

CHAPTER ONE:

General introduction

Note: Some of the material presented within this general introduction has been reproduced in Chapter Two and Chapter Five, due to the stand-alone nature of these chapters as empirical research papers prepared for submission to a scientific journal.

1. General Introduction

1.1. Research question

The research reported within this thesis was designed to examine the efficacy and underlying mechanisms of Cognitive Training as an early intervention technique for secondary prevention of dementia in older prodromal adults. The research included an application of a novel neurophysiological paradigm to this field in order to:

- a) investigate the utility of a specific neurophysiological response (an event related potential) as a biomarker of increased risk for dementia;
- b) examine this response as a potential outcome measure of treatment efficacy following a multifaceted Cognitive Training program
- c) investigate the utility of this response as an indicator of underlying neural change following Cognitive Training

The introduction that follows provides an overview of the literature regarding identification of older adults ‘at risk’ for cognitive decline and dementia. In addition, the literature pertaining to early intervention strategies aimed at slowing down or preventing ongoing decline in these groups is reviewed. Cognitive Training as a secondary preventive technique is discussed and a rationale for the investigation of novel neurophysiological biomarkers for ‘at risk’ groups is provided. The use of those biomarkers as surrogate outcome measures of treatment efficacy and indexes of neuroplastic mechanisms underlying cognitive interventions is subsequently discussed. Finally, the overarching aims and hypotheses of the research are presented.

1.2. The ageing population

The rapidly expanding ageing population is becoming an internationally recognised dilemma. In Australia, for example, the combination of a declining birth rate and increasing longevity has resulted in a 144% projected increase in people aged over 60 years by 2050; that is, from 4.1 million in 2009 to approximately 10.0 million in 2050 (Access Economics, 2009). With this expansion comes the increased risk of emerging neurodegenerative disease, with prevalence rates for Alzheimer's disease (AD) alone doubling every five years after the age of 60 (Lobo et al., 2000; National Institute on Aging, 1999). In Australia, dementia prevalence is projected to increase over four-fold from 245,400 people in 2009 to approximately 1.13 million people in 2050, with many others affected by less severe forms of cognitive impairment (Access Economics, 2009). Worldwide, dementia prevalence is expected to rise to 81 million people in 2040 (Ferri et al., 2005). The current and projected healthcare, psychosocial and financial burden associated with increasing rates of dementia are well-documented; for example, total direct and indirect costs associated with dementia are expected to account for 3.3% of Australia's gross domestic product in 2051 (rising from 0.91% in 2009) (Australian Government Department of Health and Ageing, 2006).

In the context of these grim projections, advances in knowledge regarding the pathophysiological progression of AD and other dementia syndromes have prompted re-evaluation of diagnostic criteria (e.g. McKhann, 2011), taking into account earlier stages of these disease processes, as well as investigation of various clinical and experimental treatment paradigms. Current treatments for established dementia are merely symptomatic and are now seen as too late due to the high burden of pathology at that stage (Dubois et al., 2007; Emery, 2011; McKhann, 2011). As such, in the absence of a cure, a focus on secondary prevention strategies (see Thal, 2006) has become paramount. This involves early identification of individuals 'at risk' of developing dementia, with a view to developing and

implementing intervention strategies. Such techniques may ultimately be able to reduce dementia incidence by targeting the underlying pathophysiology at the prodromal stage (see Chapter Two: Mowszowski, Batchelor, & Naismith, 2010; Naismith et al., 2009).

1.3. Targeting ‘at risk’ groups

In terms of likely candidates for secondary prevention, it is clear that some individuals are more likely to progress to dementia syndromes. For example, epidemiological research has demonstrated strong associations between ageing, genotype (e.g. apolipoprotein in AD), lifestyle and vascular risk factors (including diabetes, hypertension and obesity) and development of dementia (Barnes & Yaffe, 2011; Fratiglioni & Qiu, 2011). Importantly, the emergence of mood or cognitive symptoms has also been shown to reflect the earlier stages of underlying neurodegeneration in many cases (Cummings, Doody, & Clark, 2007; Emery, 2011). As such, those individuals with depression, subjective cognitive complaints and mild cognitive impairment are widely considered to be ‘at risk’ for developing dementia longitudinally, and are therefore worthwhile candidates for targeted prevention strategies.

1.3.1. Mild Cognitive Impairment

In characterising groups ‘at risk’ of developing dementia, much research has focused on the clinical syndrome of Mild Cognitive Impairment (MCI) (Gauthier et al., 2006; Petersen et al., 2009). By definition, individuals with MCI remain ‘functional’ and independent in everyday activities; however they subjectively report cognitive decline which is corroborated by a close informant and which is evident on objective neuropsychological testing (Petersen et al., 2001). The significance of MCI as an ‘at risk’ or transitional state to dementia, particularly AD, lies in data suggesting transition rates of around 10-15% per year in clinical samples and approximately 45% over a five year period, a much higher rate than that observed in the

general healthy elderly population (Gauthier, et al., 2006; Petersen, et al., 2001). The validity of the MCI syndrome has been questioned on the basis that elevated transition rates stem from clinical samples, obtained through memory clinics and specialist research centres. However, community-based, epidemiological samples demonstrate a transition rate of 6-10% per year – lower than the clinical samples, but still much higher than the 1-2% base incidence rates of dementia per year (Petersen, et al., 2009). Importantly, dementia may not be a definitive outcome of MCI, as approximately 40-50% of individuals diagnosed with MCI have been shown to stabilise or revert to normal functioning (Ganguli, 2006; Gauthier, et al., 2006; Mitchell & Shiri-Feshki, 2009).

Over time, the concept of MCI has been developed further and two subtypes are now widely acknowledged, differentiating those individuals with specific deficits in memory (amnesic or aMCI) from those with deficits in other cognitive domains such as language, visuospatial skills or executive functions (non-amnesic or naMCI) (Petersen, 2004). Furthermore, individuals may demonstrate deficits within a single cognitive domain or within multiple cognitive domains. These subtypes are not only clinically useful but may also provide more specific prognostic information. While it is widely acknowledged that factors such as varying definitions of MCI, variable methodologies and heterogeneous samples may contribute to heterogeneity in transition outcomes (e.g., Ganguli, 2006; Mitchell & Shiri-Feshki, 2009; Petersen, 2004), it is also clear that certain subtypes of MCI may bear a higher risk for conversion to dementia. Multiple-domain MCI (particularly when memory impairment is evident) is more likely to result in conversion to dementia and therefore appears to represent a more severely advanced disease state, while single-domain MCI may represent a more benign condition, and data have shown that a large number of this subgroup may revert to normal functioning over follow-up periods of two to three years (Forlenza et al., 2009; Hughes, Snits, & Ganguli, 2011; Mitchell & Shiri-Feshki, 2009; Nordlund et al.,

2010). Furthermore, it appears that clinical subtypes may have some significance with respect to aetiology and disease trajectory: aMCI has been associated with increased conversion to AD. While naMCI has been associated with increased conversion to vascular dementia, frontotemporal dementia or dementia with Lewy bodies (Gauthier, et al., 2006; Hughes, et al., 2011; Petersen, 2004; Yaffe, Petersen, Lindquist, Kramer, & Miller, 2006), recent studies have demonstrated that a high proportion of these individuals may also go on to develop AD (Duara et al., 2011; Fischer et al., 2007). Advances in the identification of pathophysiological biomarkers associated with the presence or progression of underlying neurodegenerative disease processes, particularly AD, have recently been extended into MCI (see Dubois, et al., 2007; Winblad et al., 2004). For example, a seminal study by Rowe et al. (2007) demonstrated two differential patterns of amyloid burden using [11C] Pittsburgh Compound B (PIB) PET scanning in individuals with MCI: one pattern was indistinguishable from that seen in an AD group, while the other pattern more closely resembled healthy controls. Such advances may also provide further clarification regarding the aetiological significance of MCI subtypes (McKhann, 2011; Petersen, et al., 2009; Vemuri, 2010).

1.3.2. Late-life depression

In recent years, depression has been recognised internationally as a prodromal feature and independent risk factor for cognitive decline (Alexopoulos, 2005; Emery, 2011; Panza et al., 2010; Steffens et al., 2007). Indeed, two large community-based studies recently demonstrated that increasing levels of depressive symptoms are associated with increasing risk for dementia (Saczynski et al., 2010), particularly for those with recurrent depression (Dotson, Beydoun, & Zonderman, 2010). In a recent systematic review of potentially modifiable risk factors associated with cognitive decline and dementia, Barnes and Yaffe (2011) calculated that more than 10% of AD cases worldwide are potentially attributable to

depression. It was estimated that a 10% reduction in depression prevalence could potentially result in a worldwide reduction of dementia incidence by approximately 326 000 cases. Similarly, a prospective seven-year cohort study of modifiable risk factors for dementia (Ritchie et al., 2010) suggested that eliminating the impact of LLD would lead to an estimated 10.3% reduction in the incidence of dementia.

While depression is widely-known to affect cognitive functioning at any age, in those over the age of 60 years ('late-life depression' or LLD) and/or those with late-onset depression (i.e. first episode after age 50 or 60) it is associated with even greater deficits in processing speed, executive functions (i.e. 'frontal' or higher-order functions) and aspects of learning and memory (Herrmann, Goodwin, & Ebmeier, 2007; Kohler, Thomas, Barnett, & O'Brien, 2010; Naismith et al., 2003; Naismith, Hickie, Ward, Scott, & Little, 2006; Sheline et al., 2006). According to a recent five-year follow-up study of depressed older adults, memory deficits and executive dysfunction best predict conversion to dementia (Potter et al., 2012). These cognitive deficits appear to be underpinned by structural and functional brain changes, particularly within frontosubcortical and frontotemporal networks (Ballmaier et al., 2004; Hickie et al., 2005a; Hickie et al., 2007; Taylor et al., 2004). Currently, it is unclear the extent to which such changes reflect underlying cerebrovascular disease, early neurodegenerative pathology, or the specific effects of depressive illness on neuronal, particularly hippocampal integrity (Duman & Monteggia, 2006; Naismith, Norrie, Mowszowski, & Hickie, in review). Possible mechanisms mediating this relationship may include down-regulation of the hypothalamic-pituitary-adrenocortical axis, neurotoxic effects of glucocorticoids and reduced expression of brain-derived neurotrophic factor (BDNF) which promotes neuronal differentiation, growth and survival (Duman & Monteggia, 2006; Hickie et al., 2005b). Importantly, it is now understood that cognitive deficits in LLD are not

merely reflective of depressive ‘state’ and tend to persist despite adequate symptom resolution (Butters et al., 2000; Devanand et al., 2003).

There is also a great deal of overlap between depression and MCI. It appears that more severe depressive symptoms represent a greater risk for MCI, with 60% of individuals with depression meeting criteria for MCI (Lee, Potter, Wagner, Welsh-Bohmer, & Steffens, 2007). Within the MCI population, rates of depression vary, with recent reviews suggesting a median depression prevalence of 44.3% in hospital-based studies and 15.7% in population-based studies (see Panza, et al., 2010 for a review). This combination of depression and MCI is associated with a twofold risk of developing AD with an earlier age of onset (Modrego & Ferrandez, 2004). Other studies suggest that those with LLD tend to progress predominantly to vascular forms of dementia (Baldwin, Gallagley, Gourlay, Jackson, & Burns, 2006; Hickie, Scott, Wilhelm, & Brodaty, 1997), likely due to the increased white matter lesion burden associated with LLD (Alexopoulos, 2005; Blazer, 2003; Santos et al., 2009).

1.3.3. Subjective cognitive impairment

While MCI and LLD have been well-established as likely prodromal phases of dementia in many cases, interest is now turning towards identifying ‘at risk’ individuals at an even earlier stage of the clinical continuum. This continuum has been operationalised in the widely-used Global Deterioration Scale (Reisberg, Ferris, de Leon, & Crook, 1982), a clinician-rated scale comprising seven clinically identifiable stages ranging from “No Cognitive Decline” (stage one) through to “Very Severe Cognitive Decline (i.e. late dementia; stage seven). In stage three, Reisberg and colleagues introduced the term ‘mild cognitive impairment’, to identify individuals who subjectively report cognitive decline *and* who demonstrate evidence of cognitive impairment on objective psychometric testing. Stage three is therefore most analogous to the currently widely-used criteria for MCI outlined above (see Petersen, 2004).

However, in recent years, Reisberg's group have argued that the earlier stage two, which identifies individuals with subjective cognitive complaints only (in the absence of objective evidence on testing), is also important in terms of prognostic value (Reisberg & Gauthier, 2008; Reisberg & Shulman, 2009).

This syndrome of 'subjective cognitive impairment' (SCI) or, similarly, 'subjective memory complaints' may initially appear somewhat superfluous as a marker of increased risk for dementia, given the frequency of subjective cognitive complaints in ageing, and the fact that some degree of cognitive decline is to be expected as part of the normal ageing process or as a symptom of other common comorbidities in ageing (e.g. depression, anxiety) (Paradise, Glozier, Naismith, Davenport, & Hickie, 2011). However, proponents of the SCI construct have generally acknowledged these limitations but maintain the utility of identifying those individuals whose subjective complaints represent the very early clinical manifestation of an underlying neurodegenerative process; particularly those individuals seeking assistance. An emerging body of literature adds empirical weight to this assertion. For example, longitudinal studies have suggested that the SCI stage may last approximately 15 years and may precede the emergence of objective evidence of cognitive decline or later functional impairment (Pritchep et al., 2006; Reisberg, 1986; Reisberg et al., 2008). Furthermore, over a seven-year observation period, individuals with subjective cognitive impairment (categorised as Global Deterioration Scale stage two at baseline) were shown to have 4.5 times greater risk of decline to either MCI or AD compared to individuals with no cognitive complaints (stage one at baseline) (Reisberg, Shulman, Torossian, Leng, & Zhu, 2010). Similar findings have been reported by groups utilising measures other than the Global Deterioration Scale to identify SCI (i.e. combination of self-report questionnaires and neuropsychological tests). For example, Duara and colleagues (2011) reported that 28.6% of individuals with SCI (termed 'pre-MCI' in this study) declined to MCI or dementia over a

two- to three-year follow-up period, compared to just 4.1% of individuals without cognitive complaints at baseline. Recent efforts to further delineate whether the type of subjective complaint (i.e. memory vs. non-memory, participant vs. informant) influences predictive value demonstrated that participant memory complaints were most accurate in predicting MCI at two-year follow-up (Slavin et al., 2011).

As with MCI, investigation of pathophysiological biomarkers identifying individuals with SCI will provide further elucidation of the underlying disease processes driving these subjective complaints. Thus far, neuroimaging markers such as Pittsburgh compound B have shown promise as potential markers of this early stage (see Dubois, et al., 2007) and one recent study has demonstrated 90% predictive accuracy of quantitative electroencephalogram features in predicting cognitive and clinical decline in SCI (Pritchep, et al., 2006).

Overall, while SCI has not been as well investigated as MCI or LLD to-date, evidence from this emerging body of research suggests that it can robustly capture an early stage of the dementia process, prior to the emergence of MCI (Reisberg & Gauthier, 2008). As such, SCI represents a ‘widening of the net’ in terms of secondary prevention and should be included as a target for early intervention strategies (Reid & MacLulich, 2006; Reisberg & Shulman, 2009). Moreover, these findings have important implications for population sampling in designing targeted secondary prevention studies. Clearly those individuals seeking contact with healthcare services are aiming to address their cognitive concerns (i.e. individuals with SCI). Thus, ‘health-seeking’ behaviour itself may be an early indicator of underlying disease in many cases where “the patient knows, but [presently] the doctor doesn’t know”, (Reisberg, et al., 2008). Thus, health-seeking groups may better represent those individuals who are truly ‘at risk’ for cognitive decline. Practically, it is frequently more difficult to recruit healthy older adults *without* cognitive complaints to participate in studies investigating

cognition (Reisberg, et al., 2010); this too suggests the utility in sampling health-seeking participants rather than community-based samples generally.

1.4. Identification of true prodromal cases within ‘at risk’ groups

Each of these ‘at risk’ groups has been characterised largely according to clinical criteria. MCI and LLD with associated cognitive impairment are diagnosed on the basis of neuropsychological assessment in conjunction with clinical interviews eliciting subjective and/or informant reports of cognitive and psychosocial functioning. SCI, by definition, is characterised solely on the basis of the individual’s subjective complaints. However, due to the noted heterogeneity of progression to dementia within these groups, increasing attention has recently been directed towards incorporating a pathophysiological biomarker approach to identifying true cases of prodromal dementia. This has occurred primarily within a research context, for two main reasons: 1) many of the biomarkers which have thus far been associated with these preclinical groups have not been validated for clinical use (McKhann, 2011); and 2) biomarker identification of true prodromal dementia enriches screening/enrolment procedures for clinical intervention trials, thus ensuring a ‘purer’ sample of prodromal cases on which to test potential disease-modifying therapies (Cummings, Doody, & Clark, 2007; Dubois, et al., 2007; Winblad, et al., 2004). In recent years, several biomarkers of underlying neurodegenerative disease processes have been extended to preclinical groups, particularly MCI but also within SCI and LLD. Most of the investigations to-date have focussed on those biomarkers which have already been identified in established dementia, particularly AD: cerebrospinal fluid markers of tau and beta-amyloid, genetic markers of mutations in amyloid precursor protein, presenilin or apolipoprotein, and neuroimaging markers of mesial temporal lobe (hippocampal and/or entorhinal) atrophy, white matter lesions, deficits in regional cerebral blood flow or glucose metabolism or cholinergic abnormalities (Gauthier, et al.,

2006; Petersen & Morris, 2005; Winblad, et al., 2004). However, these investigations often involve costly, invasive and time-consuming measures and can therefore be difficult to implement for added diagnostic clarity in screening large pools of potential research participants. As such, other techniques such as neurophysiological assessment via electroencephalography (EEG) have been recommended for their wide availability, time efficiency and non-invasiveness, and are also emerging as viable biomarkers in these ‘at risk’ groups (see Chapter Three: Mowszowski et al., 2012; Chapter Four: Naismith et al., 2012; Winblad, et al., 2004).

