In an EEG study of recognition memory performance, it was found that amnesic patient Jon lacked a late positive component in his EEG profile (an increase in amplitude between 500-700

ms after the onset of stimuli presentation), which signifies recollection processes in healthy participants. On the other hand, Jon's EEG had a preserved N400 component, related to familiarity-based recognition (Düzel, Vargha-Khadem, Heinze, & Mishkin, 2001; Rugg & Curran, 2007). The electrophysiological outcomes were congruent with his disrupted performance on recollection tasks in the face of intact performance on familiarity tests (Düzel et al., 2001).

In summary, the majority of research evidence from a range of measurement methods and research paradigms supports the Aggleton and Brown model and implicates differential roles of the hippocampus and perirhinal cortex in dual aspects of recognition memory.

The Rationale for Development of the Recognition Memory Study

Two bodies of research contributed to the theoretical foundations for developing a cognitive marker of very early changes in Alzheimer's disease. The first body of research originated from autopsy findings of AD patients, which established the hierarchial progression of AD neuropathology in the trajectory of the disease, in which amyloid plaques and neurofibrillary tangles initially infiltrate entorhinal and perirhinal cortices before extending their pathogenic effects to the hippocampus (Braak & Braak, 1991, 1994, 1997a, 1997b). The second body of research stemmed from Aggleton and Brown's (1999) neuro-anatomical model of recognition memory, in which the hippocampal network has a special role in mediation of recollection processes while the perirhinal network has a special role in supporting familiarity-based

recognition memory (Aggleton & Brown, 1999). Evidence supporting the efficacy of this model was evaluated in this chapter.

Together these findings suggest that assessing familiarity and recollective recognition memory, which are reliant on distinct medial temporal lobe structures that are differentially impacted in early stages of the disease process, may provide a cognitive marker of the earliest stages of Alzheimer's disease. Given the early involvement of perirhinal and entorhinal cortices in AD neuropathology, the earliest changes in memory should involve familiarity recognition memory, while recollective recognition memory should remain intact. As the disease progresses, the neuropathology will extend into the hippocampi, at which point both familiarity and recollective recognition process will be impaired.

Numerous studies have reported that AD patients manifest profound deterioration in recognition memory, with deficits present in both auditory and visual modalities (Budson, Desikan, Daffner, & Schacter, 2001; Budson, Michalska, Sullivan, Rentz, Daffner, & Schacter, 2003; Diesfeldt, 1990; Lee, Rahman, Hodges, Sahakian, & Graham, 2003; Lekeu et al., 2003; Moss, Albert, Butters, & Payne, 1986; Simons, Graham, & Hodges, 2002; Tierney et al., 2001). In most of these studies, however, recognition memory was examined by neuropsychological measures that were not designed to differentially tap recollection and familiarity processes.

We found only three studies that have investigated dual processes of recognition memory in MCI and AD using tasks that possessed functional characteristics necessary to differentiate recollection and familiarity (Barbeau et al., 2004; Westerberg et al., 2006; Wolk, Signoff & DeKosky, 2008). Their findings are in disagreement with each other and are discussed below.

Wolk, Signoff, and DeKosky (2008) measured recognition memory performance in a group of MCI individuals by means of a process-dissociation procedure (Jacoby, 1991; Yonelinas, 2002). Participants were asked to study an association between pairs of items: word-word, picture-location, and word-colour. During testing phases, participants were shown intact pairs (e.g., both words previously studied together) and non-studied pairs and instructed to identify the targets (studied pairs). Some of the non-studied pairs were completely novel, but others were very similar to studied pairs, but rearranged (e.g., both words were previously studied as part of different pairs). The accurate identification of target pairs and correct rejection of foils (including rearranged and novel pairs) was hypothesized to measure recollection and inaccurate recognition of re-arranged pairs as targets was thought to assess activity of familiarity processes.

Findings indicated that MCI individuals displayed significant deficits in both recollection and familiarity compared to their healthy counterparts. The level of impairment within the MCI group, however, was greater for familiarity relative to recollection. The results of their study were consistent with the predictions outlined above and with the findings of an earlier study. Barbeau et al. (2004) found that AD and MCI patients were impaired on a familiarity-based recognition test, which was specifically developed by this group of researchers to assess

familiarity-based recognition of visual stimuli. During the study phase, participants were shown 48 pictures and asked to say whether each picture contained more or less than three colors. During the testing phase (an hour later), each target (studied item) was presented simultaneously with a foil (unstudied item) and participants were requested to identify the target. Targets and foils were divided into three categories: abstract items (targets and foils are abstract objects that cannot be verbalized); concrete items (targets and foils are concrete objects belonging to the same semantic category that appear very similar) and unique items (targets and foils are dissimilar concrete objects). It was found that performance of MCI and AD groups for all types of stimuli were significantly compromised compared to the control group. It should be noted, however, that this study did not include a measure of recollective processes. This means it is not possible to examine any the differential effects of MCI and AD on recollection or to compare the effects of these clinical conditions on the two recognition dual processes.

In contrast, Westerberg et al. (2006) found that compared to a healthy control group, the performance of MCI patients was intact on a test of familiarity, while significantly disrupted on a test of recollection. AD patients showed significantly diminished performance on both tests with greater impairment on the test assessing recollection. The authors measured visual recognition memory using two tests, one designed to be sensitive to recollection (the yes-no test) and the other to familiarity (the forced-choice test). In both tests foils closely resembled studied stimuli. Westerberg and collaborators used stimuli from an experimental task developed by Holdstock et al. (2002), which were posited to have selective sensitivity in measuring dual processes of recognition memory. (A detailed theoretical background and the approach used to design and validate the measures can be found in Chapter 4).

Westerberg and investigators provided a number of hypotheses to explain intact performance of MCI patients on the test assessing familiarity (Westerberg et al., 2006). They suggested that damage to perirhinal cortices might have not reached the critical threshold of deterioration required to fully deactivate the function of those structures. Additionally, they proposed that other structures engaged in supporting activity of familiarity processes outside of perirhinal areas might have facilitated relative sparing of familiarity performance.

What might underlie the inconsistent findings across studies concerning performance of MCI patients? The characteristics of the tests used to examine familiarity-based recognition by Barbeau et al. (2004) and Westerberg et al. (2006) appeared superficially comparable. Both studies used a forced-choice test format with targets that closely resembled foils. There were, however, marked differences in the learning procedures employed in the two studies. Differences include the number of stimuli participants were required to study, the number of stimulus exposures during the learning phase, and the instructions directing attention to the stimuli during the study phase. For instance, Websterberg et al.'s participants were presented with 12 stimuli twice during the learning phase and were asked to study the details of each object. In contrast Barbeau et al.'s participants were shown 48 stimuli once and instructed to note one aspect of the stimuli (colour). It is possible that the additional learning exposure, smaller number of stimuli, and instructions facilitating detailed studying in Westerberg et al.'s study, leading to a conscious learning of stimuli details. When identifying the target item on the familiarity test, participants might have recruited either or both of the dual recognition processes

depending on how well they had learnt visual details of the target. This implies that performance on the "familiarity test" in some cases might have been aided by conscious recollection, so that overall performance was the sum of the outputs of the two memory processes. Thus, intact performance of MCI patients and mildly disrupted performance of AD individuals on this test might have reflected the combined effect of residual functional capacities of the structures involved in mediation of both hippocampal and perirhinal networks. Further research is therefore needed to clarify the nature of impairments of recognition memory processes in MCI and AD. One focus of the research in this thesis was to further refine and test the paradigm increasing the chances that the recognition memory test might distinguish recollection versus familiarity.

The main goal of the recognition memory study in this thesis was to identify task parameters that would increase the likelihood of differentiating the dual processes of recognition memory for future application with AD and MCI patients. To test whether the parameters used by Westerberg et al (2006) enabled recollective retrieval to influence performance on the familiarity task, the following research studied the performance of a group of healthy older adults on two different versions of the tasks. One version was a replication of the task used by Westerberg et al. and the second was a new version of the task, in which the number of stimuli were increased from 12 to 17 and which used only a single stimulus exposure during the learning phase. The test format and the level of similarity between foils and targets remained unchanged between the two studies and two tasks, as their validity for differentiating the dual recognition memory processes has been established in previous research (Holdstock et al., 2002).

CHAPTER 3

Long-term Potentiation

This chapter will provide background information pertinent to the development of the electrophysiological component of this thesis. First, mechanisms underlying acquisition of learning, known as long-term potentiation, will be defined, followed by a review of research elucidating disruptive actions of neuropathological processes of AD on long-term potentiation. Research endeavours that have established an experimental protocol for measurement of long-term potentiation non-invasively in humans will be then described.

Long-Term Potentiation

One of the first notable symptoms of Alzheimer's disease is a profound deficit in the ability to acquire and retain new information. Emerging research attributes this early clinical sign to disruption of synaptic plasticity by the effects of amyloid plaques, which are prime features of AD pathogenesis (Klein, 2006; Lacor et al., 2004).

Synaptic plasticity is thought to constitute the physiological basis of learning and memory as well as perceptual and sensory acquisition of information, thereby providing a mechanism that enables successful adaptation of an individual to the surrounding environment (Kirkwood,

Rioult, & Bear, 1996; Malenka, 2003; Squire, 1986). It is widely recognized that synaptic plasticity is mediated by the process of long-term potentiation (LTP) (Bliss & Collingridge, 1993; Bliss & Lomo, 1973; Cooke & Bliss, 2006; Martin, Grimwood, & Morris, 2000; Teyler & DiScenna, 1987). LTP is an intricate molecular process by which an experience with a stimulus produces neural changes resulting in an increase in the efficacy of communications between neurons (Bliss & Collingridge, 1993; Bliss & Lomo, 1973; Martin et al., 2000; Teyler & DiScenna, 1987).

In 1973, Bliss and colleagues made a revolutionary discovery in revealing neurophysiological mechanisms of synaptic plasticity (Bliss & Lomo, 1973; Bliss & Gardner-Medwin, 1973). They found that application of a high-frequency repetitive electrical stimulation to afferent projections in the rabbit hippocampus stimulated adjacent postsynaptic neurons, thereby inducing a long-lasting enhancement in the strength of the stimulated synapses (Bliss & Lomo, 1973; Bliss & Gardner-Medwin, 1973). This effect became known as long term potentiation (Bliss & Lomo, 1973).

Subsequently a substantial body of molecular, genetic, and electrophysiological experiments demonstrated that the production of LTP is universal across species and occurs through a complex interplay of molecular and physiological processes (Bliss & Lomo, 2006). A simplified description of LTP production is depicted below. It should be noted that data about molecular mechanisms of LTP are derived from experiments conducted on hippocampal slices.

Molecular processes enabling generation of LTP are complex. They are mediated by the primary excitatory neurotransmitter of the central nervous system, glutamate (Collingridge, Kehl, & McLennan, 1983; Fonnum, 1984). A simplified description of mechanisms involved in LTP formation includes the following processes. An incoming stimulus evokes an action potential (AP) in a pre-synaptic glutamatergic neuron. Arrival of an AP at the terminal button of the neuron stimulates release of glutamate into the synaptic cleft (Collingridge et al., 1983; Gustafsson & Wigstrom, 1988; Madison, Malenka, & Nicoll, 1991). Once in the synapse, glutamate binds to and activates N-Methyl-D-aspartate (NMDA) receptors at post-synaptic neurons, leading to an influx in intracellular calcium Ca^{2+} ions (Gustafsson & Wigstrom, 1988; Madison et al., 1991; Nicoll, Kauer, & Malenka, 1988) (refer to Figure 2 for a detailed description). The rise in Ca^{2+} ions triggers a cascade of biochemical reactions, which promote phopshorylation of existing proteins and initiate the synthesis of new proteins to induce the growth of novel synaptic connections that have now come to represent the experience with the process-evoking stimulus (Ginty, 1997; Kelleher, Govindarajan, & Tonegawa, 2004; Lynch, Larson, Kelso, Barrionuevo, & Schottler, 1983; Malenka, Kauer, Zucker, & Nicoll, 1988; Nayak, Zastrow, Lickteig, Zahniser, & Browning, 1998; Rosenblum et al., 2002; Waltereit & Weller, 2003; Wong et al., 1999).

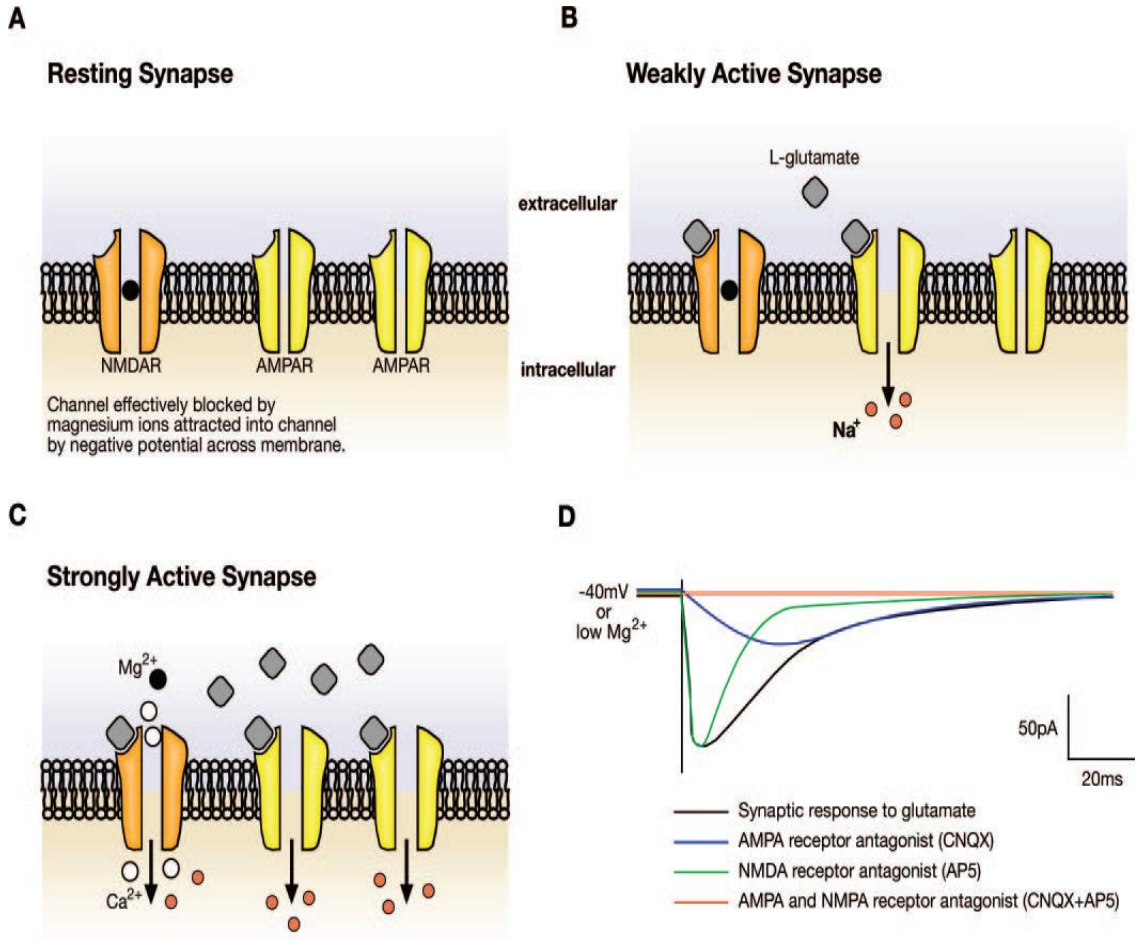


Figure2: This figure depicts molecular processes underlying induction of LTP. The glutamatergic postsynaptic membrane contains AMPA and NMDA subtypes of glutamate receptor. Under conditions of rest or low levels of input activity, the channel of the NMDA receptor is blocked by positively charged magnesium ions (Mg2+) (A). Glutamate molecules released from the pre-synaptic terminal diffuse across the synaptic cleft and bind to both sub-types of receptor, opening AMPA receptor channels. The resulting inward current flow carried by Na+ ions depolarises the post-synaptic membrane to produce an excitatory post-synaptic potential (EPSP). (B). High concentrations of glutamate released at a strongly active synapse produce strong depolarisation of the post-synaptic membrane, resulting in the expulsion of magnesium ions from the NMDA receptor channel, and allowing influx of Na+ and Ca2+ ions (C). Panel D illustrates intracellular recordings of excitatory synaptic currents under four different conditions, illustrated in the diagram, adapted from Cooke and Bliss (2006).