1.5. Early intervention strategies

It is clear that identification of therapeutic targets for improving cognitive functioning in ‘at risk’ groups such as MCI, LLD and SCI is warranted, both for symptomatic improvement as well for potential disease modification (Cummings, et al., 2007; Naismith, et al., 2009). Advances in knowledge of the underlying pathophysiology of neurodegenerative diseases have led to investigations of pharmacotherapy as an early intervention strategy in MCI. However, large-scale clinical trials of acetylcholinesterase inhibitors such as donepezil, galantamine and rivastigmine for aMCI, and other drugs including vitamin E and ginkgo biloba have demonstrated only modest symptomatic effects and limited delay of conversion to AD beyond 12-18 months (Ames, 2011; Gauthier, 2004; Gauthier, et al., 2006; Winblad, et al., 2004). Furthermore, these drugs have been associated with side-effects including gastrointestinal symptoms, haemorrhaging or other toxicities, such that the risk-benefit ratio has been questioned (Ames, 2011; Winblad, et al., 2004).

Overall, in the absence of convincing evidence for the efficacy of pharmacological interventions, recommendations for early intervention for dementia generally point towards management of modifiable (i.e. vascular) risk factors, increased cognitive activity, and

management of mood and psychosocial functioning (Emery, 2011; Naismith, et al., 2009). Furthermore, it has been suggested that these approaches may be most efficacious when implemented in combination, and that systematic evaluation of such multifaceted intervention programs is now required (Barnes & Yaffe, 2011; Emery, 2011; Naismith, et al., 2009).

1.6. Cognitive Training as an early intervention technique

Recently, Cognitive Training (CT) has been identified as a viable secondary preventive tool in ‘at risk’ groups such as MCI and LLD (Gates, Sachdev, Fiatarone Singh, & Valenzuela, 2011; Jean, Bergeron, Thivierge, & Simard, 2010; Chapter Two: Mowszowski, et al., 2010; Naismith et al., 2011). CT refers to a specific approach within the broader field of Cognitive Remediation, a cognitive/behavioural intervention which also includes cognitive stimulation and cognitive rehabilitation (see Figure 1 in Chapter Two: Mowszowski, et al., 2010). The CT approach refers to programs which enhance cognition by providing theoretically-driven strategies and skills, usually involving ‘guided practice’ on tasks reflecting various cognitive functions. CT techniques are categorized as compensatory or restorative (Sitzer, Twamley, & Jeste, 2006). Compensatory tactics aim to develop new ways of performing tasks, bypassing deficient cognitive processes and teaching alternative approaches to achieving goals. Both internal (e.g. categorizing, visualizing or paraphrasing information during learning) and external techniques (e.g. using calendars or environmental cues) are encouraged. Restorative methods, however, aim to improve functioning in specific domains, thus recovering impaired skills. Examples include spaced retrieval, repeated attention and memory tasks, vanishing cues and errorless learning. As discussed in Chapter Two, CT may be strategy-based; i.e. following a compensatory approach incorporating both internal and external techniques to strengthen intact cognitive functions and adapt to areas of weakness or decline. CT may also be computer-based; for example, following a restorative approach by

utilizing repeated exercises which typically incorporate multiple cognitive skills and allow for graded difficulty and independence on learning tasks (e.g. *CogPack* (Sartory, Zorn, Groetzinger, & Windgassen, 2005) and *NEAR* (Medalia & Freilich, 2008)).

1.7. Efficacy of CT in ‘at risk’ groups

Over the last decade, a body of literature has emerged documenting the promising effects of CT in ‘at risk’ groups, predominantly focusing on MCI. Several reviews of CT trials in MCI have been published within the last two years, including the review presented in Chapter Two (Mowszowski, et al., 2010), which also included the only known study to-date which has investigated the efficacy of CT in LLD (Naismith, et al., 2011). This literature will be presented in Chapter Two, which also includes an update of additional research published after completion of the review in 2010. No known trials have evaluated CT in health-seeking individuals or those with SCI.

Overall, the balance of evidence suggests that CT is effective in improving cognitive functioning in ‘at risk’ groups, especially MCI, which has been most widely studied. Further research is needed to elucidate the efficacy of CT in other ‘at risk’ groups such as LLD and SCI. However, a major limitation within the literature has been the lack of focus on concomitant effects on brain physiology to delineate the underlying neural mechanisms of CT.

1.8. Neuroplasticity as the underlying mechanism of CT

The underlying mechanism of CT is thought to be related to increasing cognitive activity, with a central component of promoting neuroplasticity. The concept of increasing cognitive activity as a protective measure against cognitive decline stems from a large body of research demonstrating the impact of ‘cognitive reserve’, a model which postulates that individuals

with higher levels of lifetime complex cognitive activity (stemming from level of education, occupational attainment and cognitively-demanding leisure activities) are more resilient to pathological brain changes, such as those resulting from neurodegenerative processes (Stern, 2011). Cognitive or neuronal reserve is thought to mediate the point at which clinical symptoms emerge, as well as their trajectory over time, in spite of the process of underlying neurodegeneration which may have been operating for many years previously (Stern, 2002). Indeed, a meta-analysis of 22 studies involving 29 000 participants overall and investigating the link between complex lifetime cognitive activity and dementia risk, reported an overall risk reduction of 46% for those individuals with high levels of lifetime complex mental activity (Valenzuela & Sachdev, 2006).

This protective effect appears to be underpinned by promotion and/or maintenance of brain structures. At a cellular level, cognitive activity likely influences spine density, synaptogenesis and vascular supply to the brain. It likely promotes glial and metabolic activity, trophic factors (e.g. brain-derived neurotrophic factor) and hippocampal neurogenesis (Stern, 2011; Valenzuela, 2008). These processes represent the mechanisms of neuroplasticity, a concept which has been well-established in animal literature (Turkstra, Holland, & Bays, 2003) and which has recently received renewed interest in human healthy and clinical populations (Kelly, Foxe, & Garavan, 2006; Mahncke, Bronstone, & Merzenich, 2006). The traditional view of the brain as a 'static' structure has been revised on the basis of numerous studies which show that neuronal connections and circuits undergo continual modification and reorganization (Fuchs, Czeh, Kole, Michaelis, & Lucassen, 2004). Neuroplasticity is also believed to be bi-directional; i.e. the same plasticity processes can either degrade (i.e. negative plasticity) or strengthen (i.e. positive plasticity) cognitive functioning. Such 'negative' plasticity may be involved in age-related cognitive decline (Mahncke, et al., 2006) and depression (Fuchs, et al., 2004). By contrast, processes that

strengthen brain function can be conceptualized as ‘positive’ plasticity and can provide a foundation for therapy. From the cognitive standpoint, it is possible that the efficacy of CT lies in its facilitation of ‘positive plasticity’. Using terminology conceptualized independently of CT, the mechanisms of neuroplasticity for rehabilitation may be either restorative (i.e. reorganization of existing networks) or compensatory (engagement of other cognitive abilities or networks) (Strangman et al., 2005). Importantly, evidence also suggests that neuroplasticity and enhancing cognitive reserve through life experiences and/or behavioural interventions can still occur in later life and that substantial restoration is possible even in the ageing brain, to delay or reverse the effects of normal ageing or neurodegenerative pathology (Greenwood, 2007; Mahncke, et al., 2006; Stern, 2011).

1.9. Neural changes associated with CT

As discussed above, it is thought that the mechanism of CT lies in its facilitation of neuroplastic processes as well as enhancement of cognitive reserve, to slow down the trajectory of cognitive decline and protect against further impairment. However, as mentioned, a significant limitation within CT literature has been the lack of focus on concomitant CT effects on brain physiology (see Chapter Two: Mowszowski, et al., 2010). The use of standardized, objective neurobiological outcome measures provides insight into neurophysiological changes which may underlie the cognitive/psychosocial effects of CT, and may also clarify whether specific CT programs influence the neurodegenerative process or whether they merely enhance cognition without impacting on underlying pathology. Such measures can also complement or even anticipate clinical outcomes, for example when the cognitive/functional effects of CT may be delayed: in these cases, the use of clinical outcomes alone would likely result in dismissal of the program as ineffective (Cummings, et al., 2007; Mueller et al., 2005). In fact, it is plausible that the underlying neurobiological

changes may occur first, *followed by* changes to higher-order cognitive functions. In addition to investigating the nature of these neurobiological changes, it is therefore also important to delineate the time course of various CT effects. The literature update in Chapter Two presents findings from studies which have utilized neuroimaging outcomes in CT trials.

1.10. The use of event-related potentials in research of ‘at risk’ groups

As discussed in Chapter Two, most of the research examining physiological biomarkers of prodromal dementia or treatment efficacy has focused on neuroimaging techniques (magnetic resonance imaging, diffusion tensor imaging, positron emission tomography etc.). However, it appears that other neurophysiological techniques such as event-related potentials (ERPs) are worthy of investigation in this context. This concept is explored in detail in Chapter Three (Mowszowski, et al., 2012) and Chapter Four (Naismith, et al., 2012). ERPs are a non-invasive, practical and objective index of fundamental sensory and cognitive processes (Jackson & Snyder, 2008; Rossini, Rossi, Babiloni, & Polich, 2007) that have shown great utility in detecting neurobiological changes in a range of psychiatric and neurological conditions. ERPs are time-locked to specific stimuli and are used to assess the speed and efficiency of information processing by examining the magnitude and latency of the waveform. While numerous ERP paradigms have been used to examine the integrity of various cognitive pathways and neural regions in MCI (Liddell et al., 2007; Papaliagkas, Kimiskidis, Tsolaki, & Anogianakis, 2008), studies have been characterized by two major limitations: firstly, cognitive paradigms are typically dependent on conscious awareness, attention and engagement with the eliciting stimuli, thus indexing later stages of information processing. This issue is important to address since neuropsychological deficits observed in ‘at risk’ groups (particularly SCI and MCI) may be partially attributable to dysfunction or inefficiency in earlier stages of information processing. Secondly, there has been a tendency

to focus on midline scalp electrodes which reflect fronto-central brain functioning. Therefore, ERP studies that employ a passive paradigm and that assess other brain regions implicated in the pathophysiology of prodromal dementia, particularly AD (e.g. the temporal lobes), are required.

1.11. The Mismatch Negativity paradigm

Chapter Three and Chapter Four specifically investigate the potential of the Mismatch Negativity (MMN) ERP as a viable neurophysiological biomarker of underlying disease in ‘at risk’ groups. The auditory MMN paradigm represents an excitatory response to novel or deviant auditory stimuli within a stream of homogenous sounds, elicited even in the absence of directed attention (see review by Naatanen, Paavilainen, Rinne, & Alho, 2007). Stimuli can be frequency-, duration- or intensity-deviant. As such, MMN reflects an automatic change detection system operating at the initial stages of information processing. The strongest generators of MMN are the temporal and frontal regions of the brain (Kujala, Tervaniemi, & Schroger, 2007). The temporal lobes (auditory cortex) process the auditory stimulus and maintain an echoic memory trace for the homogenous sounds, which allows for discrimination of the deviant sound as incongruent. The prefrontal cortex then triggers an involuntary switching of attention to the novel stimulus. Regarding cognitive correlates, auditory MMN has been associated with verbal memory deficits, poor executive functioning and reduced psychosocial functioning in schizophrenia (Hermens et al., 2010). The integrity of these lower-level sensory processes is thought to be essential for efficient functioning of higher-level processes (Light, Swerdlow, & Braff, 2007), which is particularly relevant as these higher-level processes may be somewhat compromised in SCI, MCI and LLD.

1.12. Research aims

In light of the literature described above, the aims of the research presented in subsequent chapters were as follows:

- 1) To examine existing evidence for the efficacy of CT as a cognitive intervention in older adults, in order to evaluate its utility as a potential selective prevention technique for ‘at risk’ groups. An additional aim was to explore existing knowledge regarding the physiological mechanisms underpinning cognitive and psychosocial gains related to CT, and to extend the understanding of such mechanisms by applying a novel neurophysiological paradigm to this field. This led to the development of the second aim.
- 2) To investigate the viability of the auditory MMN response as a biomarker of ‘at risk’ status in older adults, by characterizing MMN and its relationship to cognitive functioning in ‘at risk’ groups.
- 3) To investigate MMN as a potential outcome measure of treatment efficacy and index of underlying mechanism of neural change following a multifaceted CT program in older adults ‘at risk’ for dementia, including those with SCI, MCI and LLD, using a randomized controlled design. A secondary goal was to examine the relationship between neurophysiological and cognitive/psychosocial changes following CT.

1.13. Hypotheses

The following hypotheses were developed in relation to the aims presented above:

- a) It was expected that the MMN response for ‘at risk’ older adults would be reduced in amplitude and/or delayed in latency relative to healthy older control participants.

Regarding cognition, it was predicted that an abnormal frontal and temporal MMN response may be related to impaired performance on tasks of executive and memory functioning, respectively.

- b) If MMN was a valid index of the neuroplastic mechanisms underlying CT, the MMN response was expected to increase in amplitude and/or decrease in latency for the trained group compared to controls at post-CT follow-up, reflecting enhanced efficiency of pre-attentive processing in relation to the CT intervention.
- c) If the CT program produced cognitive/psychosocial gains on neuropsychological testing or clinical measures at follow-up, it was expected that those gains would be positively correlated with changes in MMN amplitude and/or latency. However, an alternative outcome was also considered, i.e. that the neurophysiological response might anticipate delayed clinical benefits, such that a change in MMN might not coincide with concomitant higher-order cognitive or psychosocial improvements at post-CT follow-up.

CHAPTER TWO:

Early intervention for cognitive decline: can cognitive training be used as a selective prevention technique?

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The published article is included in Appendix 2.

Note: the final sections of this chapter, entitled “Addendum to methods”, “Literature update since publication” and “Additional considerations following publication of this review”, were not included in the original manuscript and are unpublished.

2.1. Abstract

Background: Cognitive training (CT) may be effective as a therapeutic strategy to prevent cognitive decline in older adults. This review evaluates CT as a preventative tool at various stages of a prevention hierarchy with specific reference to healthy older adults, ‘at risk’ and clinical populations. It also considers the underlying mechanism of CT, namely that which suggests that CT acts via promoting neuroplasticity.

Methods: Evidence for CT in healthy, ‘at risk’ and clinical populations has been systematically reviewed elsewhere. This review re-examines several studies in each group to clarify the potential of CT as a preventative technique.

Results: Studies in healthy older adults and Mild Cognitive Impairment are largely positive and suggest that CT has the potential to improve cognition. However, findings in Alzheimer’s disease are mixed. Limitations of existing research include diverse methodologies and CT programs, small samples, insufficient focus on functional outcomes, sustainability and generalization of effects and the need for imaging data to delineate mechanisms of change. Additionally, there is limited data on those with late-life depression, despite this being an independent risk factor for dementia.

Conclusions: CT offers promise as a preventative therapeutic technique in healthy older adults and particularly as a secondary prevention method for ‘at risk’ groups. Future investigations need to focus on methodological constraints and delineating possible neuroplastic mechanisms of action. Nonetheless, CT programs may represent a viable, non-pharmacological, early intervention strategy, as they are easily-implemented, engaging and promote social interaction in group settings.

2.2. Introduction

With the rapidly aging population and associated increased rates of dementia, interventions aimed at decreasing the social and financial costs of declining cognitive function are irrefutably worth pursuing (Naismith et al., 2009b). While cholinesterase inhibitors offer symptomatic treatment, they are indicated only for some patients with clear neurodegenerative disease and do not alter the disease course. An alternative approach is early intervention, through selective prevention programs in ‘at risk’ groups to reduce the social, financial and medical burden of cognitive decline and ultimately reduce the incidence of dementia. Such programs should target prevention of cognitive decline and promote neuroplasticity. One potential method in this regard is cognitive training (CT). This paper will discuss some of the key findings in studies utilizing CT programs and evaluate the evidence for their efficacy within a novel framework - that is, at different stages of a prevention hierarchy - and in particular, suggest that CT may be employed as a ‘preventative’ technique (Mahncke, Bronstone, & Merzenich, 2006a; Naismith, et al., 2009b) for cognitive decline in ‘at risk’ groups. Throughout this paper, the term prevention may refer to the capacity of CT to ameliorate or delay cognitive decline by slowing the progression of neurobiological changes contributing to cognitive decline and/or dementia. By contrast, protection may be achieved through increased cognitive reserve. Both mechanisms may act through promoting neuroplasticity.

2.2.1. Cognitive Remediation and Cognitive Training

Cognitive remediation refers to behavioral interventions, aimed at improving cognition in individuals who have experienced a decline in cognitive functioning or enhancing and extending functioning in those who are cognitively intact (Acevedo & Loewenstein, 2007; Medalia & Richardson, 2005). These interventions may be administered in individual or

group formats over several sessions, and involve a range of activities including general mental activity, guided practice on cognitively-demanding tasks, strategy use and computerized exercises. The literature uses many terms to describe cognitive remediation techniques, such as cognitive stimulation, cognitive rehabilitation and cognitive training, all of which differ in their approach (Belleville, 2008; see Figure 1). This review will focus on cognitive training (CT), referring to programs which enhance cognition by providing theoretically-driven strategies and skills, usually involving ‘guided practice’ on various tasks reflecting different cognitive functions. CT techniques are categorized as compensatory or restorative (Sitzer, Twamley, & Jeste, 2006). Compensatory tactics aim to develop new ways of performing tasks, bypassing deficient cognitive processes and teaching alternative approaches to achieving goals. Both internal (e.g. categorizing, visualizing or paraphrasing information during learning) and external techniques (e.g. using calendars or environmental cues) are encouraged. Restorative methods, however, aim to improve functioning in specific domains, thus recovering impaired skills. Examples include spaced retrieval, repeated attention and memory tasks, vanishing cues and errorless learning. As shown in Figure 1, CT may be strategy-based which follows a compensatory approach, incorporating both internal and external techniques to strengthen intact cognitive functions and adapt to areas of weakness or decline. CT may also be computer-based, utilizing exercises which typically incorporate multiple cognitive skills and allow for graded difficulty and independence on learning tasks (e.g. *CogPack* (Sartory, Zorn, Groetzinger, & Windgassen, 2005) and *NEAR* (Medalia & Freilich, 2008)).

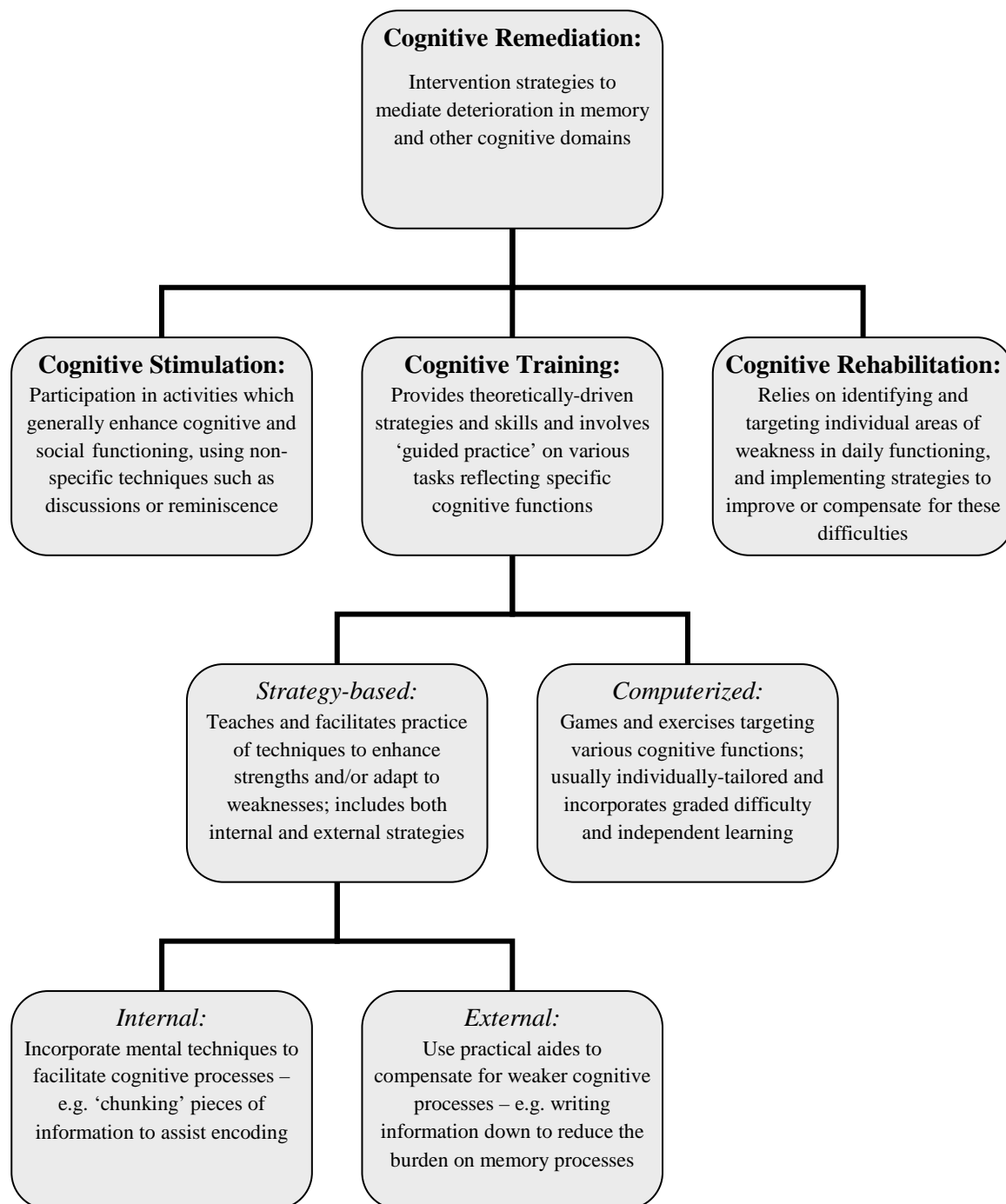


Figure 1: Cognitive Remediation terminology (Sources: Acevedo & Loewenstein, 2007; Belleville, 2008; Clare & Woods, 2008; Medalia & Richardson, 2005; Sitzler, et al., 2006)

2.2.2. CT as a preventive technique

Thal (2006) describes a three-tiered prevention hierarchy for Alzheimer's disease (AD) (see Table 1) in explaining the role of prevention programs. We suggest that CT has the ability to

target each of these stages in different populations. For example, CT may act as a primary preventative tool for healthy older adults, reducing the incidence of disease by delaying cognitive decline or perhaps building cognitive reserve (Valenzuela, 2008). In ‘at risk’ groups such as individuals with Mild Cognitive Impairment (MCI) who have a higher risk of conversion to dementia (Petersen & Morris, 2005), CT is more appropriate as a secondary preventative technique, delaying preclinical disease from converting to the clinical stages. Further, CT may act as a tertiary prevention strategy for those individuals with established dementia such as AD, aiming to reduce disability and disease progression. Investigation of the efficacy of CT in each of these populations allows for clarification of its value at each stage of this prevention hierarchy.

Table 1: Stages of a prevention hierarchy for dementia (Thal, 2006)

Primary Prevention	Secondary Prevention	Tertiary Prevention
Reduces incidence of disease by delaying cognitive decline	Prevents pre-clinical decline from converting to clinical, disease stage	Reduces disability and disease progression in individuals with established dementia

2.3. Methods

Having established likely populations coinciding with each level of prevention, this review sought to focus on secondary prevention areas. For primary and tertiary levels, evidence for CT in healthy older adults and AD respectively has been systematically reviewed elsewhere (Clare & Woods, 2008; Sitzer, et al., 2006; Valenzuela & Sachdev, 2009) and therefore has not been reviewed in depth. Findings have been generally positive in healthy older adults, though inconsistent in AD. Given the inherent nature of ‘at risk’ populations as targets for early intervention, this review will focus on CT as a secondary prevention technique. To our

knowledge, nine studies have been published investigating the efficacy of CT in MCI. Seven of these were reviewed by Belleville (2008) with a further two studies published this year (Kinsella et al., 2009; Kurz, Pohl, Ramsenthaler, & Sorg, 2009). Additionally, one recent study (Naismith et al., 2009a) examined CT in those with late-life depression, a group also considered to be 'at risk' of cognitive decline and in whom early intervention for cognitive decline may be beneficial (Naismith, et al., 2009b).

2.4. Results and Discussion

2.4.1. Effectiveness of CT as primary prevention tool

Research in healthy older adults suggests that CT offers considerable promise as a preventative technique. While studies have employed a variety of training programs and targeted a range of cognitive domains, results have generally indicated improvement or delayed decline following strategy- or computer-based training. Specifically, Valenzuela and Sachdev (2009) recently conducted a meta-analysis of seven randomised controlled trials and demonstrated large effect sizes (cumulative weighted mean difference effect size = 1.07) indicating improvement across cognitive outcomes including memory, processing speed, working memory and instrumental activities of daily living following CT. A pioneering study in this area was the ACTIVE study (Advanced CT for Independent and Vital Elderly, Ball et al., 2002). This study implemented strategy-based memory, reasoning or speed-of-processing training versus a no-contact control condition in 2832 adults (mean age = 74 years), over ten sixty-minute sessions, and demonstrated significant improvement from baseline in the targeted cognitive ability for each intervention group. Longitudinal analysis also indicated sustainability over two years (particularly when booster training sessions were included after eleven months) and at five-year follow-up, where effects were maintained in each targeted domain. However, transfer of effects was limited, with reasoning training alone

associated with less difficulty in self-reported functional outcomes compared to controls (Willis et al., 2006). Similar positive findings were recently demonstrated by Stuss *et al.* (2007) who, utilizing a randomized crossover design, provided 49 participants (mean age = 79 years) with strategy-based Memory Skills, Goal Management and Psychosocial training over twelve weeks. Neuropsychological testing following CT demonstrated significant benefits in all domains, which also generalized to functional improvements in simulated real life tasks and performance on non-trained cognitive functions (results reported by Winocur et al., 2007). Furthermore, benefits were sustained at six-month follow up (though not all participants were tested at this time).

Encouraging results have also been shown for computer-based CT. Smith *et al.*'s (2009) IMPACT study included 487 healthy older adults (mean age = 75.3 years), randomly assigned either to CT targeting improved speed and accuracy of auditory information processing, or to an active control group, with activities carried out five days per week for eight weeks. Follow-up testing revealed significantly greater improvement in the intervention group on both trained and untrained tasks (suggesting generalization) measuring memory and attention. Though well-controlled and using a large sample size, it is unclear whether effects were sustainable over time. Notably, this study also explored the mechanisms underlying CT effects by designing and testing a computer-based intervention specifically centered on the principles of positive neuroplasticity, whereby plastic brain changes mediate improvement through intensive learning and practice. Few other human-based studies have specifically addressed underlying mechanisms, despite data supporting the notion of neuroplasticity.

Generally positive findings in healthy older adults have suggested that CT programs represent a viable preventative strategy against cognitive decline in later life. However, broad conclusions are limited by vast differences in methodological rigor, study design and

nature of each CT program as demonstrated even in the abovementioned trials. Many other studies are not as well-controlled, include small sample sizes and differ in factors such as group-based versus individual; and home-based versus on-site training, or inclusion of homework assignments. Furthermore these individuals, in meeting fairly rigorous inclusion criteria, may be more resilient at baseline than the average ‘healthy’ older adult and therefore less likely to experience noticeable functional decline in a given time period. Accounting for this and for slower rates of cognitive decline in non-demented older adults necessitates longer observation periods (e.g. five to seven years; Mueller et al., 2005) in order to make definitive statements regarding the preventative capacity of CT, particularly if it is to be employed as a primary prevention strategy.

2.4.2. Evidence for CT as a secondary prevention tool

As a secondary prevention tool, CT could be used to prevent conversion of minor cognitive impairment to clinical dementia. This is particularly important for groups who have a higher risk of developing dementia, such as those with MCI. This group are by definition ‘functional’, yet have observable deficits on neuropsychological testing and are thus considered to be ‘at risk’ (Petersen et al., 2001).

A recent review (Belleville, 2008) reported that six out of seven studies demonstrated cognitive improvements following CT. These studies differed in that their training programs varied, they incorporated computerized exercises and/or strategies, they were conducted over differential time periods and they targeted various cognitive domains (though all included memory). Samples included community-dwelling participants and individuals living in geriatric residential facilities. For example, Talassi *et al.* (2007) recently showed that a computer-based program targeting a range of cognitive functions (along with occupational therapy and behavior training) resulted in significant improvement in visuospatial perception

and visual recall in community-dwelling MCI participants (mean age = 76 years), compared to a control group receiving only occupational therapy and behavior training. Similarly, Belleville *et al.* (2006) demonstrated significantly improved performance on objective memory measures in MCI participants (mean age = 62 years) following eight weeks of strategy-based memory training including pre-training in executive control and cognitive speed. This program also included homework and guidance in using the strategies in real-life situations. No improvements were seen in controls who did not receive the intervention.

Several of these studies also demonstrated evidence for long-term maintenance of cognitive improvements for older individuals with MCI following CT. Gunther and colleagues (2003) reported maintenance of improvements in verbal memory at five months following computer-based training. Likewise, individualized computer-based training for eight weeks employed by Cipriani, Bianchetti and Trabucchi (2006) resulted in a significant improvement in behavioral memory at three-month follow-up. Rozzini *et al.* (2007) presented evidence for maintenance of training effects after 12 months in association with anti-cholinesterase treatment: in this study, 15 older adults with MCI taking cholinesterase inhibitors underwent sixty sessions of computerized training in attention, memory, abstract reasoning, language and visuospatial skills. At one-year follow-up, trained participants demonstrated improvements on unrelated memory and reasoning tasks, as well as a decrease in depressive symptoms. Conversely, MCI participants who had received cholinesterase inhibitors alone (i.e. no CT) showed a decrease in depressive symptoms but no change on neuropsychological testing.

A limitation of the studies conducted in MCI, however, is the diverse group of methodologies. This was noted by Belleville (2008) who included the findings of Olazaran *et al.* (2004) as cumulative evidence for the efficacy of CT in MCI, but acknowledged that this

program did not include memory training strategies per se but rather ‘general’ cognitive activity (i.e. cognitive stimulation).

There has been one negative study in this area (Rapp, Brenes, & Marsh, 2002) which utilized a strategy-based memory training program in community-dwelling MCI participants over a six week period and did not demonstrate improvement on objective memory tests despite subjective improvement in memory reported by participants. It has been suggested that negative results may be due to a combination of small sample size and sub-optimal intervention (Belleville, 2008).

Since the time of Belleville’s review, two studies have also demonstrated evidence for improvement in cognition following strategy-based CT. Kurz *et al.* (2009) reported significant improvement in episodic memory and informant-rated activities of daily living, and decreased depressive symptoms in MCI participants (mean age = 70 years) compared to waitlist controls following an intensive four-week group program, which included strategy-based memory training as well as practical problem-solving, self-assertiveness training, relaxation techniques, stress management, and motor exercises. However, the authors acknowledge limitations including an inability to determine the relative contribution of each intervention component to the outcome, and a lack of long-term follow-up to clarify sustainability of effects. Kinsella *et al.* (2009) demonstrated improved performance on objective measures of prospective memory in 22 participants with amnesic MCI (mean age = 79 years), following five weekly sessions of memory and problem-solving strategy training and practice. Additionally, participants and their family-members who also took part in training reported increased knowledge and use of memory strategies at two-week follow-up compared to waitlist controls.

Of the seven studies described above as demonstrating cognitive improvements following CT in MCI, two were randomized controlled trials (Kinsella, et al., 2009; Rozzini,

et al., 2007). All included some standard of control except for Gunther *et al.* (2003), who argued that within a residential setting, control participants not allowed to partake in computer activities might feel devalued. However, the range of conditions included as control must be considered – for example, some studies used a non-intervention group whilst others used an active control group without the critical CT element. Cipriani *et al.* (2006) used participants with a different diagnosis (AD) as a control, and both Talassi *et al.* (2007) and Belleville *et al.* (2006) included control groups with approximately one-third the sample size of their treatment groups. Thus, whilst these findings are encouraging in suggesting that different CT programs conducted in both residential facilities and community settings may be valuable secondary prevention tools (insofar as they improve cognitive functioning in this ‘at risk’ group), methodological variability suggests that further randomized, controlled trials are warranted. Furthermore, as with healthy populations, slower rates of decline in non-demented individuals necessitate longer observation periods (e.g. three to four years) to truly clarify prevention (Mueller, et al., 2005). Additionally, given the contribution of multiple factors to MCI (e.g. vascular risk factors, psychiatric status, genetics, hormonal changes and anticholinergic medication (Gauthier et al., 2006)), CT may be more efficacious in combination with psychoeducation aimed at controlling risk factors for further cognitive decline (Naismith, et al., 2009b).

In terms of underlying mechanisms, preliminary evidence suggests that CT in MCI may be associated with other probes reflective of brain function, thus supporting the notion of neuroplasticity. For instance, in patients with MCI, Belleville, Chertkow and Gauthier (2007) reported CT-associated increased neural activity (increased amplitude of the P2 component related to active retrieval of information) seen in event-related potential (ERP) measures. However, a general dearth of reference to imaging data in the literature limits knowledge of the extent or mechanisms of neural changes occurring with CT.

An additional consideration within this body of research is the concentration on the classical definition of MCI as an amnestic syndrome, whereby diagnosis emphasizes memory loss through the presence of subjective complaint and impairment on objective testing (Petersen, et al., 2001). However, conceptual development of MCI has indicated the importance of other subtypes such as non-amnestic (Gauthier, et al., 2006; Petersen, et al., 2001; Petersen & Morris, 2005). Whilst the prognostic pathway of non-amnestic MCI is yet to be clarified to the same extent as amnestic MCI, it is reasonable to hypothesize that CT programs incorporating multiple cognitive domains may similarly improve cognition in individuals with this non-amnestic subtype.