Properties of LTP

LTP has been shown to possess a number of important functional properties including input-specificity, co-operativity, and associativity (Bliss & Collingridge, 1993; Cooke & Bliss, 2006; Gustafsson & Wigstrom, 1988; Malenka & Nicoll, 1999). Co-operativity is defined by a process whereby a synchronic activation of pre- and postsynaptic cells evokes a threshold of potentiation that instigates LTP induction (Cooke & Bliss, 2006; Gustafsson & Wigstrom, 1988; Teyler & DiScenna, 1987). Input-specificity is an instrumental feature of LTP. It signifies a mechanism, wherein a high-frequency repetitive presentation of stimuli (known as "tetanus") exerts LTP-inducing actions at a limited number of synapses. Specifically, only those synaptic connections that are active during LTP induction will be potentiated, while neighbouring synapses that have been inactive during LTP induction will not be potentiated (Cooke & Bliss, 2006; Gustafsson & Wigstrom, 1988; Teyler & DiScenna, 1987). This process enables formation of a unique association between specific synapses and the stimulus engendering their activation (Gustafsson & Wigstrom, 1988). The property of associativity ensures that a weak stimulus, which is unable to initiate LTP on its own, can trigger LTP induction through association with a stronger co-active stimulus (Cooke & Bliss, 2006; Malenka & Nicoll, 1999).

Another property of LTP is the temporal activity of potentiation (Bliss & Collingridge, 1993). Three temporal phases have been distinguished, which are contingent upon the endurance of potentiated effect. Initial potentiation has a short-term effect, known as short-term potentiation (STP), lasting 15-30 minutes (Malenka, 1991; Nicoll et al., 1988). It is followed by the early phase of LTP which exhibits a longer effect, ranging from 30 minutes to 3 hours (Abraham,

Logan, Greenwood, & Dragunow, 2002; Kelleher et al., 2004). The final phase of potentiation, late-LTP, produces a long-lasting action that persists for many hours, days and even years (Abraham et al., 2002; Kelleher et al., 2004).

The development of temporal phases is modulated by molecular processes discussed above. Induction of STP is achieved through activation of NMDA receptors and subsequent influx of Ca^{2+}, with the amount of Ca^{2+} entry determining the longevity of the potentiatiated action (Abraham et al., 2002; Bliss & Collingridge, 1993; Kelleher et al., 2004). Generation of early-LTP is facilitated by phosphorylation of existing proteins without synthesis of new proteins, while development of late-LTP requires gene transcription and protein synthesis to establish new synaptic connections (Abraham et al., 2002; Kelleher et al., 2004).

LTP and Alzheimer's disease

Animal Studies

Numerous research trials using animal models and nerve cell biology methods have revealed the deleterious impact of beta-amyloids on induction and maintenance of LTP. For example, it has been reported that induction of LTP was suppressed in transgenic mice whose medial temporal structures were infiltrated with deposits of amyloid plaques due to amyloid precursor protein (APP) mutations (Chapman et al., 1999; Dewachter et al., 2002). Similar results were documented in nerve cell biology studies. They showed that perfusion of beta-amyloids into hippocampal tissue of rodents prior to a tetanus administration inhibited LTP induction, which

was in contrast to intact LTP induction in mice injected with control saline solution. This was evident in vivo and in vitro analyses (Chen, Kagan, Hirakura, & Xie, 2000; Chen, Wei, Shimahara, & Xie, 2002; Freir, Costello, & Herron, 2003; Freir, Holscher, & Herron, 2001; Stephan, Laroche, & Davis, 2001; Walsh et al., 2002; Wang et al., 2002). Furthermore, injection of beta-amyloids has been found to occlude production of late phases of LTP after its initial induction and this phenomenon was also notable in vivo and in vitro examinations (Chen et al., 2002; Puzzo, Vitolo, Trinchese, Jacob, Palmeri, & Arancio, 2005).

Animal research using randomized controlled trials has identified that memory deficits caused by aggregations of beta-amyloids in rodents' medial temporal regions imitate a pattern of memory disturbance observed in the early phase of AD. It has been repeatedly demonstrated that mice injected with beta-amyloid peptides to hippocampal tissues before task-training exhibit pervasive difficulties in learning a wide range of spatial navigation tasks (Nitta, Fukuta, Hasegawa, & Nabeshima, 1997; Stephan et al., 2001). Moreover, infusion of beta-amyloids after training has also been found to disturb an animal's ability to perform previously well-learned tasks (Sweeney, Luedtke, McDonald, & Overmier, 1997). Parallel observations are reported by studies with transgenic mice expressing APP mutations, registering potent deficits in the ability of mice to learn a series of mnemonic tasks following the formation of beta-amyloid aggregates in the rodent's hippocampus (Arendash et al., 2001; Berger-Sweeney, McPhie, Aters, Greenan, Oster-Granite, & Neve, 1999; Chapman et al., 1999; Holcomb et al., 1998; Hsiao et al., 1996; Irizarry, McNamara, Fedorchak, Hsiao, & Hyman, 1997; Moran, Higgins, Cordell, & Moser, 1995; Nalbantoglu et al., 1997). Importantly, some of those experiments attempted to investigate whether there was a relationship between beta-amyloid induced memory deficits and LTP

activity and found a direct association between these two variables (Chapman et al., 1999; Nalbantoglu et al., 1997; Stephan et al., 2001).

The mechanism by which beta-amyloids impair synaptic plasticity is complex and not fully understood. The outcomes from numerous studies suggest that beta-amyloids suppress LTP by directly blocking NMDA receptors and by deactivating biochemical signalling cascades downstream of NMDA receptor activation, with these destructive events fostering destabilisation of Ca^{2+} homeostasis (Brorson, Bindokas, Iwama, Marcuccili, Chisholm, & Miller, 1995; Mattson, Partin, & Begley, 1998; Ueda, Shinohara, Yagami, Asakura, & Kawasaki, 1997). It is well established that disruption of Ca^{2+} homeostasis sets into motion a chain of molecular reactions resulting in apoptosis of neurons and subsequent cortical degeneration (Lipton, 1999; Meldrum, & Garthwaite, 1990; Novelli, Reilly, Lykso, & Henneberry, 1988; Olney, Ho, & Rhea, 1971). Although the mechanisms are yet to be fully elucidated, nevertheless, animal studies provide compelling evidence that loss of synaptic plasticity precedes neuronal death in rodent models of AD. The above research also suggests that this patho-physiological process may account for the difficulty of AD individuals in forming new memories (Klein, 2006; Lacor et al., 2004).

Research with AD patients

Further evidence for dysfunction of synaptic plasticity in early AD stems from autopsy research. A number of autopsy studies using electron microscope and immunocytochemical analyses detected damage in glutamatergic systems in AD patients (Arendt, 2001; Francis, 2003).

Specifically, relative to healthy counterparts, patients with early AD were found to have a significant reduction in the number and concentration of NMDA receptors, a considerable loss of glutamatergic synapses, and structural abnormalities in glutamatergic neurons (Carlson, Penney, & Young, 1993; Davies, Mann, Sumpter & Yates, 1987; DeKosky, Scheff, & Styren, 1996; Kowall & Beal 1991; Lowe, Bowen, Francis, & Neary, 1990; Masliah, 1995,1998; Masliah et al., 1992; Masliah, Mallory, Hansen, DeTeresa, Alford, & Terry, 1994). An analogous pattern of results has also been documented in MCI patients. A considerable proportion of MCI individuals suffered from loss of and damage to glutamatergic synapses (Scheff, Price, Schmitt, & Mufson, 2006). These findings indicate that disruptions in LTP activity are the first neuropathological changes that accompany the early stage of AD. Research attempts to study the relationship between LTP functioning and memory impairment in AD and MCI patients have been impeded by the absence of a valid and reliable protocol of LTP measurement in the intact human brain.

Non-Invasive LTP in Humans

Until recently, there have been no direct demonstrations of LTP activity in the intact human brain as LTP induction is a grossly invasive procedure, which requires isolation of cortical tissue and administration of a high-frequency electrical stimulation to segregated neurons. To date, LTP has only been directly observed in humans in isolated cortical tissue attained from patients undergoing neuro-surgery, where it has shown to display properties identical to those seen in non-human experiments (Beck, Goussakov, Lie, Helmstaedter, & Elger, 2000; Chen, Lee, Kato, Spencer, Shepherd, & Williamson, 1996). Research conducted at the University of Auckland was the first to create a protocol that provides a sensitive and reliable method of LTP induction

and measurement in the intact human brain (McNair, Clapp, Hamm, Teyler, Corballis, & Kirk, 2006; Ross et al., 2008; Teyler, Hamm, Clapp, Johnson, Corballis, & Kirk, 2005).

Teyler et al. (2005) initially attempted to induce LTP in superficial structures of the neocortex, such as visual cortical areas, by presenting individuals with repetitive and frequent stimuli and measuring their electrophysiological activity in vivo. Participants were shown a checkerboard stimulus on a computer screen while their electrical activity was recorded via electroencephalography. Stimuli were first presented at a low rate (1Hz: pre-tetanus), followed by a high rate of presentation (9Hz: photic tetanus), after which a low rate of presentation was reinstated (post-tetanus). A comparative analysis of pre- and post-tetanus conditions determined that exposure to a photic tetanus, a high presentation rate of visual stimuli, led to a persistent and prolonged increase in the amplitude of an early electrical component of LTP (N1b), which is one of the chief electrophysiological components of LTP activity (described in Method section).

This pattern of activity was localized at bilateral extra striate regions by the means of low resolution source localization technique (LORETA; Pascual-Marqui, Michel, & Lehmann, 1994). Subsequently this study was replicated using fMRI, a technique with greater spatial resolution, and confirmed the findings of Teyler and colleagues (2005), identifying a marked increase in activity of visual cortex (area V2) following administration of the photic tetanus (Clapp et al., 2005).

This protocol was then translated into an auditory paradigm. Clapp, Kirk, Hamm, Shepherd and

Teyler (2005) showed that a repetitive high-frequency presentation of tone tips (sinusoidal tones of 1000 Hz) evoked long-lasting potentiation in the auditory cortex, demonstrating that the protocol can be generalized to another sensory modality.

Later studies provided evidence that LTP activity evoked by visual stimuli in the intact human brain shares functional characteristics and molecular properties with LTP induced in medial temporal regions of animals (McNair et al., 2006; Ross et al., 2008). Specifically, it was determined that visual-induced LTP in the intact human brain is input-specific and NMDA receptor-dependent.

Input specificity of visual-elicited LTP in vivo was tested with visual stimuli that relied on recruitment of distinct and individual populations of neurons in the visual cortex (McNair et al., 2006). It is well-known that cells in the visual cortex are selectively responsive to specific aspects of visual information, including orientation, spatial frequency, motion and shape (Blakemore & Campbell, 1969; De Valois, Yund, & Helper, 1982; Hubel & Wiesel, 1968; Kamitani & Tong, 2005; Mansfield, 1974; Tootell et al., 1998). Given this, it was predicted that visual potentiation would be specific to a precise visual stimulus used during the tetanus presentation.

In the first demonstration, two stimuli comprising gratings of spatial frequency that differed in frequency (low and high) were used. Initially, baseline readings were recorded consisting of presentation of both stimuli (low and high spatial frequency) at a low rate. This was followed by

the photic tetanus, which involved rapid presentation of one type of grating at a high rate (either the low, or high, spatial frequency). The type of grating used as the photic tetanus was randomly assigned across participants. Participants were then exposed to stimuli at a low rate (the post-tetanus phase), comparable to the pre-tetanus phase. Comparison of pre-tetanus and post-tetanus conditions revealed that visual-evoked LTP in the intact human brain is input-specific, that is, increase in potentiation following the tetanus was specific to the spatial frequency used for tetanization (McNair et al., 2006). Identical findings were reported by Ross et al. (2008), whose study replicated McNair's paradigm but employed grating stimuli of the same spatial frequency but different orientation (vertical and horizontal).

Research exploring the molecular mechanisms of visual LTP in vivo has concluded that evoked potentiation is modulated by NMDA-receptor activation. A number of studies have assessed the impact of the NMDA-receptor antagonists on visual-evoked potentiation in humans and rodents using the experimental paradigm described above (Cavus et al., 2009; Clapp, Eckert, Teyler, & Abraham, 2006). Treatment with NMDA receptor antagonists blocked induction of visual LTP in animals and human participants (Cavus et al., 2009; Clapp et al., 2006).

Thus, findings from a series of research experiments provide strong support for the contention that visual-evoked potentiation measured via EEG in the intact human brain represents LTP activity in the visual cortex. These observations are also consistent with research observing LTP activity throughout regions of the neocortex, including tissue slices from the visual cortex (Heynen & Bear, 2001; Kirkwood & Bear, 1994; Komatsu, 1994; Malenka, 2003). The activity of LTP in those regions was shown to be governed by molecular mechanisms and to exhibit

functional and electrophysiological properties akin to those in medial temporal structures (Clothiaux, Bear, & Cooper, 1991; Heynen & Bear, 2001; Inagaki et al., 2008; Kirkwood & Bear, 1994; Kirkwood et al., 1996; Komatsu, Fujii, Maeda, Sakaguchi, & Toyama, 1988; Tsumoto & Suda, 1979; Zhang, Tao, & Poo, 2000).