Generally positive findings despite vast methodological and program differences, as well as preliminary evidence for concurrent neural changes, suggest that CT represents a promising tool that may be effective as a selective secondary preventative technique in individuals ‘at risk’ for cognitive decline. Nonetheless, further research incorporating tighter methodological control and extending the observation period would help to clarify this proposal.

2.4.3. Opportunity to develop CT in other ‘at risk’ groups: late-life depression

Depression is associated with impairments in learning, memory and executive functions (Naismith et al., 2003; Naismith, Hickie, Ward, Scott, & Little, 2006). Furthermore, late-life depression (first episode after age 50) is characterized by cognitive deficits in executive functioning, processing speed and memory (Naismith, et al., 2003). Unfortunately, cognitive deficits often remain despite adequate resolution of depressive symptoms (Butters et al., 2000). Depression has been recognized internationally as a prodromal feature for cognitive decline (Steffens et al., 2007), with more severe symptoms representing a greater risk for MCI (Barnes, Alexopoulos, Lopez, Williamson, & Yaffe, 2006). Indeed, 60% of individuals

with depression meet criteria for MCI. The combination of depression and MCI is associated with a twofold risk of developing AD with an earlier age of onset (Modrego & Ferrandez, 2004). This is likely associated with the high rates of cerebrovascular disease. Additionally, depression itself presents an independent risk factor for cognitive decline. Possible mechanisms include the down-regulation of the hypothalamic-pituitary-adrenocortical axis, neurotoxic effects of glucocorticoids and reduced expression of brain-derived neurotrophic factor (BDNF) (Duman & Monteggia, 2006; Hickie et al., 2005). BDNF is a neurotrophin that promotes neuronal differentiation, growth and survival and is decreased in persons with depression and during exposure to stress. It plays a role in use-dependent plasticity mechanisms such as long-term potentiation and is critical in cognitive processes such as learning, memory and executive functions (Shimizu et al., 2003).

Given the increased risk for cognitive decline associated with depression, it is very possible that CT again represents a viable secondary prevention tool in this 'at risk' group. Unfortunately, this group has largely been overlooked in CT literature. Whilst some studies have measured depressive symptoms in general terms using self-report measures and reported a decrease following CT (e.g. Kurz, et al., 2009; Rozzini, et al., 2007; Talassi, et al., 2007), many have directly excluded individuals with a current psychiatric disorder or lifetime psychiatric history (e.g. Kinsella, et al., 2009; Rozzini, et al., 2007; Smith, et al., 2009; Stuss, et al., 2007). We have recently examined the efficacy of CT in late-life depression using a combined psychoeducation and computer-based training program (Naismith, et al., 2009a). In this study, a ten-week course of CT was associated with significant improvements in both verbal and visual memory. We are unaware of any other study evaluating the effects of CT in elderly samples (i.e. >60 years), though three studies have shown positive effects in younger samples with a lifetime history of Major Depressive Disorder. One study (Elgamal, McKinnon, Ramakrishnan, Joffe, & MacQueen, 2007) showed that ten weeks of

computerized CT given to euthymic patients was associated with improvements in memory, attention, executive functioning and psychomotor speed. The effect was unrelated to improvements in mood symptoms over the ten week training period. Additionally, Alvarez and colleagues (2008) demonstrated a reduction in depressive symptoms and improvement on cognitive measures in university students with Major Depressive Disorder following twice-weekly computer-based CT, both alone and in conjunction with anti-depressant medication. More recently, Naismith *et al.* (in press) reported greater improvements on objective memory tests following 10 weeks of twice-weekly CT using the NEAR approach (Medalia & Freilich, 2008) in participants with a lifetime diagnosis of major depressive disorder compared to waitlist controls.

These studies provide preliminary yet encouraging results and suggest that therapies targeting neuroplastic processes in this ‘at risk’ group warrant further development and research. Additionally, such programs may be best delivered in conjunction with other mediators of mood and cognition (Naismith, et al., 2009b) such as sleep-wake cycle, social networks, physical co-morbidities, underlying cerebrovascular disease, limited mobility and access to community resources.

2.4.4. Effectiveness of CT as a tertiary prevention tool

Investigation of CT in populations with established dementia aim to determine whether CT can be used as a successful tertiary intervention to prevent further decline once cognitive impairment has already manifested. Overall, the literature is disparate regarding the capacity of CT to improve cognition in AD. A recent review by Clare and Woods (2008) reported a lack of evidence for the efficacy of CT in early-stage AD. However, the authors note considerable methodological limitations amongst the nine included studies (e.g. small samples, insufficient frequency, intensity and duration of treatment) and variability in patient

groups (e.g. age, MMSE), interventions and outcome measures, which may have contributed to trivial results. Additional confounders among studies were the inclusion of mixed-diagnosis patient groups, concomitant use of cholinesterase inhibitors and non-specific interventions. Other reviews and non-randomized trials have reported promising results for strategy-based (De Vreese, Neri, Fioravanti, Belloi, & Zanetti, 2001) and computerized CT programs targeting several cognitive domains (Cipriani, et al., 2006) in early-stage AD, in conjunction with acetylcholinesterase-inhibitor treatment. Additionally, when considered across the range of disease severity, a meta-analysis of nineteen controlled studies reported generally positive effects for CT (Sitzer, et al., 2006). Despite clear heterogeneity in procedures and methodologies (e.g. differences in sample characteristics and CT programs), Sitzer and colleagues concluded that CT can indeed improve cognitive functioning in mild to moderate AD. Whilst this is encouraging, this review also included several non-randomized studies and intervention programs comprising cognitive stimulation rather than a strict definition of CT.

Such disparate findings may reflect the possibility that CT programs as tertiary prevention tools are ‘too late’ in individuals with established, progressive, dementia. It is possible that the capacity to benefit from CT may depend on the underlying etiology. For example, due to its more predictable progressive course and/or a higher burden of pathology resulting in less opportunity for plasticity, patients with AD may benefit to a lesser extent, or less consistently, than healthy older adults or those with MCI. Indeed, in many neurological and medical intervention studies of older adults with pre-existing cognitive impairment, effects have generally been limited. For instance, there is little evidence to support the use of folate supplementation in people with dementia, and many cardiovascular interventions show limited effects on cognition (see review by Naismith, et al., 2009b). Perhaps, then, the value

of CT lies less in tertiary prevention and more in earlier implementation in healthy older adults or 'at risk' populations.

2.4.5. Limitations of Cognitive Training research

Though evidence for the efficacy of CT in healthy and clinical populations is promising, few studies are well-controlled, many include small samples and investigations have generally employed diverse methodologies, with varying treatment times and outcome measures. Differences in the design of CT programs may be understandable insofar as they follow differing theoretical approaches; however they add to the complexity of synthesizing findings from an already heterogeneous field. Such differences have been noted in many recent review papers (Belleville, 2008; Clare & Woods, 2008; Medalia & Richardson, 2005; Sitzler, et al., 2006).

Few studies have incorporated performance-based functional outcome measures (i.e. IADLs) and of those that have, findings are mixed. For example, though the ACTIVE study (Ball, et al., 2002) reported no impact of training on IADLs on initial testing, an effect was seen at five-year follow-up in one training group (Willis, et al., 2006). Additionally, speed of processing training has been associated with improved performance on timed IADLs (Edwards et al., 2002), with faster performance on both trained and untrained tasks (Zanetti et al., 1997). Talassi *et al.* (2007) reported significant improvement on a physical performance test following computerized CT within a cognitive rehabilitation program, but no concurrent change on an IADL measure. The inconsistency in findings is compounded by the argument that these IADLs are simplistic in comparison to more cognitively demanding tasks faced by independent older adults in a more technologically-dependent world (such as interacting with automated, menu-based telephone systems and the Internet (Acevedo & Loewenstein, 2007). As such, the ecological validity of CT effects should be addressed more uniformly, with the

inclusion of measurement tools commensurate with real-life situations such as tasks requiring organization of simulated car-pools, as used by Levine *et al.* (2007), or coin sorting and compiling bills as described by Manly *et al.* (2002).

Whilst CT in younger populations with schizophrenia has shown generalization and sustainability of improvements (see McGurk *et al.* (2007) for review), these issues have not been widely addressed in older groups. Again, studies that have explored generalization have returned both positive (e.g. Mahncke *et al.*, 2006b; Smith, *et al.*, 2009; Winocur, *et al.*, 2007) and negative (e.g. Acevedo & Loewenstein, 2007; Edwards, *et al.*, 2002) results, indicating a need for further consideration of this issue.

Though still a lesser focus of existing research, some studies have addressed the issue of sustainability, with some positive findings. As described above, sustained improvements have been reported in healthy older adults for as long as five years (Oswald, Gunzelmann, Rupprecht, & Hagen, 2006; Willis, *et al.*, 2006), and at least one year in MCI (Rozzini, *et al.*, 2007). As reviewed by Sitzler *et al.* (2006), improvements following training in AD may be maintained for four-and-a-half-months (on average); however given the progressive nature of the disease, maintenance of cognitive gains over time is difficult to ascertain. Nonetheless, some longitudinal studies have indicated that CT may slow the rate of decline. Notably, several studies have reported enhanced maintenance of CT effects with adjunct therapy, such as physical therapy (Oswald, *et al.*, 2006), booster sessions following program cessation (Ball, *et al.*, 2002) and acetylcholinesterase-inhibitor treatment (Cipriani, *et al.*, 2006; Rozzini, *et al.*, 2007). Again, differences in study methodologies, populations and CT parameters preclude any definitive conclusions regarding the sustainability. These encouraging results, however, suggest a need for clearer delineation of those factors comprising a CT program (such as type, duration, intensity and adjunct therapies) which are most effective for long-term gain within each population.

A further limitation which has not been widely discussed is the dearth of investigation into underlying neural changes occurring with CT. Incorporation of imaging data with CT will also help to delineate the neuromechanisms of change. Particularly given recent interest in the potential for neuroplasticity in the aging brain, it is as important to investigate evidence for CT efficacy as it is to explore how these changes occur. Fortunately, advances in physiological and functional imaging techniques such as magnetic resonance imaging (MRI; functional and spectroscopy), positron emission tomography (PET) and ERP readily afford this opportunity (Belleville, et al., 2007; Valenzuela, Breakspear, & Sachdev, 2007; Valenzuela & Sachdev, 2006) though have not, as yet, been capitalized in this area. We thus propose the need for further discussion of, and focus on, the underlying mechanisms of CT, beginning with the central component of increasing cognitive activity.

2.4.6. Cognitive activity protects against decline

Considerable epidemiological evidence suggests that there is a dose-dependent relationship between cognitive activity (e.g. education, occupation complexity) and dementia risk (see review by Valenzuela and Sachdev (2009)). This protective effect or ‘cognitive reserve’ appears to be underpinned by *promotion* or *maintenance* of brain structures. At a cellular level, cognitive activity likely influences spine density, synaptogenesis and vascular supply to the brain. It likely promotes glial and metabolic activity, trophic factors (e.g. BDNF) and hippocampal neurogenesis. Indeed, in older people, higher mental activity levels have been associated with lower rates of hippocampal atrophy over a three-year period (Turkstra, Holland, & Bays, 2003; Valenzuela, Sachdev, Wen, Chen, & Brodaty, 2008). CT programs represent an opportunity for individuals to increase their cognitive activity during training and following cessation of the program by incorporating strategies and skills into everyday life.

2.4.7. Mechanisms of neuroplasticity

‘Neuroplasticity’ refers to the ability of the brain to undergo structural and functional change in response to internal and external stimuli. For decades, animal research has shown that cognitive activity contributes to dendritic arborisation, increased synaptogenesis and brain plasticity (Turkstra, et al., 2003). More recently, investigators have applied these principles to healthy and clinical populations and the field of neuroplasticity has received renewed interest (Fuchs, Czeh, Kole, Michaelis, & Lucassen, 2004; Kelly, Foxe, & Garavan, 2006; Mahncke, et al., 2006a; Strangman et al., 2005).

The traditional view of the brain as a ‘static’ structure has been recently revised on the basis of numerous studies which show that neuronal connections and circuits undergo continual modification and reorganization (Fuchs, et al., 2004). Using terminology conceptualized independently of CT, the *mechanisms* of neuroplasticity for rehabilitation may be either restorative (i.e. reorganization of existing networks) or compensatory (engagement of other cognitive abilities or networks) (Strangman, et al., 2005). Neuroplasticity is also believed to be bi-directional. That is, the same mechanisms and plasticity processes can either degrade (i.e. negative plasticity) or strengthen (i.e. positive plasticity) cognitive functioning. Such ‘negative’ plasticity may be involved in age-related cognitive decline (Mahncke, et al., 2006a) and depression (Fuchs, et al., 2004). By contrast, processes that strengthen brain function can be conceptualized as being ‘positive’ plasticity and can provide a foundation for therapy. In this sense, therapies could theoretically target sensory, cognitive, motor and mood systems in aging (Mahncke, et al., 2006a). From the cognitive standpoint, it is possible that the efficacy of CT in preventing cognitive decline lies in its facilitation of ‘positive plasticity’.

2.4.8. CT as a promoter of neuroplasticity

In terms of underlying neuroplasticity, further corroborative evidence from employing other neurobiological assessment techniques is needed to determine the therapeutic mechanism of action for CT. As the animal literature has demonstrated increased synaptogenesis, dendritic arborisation and neurogenesis, it is reasonable to speculate that such processes are operative. However, this has not been demonstrated empirically in humans and only a few studies in healthy older adults and MCI have shown concomitant effects on brain physiology (Belleville, et al., 2007; Valenzuela, et al., 2007; Valenzuela et al., 2003) or structure (Valenzuela & Sachdev, 2006). Further structural and functional imaging studies may help to delineate the specific effects on functional neuronal networks, neurochemistry and glial cell function and may help to determine if mechanisms are restorative or compensatory, or whether there are pre-existing predictors or mediators of CT effectiveness. Additionally, longer observation periods will clarify the stability of improvements seen following CT and indicate whether such effects are due to neuroplastic changes.

Key Points:

- Epidemiological and case control data supports the effectiveness of cognitive training (CT) programs in healthy elderly and ‘at risk’ older individuals, suggesting utility as a primary and secondary prevention tool;
- Findings are mixed for Alzheimer’s disease;
- CT has not been investigated as a preventative tool in older people with depression, thus overlooking a further group ‘at risk’ of cognitive decline;
- Though the mechanisms of effectiveness are unclear, CT may promote neuroplasticity; and
- Further studies are needed to address methodological limitations, define mechanisms of neuroplasticity and to determine mediators of efficacy, generalization and sustainability.

2.5. Summary and conclusions: CT as a preventive technique for cognitive decline

Despite mixed findings in AD, studies in healthy older adults and MCI largely suggest that CT can be implemented as an early intervention technique. Whilst further neurobiological research in humans is required to delineate whether the underlying mechanism is neuroplasticity (Naismith, et al., 2009b; Valenzuela & Sachdev, 2009), data suggests that CT represents a promising selective prevention technique for older adults ‘at risk’ of cognitive decline. Though as yet CT has not been investigated in older adults with depression, future studies on programs incorporating CT and other indicated prevention programs are warranted to determine the clinical and scientific utility of CT as an early intervention and non-pharmacological treatment strategy in this ‘at risk’ group.

As the increasing aging population presents with age- or disease-related cognitive decline, early intervention and prevention strategies targeting neuroplasticity are likely to gain increasing interest and demand. CT programs offer promise for these groups for several reasons. They are easily implemented across a variety of settings, including aged-care facilities, community centers or individual homes by facilitators who require relatively uncomplicated training. They engage participants and therefore offer an enjoyable experience. Training can be conducted in one-on-one or group settings, with the latter offering the additional benefit of social interaction. Additionally, data suggests that older adults are increasingly opting for non-pharmacological forms of therapy for psychological and cognitive difficulties (Jorm et al., 1997). As shown in other areas of psychiatry, it is likely that combined pharmacological and non-pharmacological approaches may be optimal. Ideally, such programs would be implemented early (e.g. ages 55 years onwards), and now require empirical examination.

In addition to observable changes on neuropsychological testing demonstrating improved cognitive functioning, some preliminary data from imaging and ERP studies suggests that CT promotes neuroplasticity. However, as discussed, a number of limitations within the existing literature are evident. These methodological constraints (such as limited sample sizes and varied outcome measures) need to be addressed in future investigations. A general lack of performance-based functional outcome measures commensurate with real-world tasks has hindered the generalization of cognitive improvement (observed on testing) to functional efficacy. Additionally, issues including the generalization and sustainability of improvements following CT and underlying mechanisms using imaging data have not been widely addressed and require further investigation. Nonetheless, CT programs represent a promising option for primary and particularly secondary prevention of cognitive decline in older adults, especially since they are easy to implement, enjoyable and offer the potential for social interaction. Resolution of limitations and further research as posited above will help to further delineate the preventative and neuroprotective utility of CT.

2.6. Addendum to methods

2.6.1. Search strategy

Searches were conducted of PsycINFO (years 1967 – 2009) and MEDLINE (years 1950 – 2009) databases to identify empirical studies and reviews on Cognitive Training in Mild Cognitive Impairment (MCI) and depression (i.e. populations identified as ‘at risk’ of developing dementia and therefore worthwhile targets at the secondary level of prevention). The searches were conducted in December 2008 and updated in April 2009. The search terms used for this review were ‘cognitive remediation’, ‘cognitive training’, ‘memory training’, ‘Mild Cognitive Impairment’, ‘cognitive decline’, ‘depression’, ‘late-onset depression’, ‘older adults’, and ‘elderly’. Searches were restricted to English-language reports. Studies were screened for eligibility based on inclusion and exclusion criteria (detailed below). In addition to database searches, the reference lists of included studies were manually examined to identify any additional, relevant studies. Authors were contacted in the case of one study where further detail was required.

2.6.2. Criteria for inclusion

Included studies were required to meet the following criteria: a) included participants older than 50 years; b) included participants with MCI or depression; c) conducted a CT intervention on more than one separate occasion aimed at improving functioning in at least one cognitive domain OR reviewed studies which had done so; and d) at least one objective cognitive or functional outcome was measured and described.

2.6.3. Criteria for exclusion

Studies were specifically excluded from this review if they a) described a Cognitive Stimulation or Cognitive Rehabilitation program (rather than CT) or b) described multi-

faceted behavioural intervention programs where the effect of CT alone could not be isolated (e.g. in combination with exercise programs). In the case of reviews which were included but referred to such studies, these issues were highlighted.

2.7. Literature update since publication of this review

2.7.1. CT in ‘at risk’ groups

Since the publication of this review in 2010, several other comprehensive reviews of CT trials in MCI have been published. As such, individual CT trials will not be described here; rather, the findings from these reviews will be summarized. However, evidence from individual CT studies which also examined neural changes in relation to cognitive effects will be discussed as this aspect of CT has not been widely reviewed to-date.

The review presented above indicated generally positive findings, suggesting that CT programs can improve cognitive functioning (particularly learning and memory) in ‘at risk’ groups and may represent a viable non-pharmacological early intervention strategy, particularly since they are easy to implement, enjoyable and offer the potential for social engagement. However, the review also highlighted several methodological limitations to generalizing across CT studies, including vast differences in CT program design, modality, location (community-based versus residential facility), observation period, standard of control and criteria for MCI. As such, further randomized controlled studies were recommended, including longer observation periods to truly clarify prevention of dementia diagnosis, increased focus on concurrent neural changes associated with cognitive improvements, measurement of generalizability and sustainability of effects, and consideration of a psychoeducation component aimed at controlling risk factors for further cognitive decline.

Similarly, a subsequent systematic review of 15 CT studies specifically involving participants diagnosed with amnesic MCI (Jean, et al., 2010) according to Peterson's criteria (Petersen, 2004) also reported promising preliminary findings regarding the efficacy of CT in this specifically amnesic 'at risk' group. According to the review, all of the intervention programs demonstrated some statistically significant cognitive improvement, especially on objective and subjective measures of memory, with additional improvement on measures of psychosocial functioning (i.e. quality of life and mood). However, the authors also raised concerns regarding methodological variability across the studies, including differences in sample sizes and design, as well as the necessity for longer follow-up periods to assess the longitudinal course of efficacy data. The review also highlighted the importance of the CT format: whilst there was no apparent relationship between efficacy and individual vs. group format, the authors emphasized the advantage in tailoring a CT program to each individual participant's complaints and level of functioning. It was recommended that guidelines be developed via a consensus meeting of experts in CT, regarding aspects of program design, format, duration and outcome measures, for improved comparability across studies.

Most recently, another systematic review attempted to further delineate the efficacy of specific CT approaches in MCI by comparing the efficacy of trials using applied memory strategy training vs. trials using repetitive multi-domain cognitive exercises (Gates, et al., 2011). Ten studies were included in this review, with these authors also highlighting vast heterogeneity in methodology and design. Nonetheless, the review reported moderate-sized effects on memory performance and global cognitive measures in the majority of studies, with stronger effect sizes and generalizability of benefits more frequently seen in those trials using a computer-based, cognitive exercise approach. It was suggested that the apparent advantage of multi-domain exercises over memory strategy training may be related to their broader range of cognitive challenges and subsequent ability to stimulate a variety of

neuroplastic processes. Despite reiterating the limitations in generalizing across studies with heterogeneous design, methodology and quality, the authors acknowledged the promising role of CT interventions in enhancing cognition in MCI, and reinforced the framework proposed in chapter two by Mowszowski et al (2010) in recognizing CT as a secondary prevention strategy for this ‘at risk’ group.

Importantly, another recent systematic review combining CT trials in healthy older adults and MCI (Martin, Clare, Altgassen, Cameron, & Zehnder, 2011) reported that while most of the CT trials had demonstrated significant improvements following training, these improvements were not specific to CT as they did not exceed improvements seen in the active control conditions. The authors therefore concluded that cognitive interventions are no more effective than alternative interventions. However, the authors also acknowledged the scarcity of their data in MCI, as only three of the 36 studies reviewed sampled participants with MCI. As such, these conclusions are arguably more appropriate for the healthy older adult samples included in their review, at the risk of de-valuing the potential of CT as a potential early intervention strategy in MCI.

In terms of clarifying the efficacy of CT in SCI, it seems that studies focusing explicitly on this group are relatively scarce. This may be related to the fact that SCI has fairly recently been established as part of the ‘at risk’ spectrum. However, it is possible that a proportion of the literature which has shown positive effects of CT in healthy older adults may also be applicable to the SCI population, since many of these studies recruit community-dwelling individuals without objective evidence of cognitive or functional impairment but with some subjective complaints of cognitive change (e.g. Stuss et al., 2007). Although it has been suggested that trials recruiting healthy populations often attract ‘supernormal’ volunteers (Valenzuela & Sachdev, 2009), it is also possible that studies advertising participation in a program designed to enhance cognitive functioning would likely attract

generally healthy individuals who feel that they would stand to benefit; i.e. who subjectively feel that their cognition has changed. Thus, it is plausible to assume that the established cognitive benefits of CT in healthy older adults may also extend to those with SCI, who perhaps have not explicitly been labeled.

Overall, the balance of evidence suggests that CT is effective in improving cognitive functioning in ‘at risk’ groups, especially MCI which has been most widely studied. However, limitations to the body of research have also been widely acknowledged and can only be remedied with further, scientifically-rigorous investigations with larger sample sizes, randomized controlled and longitudinal designs, and improved standardization of CT programs for increased comparability of effects. In particular, further research is needed to further elucidate the efficacy of CT in other ‘at risk’ groups such as LLD and SCI.

2.7.2. Neural changes associated with CT

As discussed earlier in this chapter, it is thought that the mechanism of CT lies in its facilitation of neuroplastic processes as well as enhancement of cognitive reserve, to slow down the trajectory of cognitive decline and protect against further impairment. However, a significant limitation within CT literature has been the lack of focus on concomitant CT effects on brain physiology. The use of standardized, objective neuroimaging outcome measures provides insight into neurophysiological changes which may underlie the cognitive/psychosocial effects of CT, and may also clarify whether specific CT programs influence the neurodegenerative process or whether they merely enhance cognition without impacting on underlying pathology. Such measures can also complement or even anticipate clinical outcomes, for example when the cognitive/ functional effects of CT may be delayed: in these cases, the use of clinical outcomes alone would likely result in dismissal of the program as ineffective (Cummings, et al., 2007; Mueller et al., 2005).

CT studies in other populations have recognized the potential of neuroimaging outcomes: for example, Draganski and colleagues (2004) utilized MRI in mid-adulthood and reported significant volumetric increases in grey matter regions associated with perception and spatial anticipation of moving objects following a three-month training course in juggling, compared to non-trained participants. Penner et al. (2006) used functional MRI (fMRI) to study the effects of CT in patients with multiple sclerosis, and reported additional recruitment of an ‘attention-associated’ network including the posterior cingulate cortex, precuneus and dorsal frontal cortex at follow-up. Recently, Takeuchi et al. (2010) utilized diffusion tensor imaging (DTI) to investigate the effect of working memory training on structural connectivity in healthy young adults. The study demonstrated increased fractional anisotropy (indexing structural connectivity) in white matter regions in parietal areas as well as adjacent to the body of the corpus callosum following training, which also correlated with the amount of training received.

Within the ageing literature, a few early CT studies demonstrated increased activation in the parieto-occipital cortex seen on PET scanning (Nyberg et al., 2003), as well as elevated neurochemical signals in the hippocampus seen on magnetic resonance spectroscopy (MRS) (Valenzuela et al., 2003), in healthy older adults following memory strategy training. Fortunately, neuroimaging outcomes have received renewed interest in recent years, with a growing body of CT studies targeting healthy older adults adding to these earlier findings. According to a recent systematic review of CT studies utilising MRI outcomes, five studies have included older adult samples and each has reported at least one significant brain-imaging outcome, most commonly reflecting training-related changes in the frontal lobes (Suo & Valenzuela, in press). For example, Lovden and colleagues (2010) reported increased white matter connectivity evident on DTI in the anterior region of the corpus callosum in older adults who received training in working memory, episodic memory and processing

speed compared to untrained controls. This increase in white matter connectivity following memory training was recently confirmed by Engvig and colleagues (2011), who also demonstrated a positive relationship between the increase in fractional anisotropy and improvements on a memory task following training. In an earlier study, this group also reported regional increases in cortical thickness in the right insular, fusiform and orbitofrontal cortices on post-CT MRI in healthy older adults who underwent eight weeks of intensive memory strategy training (Engvig et al., 2010). Again, these increases were positively correlated with improvement in performance on a memory task. Furthermore, increases in resting cerebral blood flow in the prefrontal cortex have recently been reported in healthy older adults following an eight-week training program targeting attention and distractibility (Mozolic, Hayasaka, & Laurienti, 2010). These increases in blood flow were larger than those seen for an active control group and were also positively associated with reduced susceptibility to distraction on a cognitive task at follow-up.

To-date, only one known study has investigated neuroimaging outcomes following CT in MCI. Forster et al. (2011) recently reported improved global cognitive scores and attenuated decline in cerebral metabolism seen on PET scanning in a group of amnesic MCI participants who received a six-month cognitive intervention focusing on cognitive training, compared to an active control group. The authors suggested that these findings represent evidence of cognitive stabilization following cognitive intervention. However, it should be noted that the active control group in this study received a program based on cognitive stimulation, which also contained elements of cognitive training. Thus, the validity of the control group is uncertain.

It is evident that most of the research examining physiological biomarkers of prodromal dementia or CT efficacy has focused on neuroimaging techniques (MRI, DTI, PET etc.). However, other neurophysiological responses such as ERPs may offer a novel

perspective and lead to further discovery within these groups. This will be discussed further in subsequent chapters.

2.8. Additional considerations following publication of this review

With the progression of this research, it has become clear that some clarification is required in relation to some of the points raised in this review.

2.8.1. Terminology of neuroplasticity / CT mechanisms

In explaining the concept of neuroplasticity, it was stated that the terminology used to describe the proposed mechanisms of neuroplasticity (i.e. restorative or compensatory) were conceptualized independently of CT. This statement was intended to clarify that whilst the terms ‘compensatory’ and ‘restorative’ have been defined and used concurrently within both the fields of CT and neuroplasticity, these definitions were not formulated in direct relation to one another.

2.8.2. CT and other indicated prevention programs

In the concluding paragraphs of this review, it was proposed that “future studies on programs incorporating CT and other indicated prevention programs are warranted”. Within this review, several other preventive strategies were mentioned (see sections 2.4.2 and 2.4.3) and it is suggested that CT may be most efficacious when delivered in conjunction with these strategies. For example, this could include provision of psychoeducation targeting multiple factors affecting cognition (e.g. vascular risk factors, mood, lifestyle factors etc.), interventions for alterations in sleep-wake cycle, social groups, community involvement and physical exercise programs.

CHAPTER THREE:

Reduced Mismatch Negativity in Mild Cognitive Impairment: associations with neuropsychological performance

This chapter has been published as:

Mowszowski, L., Hermens, D. F., Diamond, K., Norrie, L., Hickie, I. B., Lewis, S. J. G., et al. (2012). Reduced Mismatch Negativity in Mild Cognitive Impairment: associations with neuropsychological performance. *Journal of Alzheimer's Disease*, 30(1), 209-219. doi: 10.3233/JAD-2012-111868

The published article is included in Appendix 3.

3.1. Abstract

Mild Cognitive Impairment (MCI) refers to a transitory state between healthy ageing and dementia. Biomarkers are needed to facilitate early identification of MCI and predict progression to dementia. One potential neurophysiological biomarker, Mismatch Negativity (MMN), is an event-related potential reflecting fundamental, pre-attentive cognitive processes. MMN is reduced in normal ageing and dementia and in neuropsychiatric samples and is associated with verbal memory deficits and poor executive functioning. This study aimed to investigate auditory MMN and its relationship to neuropsychological performance in MCI. Twenty-eight MCI participants and fourteen controls, aged ≥ 50 years, underwent neurophysiological and neuropsychological assessment, and completed questionnaires pertaining to disability. Relative to controls, the MCI group demonstrated reduced temporal MMN amplitude ($p < 0.01$). Reduced right temporal MMN was significantly associated with poorer verbal learning ($r = 0.496$; $p < 0.01$) and reduced left temporal MMN was significantly associated with increased self-reported disability ($r = -0.419$; $p < 0.05$). These results indicate that patients with MCI exhibit altered pre-attentive information processing, which in turn is associated with memory and psychosocial deficits. These findings overall suggest that MMN may be a viable neurophysiological biomarker of underlying disease in this ‘at risk’ group.

3.2. Introduction

Given the burgeoning ageing population and the associated increase in dementia prevalence (Ferri et al., 2005), early identification and intervention for individuals ‘at risk’ of dementia has received considerable attention (for review, see Mowszowski, Batchelor, & Naismith, 2010; Naismith, et al., 2009b). Indeed, much research has focused on the syndrome of Mild Cognitive Impairment (MCI) as an ‘at risk’ condition for dementia, particularly Alzheimer’s Disease (AD) (Gauthier, et al., 2006; Petersen et al., 2009). By definition, individuals with MCI remain ‘functional’ and independent in their daily activities; yet have corroborated cognitive complaints and observable deficits on neuropsychological testing (Petersen, et al., 2001). Over time, the concept of MCI has been further developed and two subtypes are now widely acknowledged, differentiating those individuals with specific deficits in memory (amnesic, or aMCI) from those with deficits in other cognitive domains such as language, visuospatial skills or executive functions (non-amnesic, or naMCI) (Petersen, 2004). Furthermore, individuals may demonstrate deficits within a single cognitive domain, or within multiple cognitive domains. Data suggests transition rates to dementia of around 10-15% per year and approximately 45% over a five year period, a much higher rate than observed in the general healthy elderly population (Gauthier, et al., 2006; Petersen, et al., 2001).

Increased sophistication in biomarker identification will ultimately assist in improved early detection of older ‘at risk’ individuals (Gauthier, et al., 2006; Petersen, et al., 2009) and over the past decade, a body of research has unveiled many underlying neurobiological changes associated with MCI. Such studies have identified that certain neuropsychological (e.g. delayed memory recall), neuroimaging (e.g. hippocampal atrophy, amyloid burden) and biological (e.g. cerebrospinal fluid) markers are important predictors of conversion to dementia (see reviews by McKhann, 2011; Winblad et al., 2004). It has also been suggested

that neurophysiological techniques may be valuable in the assessment of neurobiological alterations in the very early or prodromal stages of dementia (Winblad, et al., 2004). In this regard, event-related potentials (ERPs) are a non-invasive, practical and objective index of fundamental sensory and cognitive processes (Jackson & Snyder, 2008; Rossini, Rossi, Babiloni, & Polich, 2007) that have shown great utility in detecting neurobiological changes in a range of psychiatric and neurological conditions. ERPs are time-locked to specific stimuli, and are used to assess the speed and efficiency of information processing by examining the magnitude and latency of the waveform.

Numerous ERPs have been shown to map onto different cognitive functions and neural regions, under various elicitation paradigms (e.g. auditory oddball, working memory N-back tasks and mental calculation), to examine the integrity of cognitive pathways in normal ageing, MCI and AD (Liddell et al., 2007; Papaliagkas, Kimiskidis, Tsolaki, & Anogianakis, 2008; Rossini, et al., 2007). However, previous ERP studies in MCI have been characterized by two major limitations: firstly, studies have typically used cognitive paradigms that are dependent on conscious awareness, attention and engagement with the eliciting stimuli, thus indexing later stages of information processing. This issue is important to address since neuropsychological deficits observed in MCI may be partially attributable to dysfunction or inefficiency in earlier stages of information processing. Secondly, there has been a tendency to focus on midline scalp electrodes which reflect fronto-central brain functioning. Therefore, ERP studies that employ a passive paradigm and that assess other brain regions implicated in the pathophysiology of MCI (e.g. the temporal lobes) are required.