LTP in the visual cortex is less likely to subserve memory function as directly as LTP in medial temporal structures and the hippocampus, which are known to have a pivotal role in mnemonic processes. Therefore, a pertinent question arises as to whether visual LTP will be useful in studying MCI and AD conditions in which memory difficulties are typically the earliest clinical feature. There is evidence that the process of LTP induction and its maintenance is universal across most brain regions, and, therefore, electrophysiological changes in LTP activity in any cortical area may reflect the existence of equivalent or similar alterations in LTP viability in other cortical areas. Furthermore, it is well-established that neural structures in visual and medial temporal cortices are interconnected and recruited in visual pathways specialised for processing and acquisition of visual information (Goodale & Milner, 1992; Mishkin, Ungerleider, & Macko, 1983; Moscovitch, Kapur, Kohler, & Houle, 1995; Ungerleider & Haxby, 1994). The visual LTP measured in the paradigm described above is likely to estimate the degree of synaptic plasticity throughout the visual pathway, including visual and medial temporal areas.

Support for this idea comes from the findings of Thompson et al, (2010). They utilizied the EEG protocol and found that individuals with a single nucleotide polymorphism in the brain-derived neurotrophic factor (BDNF) gene, which modulates generation of early and late-phases of

potentiation, displayed a significant decline in visual-evoked LTP and diminished scores on a number of visual recognition tests compared to healthy individuals without the polymorphism (Dragunow, Beilharz, Mason, Lawlor, Abraham, & Gluckman, 1993; Lu, 2003; Lu, Christian, & Lu, 2008; Poo, 2001). This research also established a positive correlation between the magnitude of LTP activity and memory performance for all participants. The results of this research support potential feasibility of detecting subtle neuropathological changes in the form of LTP in early AD and MCI.

Thus, the EEG protocol designed by the Research Centre for Cognitive Neuroscience at the University of Auckland affords a novel opportunity to measure activity of visual LTP in MCI and AD patients. The research conducted in this thesis, described in Chapter 5, applied the EEG protocol to healthy older participants in order to assess whether older adults generate reliable visual LTP. If so, measurement of visual LTP in MCI and AD individuals becomes a viable option for further research endeavours. If LTP disruption precedes neuronal degradation in AD and MCI, and changes in LTP emerge with early appearance of amyloid plaques, it is possible that measuring visual LTP may reveal subtle neuropathological deficits in MCI and early AD, otherwise undetectable by currently available means of measurements in living patients, including fMRI and CT (computerized tomography) scans.

To summarise, the main aim of research in this thesis was to develop a protocol that may lead to identification of an early marker of AD. The protocol to be evaluated emerged from two diverse fields of research linked by processes occurring during Alzheimer's disease and comprises measures of recognition memory and visual LTP. In the first phase of the research, which is

reported in this thesis, a group of healthy older participants were tested to establish whether this protocol constitutes a reliable and valid method of testing these domains of functioning, and whether there is a relation between performance on these domains in the healthy older population. If the results of this research support the use of this protocol, the next phase of the research will be to test the protocol in AD and MCI patients. The specific hypotheses for each study in this thesis are described in Chapters 4 and 5.

Chapter 4

Recognition Memory Study

A small number of studies to date have examined familiarity and recollection recognition memory in individuals with AD and MCI, presenting inconsistent findings. Westerberg et al. (2006) used stimuli and tasks developed by Holdstock et al. (2002), who had designed two tests of equal difficulty with selective sensitivity to familiarity and recollection processes of recognition memory. Westerberg's results were surprising: MCI participants, theoretically with differential damage to perirhinal cortices, were impaired on the recollection (yes-no) task, but not the familiarity (forced-choice) task, which is contrary to the predictions of the recognition memory model proposed by Aggleton and Brown (1999).

One possible explanation for these findings is that the learning procedure used by Westerberg et al. (2006) may have enabled consolidated learning of some items, implying that recollection as well as familiarity processes may have contributed to performance on the familiarity test. To test this possibility in the following study we first replicated the procedures and measures used by Westerberg and colleagues for testing recollection and familiarity in a sample of healthy older adults. We then tested the same participants on a second pair of tasks of the same general format, in which we manipulated parameters in the learning phase to force use of familiarity-based recognition memory on the forced-choice test, specifically increasing the number of

stimuli from 12 to 17 and having only 1 learning trial. As the stimuli and experimental paradigm of these recognition memory tasks have been derived from Holdstock et al. (2002), a brief account of the theoretical background, design and validation of the measures will be provided.

In designing the tests, Holdstock et al. (2002) were guided by Complementary Learning Systems model (CLS). The model integrated mathematical-modeling and cognitive neuroscience approaches to understanding mechanisms of memory, including the function of different components of recognition memory and neural substrates mediating its processes (McClelland, McNaughton, & O'Reilly, 1995; Norman & O'Reilly, 2003). In essence, it presents an explanatory account of modes through which stimuli are processed, encoded, and retrieved in the hippocampus and neocortex. This model compliments the Aggleton and Brown (1999) proposition, suggesting that hippocampal activity is responsible for recollective recognition while perirhinal activity is crucial for familiarity-based recognition.

According to the CLS, during the encoding process the hippocampus segregates information about an incoming item as well as details accompanying that item presentation into separate and distinctive features and assigns non-overlapping representations to those features in order to form a memory of a specific, unique episode. During the retrieval of that item, the hippocampus, with support and mediation of activity of the frontal cortex, binds all stimuli-associated information together. This process allows an individual to retrieve the item and also details which were present during the encoding of that item. This mnemonic association can be formed through a single encounter of an individual with the item, although the association becomes stronger if the

item is represented repeatedly (McClelland et al., 1995; Norman & O'Reilly, 2003). Based on the above proposition, the hippocampus supports the activity of recollection, which involves conscious re-experiencing of a memory and is aided by elaborate information processing during encoding and retrieval, consistent with the Aggleton and Brown neuro-anatomical model (1999) of recognition memory.

The CLS additionally posits that the perirhinal cortex operates through assigning similar and overlapping representations to similar stimuli. Specifically, it processes novel stimuli based on their similarity to ones that were previously encountered without differentiating contextual details of that stimuli. Hence, at retrieval it can only provide a general sense that the item has been experienced previously, devoid of any information bound to that stimulus. This type of learning usually occurs via a single exposure to stimuli (McClelland et al., 1995; Norman & O'Reilly, 2003). This, therefore, suggests that perirhinal cortex is likely to facilitate processes of familiarity-based recognition as posited by Aggleton and Brown (1999).

Taking into account the distinct modes through which information is processed, encoded and retrieved in the hippocampus and perirhinal cortex, Holdstock and colleagues (2002) have suggested that dual processes of recognition memory can be differentiated in research settings under two conditions: 1) foils need to be very similar to targets and 2) different test formats need to be utilized in the recognition phase. Provided foils are very similar to studied stimuli, they argue that a forced-choice recognition test will measure the function of familiarity, while a yes-no recognition test will tap the function of recollection.

The explanation for this claim is as follows. In a forced-choice format, targets and foils are presented simultaneously: the participant must evaluate these together, and following a comparative analysis, select the item with the strongest familiarity signal, or activation. There is no requirement for a participant to forcefully retrieve features of the studied item, but rather a comparative strategy of the strength of familiarity signals is used to guide responses. This type of performance is supported by the perirhinal cortex, which processes incoming information via a comparative mechanism.

In a yes-no test format, under conditions where targets and foils are highly similar, each item is shown separately and a strategy of responding to items that are familiar would lead to many errors. This is because it would require setting a "familiarity threshold" to use to respond "yes"; such a threshold would not distinguish targets of low familiarity from foils associated with a highly familiar target. Instead, to accurately detect the target the participant would need to recollect specific features of the target items, in order to activate representations in the hippocampus, which are relatively distinct.

Based on the above rationale, Holdstock and colleagues (2002) designed two tests that were postulated to have selective sensitivity to measurement of familiarity and recollection. Additionally, they evaluated the level of difficulty of these tests in a population of healthy adults (50-60 years of age) and concluded that the tests possess equal levels of difficulty (Holdstock et al., 2002). Given these characteristics, these tests appear to have utility in distinguishing

activities of dual processes of recognition memory and are likely to shed light upon the function of neural substrates in supporting these cognitive processes.

There is a significant literature investigating the dual processes of recognition memory in healthy older adults using a variety of testing procedures (Howard, Bessette-Symons, Zhang, & Hoyer, 2006; Jennings & Jacoby, 1997; Mantyla, 1993; Naveh-Benjamin, 2000; Parkin & Walter, 1992). Negative effects of aging on recollection have usually been explained by neuropathological changes occurring in the prefrontal cortex (Buckner, 2004; Moscovitch & Winocur, 1995; Wheeler & Stuss, 2003).

A large body of research using neuroimaging and postmortem tissue analysis identified selective susceptibility of prefrontal cortex to the effects of aging (Buckner, 2004; Moscovitch & Winocur, 1995; Parkin & Walter, 1992), including a loss of grey matter (Michielse et al., 2010; Raz & Rodrigue, 2006; Raz et al., 1997; Salat et al., 2004); damage to white matter fibers (Head et al., 2004; Madden, Bennett, & Song, 2009; O'Sullivan, Jones, Summers, Morris, Williams, & Markus, 2001); deterioration in axonal myelin (Bennett, Madden, Vaidya, Howard, & Howard, 2010; Madden et al., 2009; Raz & Rodrigue, 2006); and neurotransmitter depletion (Albert, 2002).

It is argued that functions of prefrontal cortex are more crucial for the formation and retrieval of recollections rather than familiarity memories (Davidson & Glisky, 2002; Greenwood, 2000;

Moscovitch & Winocur, 1995; Spencer & Raz, 1995; Wheeler & Stuss, 2003). The prefrontal cortex is known to participate in a myriad of executive functions, such as planning and organization, problem-solving, attention and concentration, regulation of emotions, and thought generation (Alexander, Stuss, Shallice, Picton, & Gillingham, 2005; Baddeley, 1996; Moscovitch & Winocur, 1995; Stuss, 2000; Stuss & Benson, 1984). With respect to memory, the role of prefrontal cortex is to coordinate and process incoming information to feedback a strategy to the hippocampus to be used for efficient information encoding and retrieval (Baddeley, 1996; Baddeley, 2010; Incisa della Rocchetta & Milner, 1993; Kimberg & Farah, 1993; Moscovitch, 1992; Moscovitch & Winocur, 1995; Spencer & Raz, 1995; Stuss & Alexander, 2005). Therefore, it has been postulated that any deficits in prefrontal activity will be more evident in recollection than familiarity, due to its greater dependence on strategic guidance from the prefrontal area (Greenwood, 2000; Moscovitch & Winocur, 1995; Wheeler & Stuss, 2003).

In summary, the motivation for this study was to explore and clarify factors that have contributed to inconsistency in the literature regarding recognition memory performance in MCI groups, particularly the findings of Westerberg et al. (2006) and Barbeau et al. (2004). The aim was to refine the procedure used by Westerberg et al. (2006) in order to establish a valid assessment tool for evaluating the dual processes of recognition memory in AD and MCI individuals in future stages of this research project.

We predicted that there would be a significant decline in performance of healthy older adults on both tests of recognition memory using the new learning paradigm, relative to tests using the

learning procedures of Westerberg et al (2006). Additionally, based on previous findings, we also predicted that participants would perform better on the tests of recollection relative to the tests of familiarity.

Method

Participants

A total of 28 healthy older adults took part in the study. Participants ranged in age from 62 to 87 years (*M*=73.04 years; *SD*=6.41 years). The majority of participants, (15), fell within the age-range of 70-80 years, 8 participants were within the 60-70 age-group, and the remaining 5 participants spanned the age-range of 80-90 years. The study participants were all European Pakeha; 18 identified themselves as New Zealand Europeans and 10 as Europeans. The gender distribution of the sample was uneven, consisting predominantly of female participants with 75% females (21 participants) and 25% males (7 participants). The sample was characterized by a high educational level with a mean of 15 years of education (*SD*=2.74 years; range: 8-19 years).

Inclusion criteria for the study were an absence of any diagnosed neurological condition, no history of any head injury, stroke or pharmacological treatment for psychiatric disorders, and corrected-to-normal vision. Participants were also screened for a history of epilepsy, as the task used in the electrophysiological study (flashing stimuli on a computer screen) could potentially trigger epileptic activity.

Exclusion criteria included presence of signs of dementia and cognitive impairment. The investigator asked participants whether they had ever been given or suspected to have a probable diagnosis of any type of dementia or mild cognitive impairment. The Mini-Mental State Examination (MMSE) was also used to screen for undiagnosed cognitive impairments, with exclusion of any individual with a score less than 24 out of 30. The cut-off score was based on findings that 24 represents the lowest score achieved by healthy older adults (Folstein, Folstein, & McHugh, 1975). The mean score of the sample was 29.86, (SD= 0.36), range 29-30. All participants were living independently and reported no difficulties in execution of everyday affairs or significant changes in cognitive functioning.

Participants were volunteers, recruited from a variety of community-based social organizations for older people, including Grey Power, University of the Third Age, and Age Concern. Out of 35 interested older adults, 28 satisfied inclusion criteria and formed the study sample.

Measures

Mini-Mental Status Examination (Folstein, Folstein, & McHugh, 1975)

The MMSE is a brief cognitive test that is widely used to screen for signs of cognitive dysfunction and dementia (Folstein, Folstein, & McHugh, 1975). A number of studies examining properties of the MMSE revealed its high reliability (test-retest = 0.89) and adequate validity: sensitivity=86%; specificity=92%; concurrent validity=78% (Mitrushina & Satz, 1991; O'Connor et al., 1989).

The MMSE evaluates, albeit not in depth, a number of cognitive functions, including memory, attention, orientation, spatial and executive abilities, with a maximum score of 30. A score of less than 24 out of 30 is frequently used as a cut-off for indicating cognitive impairment or dementia, which implies a need for further neuropsychological assessment to elucidate low performance on the MMSE (Folstein, Folstein, & McHugh, 1975; O'Bryant et al., 2008).

Recognition Memory Tasks

Stimuli were obtained from Holdstock and colleagues (2002). They consisted of black pictures, half of which were naturally occurring and half of which were manmade nameable objects (refer to Figure 3). In total 58 targets and 174 foils were used for experimental and replication procedures. The replication task comprised 12 targets and 36 foils for the yes-no task, and the same number for the forced-choice task. The experimental task comprised 17 target items and 51 foils for each test.