Mismatch negativity (MMN) is an ERP ideally suited to address these needs. It is elicited in the absence of directed attention, reflecting an automatic change detection system operating at the pre-attentive stages of information processing, and it has been shown to have

both a frontal and a temporal generator (Giard, Perrin, Pernier, & Bouchet, 1990). The MMN response is typically elicited using an auditory paradigm, and represents an excitatory response to novel or deviant stimuli within a stream of homogenous sounds (see review by Naatanen, Paavilainen, Rinne, & Alho, 2007). In terms of neurobiological mechanisms, there are two distinct steps: first, the temporal lobes (auditory cortex) process the auditory stimulus and maintain an echoic memory trace for the homogenous sounds, which allows for discrimination of the deviant sound as incongruent. The prefrontal cortex then triggers an involuntary switching of attention to the novel stimulus (Giard, et al., 1990; Naatanen & Alho, 1995). The integrity of these lower-level sensory processes is essential for efficient functioning of higher-level processes; MMN is therefore advantageous in its ability to detect subtle, early physiological changes which may underlie cognitive difficulties.

MMN has been most extensively investigated in neuropsychiatric disease, where data examining psychotic, and to a lesser extent affective disorders has shown strong, robust correlations between reduced MMN amplitude, cognitive impairment (including deficits in verbal memory, working memory and executive functioning) and psychosocial functioning (Baldeweg, Klugman, Gruzelier, & Hirsch, 2004; Hermens et al., 2010; Kaur et al., 2011; Light & Braff, 2005). This measure has also been shown to relate to underlying neurobiological changes in the temporal lobes (Rasser et al., 2011; Salisbury, Kuroki, Kasai, Shenton, & McCarley, 2007), areas which are implicated early in the course of AD (Dubois & Albert, 2004). Given the apparent utility of this measure as a marker of fundamental pre-attentive processing deficits in these disease groups, it is plausible to hypothesize that MMN may also relate to early neurobiological change in MCI patients.

While initial studies examining the effect of normal ageing on MMN were inconsistent (see Pekkonen, 2000 for review), the majority of studies have shown reduced MMN amplitude and/or delayed latency with increasing age (Cooper, Todd, McGill, &

Michie, 2006; Gaeta, Friedman, Ritter, & Cheng, 1998; Kisley, Davalos, Engleman, Guinther, & Davis, 2005), and as such, MMN has emerged as a potential marker of altered cognitive processing in ageing (Naatanen et al., 2011). For example, reduced MMN amplitude has been correlated with poorer performance on neuropsychological tests of verbal learning, planning, working memory and response inhibition in healthy elders (Kisley, et al., 2005). As in normal ageing, individuals with established dementia such as AD also demonstrate reduced MMN amplitude compared to younger adults (see review by Vecchio & Maatta, 2011), as well as a reduced response relative to age-matched healthy controls (Kazmerski, Friedman, & Ritter, 1997).

To our knowledge, only two studies have investigated MMN in MCI; one demonstrated a mismatch response to deviant auditory stimuli in ten MCI participants (Borghetti et al., 2006) and the other reported an “abnormal” MMN response to visual stimuli in eight MCI participants (Tales, Haworth, Wilcock, Newton, & Butler, 2008). However, both studies were limited by small samples sizes and by difficulties with control comparisons: the former had no control group and the latter did not elicit an MMN in the control group. These limitations warrant further research to determine whether MMN has utility as a biomarker for MCI.

The primary aim of this study was to investigate the auditory MMN response in a larger sample of individuals with MCI compared to healthy older adults. We also aimed to determine whether MMN differs according to MCI subtype (i.e. aMCI and naMCI) and whether altered MMN relates to clinical features such as neuropsychological functioning and disability.

3.3. Material and methods

3.3.1. Participants

28 health seeking older adults aged between 50 and 90 years meeting criteria for multiple domain MCI (i.e. based on decrements of at least 1.5 standard deviations on at least two domains of neuropsychological functioning (Gauthier, et al., 2006; Petersen, et al., 2001)) were recruited from the “Healthy Brain Ageing” Clinic, a specialist research program at the Brain & Mind research Institute, which preferentially recruits older people with new onset mood or cognitive disorders. The clinic receives referrals from psychiatry, psychology and neurology clinics as well as from local geriatricians and General Practitioners. 14 age-matched controls were recruited from the community, via local advertisement and resided within the same geographical location (i.e. Sydney metropolitan area). Exclusion criteria comprised a Mini-Mental State Examination (MMSE) score < 24, use of cholinesterase inhibitors and/or established dementia (i.e. sufficient to impair function); previous head injury with loss of consciousness \geq 30 minutes; history of schizophrenia or neurological condition; previous stroke or transient ischaemic attack; current substance abuse or history of significant substance misuse; intellectual disability or insufficient English language skills for assessment. Additionally, individuals who met DSM-IV criteria for current major depression were excluded. Additional exclusion criteria for control participants were subjective cognitive complaints and/or a previous psychiatric diagnosis. The study was approved by the University of Sydney Human Research Ethics Committee. Written consent was obtained from all participants.

3.3.2. Psychiatric and medical assessment

A semi-structured assessment was conducted by an Old Age Psychiatrist to document history of cognitive decline, lifetime and current psychiatric diagnoses and medical history.

Measures included the 17-item Hamilton Depression Rating Scale where scores ≤ 7 indicate normal levels of depressive symptoms (HDRS; Hamilton, 1960), the Structured Clinical Interview for Psychiatric Disorders (First, Spitzer, Gibson, & Williams, 1996), the Cumulative Illness Rating Scale – Geriatric version (Miller & Towers, 1991) and the Global Assessment of Functioning Scale (GAFS; American Psychiatric Association, 1994), a clinician-rated measure of psychosocial functioning.

Subjective ratings of disability were measured using the 36-item self-administered World Health Organization Disability Assessment Schedule (WHO-DAS) (World Health Organisation, 1999). Domains of functioning included understanding and communicating, getting along with others, participation in society, self-care, getting around, and life activities. A standardized summary score was calculated to reflect a total disability score. Higher scores indicate greater disability.

Several participants in this sample were taking psychotropic medications in the context of ‘treatment as usual’ management of comorbid neuropsychiatric conditions (e.g. depression, anxiety or sleep disturbance), which are often observed in older adults. As such, a detailed medication history was taken. In the MCI group, psychotropic medication usage was evident in a total of 12 participants. All 12 were taking newer-generation antidepressants, including eight taking SSRIs, three taking SNRIs and one unspecified. Of these 12 participants, three were also taking benzodiazepines, two were taking mood stabilisers and three were taking adjunctive atypical antipsychotics. In the control group, only two participants were taking psychotropic medications, both of whom were taking newer-generation antidepressants (SSRIs), and one of whom was also taking an adjunctive benzodiazepine.

3.3.3. Neuropsychological assessment

Clinical Neuropsychologists conducted a semi-structured interview and a standardised battery of neuropsychological tests that were selected on the basis of prior research (Naismith et al., 2010) and sensitivity to early dementia. For clinical diagnostic and descriptive purposes, premorbid intellectual ability was estimated using the Wechsler Test of Adult Reading (WTAR) (Psychological Corporation, 2001) and global cognition was measured using the MMSE (Folstein, Folstein, & McHugh, 1975). Visuomotor processing speed was measured using the Trail Making Test, part A (Reitan, 1979) and confrontation naming was measured using the Boston Naming Test (Kaplan, Goodglass, & Weintraub, 1983). Standardized scores (i.e. z scores or age scaled scores) were calculated for all neuropsychological variables in order to account for differences in age (and level of education, where available).

Also for descriptive purposes, we used Petersen's criteria (Petersen, 2004) to document those having either amnesic or non-amnesic forms of mild cognitive impairment. That is, diagnosis of MCI was based on decrements of at least 1.5 standard deviations in comparison to normative data in at least one neuropsychological domain and was made via consensus of three raters (SLN, KD, LN). aMCI was diagnosed if deficits were of the 'hippocampal-type' (i.e., present on tests of delayed memory recall) (Dubois & Albert, 2004). naMCI was diagnosed if deficits were present on tests of other cognitive domains (e.g. executive functioning, processing speed, language, working memory).

Based on our hypothesised relationship to frontal and temporal lobe functioning, we specifically examined the following domains in relation to MMN:

- a) Verbal memory: The *Rey Auditory Verbal Learning Test* (RAVLT) (Spreen & Strauss, 1998) was administered to measure unstructured verbal learning. Total

learning over the five trials was examined (*RAVLT 1-5*) as well as delayed recall (*RAVLT-7*).

- b) Language: Language generativity was assessed using *phonemic* (letters F,A,S) and *semantic* (animal names, total words in 1-minute) verbal fluency (see Tombaugh et al., in Spreen & Strauss, 1998).
- c) Working memory: The total digit span score from the Wechsler Adult Intelligence Scale – III *Digit Span* (Wechsler, 1997) subtest was used as a measure of auditory working memory.
- d) Executive functioning: This encompassed the *Trail Making Test Part B* (seconds) (Reitan, 1979) to assess mental flexibility.

3.3.4. Neurophysiological testing

As described previously (Hermens, et al., 2010), participants were fitted with a cap for electroencephalography (EEG) recording and presented (via headphones) with 2500 binaural pure tones (1000Hz, 75dB SPL, 10ms rise/fall) at a 500 ms stimulus onset asynchrony; comprising a pseudo-random sequence of 2300 (92%) 50ms standard (short) tones and 200 (8%) 100ms deviant (long) tones. During presentation of the tones, participants watched a silent comedy film and were asked to report the storyline at the end of the task. A 64-channel Quik-Cap (NeuroScan) acquired EEG data from sites according to the standard 10-10 International System (including mastoids). Data was referred to a nose electrode. Vertical and horizontal electro-oculogram (EOG) was monitored for eye-blink artefact with correction based on established methods (Semlitsch, Anderer, Schuster, & Presslich, 1986). Scalp and EOG potentials were amplified and digitized continuously by SynAmps2 via SCAN 4.3.1

software with a frequency response from 0.01 to 100 Hz (and a gain of 20,000). Segments of the EEG record which were contaminated by other artefacts ($\pm 100 \mu\text{V}$) were rejected. MMN difference waveforms were obtained by subtracting ERP waveforms elicited by the deviant stimuli from those of the standard stimuli. The mean amplitude, peak amplitude and peak latency for the MMN component were determined within an epoch of 100-250ms, according to previous studies in older adult populations (see Cooper, et al., 2006; Gaeta, et al., 1998; Tales, et al., 2008). MMN measures were obtained at four sites: midline fronto-central (Fz and Cz) and temporal (left and right mastoid: M1 and M2, respectively).

3.3.5. Statistical analyses

Statistical analyses were performed using SPSS for Windows 18.0.0 Chicago: SPSS Inc. Histograms of all variables were inspected visually for skewness or kurtosis. Between-group differences were examined using independent t-tests for normally-distributed variables, with corrected degrees of freedom and p-values reported when equality of variance was compromised (according to Levene's test). For variables with a non-normal distribution, Mann-Whitney U tests were used. The relationship between continuous variables was examined using Pearson correlation coefficients while categorical variables were analysed using chi-square. All analyses were two-tailed and employed an alpha level of 0.05.

3.4. Results

3.4.1. Sample descriptive, clinical and social functioning data

The total sample comprised 28 MCI and 14 control participants ranging in age from 51 to 79 years. Of the 28 participants with multi-domain MCI, 50% (14/28) met criteria for the amnesic subtype, while 50% (14/28) met criteria for the non-amnesic subtype. As shown in Table 2, there were no significant MCI vs. control group differences in age, gender, years of

education or estimated premorbid IQ. However as expected, MCI participants demonstrated a significantly lower MMSE score.

Group differences were also evident on clinical variables. Mean HDRS scores were significantly increased in MCI participants (although both groups indicated normal levels of depressive symptoms). As expected, clinician ratings on the GAFS indicated significantly worse functional decline in the MCI group (i.e. mild decline) compared to the control group (i.e. absent/minimal decline). Self-reported disability on the WHO-DAS was significantly higher in the MCI group.

Table 2.

Mean (SD) scores for sample demographic, clinical and social functioning variables in MCI and control groups, with corresponding between-group test statistics.

Measure	MCI	Control	Between-group differences
Gender, m/f	13/15	5/9	$\chi^2 = 0.438, df = 42, p = 0.51$
Age, years	67.32 (8.05)	64.86 (4.0)	$t = 1.33, df = 39.995, p = 0.19$
Education, years	13.34 (3.52)	13.43 (2.82)	$t = -0.08, df = 40, p = 0.94$
Premorbid IQ*	104.07 (7.64)	106.21 (7.71)	$U = 153.00, Z = -0.99, p = 0.32$
MMSE, raw score	27.86 (1.58)	29.14 (1.03)	$U = 101.00, Z = -2.60, p = \mathbf{0.009}$
HDRS, score	4.79 (3.55)	0.93 (1.86)	$U = 52.50, Z = -3.68, p = \mathbf{0.000}$
GAFS [#]	67.75 (11.30)	83.1 (9.9)	$U = 58.50, Z = -3.50, p = \mathbf{0.000}$
WHO-DAS	22.43 (13.85)	9.55 (8.52)	$t = 3.71, df = 38.064, p = \mathbf{0.001}$

Significant values are represented in bold. Note: HDRS = Hamilton Depression Rating Scale, 17-item; GAFS = Global Assessment of Functioning Scale; WHO-DAS = World Health Organization Disability Assessment Schedule, summary score * Premorbid IQ score from the Wechsler Test of Adult Reading was not calculated for one MCI participant due English being her second language. [#]GAFS score was not calculated for one control participant who did not complete the medical assessment.

3.4.2. Neurophysiological data

Grand average MMN waveforms for MCI and control groups are shown in Figure 2. Means and standard deviations of MCI and control groups for each neurophysiological variable with corresponding results of *t*-tests are provided in Table 3. As illustrated, peak and mean amplitudes were significantly reduced at both M1 and M2 in the MCI group compared to controls, although the difference was more marked at M2 and marginal at M1. There were, however, no significant group differences in amplitude at Fz or Cz. The peak latency did not differ significantly between MCI and control groups at any of the four sites.

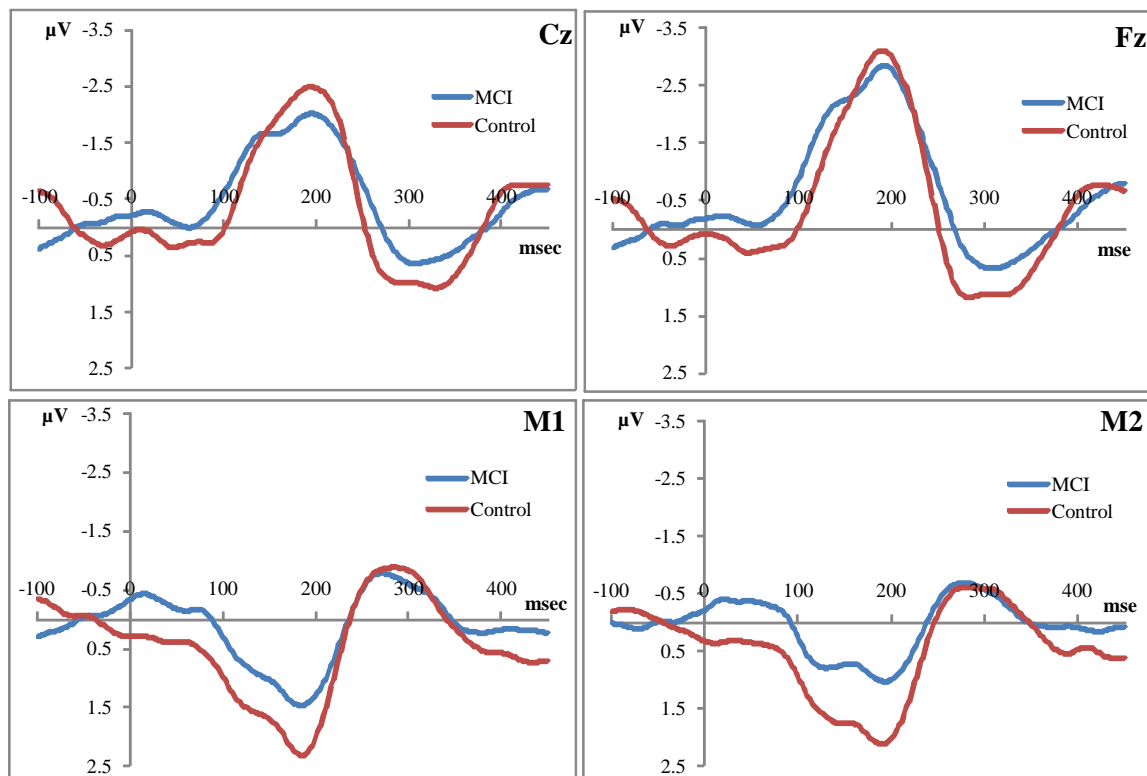


Figure 2.

Grand Average MMN waveforms for MCI (red, N=28) and control (blue, N=14) groups at (clockwise from top left) central (Cz), frontal (Fz), left temporal (M1) and right temporal (M2) sites. The MCI group showed reduced MMN (100-250ms) amplitudes (μ V) at the right temporal site (M2) compared to controls. Note: M1 and M2 waveforms are reversed in polarity due to the nose-referenced recording.

Table 3.

Mean (SD) scores for neurophysiological (MMN) variables in MCI and control groups, with corresponding between-group test statistics.