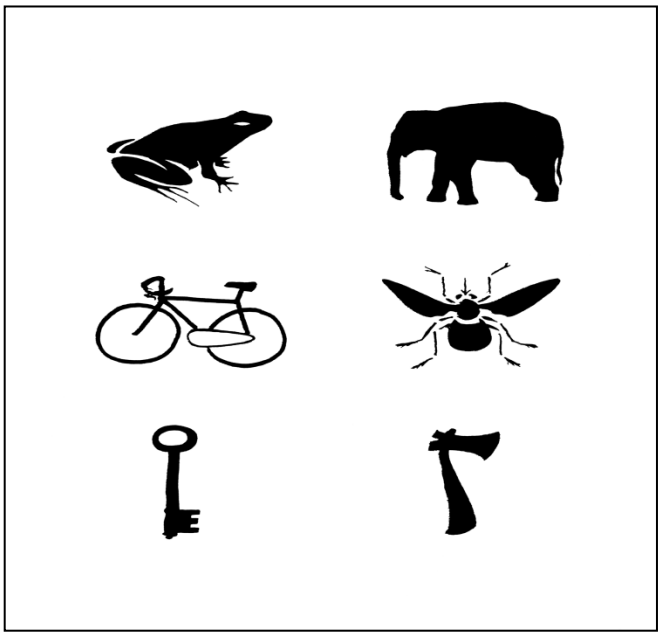


Figure 3: Exemplars of visual stimuli: pictures of manmade and naturally occurring objects (Holdstock et al. 2002).

Two recognition memory tasks (replication and experimental), each consisting of two tests: a forced-choice recognition test and a yes-no recognition test, were administered. Each participant, hence, completed four tests. A different set of stimuli were employed in each test, however, stimuli in each test didn't differ across participants.

Replication Recognition Memory Task

Learning Phase

The procedure used to study stimuli was identical for both the "yes-no" and "forced-choice" recognition tests. During the learning phase, participants were shown 12 target objects at a rate of 3 seconds per object, with each target presented twice. Objects were approximately 5 x 4 cm

in size and were presented on 9 x 9 cm cards on a white background one at a time. Stimuli were presented manually by the investigator.

For the first presentation, participants were asked to decide whether each object was natural or manmade. This was followed by the second presentation, in which participants were instructed to study the details of each object. Immediately after the completion of stimuli presentations, participants were given a distraction task (counting backwards) for approximately one minute to minimise rehearsal of the recently viewed objects. Testing was initiated immediately after the administration of the distraction task.

Testing Phase

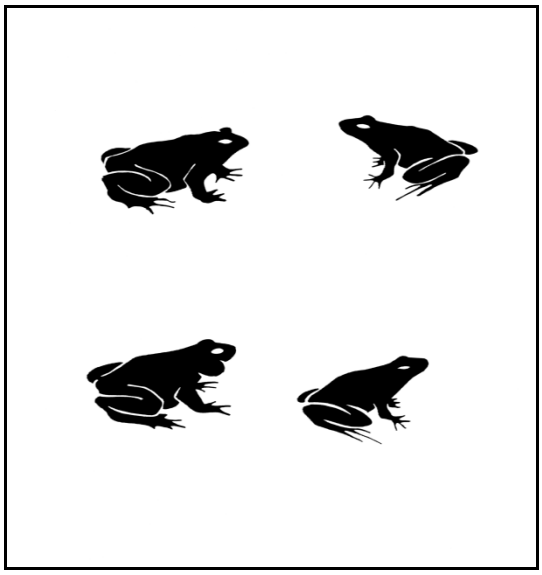
i.) Forced-choice recognition test: "Familiarity test"

This test comprised 12 randomly-ordered trials. In each trial, participants were shown a target object and three corresponding foils evenly distributed on an A4 page and were asked to identify the target object among four presented objects. Foils closely resembled the targets in their visual presentation (see Figure 4).

ii.) Yes-No recognition test: "Recollection test"

The test consisted of 48 trials, which included a presentation of 12 target objects and 36 foils (three for each of the target objects, closely resembling the targets). In each trial, participants

were shown an object and were asked to say “yes” if they thought the object was the target object and “no” if not. Objects were presented one at a time on 9 x 9 cm cards in a random order.



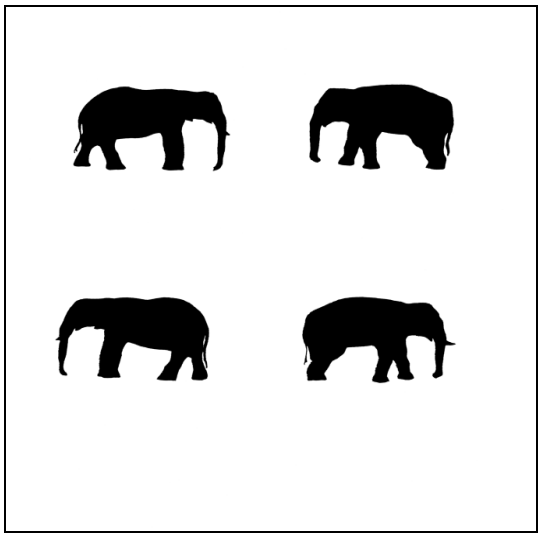


Figure 4: Examples of two trials used in the forced-choice recognition test. Each trial consisted of a presentation of four objects: a target and three corresponding foils, which are similar in their visual presentation to the target.

Experimental Task

Learning Phase

The same procedure was used in the learning phase for both tests. It involved the presentation of 17 objects, only once, at a rate of 3 seconds per object. Objects were approximately 5 x 4 cm in size and were shown on 9 x 9 cm cards one at a time. During the presentation, participants were asked to study the details of each object. This was followed by the distraction task, which was administered for approximately one minute to prevent rehearsal of the recently viewed objects. Testing began immediately after the task was completed.

Testing Phase

i.) Forced-choice recognition test: "Familiarity" test

The test comprised 17 trials, which were randomly ordered. In each trial, participants viewed a target object and three corresponding foils evenly distributed on A 4 page and were asked to select the target object among four presented objects. Foils were very similar to the targets in their visual presentation.

ii.) Yes-No recognition test: "Recollection" test

The test consisted of 68 trials, which included the presentation of 17 target objects and 51 foils (three for each of the target objects, closely resembling the targets). In each trial, participants were presented with an object and were asked to say "yes" if they thought the object was the

target object and "no" if not. Objects were shown one at a time on 9 x 9 cm cards in a random order.

General Procedure

All aspects of participant selection, recruitment, and procedures used in data collection were approved by the University of Auckland Human Participants Ethics Committee.

Information about the research was provided to members of the organizations (Grey Power, University of the Third Age, and Age Concern) via newsletters or brief presentations given in social meetings. Older adults interested in participating in the study contacted the investigator by telephone, who explained the purpose and nature of the study and answered any questions. Additionally the researcher asked screening questions pertaining to eligibility criteria of the current study.

Prior to data collection, participants were given a participant information sheet (Appendix B) and signed a written consent form (Appendix C). The Participant Information Sheet included a description and rationale of the study and a statement informing participants of their right to withdraw from the study at any time. For most participants, the recognition memory study took approximately an hour to 1.5 hours to complete and was conducted in participants' homes.

Prior to testing, participants were introduced to the test procedure with an administration of two practice trials, corresponding to each type of test: a yes-no test and a forced-choice test. The practice tests were identical to the ones used in the experiment employing pictures of the same style with comparable target-foil similarity, although utilizing a limited number of stimuli. This provided participants with an opportunity to become accustomed to the procedure and familiarized with the level of difficulty of the testing paradigm. Participants were also informed that they would be required to perform four tests and that the number of stimuli and amount of stimuli exposure would vary across the tests.

The presentation of the replication and experimental tasks was separated by administration of the MMSE to help to reduce visual interference from the first procedure presentation. To control for the task-order effect, the order of presentation of tests (yes-no and forced-choice) in each task was counterbalanced across participants. The order of task presentation was also counterbalanced.

At the conclusion of the study, participants were thanked for their participation and the researcher checked for any possible distress arising from participation. There was no reported distress evoked by participation, neither was there evidence of psychological distress noted by the researcher following the completion of the study. Participants were also advised to contact the researcher if they felt emotionally unwell (anxious, distressed, low, or tearful) due to participation in the study. No contact was made by any of the participants in respect to that matter.

Data Analysis

Accuracy scores across the forced choice and yes-no memory tests had quite different chance performance rates. To enable direct comparisons, estimates of recognition sensitivity, (*d'*), were calculated for each task for each participant (Macmillan & Creelman, 2004). Appendix A provides background information about this sensitivity measure.

Yes-No Test Format

For each individual, hits and false alarms were converted to raw proportions of hit rates and false alarm rates, where the number of hits and false alarms was divided by N. For hits, N denotes the number of target trials (12 in the replication task and 17 in the experimental task) and for false alarm, the number of foil trials (36 in the replication task and 51 in the experimental task).

To correct for perfect performance and the possibility of a ceiling effect, new proportions of hit and false alarm rates were estimated by adding 0.5 to hits and false alarms and dividing these by N+1 (as recommended by Hautus, 1995; Miller, 1996; Snodgrass and Corwin, 1988). Proportions of hit rates and false alarm rates were then transformed to z scores using a transformation table (Table A5.1, Appendix 5) in Macmillan & Creelman, (2004). Finally, z scores were placed into the formula to calculate $d' = z(HR) - z(FA)$.

Forced-choice Test Format

The initial step involved a calculation of proportion correct (p(c)), where the number of hits was divided by the number of target trials (12 in the replication task and 17 in the experimental task). This was followed by a transformation of p(c) into sensitivity values, using the transformation table from Macmillan & Creelman, 2004 (Table A5.7). This table provides *d'* values for each possible proportion correct and for different numbers of alternatives used in forced-choice designs. Although these *d'* values were calculated with corrections for response bias using appropriate algebraic adjustments, the format of the forced-choice test does not allow a direct estimation of false-alarms and, hence, cannot totally account for response bias which can affect a participant's performance (Hacker & Ratcliff, 1979; Macmillan & Creelman, 2004). In the present experiment, where one target and three foils were distributed evenly in four locations, one potential response bias would be a location bias reflected in participants' preference to select one location over the others. To ascertain whether the forced-choice recognition tests were confounded by a response bias towards location, the number of times each of four locations was selected out of 12 trials in the replication task and out of 17 trials in the experimental task was converted to a percentage for each participant. Data were then subjected to analyses described below.

Statistical Analysis

The primary aim of the recognition memory study was to explore whether manipulation of the learning procedures directly influenced recognition memory scores on the yes-no test ("recollection") and the forced-choice test ("familiarity"). A secondary aim of the study was to

establish if a difference existed between forced-choice and yes-no test formats in recognition memory performance in either of the tasks.

To determine whether manipulation of learning procedures influenced scores on the "yes-no" and "forced choice" recognition memory tests, a 2 factor repeated measures analysis of variance (ANOVA) was performed with test format (yes-no or forced- choice) and learning procedure (replication and experimental) both within-subjects factors.

To check whether there was a response bias towards specific locations in the forced-choice tests one-way ANOVAs were conducted for each forced-choice task, using percentage of each location (one, two, three, & four) selected as the within-subject variable.

Results

Table 1 displays mean performance of participants on four recognition memory tests, including raw proportions of hit rates and false alarm rates and *d*'. The repeated measures ANOVA revealed a significant main effect of learning procedure on memory performance, $F_{(1, 27)} = 12.40$, $p = 0.002$), with lower recognition sensitivity on the experimental procedure than the replication procedure. There was no significant effect of test format on memory performance ($F_{(1, 27)} = 2.77$, $p = 0.108$), indicating no significant difference in overall performance between forced-choice (familiarity) and yes-no (recollection) test formats. There was also no significant interaction between test format and learning procedure ($F_{(1, 27)} = 1.19$, $p = 0.284$).

Table 1: Mean performance on the forced-choice tests and the yes-no recognition memory tests for replication and experimental tasks.

	Replication Tasks				Experimental Tasks			
	Forced-choice		Yes-No		Forced-choice		Yes-No	
	M	*SEM*	*M*	*SEM*	*M*	*SEM*	*M*	*SEM*
HR	0.76	0.03	0.79	0.02	0.65	0.03	0.75	0.03
FAR			0.25	0.03			0.29	0.02
d'	1.72	0.12	1.48	0.09	1.33	0.09	1.29	0.10
p *(c)*	75.64	0.03	78.25	0.02	65.57	0.03	74.89	0.03

Note: Statistical analysis was based on measurements of *d'*. HR = hit rate; FAR = false alarm rate; *d'* = estimated sensitivity; p *(c)* = percent correct; *M* = mean; *SEM* = standard error of the mean. HR and FAR represent performance data, without correction for ceiling effect.

To determine whether recognition memory performance on forced-choice tests was contaminated by a response bias to location, a within-subjects ANOVA was conducted. There was no significant effect of location on recognition responses for either the experimental or replication procedures (experimental procedure: $F_{(3, 81)} = 1.52$, $p = 0.255$; replication procedure: $F_{(3, 81)} = 0.96$, $p = 0.414$). The results indicate that participants did not show a preference for a specific location while selecting an object, suggesting these was no response bias for location on tests with forced-choice format.

Discussion

The recognition memory study yielded a number of important findings. The results revealed that the learning procedure of the experimental task significantly reduced participants' performance on the tests of recognition memory. The study also found that healthy older adults demonstrated relatively equal levels of performance on tests of dual processes of recognition memory.

The Effects of the Experimental Procedure on Recognition Memory Performance

It is highly likely that properties of both the study procedure and the test, including stimuli used and test format, can influence involvement of the dual processes of recognition memory. Consequently, parameters of the test and learning procedure need to be taken into account when designing a protocol aiming to tease apart activities of familiarity and recollection.

As previously described, both the replication and experimental tasks in the current study were comprised of tests which possessed analogous characteristics. The tests were of distinct formats (yes-no and forced-choice) and consisted of targets that closely resembled foils. Previous research indicates that under a condition where targets are similar to foils, a yes-no format will tap into recollection processes, while a forced-choice will measure familiarity-based recognition (Holdstock et al., 2002; McClelland et al., 1995; Norman & O'Reilly, 2003).

The tasks in the present study, however, consisted of procedures which differed on two dimensions, the number of items and number of stimulus exposures used during the study phase. The experimental task comprised 17 items which were shown only once, while the replication task included 12 items which were presented twice. Thus any identified difference in recognition performance between these tasks would be due to the differences in procedure.

The experimental procedure led to a significantly lower level of performance overall by participants on measures of the dual processes of recognition memory. This pattern of results is consistent with the hypothesis that an increase in memory load, through a reduction in stimulus exposures and increase in number of study items, would negatively affect participants' performance on tests of familiarity and recollection and would decrease the likelihood that recollection and familiarity-based recognition processes would be used on the forced-choice task.