Site	MMN variable	MCI	Control	Between-group differences
Cz	Peak amp	-2.72 (1.38)	-2.95 (2.31)	$t = 0.40, df = 40, p = 0.69$
	Mean amp	-1.53 (1.23)	-1.59 (1.82)	$t = 0.13, df = 40, p = 0.90$
	Peak lat	182.64 (37.18)	190.14 (25.82)	$t = -0.68, df = 40, p = 0.50$
Fz	Peak amp	-3.43 (1.66)	-3.34 (2.61)	$t = -0.12, df = 18.40, p = 0.91$
	Mean amp	-2.05 (1.44)	-1.85 (2.09)	$t = -0.37, df = 40, p = 0.71$
	Peak lat	178.07 (32.18)	186.29 (13.63)	$U = 183.00, Z = -0.35, p = 0.73$
M1	Peak amp	1.90 (1.05)	2.61 (1.13)	$t = -2.03, df = 40, p = \mathbf{0.05}$
	Mean amp	0.82 (0.82)	1.39 (0.90)	$t = -2.03, df = 40, p = \mathbf{0.05}$
	Peak lat	169.00 (28.41)	164.29 (35.12)	$U = 193.00, Z = -0.08, p = 0.94$
M2	Peak amp	1.59 (0.78)	2.47 (1.0)	$t = -3.16, df = 40, p = \mathbf{0.003}$
	Mean amp	0.65 (0.61)	1.39 (0.82)	$U = 78.00, Z = -3.15, p = \mathbf{0.002}$
	Peak lat	170.36 (38.78)	166.71 (36.64)	$U = 187.00, Z = -0.24, p = 0.81$

Significant values are represented in bold. Note: amp = amplitude (μV); lat = latency (ms).

Amnesic and non-amnesic subtypes within the MCI group did not differ significantly on any of the neurophysiological variables ($df = 26$; $p = > 0.05$ for all comparisons); therefore correlations between the neurophysiological, demographic, symptom and neuropsychological variables were analysed for the pooled MCI sample.

Additionally, in order to clarify the potential effect of psychotropic medication use on MMN in this sample, the MMN response was compared for the 14 participants in total taking psychotropic medications and the remainder not taking such medications. There was no difference in MMN mean amplitude between these two sub-groups (Cz, $t(26) = 0.41, p = 0.69$; Fz, $t(26) = 0.03, p = 0.98$; M1, $t(26) = 1.50, p = 0.15$; M2, $t(26) = 0.45, p = 0.66$).

3.4.3. Neuropsychological data

Neuropsychological data are provided in Table 4. As illustrated, MCI participants' scores were significantly poorer on measures of learning (i.e. RAVLT 1-5) and delayed recall (i.e. RAVLT-7) compared to controls. The MCI group also demonstrated significantly poorer semantic fluency and cognitive flexibility.

Table 4.

Mean (SD) scores for neuropsychological variables in MCI and control groups, with corresponding results for between-group test statistics.

Measure	MCI	Control	Between-group differences
Digit Span, age-scaled score	10.33 (3.22)	11.36 (1.95)	$U = 129.50, Z = -1.80, p = 0.07$
RAVLT 1-5, z-score	-0.37 (1.10)	0.32 (0.46)	$t = -2.79, df = 37.76, p = \mathbf{0.008}$
RAVLT 7, z-score	-0.66 (1.18)	0.28 (0.51)	$t = -3.56, df = 38.19, p = \mathbf{0.001}$
COWAT FAS, z-score	-0.16 (1.10)	0.16 (0.86)	$U = 161.00, Z = -0.93, p = 0.35$
COWAT Animals, z-score	-0.36 (1.30)	0.24 (0.68)	$U = 97.00, Z = -2.64, p = \mathbf{0.008}$
TMT-B, z-score	-0.88 (1.70)	0.10 (0.58)	$U = 113.00, Z = -2.22, p = \mathbf{0.03}$

Significant values are represented in bold. Note: RAVLT 1-5 = Rey Auditory Verbal Learning Test, total learning over trials 1-5; RAVLT 7 = Rey Auditory Verbal Learning Test, delayed recall of word list; COWAT FAS = Controlled Oral Word Association Test, total for letter trials over F, A, S; COWAT Animals = Controlled Oral Word Association Test, total for animals trial; TMT-B = Trail Making Test Part B, completion time.

3.4.4. Correlations between neurophysiological and neuropsychological data

Table 5 displays correlations between MMN mean amplitude at the temporal sites (M1 and M2) and the demographic and neuropsychological variables for MCI and control participants (note: results for peak amplitude showed the same overall pattern and therefore have not been shown). As illustrated, there were no significant associations between MMN and

demographic or clinician-rated clinical variables (age, gender, level of education, current depressive symptoms or psychosocial functioning) in either group. However, increased self-reported disability was significantly associated with reduced left temporal MMN amplitude in the MCI group. This relationship is illustrated in a scatterplot, shown in Figure 3.

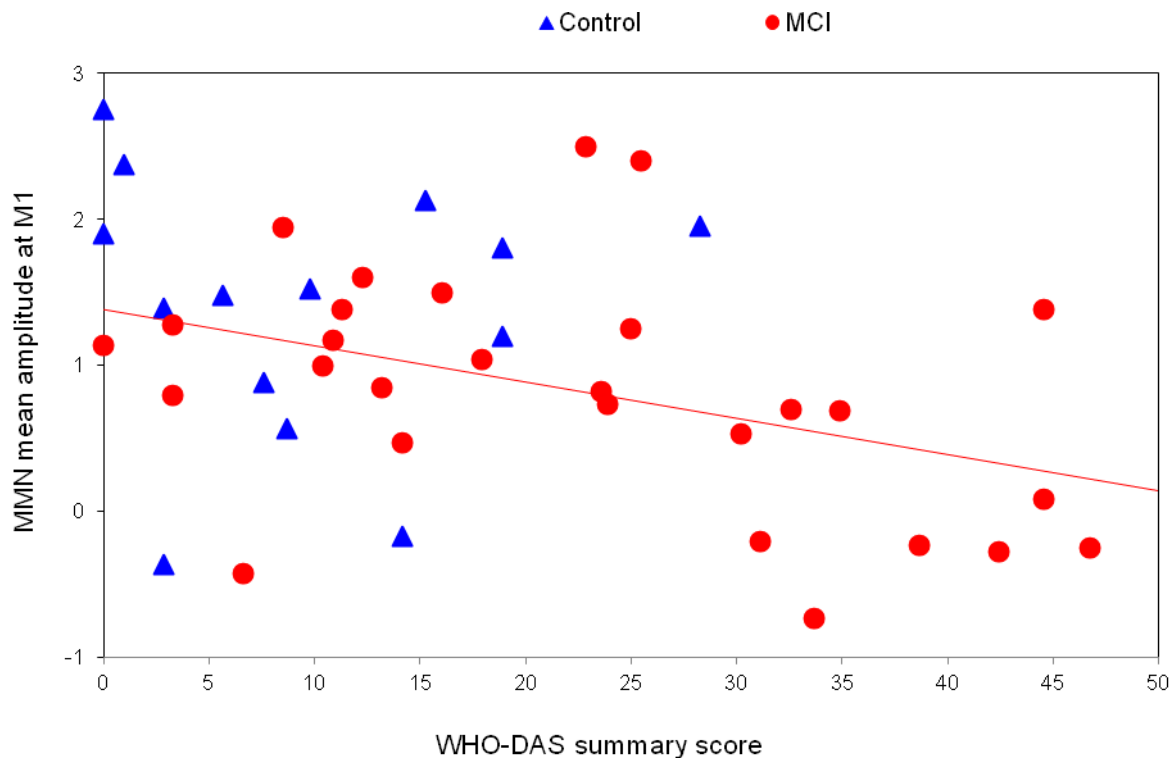


Figure 3.

Scatter plot for mean amplitude at M1 versus self-reported disability (WHO-DAS summary score) for control subjects (N=14) and patients with MCI (N=28). The (red) regression line demonstrates the significant ($p < 0.05$) association between reduced MMN response and greater disability in the MCI group.

In terms of neuropsychological variables, the magnitude of the MMN response was associated with some domains of neuropsychological performance. In the MCI group, reduced mean amplitude at the right temporal site (M2) was significantly associated with poorer performance on verbal memory encoding. This relationship is illustrated in a scatterplot, shown in Figure 4. Note that this data was analysed with inclusion and exclusion

of the outlier evident in Figure 4; however, the results did not change ($n = 27$, $r = 0.455$, $p = 0.017$) and the relationship remained significant using Spearman's rho. As such, the outlier was included in these results. The MCI group did not demonstrate any other significant associations between the magnitude of the temporal MMN response and performance in other cognitive domains. There were no significant relationships between temporal MMN amplitude and cognitive functioning in the control group.

Table 5.

Pearson correlation coefficients and corresponding p-values between MMN mean amplitude at sites M1 and M2 and demographic, symptom and neuropsychological variables for MCI and control groups.

	GROUP							
	MCI				CONTROL			
	M1		M2		M1		M2	
	r	p-value	r	p-value	r	p-value	r	p-value
Age	-0.04	0.844	-0.32	0.100	-0.14	0.642	0.04	0.890
Education	-0.09	0.640	-0.09	0.658	-0.20	0.501	-0.39	0.167
HDRS	0.05	0.817	0.27	0.161	0.14	0.644	0.11	0.715
GAFS	0.30	0.121	0.29	0.141	-0.32	0.280	-0.24	0.430
WHO-DAS	-0.42	0.027^a	-0.30	0.121	-0.04	0.902	-0.03	0.919
Digit Span	0.08	0.684	0.10	0.608	-0.02	0.940	0.47	0.091
RAVLT 1-5	0.23	0.236	0.50	0.007^a	0.14	0.646	0.16	0.593
RAVLT 7	0.25	0.204	0.37	0.065	-0.03	0.920	-0.17	0.551
COWAT FAS	0.15	0.453	0.27	0.166	0.11	0.722	0.37	0.192
COWAT Animals	0.01	0.968	0.14	0.494	-0.36	0.205	-0.11	0.711
TMT-B	0.29	0.142	0.32	0.099	0.10	0.748	0.23	0.420

Significant values are represented in bold. Note: HDRS = Hamilton Depression Rating Scale, 17-item; GAFS = Global Assessment of Functioning Scale; WHO-DAS = World Health Organization Disability Assessment Schedule, summary score; RAVLT = Rey Auditory Verbal Learning Test; COWAT = Controlled Oral Word Association Test, TMT-B = Trail Making Test Part B. Note: ^a denotes relationship remained significant using Spearman's rho.

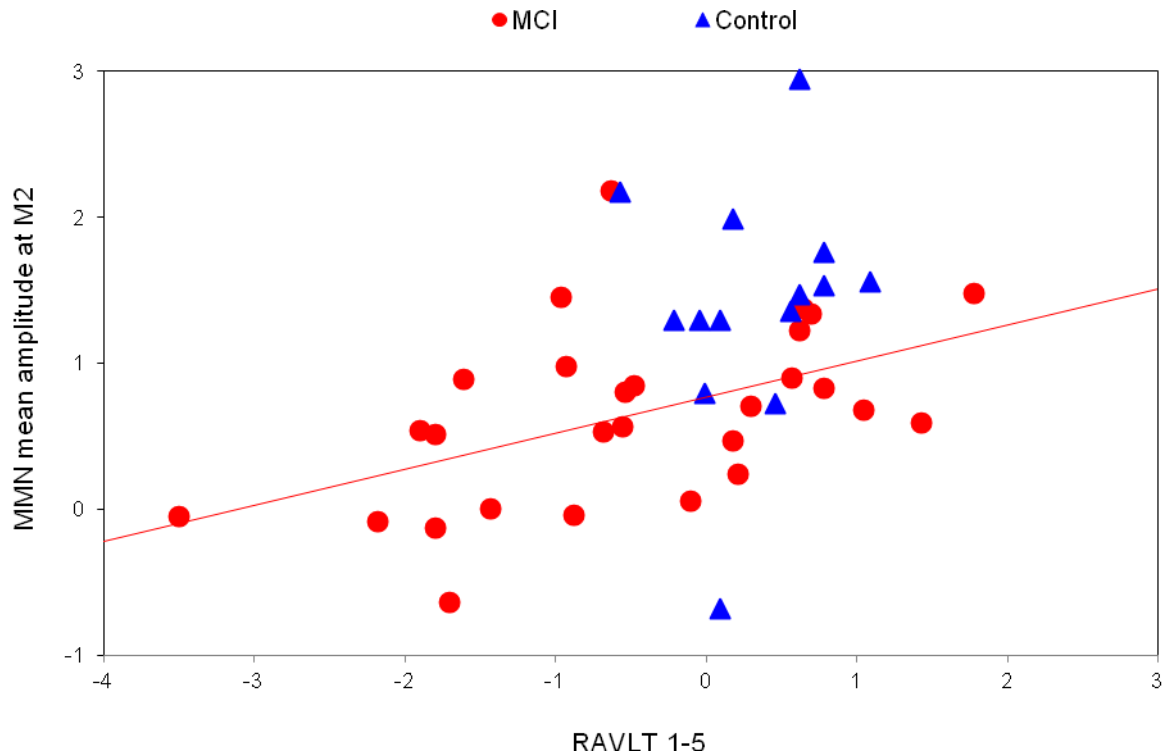


Figure 4.

Scatter plot for mean amplitude at M2 versus verbal learning (z score for summed trials 1 to 5 on the Rey Auditory Verbal Learning Test; RAVLT 1-5) for control subjects (N=14) and patients with MCI (N=28). The (red) regression line demonstrates the significant ($p < 0.01$) association between reduced MMN response and poorer verbal learning in the MCI group.

3.5. Discussion

This study is the largest known study to examine MMN in MCI patients. Results show that the MMN response in MCI is significantly reduced in the temporal region compared to healthy cognitively-intact older adults. This finding is consistent with our hypothesis that MCI is associated with inefficiency of information processing at an early, pre-attentive stage, and we are not aware of any other study reporting that MMN is a marker of these subtle neurophysiological changes. Importantly, these findings have functional significance for the MCI group: the right temporal MMN decrement was significantly associated with poorer

performance on a task of verbal learning, and the left temporal MMN decrement was significantly associated with increased self-rated disability. These findings further suggest that the attenuation of early information processing mechanisms may underpin aspects of higher-order cognitive and psychosocial functioning in MCI. As such, MMN may be a viable biomarker of this transitory stage between healthy ageing and dementia, thus representing a practical, time-efficient and non-invasive tool for early identification of 'at risk' individuals. Given its cognitive implications, MMN may also have utility as an outcome measure of individually-tailored cognitive interventions (e.g. cognitive training programs). This study has extended the limited understanding of MMN in MCI through its increased sample size, direct comparison with healthy elderly controls and investigation of the link with higher-order cognitive functions.

Interestingly, only the magnitude, but not the latency of the MMN response was reduced in this MCI group. This is not an uncommon finding amongst studies investigating MMN in AD, whereby the difference between AD and normal ageing often appears to be specific to amplitude and not latency (see reviews by Pekkonen, 2000; Vecchio & Maatta, 2011). Based on such evidence, it would appear that prolonged MMN latency is a more general, age-related finding (Pekkonen, 2000) rather than an additive effect of cognitive decline.

The association between reduced temporal MMN response and increased self-rated disability is consistent with findings in schizophrenia and psychosis, which have indicated a similar relationship between reduced MMN response and poor psychosocial functioning (Hermens, et al., 2010; Kaur, et al., 2011; Light & Braff, 2005). This association further suggests that MMN has utility as a marker of the subjective difficulties reported by individuals with MCI, and that it indexes fundamental processes that impact upon daily functioning.

The relationship between reduced temporal MMN response and poorer verbal learning in the MCI group is consistent with results reported by Kisley and colleagues (2005), who also demonstrated a positive association between MMN amplitude and the RAVLT total learning score (i.e. reduced MMN amplitude in individuals with poorer verbal learning) in healthy older adults; however the association was seen at the frontal midline site (Fz), which was the only electrode considered in their correlation analysis. As suggested by the authors, information acquisition or ‘encoding’ does involve the prefrontal cortex, thereby explaining the association. However, the relationship between temporal MMN and learning reported in the present study is also consistent with the anatomical basis of learning and memory processes, which are primarily subserved by structures within the temporal lobes. Neuroimaging activation studies (i.e. positron emission tomography and functional magnetic resonance imaging) have reported an association between performance on learning tasks (including the RAVLT) and both medial and lateral temporal lobe activation, with additional involvement of prefrontal regions acting within a fronto-temporal ‘memory consolidation’ network (Desgranges, Baron, & Eustache, 1998; Kopelman, Stevens, Foli, & Grasby, 1998). Furthermore, other neuroimaging studies have also demonstrated a reduction in temporal lobe activation during encoding in MCI versus healthy controls (e.g. Johnson et al., 2006; Machulda et al., 2009).

Another intriguing finding of the present study is the laterality of the relationship between reduced right temporal MMN and poorer verbal learning. This finding is consistent with the lateralised temporal MMN response reported by Borghetti et al. (2006). It has been shown that the MMN to non-linguistic (i.e. tonal) sound changes can be elicited more strongly in the right hemisphere compared to the left, which is more responsive to language-based (i.e. phonemes, syllables and words) changes (see Kujala, Tervaniemi, & Schroger, 2007). Since the present study used a tonal paradigm, it may follow that the resultant MMN

was stronger in the right hemisphere, and therefore robust enough at that site to demonstrate a relationship with impaired performance on the higher-level learning task, which recruits temporal circuitry (as explained above). Ultimately, replication of these findings within other MCI samples will help to clarify patterns such as laterality.