Poorer performance on the experimental yes-no test is consistent with the theoretical foundation that guided development of the experimental procedure. It is well-established that recollection mediates activity of one type of recognition memory that allows an individual to recollect the item and its associated features at the ensuing encounter (Gardiner, 1988; Jacoby, 1991; Mandler, 1980; Tulving, 1985; Yonelinas, 1999, 2001, 2002; Yonelinas et al., 1996; Yonelinas & Jacoby, 1996). Research further suggests that formation of recollective experiences depends upon an individual's ability to attend, process and encode as many features of that stimuli as possible, enabling an individual to differentiate that specific item from similar ones (Aggleton & Brown, 1999; Aggleton & Brown, 2006; McClelland et al., 1995; Norman & O'Reilly, 2003). Therefore, it can be inferred that cognitive variables, such as exposure duration and the number of item presentations, are likely to affect an individual's ability to form recollective memory.

Under conditions of the experimental procedure, participants were disadvantaged by reduced opportunities to encode and consolidate as many details of stimuli as they would have done under more favourable conditions of the replication procedure. Accurate recognition of the target on the yes-no test where targets are very similar to foils is likely to be contingent upon the ability of an individual to remember as many distinguishable features of that target as possible, hence, elimination of additional stimulus exposures during learning is likely to have led to a decline in the yes-no test in the experimental task.

The decrease in performance on the forced-choice test in the experimental task relative to performance on the same test in the replication task is likely to reflect an enhanced ability of the

experimental procedure to test familiarity processes. The single item exposure and greater number of items employed in the experimental procedure likely reduced the efficacy of enhanced learning which underlies recollection processes.

The additional exposure used in the replication procedure might have led to memorization of a greater amount of details of the item enabling formation of recollective memory of some items during the encoding phase and its subsequent activation during retrieval. Thus, the performance of participants on the forced-choice test in the replication task is likely contaminated by simultaneous use of recollective and familiarity retrieval, while their performance on the experimental task is likely to have reflected a more pure assessment of familiarity processes. This proposition is supported by a finding of our study showing a negative effect of the experimental learning procedure on the familiarity–based recognition task.

The results found no significant difference in overall performance between forced-choice (familiarity) and yes-no (recollection) test formats in either of the procedures. This suggests that the tests in the experimental procedure (as well as the original procedure) show an equal level of difficulty. Thus the new learning parameters may be useful for future research with patient groups as interpreting a difference in performance on the yes-no and forced-choice tasks will not be confounded by differential difficulty of the two tasks.

The results of the current study compliment research findings reporting differential effects of manipulation of study variables on recognition memory performance. Numerous studies have reported that an increase in memory load, using a greater number of study items and limited item exposure, significantly reduced performance on recognition memory tasks, while provision of variables that facilitate memory performance, such as repeated stimuli exposure and fewer number of study items, enhanced recognition memory (Algrabel & Ruiz, 1986; Daniel & Ellis, 1972; Jacoby, 1999; Kausler, Dalezman, & Yadrick, 1977; Kausler, Dalezman, & Yadrick, 1978; Light, Chung, Pendergrass, & Van Ocker, 2006; Nahinsky & Dodd, 1965). Of most relevance to the present study are findings that identify mechanisms through which number of item exposure influences dual processes of recognition memory (Brandt, Cooper, and Dewhurst, 2005; Daniel & Ellis, 1972).

Brandt and colleagues (2005) examined the effect of repeated item exposure on recognition performance of students who were experts at a particular subject. Radiography and psychology students were randomly assigned to two conditions: a single item exposure and repeated exposure. Hence, half of the participants were shown a set of words from radiography and psychology terminology once and the other half three times, following which they were given a recognition test using a Remember/Know procedure. Results of this study identified an expertise effect in the single exposure condition: participants who had seen items once correctly recognized more words from their own domain of expertise. On the other hand, participants who had seen items three times were equally good at recognizing items from both domains of subjects. Brandt et al. (2005) also showed that a significant increase in recollection responses was a key factor responsible for the elimination of the expertise effect as there was a significant

increase in "remember" responses indexing recollection and a reduction in "know" responses reflecting familiarity. In other words, repeated item exposure evoked activity of recollective processes, which is echoed by the findings of the present study, demonstrating that additional item exposure improved recognition memory performance through induction of recollective processes.

A series of other studies have also observed the beneficial effect of repetition on recollection. In those experiments, repetitive item exposure, varying from two to four exposures, increased the likelihood that participants "remembered" rather than "knew" that an item was previously presented (Daniel & Ellis, 1972; Mantyla & Cornoldi, 2002; Parkin, Gardiner, & Rosser, 1995; Parkin & Russo, 1993).

The results of our study in collaboration with data of the previously reviewed research provide some insight into the disparity between the findings of Westerberg et al.'s (2006) and Barbeau et al.'s (2004) experiments. The findings of the current study indicate that the superior overall performance of participants on the replication task, which was identical to the one used in Westerberg et al.'s study, was due to enhanced acquisition of study materials. This implies that the procedure used in Westerberg et al.'s study is likely to have formed optimal conditions for the test of yes-no format to gauge recollection processes, while measurement of familiarity processes on the forced-choice test was likely confounded by the use of combined recollective and familiarity processes. In other words accurate recognition of a target on the Westerberg et al. forced-choice test could have been made through utilization of either familiarity or

recollection, dependent upon the degree of memory strength pertaining to specific details of a target.

Given recollection is mediated by the hippocampal network, while familiarity is supported by activity of the perirhinal network (Aggleton & Brown, 1999; Aggleton & Brown, 2006; Yonelinas, 2002), the observation of intact performance of MCI individuals on the forced-choice test of familiarity in Westerberg et al.'s study may reflect the recruitment of residual activities from a combination of neural structures, including perirhinal cortex and hippocampus. In contrast to Westerberg et al. (2006), Barbeau and colleagues (2004) reported a significant deficit in performance of MCI individuals on a forced-choice familiarity test. The procedure employed by Barbeau et al. which was similar to the experimental task of our study (although with many more items), is likely to have possessed greater sensitivity in assessing familiarity-based recognition. Their findings of impoverished familiarity recognition memory of MCI individuals is consistent with neuropathological findings that damage to perirhinal cortex precede the impairment of hippocampal formation (Braak & Braak, 1991, 1994, 1997a, 1997b; Braak et al., 1993).

The Impact of Aging on Recognition Memory

This study also found that participants demonstrated an equal level of performance on the tests of yes-no and forced-choice formats. This pattern of results was observed in both the experimental and replication tasks as no interaction effect between the tests and tasks was found. Hence, the

present research suggests that healthy older adults showed no differential difficulty on these tests of recollection and familiarity.

These findings contrast with several studies which suggest that aging negatively affects recollection, with relative sparing of familiarity processes (Java, 1996; Jennings & Jacoby, 1993; Jennings & Jacoby, 1997; Mantyla, 1993; Parkin & Walter, 1992). As already noted, an age-related decline in recollection has been commonly attributed to neural deficits in the prefrontal cortex (Buckner, 2004; Moscovitch & Winocur, 1995; Wheeler & Stuss, 2003).

As well as reducing executive resources, the neural changes occurring with aging reduce speed of information processing (Madden et al., 2009; Salthouse, 1996; Stuss et al., 2005). Both of these changes are thought to slow down the generation and provision of executive strategies necessary for efficient information acquisition, which is more critical for formation of recollective recognition memory than familiarity-based recognition (Madden et al., 2009; Salthouse, 1994a; Salthouse, 1996; Stuss et al., 2005).

In support of this view fMRI studies have demonstrated that in contrast to unilateral recruitment of prefrontal areas by young adults, older adults recruit bilateral prefrontal areas during performance of executive and recognition memory tasks, presumably to compensate for the decline in functional integrity of prefrontal cortex (Cabeza, Anderson, Locantore, & McIntosh,

2002; Duverne, Motamedinia, & Rugg, 2009; Grady et al., 1995; Logan, Sanders, Snyder, Morris & Buckner, 2002; Morcom, Good, Frackowiak, & Rugg, 2003; Rosen et al., 2002).

Furthermore, numerous studies demonstrate a significant decrease in the speed of information processing in older adults (Palfai, Halperin, & Hoyer, 2003; Salthouse, 1992; Salthouse, 1994c; Salthouse, 1995; Salthouse & Babcock, 1991; Salthouse & Ferrer-Caja, 2003), with some suggesting a causal link between a decline in processing speed and age-associated deficits in recall and recollection. A reduction in cognitive speed of information processing has been found to account for 80-90 % of age-related variance in recall and recollection (Park et al., 1996; Salthouse, 1994b; Salthouse, 1995; Salthouse, 1996; Salthouse, Toth, Hancock, & Woodard, 1997). In contrast, no association between reduced processing speed and familiarity-based recognition has been observed (Salthouse et al., 1997).

These findings indicate that provision of strategies, aiming to counteract deficiencies in processing speed and executive resources, may compensate for the negative effects of aging on recollection. Data from several studies support this hypothesis (Craik, 1994; Logan et al., 2002; Multhaup, 1995). It has been repeatedly found that when older adults are given instructions which facilitate deep information processing (e.g., guiding participants to form an imagery association with a stimuli), their recollection performance improve to the level of their younger counterparts (Hay & Jacoby, 1999; Perfect, Williams, & Anderton-Brown, 1995). A similar pattern of results is noted in a condition in which healthy older adults are provided with additional study time (Hay & Jacoby, 1999; Palfai et al., 2003). Hence, research indicates that

older adults exhibit good recollection performance if they are afforded appropriate environmental support, permitting effective processing of information.

The collective findings of the research reviewed have important implications for the current study. As previously stated, the present research failed to find a significant difference in performance of older adults between tests of yes-no and forced-choice format in either the replication or experimental tasks. This suggests that the group of healthy older adults didn't show any differential difficulty between tasks assessing recollection and familiarity processes of recognition memory. A number of supportive conditions were included in the task design, which possibly elicited generation of strategies that benefitted recollection memory performance. First, participants were given a practice opportunity prior to data collection to familiarise them with the procedure and the level of difficulty of the testing paradigm. Second, study instructions encouraged participants to attend to object details. A combination of these environmental cues may have created advantageous conditions for generation of executive strategies necessary to build recollective experiences. Hence, it is possible that the provision of environmental cues through task practice and guiding instructions in this study eliminated the expected disparity between familiarity and recollection processes.

This proposition is compatible with findings of research which employed stimuli and study instructions analogues to the current study. A study conducted by Koutstaal and colleagues investigated the effect of environmental task conditions on recollection performance in older adults (Koutstaal, Schacter, Galluccio, & Stofer, 1999). During the study phase, older and

younger adults were presented with objects. One group of participants was presented with objects without any specific learning instructions, while the other group was instructed to attend to specific details of each object. In a subsequent retrieval phase, participants were shown one item at a time (yes-no format) with targets being very similar to foils and asked to identify the studied items. It has been demonstrated that supportive encoding instructions significantly reduced age-related variance on recollection performance, compared to the condition with no learning guidance.

In summary, the study in this thesis provides a strong foundation on which to select task properties that will exhibit discriminative sensitivity in assessment of familiarity and recollection. The outcomes of the current study clearly illustrate that additional exposure led to memorization of greater amount of item details. This profile of results is consistent with research evidence revealing that repeated exposure is crucial to the binding and strengthening of mnemonic connections, which underlies recollective processes (Johnson, 1992; Malenka, 2003; Squire, 1986). Research also suggests that retention of the encoded information is likely to be stronger with presentation of fewer items (Johnson, 1992; McClelland et al., 1995; Norman & O'Reilly, 2003; Squire, 1986). This indicates that repeated exposure of fewer items is likely to maximize processes of recollection.

A single item exposure, on the other hand, affords an equal opportunity for an individual to process an item through either an elaborative encoding or less effortful, automatic process. Hence, a procedure consisting of a single item exposure is likely to create optimal conditions for

a test to display its characteristics in measuring familiarity while a procedure consisting of a double item exposure is likely to enhance test characteristics in assessing recollective recognition.

Thus, the present results suggest that a task that is most likely to display high sensitivity in discriminating between processes of recollection and familiarity might possess the following test and procedure characteristics. To assess familiarity-based recognition the task should consist of the learning procedure directing individuals to note whether an item was manmade or naturally occurring and involving a single stimuli exposure of more than 12 items, using a forced-choice test format with targets closely resembling foils. To measure recollection, the task should consist of the learning procedure directing participants to study details of the items and comprising of a double item exposure of at least 12 items and of the test characteristics involving the yes-no format with targets very similar to foils.

Chapter 5

Electrophysiological Study

A body of research conducted at the Cognitive Research Centre at the University of Auckland developed a protocol that elicited and measured visual LTP in humans non-invasively via EEG recordings (McNair et al., 2006; Ross et al., 2008; Teyler et al., 2005). Repeated presentation of visual stimuli at high frequency induced a persistent increase in the amplitude of the N1b component of the EEG. Additionally, research demonstrated that visual evoked potentiation in vivo possesses molecular and functional properties of LTP identified in vitro, that is, NMDA-receptor dependency and input-specificity (Cavus et al., 2009; Clapp et al., 2006; McNair et al., 2006; Ross et al., 2008).

The current study employed the protocol and procedure developed in this EEG laboratory to study visual LTP in healthy older adults. The primary aim was to discover whether it was possibly to induce measurable LTP activity in healthy older adults to help determine the utility of the protocol for further application with AD and MCI individuals.

Given that healthy older adults are able to acquire new information (presumably indicative of synaptic plasticity), it was hypothesised that participants would demonstrate evidence of visual evoked potentiation. Specifically, it was expected that the amplitude of the N1b component of

tetanised stimuli will be significantly increased after immediately following the photic tetanus compared to pre-tetanus amplitude and relative to non-tetanized stimuli, and that this increase in amplitude will be maintained 30 minutes later.

This study will also explore the relationship between the magnitude of visual LTP and visual recognition memory in healthy older adults by correlating individuals' memory scores on four recognition memory tests with the degree of the amplitude increase in their LTP activity. We hypothesised that the scores of the recognition memory will be positively associated with magnitudes of visual-induced potentiation, that is, individuals with greater increase in LTP will have higher scores on memory tests.

Method

Participants

Twenty four out of 28 participants consented to take part in the electrophysiological study. The four participants who elected not to participate in this study were all females. Three participants indicated that they didn't want to experience the inconvenience associated with EEG set-up. The other participant went overseas due to urgent personal circumstances. This group did not perform significantly differently from the group who chose to take part in the EEG study on any of the four recognition memory tests (Mann Whitney independent sample tests: replication forced-choice test Z = - 0.30, p = 0.764, the replication yes-no test Z = -0.72, p = 0.47; the experimental forced-choice test Z = - 0.13, p = 0.924; or the experimental yes-no test Z = - 0.72, p = 0.505). However, the

there was a marginally significant difference in age, with the group who declined participation being greater in age (Z = - 1.94. p = 0.052). Exclusion of these four participants led to a drop in mean age from 73.04 to 72.0 (SD = 5.93).

EEG Set-up

The circumference of each participant's head was first measured to determine the appropriate net size (large, medium or small). The selected net was then soaked in a solution containing one litre of warm water, two teaspoons of potassium chloride (to enhance electrical conductance) and 15 millilitres of shampoo (to break down natural fatty acids on the scalp to reduce resistance). After soaking for a few minutes, the net was removed and gently dried with a towel to eliminate excess moisture before being fitted over the participant's head and face. When the net was accurately fitted, each of the electrodes on the net was adjusted to a vertical position to ensure optimal recording and connection to the EEG amplifier.

Prior to the EEG recordings, the participants were shown their real-time ongoing EEG on the computer screen to demonstrate the effect of motor artefacts induced by eye blinking, jaw clenching, and body movement on the EEG activity. Participants were encouraged to be as relaxed as possible to avoid rapid, frequent eye blinking and body movements during the process of data acquisition.

EEG Acquisition

The experiment was conducted in a dimly lit, electrically-shielded and sound-attenuated room. Participants were monitored via a closed circuit video camera and were also instructed to raise their hand if they felt unwell or needed assistance at any time over the period of data collection.

EEG activity was recorded continuously (under 250 Hz sampling rate, 0.1-100 Hz analogue bandpass filter) using 128-channel Ag/AgCl electrode nets (supplied by Electrical Geosides Incorporated, Eugene, OR, USA). Electrode impedances were maintained below 50 kΩ (range 30 to 50kΩ), a value defined as acceptable for this system (Ferree, Luu, Russell, & Tucker, 2001). EEG was initially attained using a common vertex (Cz) reference and was later re-referenced to the average reference in off-line analyses. Acquisition software was run on a Macintosh G4 computer with a 16-bit analogue-to-digital converter.

Stimuli

The stimuli were horizontal and vertical sine gratings, each with a spatial frequency of one cycle per degree (cpd) (see Figure 5). The gratings were circular with the diameter subtending a visual angle of 8°, and shown at full contrast on a grey background (see Figure 5). Stimuli were displayed on a SVGA (super video graphics array) computer monitor (1024 × 768 pixel resolution; 60 Hz refresh rate) at a distance of 57 cm (distance measured from computer screen to the face of a participant). Stimulus presentation, timing routines for visual displays and pulse generation were programmed and controlled using the E-Prime User Guide (Psychology Software Tools, Pittsburgh, PA, USA).

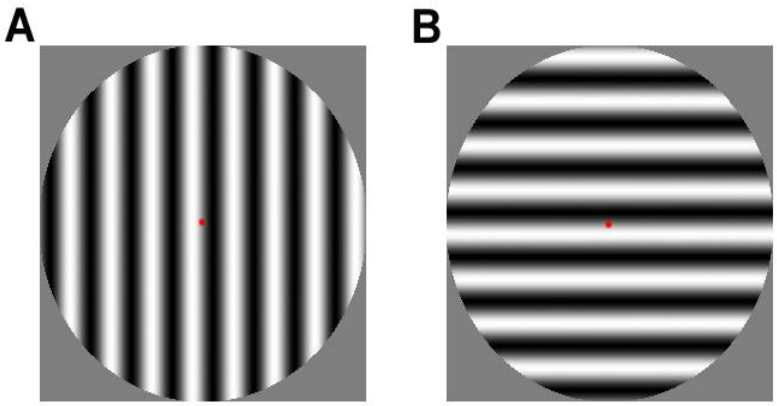


Figure 5. Experimental stimuli: A) vertical or B) horizontal circular sine gratings with a spatial frequency of 1cpd. Both stimuli were presented on a grey background at full contrast.

Procedure

The experiment consisted of four phases: two baseline blocks, a photic tetanus, two early post-tetanus blocks, and two late post-tetanus blocks. The first phase (baseline condition) consisted of two pre-tetanus blocks during which sine gratings of both vertical and horizontal orientations were shown to participants at a low frequency rate (1 Hz). This was followed by a photic tetanus, in which sine gratings of either vertical or horizontal orientation were presented at a high frequency rate (6.8 Hz). The type of grating used for the photic tetanus was randomized across participants. The third phase consisted of two early post-tetanus blocks, in which sine gratings of both horizontal and vertical orientations were shown at a low rate (1Hz) immediately following the tetanus. The final phase was composed of two late post-tetanus blocks which were administered 30 minutes later

and involved a presentation of sine gratings of both vertical and horizontal orientations at a low frequency rate (1Hz). During the 30 minute rest period participants were asked to keep their eyes closed.

The pre-tetanus, early post-tetanus, and late post-tetanus blocks were each comprised of the presentation of 120 vertical-grating stimuli and 120 horizontal-grating stimuli, which were presented in a random order. Each stimulus was displayed in the centre for 33 ms with a randomly jittered inter-stimulus interval of 1000-15000 ms, a temporal frequency of 1 Hz. The duration of each block was approximately 5 minutes. The photic tetanus consisted of 1000 presentations of either a vertical sine grating or a horizontal sine grating, which lasted for approximately 2 minutes. Each photic stimulus was shown for 33 ms with a randomly jittered inter-stimulus interval of 67-100 ms, a temporal frequency of 8.6 Hz. This level of frequency is found to be effective in inducing potentiation, but at the same time minimizes the possibility of tetanus-evoked perceptual fusion (McNair et al., 2006; Teyler et al., 2005). Participants were requested to focus their sight on a red circular dot at the centre of the stimuli throughout the experiment.

General Procedure

Each participant was transported from their home to the University of Auckland. EEG was measured at the EEG laboratory at the University of Auckland. Prior to the initiation of the experiment, the methods, instructions, and rationale of the electrophysiological experiment were explained to each participant. Following the completion of the experiment, each participant was thanked for their participation in the experiment and commuted to their home by the investigator. Each participant was also informed that they could contact the researcher if they thought that

participation in the experiment evoked emotional discomfort for them. No contact was made by any of the participants in respect to that matter. The completion time of the electrophysiological (EEG) study varied between two to three hours depending upon time required to set up the EEG apparatus for each participant.

EEG Analysis

Acquired EEG readings were initially segmented into 600 ms epochs, consisting of 100 ms pre-stimulus onset and a 500-ms period post-stimulus onset. Automatic eye-movement correction was then applied to all segments using the procedure designed by Jervis, Nichols, Allen, Hudson, and Johnson (1985). The corrected data were subsequently averaged according to orientation (horizontal or vertical gratings) and block (pre-tetanus, early post-tetanus or late post-tetanus). These manipulations were applied to the data of each participant individually prior to measurement of the amplitude of the N1b component. The amplitude of the N1b component was calculated using the protocol developed by researchers at the Cognitive Research Centre at the University of Auckland (Teyler et al., 2005; McNair et al., 2006; Ross et al., 2008). The N1b component was defined as the part of the waveform extending from the peak of the N1 component to halfway between the N1 and P2 components, which were generated approximately 150-190 ms following a stimuli onset.

The N1b component was determined by estimating the N1b components for a cluster of seven electrodes centred on areas of P7 and P8 (see Figure 6). To calculate the N1b component, values of the N1amplitude peaks across the seven electrodes were summed and averaged and then the values of P2 amplitude peaks across the seven electrodes were summed and averaged. Following this step, the estimated averaged values of the N1 and P2 amplitude peaks were summed and divided by 2,

which provided the value of the N1b component. N1b amplitude was measured for each block (pre-tetanus, early post-tetanus, and late post-tetanus) and each condition (vertical and horizontal), hence, data for both tetanised and non-tetanized gratings for each block were processed. The last step involved the identification of a change in amplitude of the N1b components of early and late post-tetanus blocks compared to the amplitude of N1b components of pre-tetanus blocks, which was measured by subtracting pre-tetanus N1b components from early post-tetanus and late post-tetanus N1b components. The data of each participant were analysed individually.

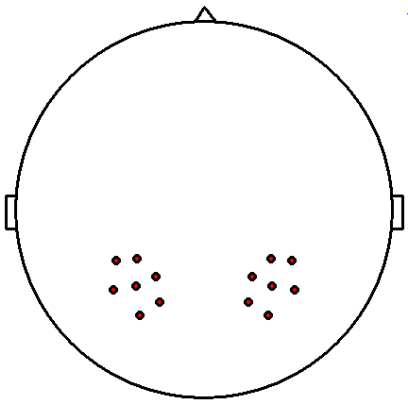


Figure 6. Approximate location of left and right hemisphere electrodes used to measure amplitude of the N1b component.

Statistical Analysis

A primary goal of the electrophysiological study was to investigate whether healthy older participants demonstrate visual LTP. To evaluate the results of the obtained EEG data, a 2 factor repeated measures ANOVA was conducted, with grating (tetanised/non-tetanised) and block (pre-tetanus, early post-tetanus, late post-tetanus) as within-subject factors. The main effect of interest was whether the amplitude (μV) of the N1b component of baseline blocks (pre-tetanus) differed from the test blocks (early post-tetanus and late post-tetanus) for the tetanised grating (treatment) relative to the non-tetanised grating (control): a block-by-grating interaction.

To determine whether there was a significant association between recognition memory performance and LTP activity, Pearson bivariate correlations were calculated between *d'* measures of the four recognition memory tests and magnitude of LTP activity. LTP activity was defined as the difference in the increase of amplitude of N1b components between tetanised and non-tetanised stimuli. To clarify, that difference was measured by first calculating the amplitude change of the N1b component between pre tetanus and early post-tetanus, and, between pre-tetanus and late post-tetanus, for both tetanised and for non-tetanised stimuli. Next, the size of the amplitude change of the N1b component for non-tetanised stimuli was subtracted from the size of the amplitude change of the N1b component for tetanised stimuli to give the difference in the amplitude change.

All statistical analyses were run using SPSS version 17, and an alpha of 0.05 was set for all analyses. In case of violation of sphericity assumption, Greenhouse-Geisser corrections were

applied to all F-statistics when investigating main effects and interactions, and Bonferroni adjustments were made in any pairwise comparisons.

Results

Twenty four participants completed the electrophysiological study, but data from only 20 participants was utilizable for EEG analysis. The data of the four excluded participants were significantly corrupted by noise artifact, which affected EEG readings across all cortical areas. A number of internal and external variables have been found to produce noise; including hair and skin conditions (i.e., thin hair, dry skin of the scalp), ocular and muscular artefacts and defaults within the EEG system (Scheer, Sander, & Trahms, 2006). These conditions may lead to diffusion, displacement and disruption of electrical signals, resulting in flat, markedly spiky and obscured EEG recordings, which was overtly observed in the EEG data of these participants (Scheer et al., 2006).

The excluded participants included one male and three females. To check whether this subgroup of participants whose data were excluded from EEG analysis differed in memory performance or age compared to the group whose data were analysed Mann-Whitney independent samples tests were conducted. There were no significant differences between the two groups in age ($Z = - 0.662$, $p = 0.508$) or in memory performance on any of the tests (replication forced-choice test $Z = - 0.864$, $p = 0.387$; replication yes-no test $Z = - 0.349$, $p = 0.727$; experimental forced-choice test $Z = - 0.391$; $p = 0.696$; or experimental yes-no test $Z = - 0.232$, $p = 0.816$).

Figure 7 displays participants' mean N1b amplitudes for tetanised and non-tetanised sine gratings. The analysis of EEG data revealed a significant interaction between block and grating, $F (2, 38) =$

5.22, $p = 0.016$. Pairwise comparisons showed that for the tetanised grating, there was a significant increase in the N1b amplitude from the pre-tetanus block to the early post-tetanus block (-0.38 µV, SEM 0.132 µV, $p = 0.029$) and to the late post-tetanus block (-0.532 µV, SEM 0.169 µV, $p = 0.016$). There was no significant change in the N1b amplitude for the non-tetanised grating from the pre-tetanus block to either the early (-0.092 µV, SEM 0.039, $p = 0.09$) or late post-tetanus blocks (-0.189 µV, SEM 0.105 µV, $p = 0.264$). There was no significant difference between the tetanised and non-tetanised gratings at the pre-tetanus block (-0.094 µV, SEM 0.146, $p = 0.527$) or at the early post-tetanus block (-0.193 µV, SEM 0.132, $p = 0.161$). A significant difference was found between the tetanised and non-tetanised gratings at the late post-tetanus block (-0.248 µV, SEM 0.101, $p = 0.023$). These findings provide an empirical basis upon which to assert that it is possible to induce visual LTP in healthy older adults and for this effect to be sustained.

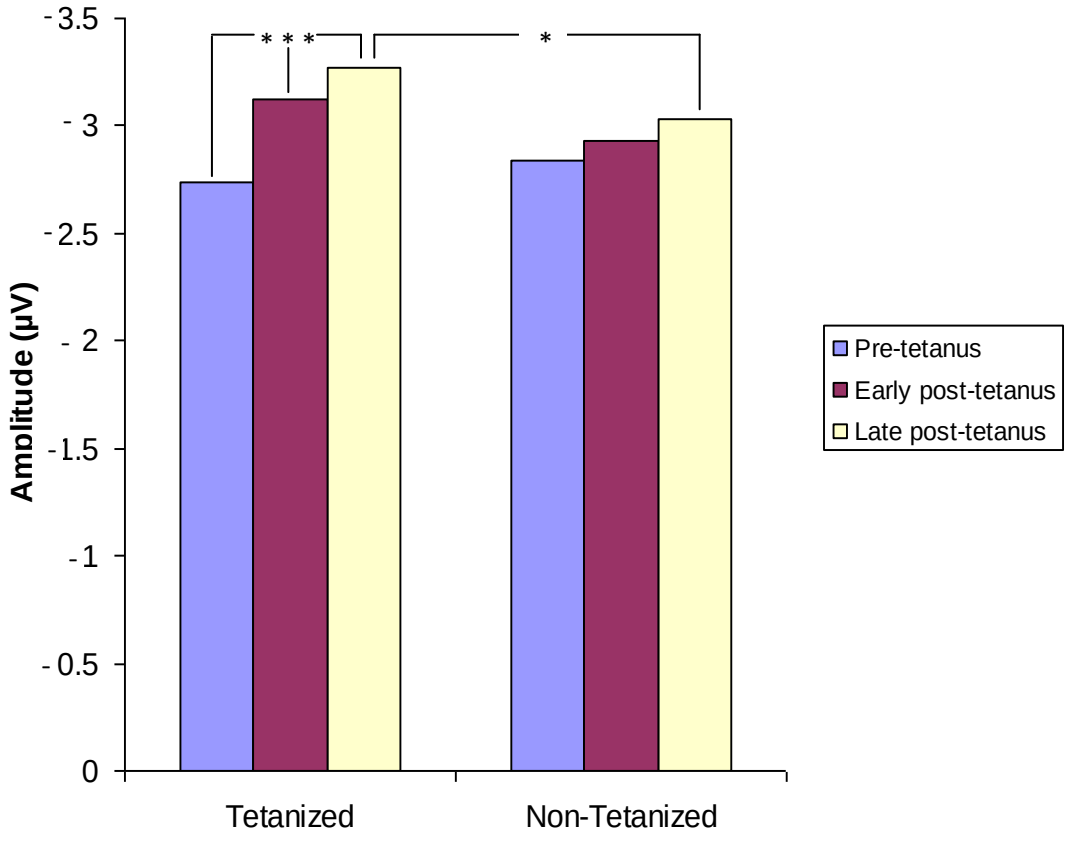


Figure 7: Mean Amplitudes of the N1b Components between Baselines, Early, and Late Blocks for Tetanized and Non Tetanized Stimuli.

To investigate the prediction that LTP activity (increase in the N1b amplitudes in early and late post-tetanus blocks) would be related to performance on the four recognition memory tests, Pearson's bivariate correlations examining relationship between these two sets of variables were conducted. Before describing the results, it should be clarified, that an increase in the N1b component is characterised by an increase in the size of the negative peak, reflected in larger negative values (see Figure 7).

Pearson's bivariate correlations identified only one significant relationship, which was between late LTP and memory performance on the forced-choice test of the experimental procedure, r = - 0.458, p = 0.021 (see Figure 8 and Table 2). Remembering that the greater the change in the N1b amplitude the more negative the μV, this finding, therefore, indicates that memory performance on the forced-choice test of the experimental procedure is linked with magnitude of LTP functioning (i.e., the amount of amplitude increase in the N1b components). The implications of these findings will be discussed in the Discussion.

Table 2: Pearson correlations between Early and Late LTP and four recognition memory tests.

	Replication Procedure		Experimental Procedure	
	Forced-Choice	Yes-No	Forced-Choice	Yes-No
Early LTP	0.01	- 0.05	- 0.02	- 0.09
Late LTP	- 0.006	- 0.19	- 0. 46*	0.07

Note: Early and LTP was measured as the difference in the increase of amplitude of N1b components between tetanised and non-tetanised stimuli.

Figure 8: Pearson correlations between the N1b components (µV) of late post-tetanus blocks and memory scores (*d'*) of the exprimental forced-choice test ($p = 0.021$). LTP is measured as the difference in the increase of amplitude of N1b components between tetanised and non-tetanised stimuli.

To check whether age may have been underlying the association between LTP magnitude and forced-choice recognition memory, Pearson's bivariate correlations were carried out between age and these variables. LTP activity was again defined as the difference in the increase of amplitude of N1b components between tetanised and non-tetanised stimuli for early and late post-tetanus blocks. The correlation analyses failed to reveal significant relationships between age and any of those variables (early LTP r = -0.112, $p = 0.639$; late LTP r = - 0.125, $p = 0.60$; age and the replication forced-choice test r = -0.139, $p = 0.558$; age and the replication yes-no test r = - 0.092, $p = 0.70$;

experimental forced-choice test r = - 0.188, $p = 0.427$; and the experimental yes-no test r = 0.17, $p = 0.942$).

Examination of EEG data revealed that although the majority of participants, 15, showed LTP activity, 5 (2 males, 3 females) demonstrated no increase in the N1b amplitude from pre-tetanus block to early and late post-tetanus blocks. The presence of LTP like-effect was defined by any increase in the amplitude of N1b component, while an absence of LTP like-effect was defined by any decrease/or no change in the amplitude of the N1b component. This was initially determined visually by examining graphs displaying N1b components for each individual and then a difference between baseline and early/late phases was calculated for each participant. It should be noted that an average difference in increase in the amplitude of the N1b component was of – 0.20 μV and an average decrease was of + 0.25 μV. A Mann-Whitney independent samples test was carried out to investigate whether the group who didn't show LTP differed in age and years of education from the group who demonstrated LTP. There were no significant differences in age (Z = - 0.963, $p = 0.336$) or years of education (Z = - 1.667, $p = 0.096$).

To assess whether the two groups of participants, with LTP and no LTP activity, differed in their memory performance on any of four recognition memory tests, a Mann-Whitney independent samples test was conducted with memory scores (*d'*) as the dependent variable. The only recognition test that differentiated the two groups of participants was the forced-choice test of the experimental procedure. There was a significant difference in memory performance on this test between individuals who exhibited LTP and those who didn't manifest LTP activity (Z = - 2.643, $p = 0.008$). No significant differences in memory performance on the other recognition tests between

the two groups of participants were observed: the forced-choice test of the replication procedure Z = - 1.25, $p = 0.212$; the yes-no test of the replication procedure Z = - 0.92, $p = 0.359$; and the yes-no test of the experimental procedure Z = - 0.611, $p = 0.541$.

To further investigate the effect of memory performance on increase in N1b amplitude, we examined the difference in LTP functioning (early/late) between two groups of participants: "good" memory performers and "poor" memory performers using participants' performance on the forced-choice test of the experimental procedure. A "poor" performer was defined by a participant's performance below the group mean while a "good" performer was defined by performance above the group mean on the experimental forced-choice task. There were 11 participants in the "good" performer group and 4 participants in the "poor" performer group. Individuals who didn't demonstrate LTP activity were excluded from the analysis, but notably this subgroup of participants performed below the group mean on the experimental forced-choice test. The good versus poor memory performers did not differ significantly in age (Z = - 0.267, $p = 0.79$).

To check whether the level of the amplitude increase in N1b components differed between the "good" and "poor" memory performer groups, Mann-Whitney independent samples tests were conducted. There were significant differences in early LTP activity between the two groups, z = - 2.09, $p = 0.037$, and a marginally significant difference in late LTP activity, z = - 1.94, $p = 0.053$. This suggests that "good" performers showed greater increase in the N1b amplitudes in early and late LTP phases compared to "poor" performers.

Discussion

A number of important findings emerged from the electrophysiological study. The results of this study demonstrated that visual LTP activity can be induced and maintained in healthy older adults. Additionally, an association was revealed between LTP activity and recognition memory performance on the familiarity test. The study also identified that performance on the familiarity test reflected the level of visual LTP activity in this sample of older adults.

LTP in Older Adults

One of the main findings of this study constitutes the novel demonstration that it is possible to induce visual LTP in healthy older adults. The results revealed that participants responded with significant increases in the N1b component during post-tetanus presentations to sine gratings of the same orientation as the tetanus stimulus, while demonstrating no significant increases in the N1b component during post-tetanus presentations of sine gratings of non-tetanic stimuli. These observations were evident in both early and late post-tetanus blocks, indicating that older adults can produce visual LTP and maintain this activity for at least 30 minutes. Although it is possible that the increase in amplitude of N1b components may have been generated by general excitability of visual after-effect, this appears unlikely for the following reasons. Research shows that elevation in electrophysiological activity induced by visual after-effect disappears within seconds and minutes with optimal longevity of 10 and 15 minutes (Blakemore & Nachmias, 1971; Poiroux, Georges, Bernard, Lannou, Lalonde, & Rebai, 2001). Furthermore, excitability invoked by after-effect phenomenon would likely alter all components of the visual

evoked response, in contrast to the selective potentiation of the N1b component following repetitive presentation of sine gratings of one orientation (e.g., Teyler et al., 2005).

The current research is the first study to the author's knowledge to identify induction of an LTP-like effect in a population of older adults. The discovery of LTP activity in normal aging converges with findings of a study suggesting that older adults display intact electrophysiological activity accompanying performance of recognition memory (Koulikova, Kirk, & Tippett, 2006). Koulikova et al. (2006) investigated the temporal and spatial characteristics of theta waves in older and young adults while they performed a spatial recognition memory task. Theta waves reflect electrophysiological activity (4-7 Hz) which underlies neural mechanisms involved in execution of working and episodic memory (Kirk & Mackay, 2003; Klimesch, 1999; Klimesch et al., 2001). It was revealed that during encoding and retrieval phases of the recognition task, temporal characteristics of theta activity, including onset, peak periods and amplitude of waveforms, were comparable between the two groups of participants. Additionally, theta oscillations were distributed in similar cortical areas in both young and older adults. Hence the findings of the present study compliment evidence which suggests that older adults exhibit intact electrophysiological activity associated with processes of information acquisition.

The outcome of the current research also provides support for the validity of the experimental protocol on which this research is based (Clapp et al., 2005; McNair et al., 2006; Ross et al., 2008; Teyler et al., 2005). These findings confirm in a population with different demographic characteristics that LTP can be induced non-invasively in the visual human system through the

repetitive presentation of visual stimuli (Clapp et al., 2005; McNair et al., 2006; Ross et al., 2008; Teyler et al., 2005). Additionally, they add to evidence that visual potentiation evoked by the photic tetanus in-vivo possesses a fundamental property of LTP, input-specificity (McNair et al., 2006; Ross et al., 2008). Using sine gratings of distinctive orientations, this study found that enhancement of visual LTP activity was specific to the orientation of the photic tetanus.

Association between LTP Activity and the Experimental Forced-Choice Test

Another key finding of this research was the discovery of a significant relationship between LTP functioning and performance on one recognition memory task. It was found that the magnitude of LTP activity induced in participants was related to their memory scores on the forced-choice test (familiarity) of the experimental task. Specifically, higher memory scores on this test were associated with greater magnitude increase of N1b amplitudes during the late potentiation phase. This pattern of results supports the study hypothesis that LTP activity in the form of visual-evoked potentials is related to memory performance.

As outlined in the Results sections, analysis of the EEG data showed that five out of 20 participants didn't generate visual evoked potentiation. When we examined whether any of the four tests had the power to differentiate individuals with LTP manifestation from those without, the results revealed that the only test that distinguished the two groups was the experimental forced-choice test. Specifically, it was demonstrated that participants who exhibited LTP activity performed significantly better on this test compared to participants with no evidence of

visual evoked potentiation. This finding suggested that the experimental forced-choice test has the potential to screen for presence of LTP activity.

Given its selective association with LTP magnitude, the efficacy of the experimental forced-choice test was further explored by testing whether the quality of memory performance on the test would predict the quality of LTP functioning. When participants were separated into two groups: "good" and "poor" test performers, based on their *d'* scores relative to the group average, subsequent analyses revealed that individuals whose memory performance was above the group mean showed greater increase in the amplitudes of potentiation during early and late LTP relative to individuals who performed below the group mean. Collectively, the findings of the present study signify that the experimental forced-choice appears to exhibit properties that are sensitive to examination of visually-evoked LTP.

A significant connection between the experimental forced-choice test (in contrast to the recollection task) and visual potentiation was initially puzzling, but perhaps may be explained by the following account. There is evidence that induction of LTP following repeated presentation of a simple visual stimulus (using this EEG paradigm) results in synaptic changes early in the visual system (Clapp et al., 2005). The recognition memory tasks used in this study were designed to tease apart memory functions associated with perirhinal and hippocampal regions. The design of the familiarity task (forced-choice) was based on the theory that perirhinal and entorhinal cortices assign similar and overlapping representations to similar stimuli and response on the task is guided by a comparison of the relative strength of signals of the target and very

similar foils (Holdstock et al., 2002; McClelland et al., 1995; Norman & O'Reilly, 2003; Westerberg et al., 2006). Thus responses are guided by a process that does not involve conscious recollection of a target or remembering of specific details. In this sense, the nature of the processing that occurs in perirhinal cortex is largely an extension of the processing that occurs through the ventral visual processing stream, which is specialized in the recognition and perception of object identity (Goodale & Milner, 1992; Mishkin et al., 1983; Ungerleider & Haxby, 1994). In contrast, the measure of recollection memory used in this study required accurate reactivation of precise details of targets via the unique and sparse underlying hippocampal representations of those items. Although there is no doubt that synaptic plasticity also underlies this hippocampal process, it may be that performance on this task by our older adults additionally reflected the efficacy of strategic and elaborate processing of stimuli (rather than simply the efficacy of the synaptic changes), hence, showing no association with visual evoked potentiation. Additionally, a possibility exists that the procedure used to induce visual LTP may have engaged activities of neural substrates earlier in the visual system rather than the perirhinal cortex that are also involved in mediation of familiarity-based recognition.

It was somewhat puzzling as to why despite the significant association found between late visual LTP and the experimental forced-choice test, no relationship was found between the forced-choice replication test and visual evoked potentiation in any of the phases (early/late). This was a surprising finding given that characteristics of this test (forced-choice format and close resemblance of foils with targets) were directly aimed at measuring familiarity processes; hence at least a slight relationship would be expected. One possible explanation is that our study participants primarily relied on recollection processes when performing the replication forced-

choice test and recollection was not linked to LTP phenomenon as measured in this study. The relationship between late visual LTP and the forced-choice experimental task was only moderate and could largely reflect use of familiarity processes, indicating successful modification of the parameters in the learning procedure which reduced use of recollective recognition on this task. . A replication of these tasks (using the new learning parameters) with greater numbers of participants and use of other tests differentially tapping recollection and familiarity is could help clarify this unexpected finding.

This study also failed to demonstrate a relationship between early LTP and any of the recognition memory tests. This lack of association could possibly be attributed to fluctuations in potentiated activity following an immediate presentation of tetanus. Experiments investigating potentiation in animals implicate a high degree of flux in potentiated activity after immediate application of tetanus (Bao, Kandel, & Hawkins, 1997; Citri & Malenka, 2008). It is possible that this electrophysiological phenomenon may have affected the magnitude of increase in early visual LTP necessary to reach sufficient potentiation in order to form a significant relationship with the recognition test scores. This hypothesis is consistent with findings in this study, namely that although there was a significant difference between the baseline phase relative to early post-tetanus for tetanised stimuli, there was no significant difference between the tetanised and non-tetanised stimuli at the early post-tetanus, which was in contrast to a significant different between the tetanised and non-tetanised stimuli at the late post-tetanus phase.

Nonetheless, the hypothesis discussed above warrants further investigation utilising fMRI, which will enable detection of neural systems underlying activity of visual LTP and regions mediating performance on the forced-choice test of the experimental task.

Clinical Implications

The findings generated by the current study make several novel contributions to aging and AD research endeavors. To the author's knowledge, this is the first study which has identified that it is possible to use an EEG paradigm to induce and maintain visual LTP in healthy older adults. Thereby, this offers a possibility of explicating the potential role of LTP in older adults in investigating potentiated activity in AD and MCI patients. The current also identified the recognition task which may prove to be sensitive in assessment of recognition memory with AD and MCI. Hence, the current research provides a platform for further longitudinal research which can clarify the contribution of results of our study as a possible biomarker of early cognitive change.

Utilization of the recognition and LTP protocols as either separate methodological or converging approaches in evaluating MCI and AD may afford potential to detect subtle neurophysiological changes affected by AD neuropathology in its earliest stage. Thus examining these specific electrophysiological and cognitive processes may generate valuable information over and above existing biomarkers, and guide the development of more accurate diagnostic procedures to

facilitate detecting the very early stages of AD and transitional stages of MCI. This protocol may be useful as a converging method in combination with biochemical biomarkers.

The findings of the present research will also provide a comparison baseline of LTP and recognition memory mechanisms associated with processes of normal aging. This data will be used in later phases of the research, aiming to investigate LTP and recognition memory functioning in AD and MCI individuals.

Identification of an earlier marker of AD has considerable clinical and ethical implications. AD is the most common form of dementia afflicting millions of older adults worldwide (Aronson et al., 1991; Lobo et al., 2000; Wimo et al., 2003). The impact of AD is deleterious and pervasive with multiple implications. It hastens death, causes considerable morbidity, and diminishes the quality of lives of victims and their families (Aronson et al., 1991; Baldereschi et al., 1999; Ewbank, 1999; Katzman et al., 1994). It also exhausts vast economic resources and greatly contributes to socio-economic burden (Richter & Richter, 2004).

Major studies are currently underway in designing therapeutic strategies to prevent and slow neuronal degradation induced by AD pathology (Aisen et al., 2011; Rafii & Aisen, 2009; Tuszynski et al., 2005). An accurate early diagnosis will permit timely implementation of preventive strategies in the trajectory of disease when such treatments are likely to be optimally conducive before irrevocable neural degeneration becomes severe and widespread (Aisen et al.,

2011; Blennow, 2010). Furthermore, diagnosing individuals at an early stage may afford vital opportunities for patients and their families to make decisions with potential to enhance quality of life. In the early phase of the disease, individuals are likely to be at a level of cognitive functioning where they can make important decisions regarding their lives and choose to use effective therapeutic treatment to ameliorate their impoverished cognitive symptoms (Diniz, Pinto, Gonzaga, Guimaraes, Gattaz, & Forlenza, 2009; Giacobini, 2001; Hsiung & Feldman, 2008; Kinsella et al., 2009; Kurz, Pohl, Ramsenthaler, & Sorg, 2009). This will ultimately enhance the quality of patients' lives and extend valuable time with their loved ones (Petersen, 2001; Richter, 2004). Identifying an early marker of AD will also aid in discerning between a stable MCI state and progressive condition, thereby rendering psychological benefits. This is likely to alleviate anxiety and uncertainty for individuals concerning their life expectancy and future psychosocial and cognitive wellbeing (Austrom & Lu, 2009; Joosten-Weyn Banningh et al., 2008; Lu & Haase, 2009; Petersen, 2001; Visser, 2004).

Despite these potential advantages, however, receiving a diagnosis of a debilitating disease for which there is no effective means of treatment (as is the current situation for AD), can for some people induce a sense of hopelessness and powerlessness, which if unattended may foster depression and anxiety (Mattsson, Brax, & Zetterberg, 2010). Hence, rather than assume that early diagnosis is good, clinicians and research practitioners should inform patients and their families about potential benefits and risks of pursuing early diagnosis, explaining very clearly the predictive accuracy (or not) of biomarker-based diagnosis and educate them regarding the efficacy of cognitive enhancers. This will enable individuals with MCI and/or early AD to make an informed choice whether to proceed with testing (Howe, 2007).

Limitations, Strengths, and Future Directions

While this study has yielded a number of important findings, it has, nonetheless, several methodological limitations which merit exploration and highlight areas for further research. The first limitation involves sample characteristics of the study. The sample consisted of predominantly females and included participants with a high level of education, which are not representative characteristics of the general older population. Thus it will be important to replicate this study with a sample containing more men and a wider range of educational backgrounds.

A second limitation is posed by the lack of a comparison group. Although the current research has demonstrated the ability of older adults to generate visual LTP and perform equally on recollection and familiarity tests, it hasn't examined possible changes in these processes in older adults relative to younger adults. Directly comparing the effect of age on visual potentiation and recognition memory performance will allow assessment of possible changes in the level of LTP functioning and dual processes of recognition memory with age. On the other hand, the research described in this thesis revealed clinically applicable findings using sensitive statistical analysis. Application of within-subject design is likely to have increased sensitivity of the study findings by controlling for individual difference variables and enhancing the study power (Coakes & Ong, 2011; Elwood, 2007). This, thereby, increases internal validity of the current research (Coakes & Ong, 2011; Elwood, 2007).

An additional consideration includes the theoretical basis of the study. The current research was founded on a number of assumptions concerning recognition memory and structures supporting its processes which guided interpretations of the study results (Aggleton & Brown, 1999; Aggleton & Brown, 2006; Yonelinas, 2002). Hence, if any of the assumptions are violated, the validity of the rationale underlying the current study will be significantly compromised. In an attempt to address this concern, a critical review of the existing literature pertaining to the proposed assumptions was undertaken and provided corroborative evidence for their utility. Additional efforts could be made to replicate the study using fMRI, which will enable identification of neural circuitry mediating performance on the replication and experimental memory tasks and detection of the structures supporting activity in the forced-choice test of the experimental task.

Another consideration warranting attention is the lack of association between LTP activity and the recollection test. Performance on the recollection test has been found in previous research to be contingent on hippocampal activity. LTP has been mainly studied in the hippocampal tissue, which is universally accepted as a region specializing in memory consolidation (Deweer, Pillon, Pochon, & Dubois, 2001). As previously discussed, the visual LTP measured in this protocol could be more directly linked with the type of information acquisition in perirhinal cortices, namely familiarity-based recognition rather than recollection. Additionally, LTP represents a universal neurophysiological phenomena enabling acquisition of sensory information with evidence of its activity across all cortical regions, including perirhinal cortex (Bilkey, 1996;

Kealy & Commins, 2009; Liu & Bilkey, 1996; Malenka, 2003; Squire, 1986; Warburton et al., 2005; Yaniv & Richter-Levin, 2000).

A final concern regards the observation that although majority of participants displayed LTP activity, some did not. This finding could arise due to a number of reasons. First, it is possible that the protocol is not entirely sensitive to identification of potentiated activity in older adults. Participants who didn't exhibit LTP might have generated a pattern of neurophysiological activity which cannot be detected by the current protocol. Another possibility is that participants without LTP manifestation may be on the cusp of clinically significant cognitive decline. Research suggests that the MMSE may not be sensitive enough to identify the presence of early stages of AD or MCI, especially if older adults possess high baseline functioning and other mitigating factors enabling them to retain average cognitive functioning during the initial stages of the disease (Brandt et al., 2005; Magni, Binetti, Cappa, & Bianchetti, 1995; Mitchell, 2009). Hence, it is possible that participants who didn't demonstrate evidence of LTP activity might have presented to the study with undiagnosed MCI or early AD. Support for this proposition comes from the findings showing that compared to participants who displayed LTP activity, participants who lacked the ability to produce LTP performed significantly worse on the familiarity test, which is reliant on the neural structure, where AD neuropathology originates. It can, hence, be inferred that inability to produce LTP activity might be due to this pathological process. Investigation of the accuracy of this proposition requires longitudinal follow-up analysis of cognitive functioning of those older adults who were not able to produce LTP. Additionally, evaluation of this protocol in longitudinal research with AD and MCI patients will

be essential to determine the utility of this protocol in detecting pre-clinical AD and in differential diagnosis of static versus evolving MCI.

Conclusion

Despite the limitations discussed, this research has provided preliminary data on which further research and development of an early AD marker can be based. In summary, the current research yielded a number of significant findings. The recognition memory study identified that the experimental procedure was more sensitive to assessment of familiarity-based recognition relative to the replication procedure in a tested group of participants. It is therefore suggested that a task sensitive to familiarity-based recognition should consist of a single stimuli exposure of more than 12 items using a forced-choice format with targets very similar to foils, with learning instructions guiding participants to note whether the item is naturally occurring or manmade. It is proposed that a task sensitive to recollective recognition could consist of a double item exposure of at least 12 items using the yes-no format with targets closely resembling foils and with learning instructions which guide the participants to study details of the item.

The electrophysiological study found that older adults demonstrate ability to generate LTP activity in the form of visual evoked potentiation. LTP activity was found to be associated with performance on the familiarity test. Additionally, it was revealed that the familiarity test has an ability to estimate LTP functioning. Hence, the present research has developed a protocol which may be sensitive to early diagnosis of AD and differential diagnosis of MCI. This protocol

involves assessment of dual processes of recognition memory, using a task selectively sensitive to recollection and familiarity recognition, and measurement of visual LTP, using an EEG protocol that is able to induce visual potentiation in vivo. Clinically, the EEG protocol may represent a cost-effective and non-invasive assessment tool of neural activity capable of identifying subtle functional changes preceding structural or metabolic abnormalities of AD. The visual recognition tests are also easy to administer, time efficient, and sensitive to language barriers and cross-cultural differences. As previously discussed, development of a protocol enabling earlier diagnosis potentially offers a plethora of social and clinical benefits, enabling implementation of interventions at an earlier stage of neural degeneration, facilitating vital decision-making opportunities related to clinical treatment, and possibly enhancing psychological adaptation and quality of life for patients and their families.

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Appendices

Appendix A: Sensitivity Measure

Sensitivity (*d'*) assesses how well a person can discriminate between a target and foils (i.e., a seen or unseen object) (Macmillan & Creelman, 2004). High sensitivity indicates good ability to discriminate between a target and foils while low sensitivity suggests poor ability. The value of *d'* prime is determined by hits and false alarms. A hit refers to the correct identification of a target (saying "yes" to the target). A false alarm is an error in which a foil is identified as a target (saying "yes" to the foils, mistaking a foil for the target). The higher the hit rates and the lower false alarm rates, the higher is *d'* and sensitivity (Macmillan & Creelman, 2004).

Estimation of *d'* prime on the basis of hit and false alarm rates takes account of response bias. Response bias includes the variability of internal and external factors that influence an individual's decision in favouring one response over another, such as motivation, fatigue, stimuli location, and many others. Other measurements of recognition judgments, such as proportion correct, don't account for false alarm rates and are highly affected by manipulations of response bias parameters (Macmillan & Creelman, 2004).

Appendix B: Participants Information Sheet

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PARTICIPANT INFORMATION SHEET

Title of Project: **Human Information Processing**

Researchers: **Dr Lynette Tippett, Assoc. Prof. Ian Kirk, Alevtina Koulikova**

Thank you for taking the time to read this information sheet. You are invited to participate in research which investigates recognition memory and electrophysiological activity accompanying visual learning in healthy older adults.

I. Electrophysiological Study

Recording the electrical activity of the brain using electroencephalography (EEG) allows us to study physiological mechanism underlying learning and formation of new memories, called long-term potentiation (LTP). By measuring LTP in healthy older adults, it is possible to determine whether healthy older adults show electrophysiological mechanisms accompanying visual learning processes.

Procedure: The experimental procedure will require up to two to three hours of your time. It will involve application of the EEG net over your head. EEG net is a cap which has electrodes attached to it allowing to detect electrical impulses generated by the brain. You will be asked to look at some visual pictures displayed on a computer screen while your electrical activity is recorded via EEG device.

This study will take place at the premises of the University of Auckland (EEG laboratory). You can choose to be transported to the university and back to your homes by the researcher or could meet the researcher at the university. The fees incurred by travel would be reimbursed to you.

II. Recognition Memory Study

Studying recognition memory will provide valuable information about memory processes in aging brain. Specifically, it will assist in understanding which aspects of memory remains preserved and which ones decline with advancing age.

Procedure: The experimental procedure will require an hour and a half of your time. It will consist of short visual memory tasks. You will be presented with pictures of different objects and asked to remember them to your best ability. You

will be then shown a set of pictures, among which will be the ones you did study and ones you didn't and you will be asked to recognize the ones that you did study.

The experiment can take place in your home, an interview room at the university, or an alternative neutral environment convenient to you.

Benefits and Implications: Your participation will greatly aid in understanding of memory processes and electrophysiological mechanisms underlying learning in aging brain. It will inform us of what memory and electrophysiological activities are expected to manifest in healthy aging. Your participation will also contribute to gaining insight about Alzheimer's disease. Your performance on memory and EEG tasks will form a baseline data to which performance of older adults with Alzheimer's disease will be compared in the future study.

Risks and discomforts: There are no expected risks although completing the tasks may be a little tiring.

Your rights as a participant: Participation in this study is entirely voluntary. If you choose to participate, you can change your mind at any time without giving a reason. Whether or not you participate will not affect your relationship with the researchers in any way. After your participation is completed you will still have the right to request that your data be withdrawn from the study for up to three months. You will be given a copy of this document to keep.

You can also request a copy of the final published report of the study. Please note, however, that there will be a significant time lag between your participation and the report being published.

You have a right to bring a support person to accompany you to any of those experiments if you wish.

Confidentiality, anonymity and data storage: Any information that identifies you as a participant will be used confidentially and kept in a secure location. Your name will only appear on the attached Consent Form, which will be coded with an identification number. Your data will only be referred to using this identification number. The Consent Form will only be seen by you and the investigators, and will be kept in a secure filing cabinet for six years, after which time it will be securely and confidentially disposed of. After completion of the study, all anonymous data, including computer files, will be kept for six years to allow for publication and future re-analysis. Research publications or presentations from the study will not contain any information that could personally identify you.

Approved by the University of Auckland Human Participants Ethics Committee on 26 April 2010 for 3 years (Reference Number: 2010/137).

APPENDIX C: Consent form for the study

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Auckland, New Zealand

CONSENT TO PARTICIPATE IN RESEARCH

(THIS FORM WILL BE HELD FOR A PERIOD OF SIX YEARS)

Title of Project: **Human Information Processing**

Researchers: **Assoc. Prof. Ian Kirk, Dr Lynette Tippett, Alevtina Koulikova**

I have read the Participant Information Sheet, and have understood the nature of the research and why I have been selected. I have had the opportunity to ask questions and have them answered to my satisfaction.

- I agree to take part in this research; Circle which part/parts you agree to participate:
  - Recognition Memory Study
  - Electrophysiological
- I understand that I am free to withdraw participation at any time, and to withdraw any data traceable to me up to a specific date (3 months from today).
- I understand my data will be kept confidential and will not identify me as its source.
- I wish / do not wish to receive the summary of findings.
- I understand that data will be kept for 6 years, after which they will be destroyed.

Name:

(please print clearly)

Signature:

Date:

Email address:

Approved by the University of Auckland Human Participants Ethics Committee on 26 April 2010 for 3 years (Reference Number: 2010/137).