Regarding the significant reduction in MMN in MCI relative to controls, as suggested by Naatanen et al. (2011), it is also possible that deficient auditory discrimination (as indexed by reduced MMN) might indicate a more general functional deficiency. This functional deficiency may emerge as cognitive impairment and/or reduced psychosocial functioning, as seen in many neuropsychiatric groups with reduced MMN including the present MCI sample. It is possible that this phenomenon of general functional deficiency is related to glutamatergic dysfunction. Reduced MMN amplitude has previously been linked to pharmacological deactivation of N-methyl-D-aspartate (NMDA) receptors which usually bind to the excitatory neurotransmitter, glutamate (Javitt, Steinschneider, Schroeder, & Arezzo, 1996; Naatanen, et al., 2011; Umbricht et al., 2000). This system plays an important role in learning, memory and attention (Javitt, et al., 1996; Malhotra et al., 1996) and has been implicated in the pathogenesis of cognitive impairment in ageing, MCI and AD (Gong, Lippa, Zhu, Lin, & Rosso, 2009; Muller, Scheuer, & Stoll, 1994). MMN is therefore thought to be a marker of post-synaptic glutamatergic activity and thus a reduced response may reflect a reduction in glutamatergic/excitatory output.

Contrary to our hypothesis, the aMCI and naMCI subgroups in the present study did not differ in their MMN response. The MCI literature has more recently focused on the varying trajectories of amnesic versus non-amnesic subtypes; aMCI is generally seen as a possible precursor to Alzheimer's disease. naMCI was originally proposed to represent an antecedent phase of other dementia types (e.g. frontotemporal dementia, dementia with Lewy Bodies and vascular dementia) (Petersen, et al., 2009), although recent data has shown that a

high proportion of those with naMCI may also progress to AD (Duara et al., 2011; Fischer et al., 2007). Thus, this data may reflect a lack of differences in underlying neurobiological changes between the subtypes. Alternatively, the underlying neurophysiological changes underpinning pre-attentive processes may be a non-specific marker of neurobiological changes in fronto-temporal networks rather than being reflective of AD pathology specifically. Longitudinal analysis of this sample and further comparison of the MMN response in larger amnesic and non-amnesic subgroups and between individuals reporting recent onset versus longstanding cognitive difficulties may help to delineate the aetiological factors contributing to altered MMN in MCI.

This study is not without limitations. Although this is the largest study of MMN in MCI, replication of these results in larger samples (including larger control groups) is now warranted. While there were no MMN differences between the naMCI and aMCI groups, a larger more homogenous sample comprising only those with aMCI may yield different findings. Furthermore, several participants within the MCI sample were taking antidepressant medications and some were also taking adjunctive mood stabilisers and antipsychotics. While there is strong evidence that antipsychotics do not affect the MMN response (Michie, 2001), less is known about the effect of mood stabilisers and antidepressants. However, our results indicate that there was no difference in MMN response for those participants taking psychotropic medications. Furthermore, recent data suggests that MMN is not modulated by either the serotonergic or dopaminergic system (Leung et al., 2010). Rather, as mentioned, MMN is modulated primarily by the glutamatergic system on which these medications have relatively little effect. Thus, it is unlikely that the observed effect in this study is due to psychotropic medication use. Ultimately, follow-up of this sample as well as direct comparison to an AD group will help to clarify whether these pre-attentive changes to information processing in MCI represent a transitional phase between

normal ageing and dementia, and will determine the true predictive validity of MMN as a biomarker for cognitive decline.

Despite these limitations, this study has presented evidence that fundamental, pre-attentive information processing is disrupted in MCI, and most importantly, that this disruption is associated with higher-level cognitive impairment. MMN may be a useful biomarker of subtle, early neurophysiological changes underlying neuropsychological deficits in MCI, and could signify general functional deficiency in this group. Ongoing clarification of the neurobiological changes associated with MCI will ultimately assist in improved early detection and targeted prevention of conversion to dementia in these 'at risk' older adults.

Section 3.6. Addendum: Additional considerations following publication

With the progression of this research, it has become clear that some clarification or further exploration is required in relation to aspects of the sample and the results.

3.6.1. Diabetes

It is noted that four participants reported a history of diabetes (all of whom had noninsulin-dependent diabetes mellitus or Type 2 diabetes).

3.6.2. Use of ‘Digit Span’ subtest for measurement of working memory

It is noted that there is some controversy within the field regarding the use of the Digit Span total score as a measure of working memory. It is widely accepted that Digits Forward is a measure of immediate auditory attention span whilst Digits Backward is a measure of the capacity to manipulate information in mind. However, it has also been proposed (based on Baddeley’s (1974) model of working memory) that Digits Forward represents the phonological loop component that feeds into the central executive system, and therefore it is also relevant in measuring working memory (Hodges, 2007). In the current study, the difference between the Digits Forward and Digits Backward maximum span scores was considered for each participant and any participant with a clinically significant difference score (according to WAIS-III normative data) was excluded from the analysis. As there were no significant outcomes relating to working memory (Digit Span) in this study, this level of detail was not provided within the chapter for the sake of brevity.

3.6.3. Measurement of cognitive flexibility

In using the *Trail Making Test* Part B as a measure of cognitive flexibility, it is acknowledged that many clinicians/researchers also calculate a derived score which takes into account the unique contribution of cognitive flexibility over and above the contribution of processing speed and perceptual tracking. This may involve calculation of a ratio score (i.e. TMT B / TMT A) or a difference score (i.e. TMT B – TMT A). These derived scores are therefore thought to represent a more ‘pure’ measure of cognitive flexibility (Hester et al., 2005). As such, the omission of a derived score from this study could be considered a potential limitation and it is recommended that future research incorporate these scores when using *Trail Making Test* Part B as a measure of cognitive flexibility.

3.6.4. Visual inspection of data for normality

As stated in section 3.3.5 above (“Statistical analyses”), histograms of all variables were inspected visually for skewness or kurtosis. It is noted that an absolute z score value of > 1.96 (where $\alpha = 0.05$) was utilised as a cut-off score in determining skewness and kurtosis.

3.6.5. Statistical power

Although this study is the largest known investigation of MMN in MCI, it is acknowledged that the small sample size may have been limiting with respect to statistical power. Therefore, there may have been insufficient statistical power to detect between-group differences or relationships between neurophysiological and neuropsychological or demographic data. As stated above, replication and extension of these results in larger samples (including larger control groups) is now warranted.

CHAPTER FOUR:

Reduced temporal mismatch negativity in late-life depression: An event-related potential index of cognitive deficit and functional disability?

This paper has been published as:

Naismith, S. L., Mowszowski, L., Ward, P. B., Diamond, K., Paradise, M., Kaur, M., et al. (2012). Reduced temporal mismatch negativity in late-life depression: An event-related potential index of cognitive deficit and functional disability? *Journal of Affective Disorders*, 138, 71-78. doi: 10.1016/j.jad.2011.12.028

The published article is included in Appendix 4.

4.1. Candidate's contribution to the present paper

In order to submit the findings pertaining to two distinct populations (MCI and LLD) for publication at the same time, the candidate's adjunct supervisor took on the role of first author for this paper while the candidate focused on preparing the manuscript for the paper already presented in Chapter Three. Despite appearing as second author, the candidate has included the present paper as an integral component of this thesis, as the findings comprise part of the justification for the final study and contribute to the formulation of subsequent hypotheses. Furthermore, these findings were a direct result of the candidate's contribution to the research trial, as the candidate was solely responsible for neurophysiological data collection and preparation. The candidate also made a substantial contribution to preparation of the manuscript: specifically, she contributed significantly to neuropsychological data collection, statistical analyses and data interpretation, preparation of figures, formulation and editing of content, and preparation of the final manuscript documents for submission.

4.2. Abstract

Background: Depression in older people has been consistently linked with a variety of neurobiological brain changes. One measure of preattentive auditory processing, the mismatch negativity (MMN), has not been previously examined in late-life depression. This study examined MMN elicited by duration deviant stimuli in older people with lifetime depression, and explored its relationship with neuropsychological functioning and disability.

Methods: Twenty-two older health-seeking patients (mean age = 65.2 years) with lifetime major depressive disorder and twelve age and sex-matched control participants (mean age = 64.6 years) completed detailed clinical and neuropsychological assessments and the WHO-DAS as a measure of disability. MMN amplitudes were elicited using a two-tone passive auditory oddball paradigm and measured at frontal (Fz), central (Cz) and temporal (left and right mastoid: M1 and M2, respectively) sites.

Results: Patients with depression demonstrated reduced mean MMN amplitude at temporal (M1, $t = 3.1$, $p < 0.01$; M2, $t = 3.8$, $p < 0.01$), but not fronto-central sites. Reduced temporal MMN amplitudes did not relate to depressive symptom severity, but were associated with reduced semantic fluency and greater self-rated functional disability.

Limitations: The contribution of depressive symptom ‘state’ and medications on MMN need to be considered.

Conclusions: Reduced mean amplitudes of mastoid MMN in older patients with lifetime depression may reflect underlying brain changes. This preattentive marker relates to neuropsychological probes of frontotemporal circuits, and importantly, is associated with disability. Longitudinal analysis of MMN in this group will determine its predictive utility as a biomarker for ongoing cognitive decline and illness chronicity.

4.3. Introduction

Depression in older people is associated with a number of structural and functional brain changes particularly in frontosubcortical and frontotemporal circuitry (e.g., Ballmaier et al., 2004; Hickie et al., 2005; Hickie et al., 2007; Naismith et al., 2010; Taylor et al., 2004). Cognitive deficits are also common and typically occur in the domains of processing speed and executive functions as well as in learning and memory (Herrmann, Goodwin, & Ebmeier, 2007; Kohler, Thomas, Barnett, & O'Brien, 2010; Naismith, Hickie, Ward, Scott, & Little, 2006; Sheline et al., 2006). Up to 54% of patients with late-life depression (LLD) may actually meet criteria for mild cognitive impairment (MCI) (Adler, Chwalek, & Jajcevic, 2004; Lee, Potter, Wagner, Welsh-Bohmer, & Steffens, 2007), a syndrome that is considered to be a prodromal or 'at risk' state for dementia. While it was previously thought that neuropsychological deficits in LLD would abate with adequate treatment, this notion is no longer widely accepted. Instead, it appears that at least some degree of cognitive dysfunction may persist even following complete symptom resolution (Devanand et al., 2003). Regardless of the underlying aetiological mechanisms, it is now recognised that depression is a risk factor for dementia (Ritchie et al., 2010; Steffens et al., 2007).

Investigating the information processing deficits that occur in older people with depression could be probed by recording event-related potentials (ERPs). Of significance, ERPs are able to probe specific regions and circuits that are implicated in brain diseases and may provide a critical insight into underlying brain dysfunction. ERPs are discrete responses, which are extracted from the ongoing electroencephalogram (EEG) and time-locked to specific cognitive events. One particular ERP component, the mismatch negativity (MMN) has been postulated to be an objective index of cognitive decline across neuropsychiatric diseases (Naatanen et al., 2011). The MMN represents an automatic response to deviant stimuli presented among an array of standard stimuli and reflects the brain's ability to extract

relevant information from an irrelevant background (Hermens et al., 2010; Kaur et al., 2011; Naatanen, et al., 2011). MMN is usually elicited using auditory stimuli, and is recorded without directing attention to such stimuli, whilst patients watch a video or perform a simple visual distraction task. This ‘pre-attentive’ element can be considered an advantage (Hermens, et al., 2010; Michie, 2001), since patients with depression may exert suboptimal effort (Naismith, et al., 2006), thus the minimal attention required reduces this potential confound. MMN is elicited after the presentation of a deviant tone that differs (for example, in pitch, duration or loudness) from a series of frequent standard tones. The negative deflection of the MMN is thought to reflect a neural mismatch between features of the current versus preceding stimuli, stored in short-term memory (Naatanen, 1990). While the MMN amplitude tends to be greatest at fronto-central sites, data suggest that the frontal generator depends on the temporal MMN generator (Giard, Lavikainen, Reinikainen, Perrin, & et al., 1995; Giard, Perrin, Pernier, & Bouchet, 1990). It has been postulated that frontal and temporal lobe sources may be associated with involuntary attentional switching and pre-perceptual change detection respectively (see review by Naatanen, Paavilainen, Rinne, & Alho, 2007). Accordingly, neuropsychological functions have been associated with each of these mechanisms including set-shifting with frontal sites and verbal memory processes within temporal sites (Oades et al., 2006).

The MMN response has been most extensively investigated in schizophrenia (Shelley et al., 1991), with meta-analyses showing MMN to be a robust “trait” marker of this disease with moderate effect size reductions, in comparison to control groups (Michie et al., 2000; Umbricht & Krljes, 2005). It has thus been suggested that MMN deficits may represent the underlying basis for attentional dysfunction in schizophrenia (Umbricht & Krljes, 2005). MMN deficits have also been shown to correlate with global functioning (Light & Braff, 2005), symptom severity (Baldeweg, Klugman, Gruzelier, & Hirsch, 2004; Naatanen &

Kahkonen, 2009), cognitive dysfunction (Baldeweg, et al., 2004) and grey matter volume reductions in frontotemporal brain regions (Rasser et al., 2011). By comparison, in depressive disorders, there is a relative dearth of MMN studies. Of those that have examined this ERP component, all were conducted in younger samples, and employed various methodologies resulting in inconsistent findings. Specifically, increased MMN amplitude was reported in two studies that were conducted in 13 middle-aged drug naïve patients with major depression (Kahkonen et al., 2007) and 22 younger patients with treatment-resistant depression (He et al., 2010). Both of these studies used frequency deviants and only reported fronto-central midline MMN amplitudes. By contrast, decreased temporal MMN has been reported in two studies. One of these studies utilised magnetoencephalography in 14 patients with mild major depression (Takei et al., 2009), while the other employed a visual MMN paradigm (Chang, Xu, Shi, Zhang, & Zhao, 2010); though notably, the latter study utilised an active (i.e. mentally count stimuli), rather than a passive cognitive paradigm. Two other studies reported no significant MMN amplitude differences between patients and controls: one utilised frequency and duration deviants in middle-aged adults (mean age of 43 years) with major depression (Umbricht et al., 2003); however, they found a significant difference in MMN topography with larger MMN amplitudes at the mastoid electrodes in the patient group. The other study was conducted in children (Lepisto et al., 2004), and was based on a phoneme-mismatch paradigm. No known studies have examined MMN in older patients with depressive disorders. Nor have they examined MMN with reference to detailed measures of neuropsychological performance or disability. Additionally, many studies have been unable to measure the temporal MMN, a region that is relevant when considering the memory deficits inherent to major depression (Hickie, et al., 2005).

If the MMN response is altered in older people with depression, this finding would have important implications for neurobiological models of illness, particularly if it exists as a

‘trait’ marker. Symptom measures, and to a lesser extent, cognitive measures may fluctuate depending on depressive state and with treatment. Thus, MMN may provide a more robust ‘trait’ marker that has predictive utility for cognitive decline. In this study, we therefore aim to examine MMN in older patients with a lifetime history of major depression. We also seek to investigate how MMN may relate to neuropsychological functioning in key areas that are known to be impaired and which may persist despite symptom resolution.

4.4. Methods

4.4.1. Sample

Twenty-two health-seeking patients meeting criteria for lifetime major depressive disorder were recruited from specialist psychiatry clinics at the Brain & Mind Research Institute, Sydney. Participants were required to: be over the age of 50 years; speak English fluently; to have had a major depressive episode in the last five years; and, to be stabilised on medication. *Exclusion criteria* were: history of stroke; neurological disorder; head injury with loss of consciousness \geq 30-minutes; medical condition known to affect cognition (e.g. cancer); psychiatric illness other than affective disorder; *Mini Mental State Examination Score* (MMSE) < 24 (Folstein, Folstein, & McHugh, 1975) and/or diagnosis of dementia. Twelve age and sex-matched control participants were recruited from the community via local advertisements and were screened according to the above exclusion criteria as well as for psychiatric disorders. This research was approved by the Human Research Ethics Committee of the University of Sydney. Written informed consent was obtained from all participants.

4.4.2. Measures

4.4.2.1. Psychiatric: An Old Age Psychiatrist performed a structured clinical assessment to derive clinical history including psychiatric history, age of depression onset,

and substance and medication use. Medical burden was recorded using the severity index of the *Cumulative Illness Rating Scale, Geriatric Version* (Miller & Towers, 1991). The affective component of the *Structured Clinical Interview for DSM-IV-R* (First, Spitzer, Gibson, & Williams, 1996) was performed to confirm lifetime and current depression diagnosis. Depression severity was rated using the *Hamilton Depression Rating Scale* (HDRS) (Hamilton, 1960), where the symptom severity ranged from euthymic to mild (range 0-14). The mean age of depression onset was 37.0 years (sd = 16.9, range 17 to 63 years), with the average number of depressive episodes being 3.1 (sd = 2.9, range 1 to 10). Only one patient had a history of ECT treatment, and this was conducted when the patient was 17 years old. Only three patients met current DSM-IV criteria for major depression. A detailed medication history was taken: Fifteen participants were taking antidepressant medications, including one taking tricyclics, seven taking SSRIs, six taking SNRIs and one taking a NASSA. Three patients took mood stabilisers and three used a low dose atypical antipsychotic.

4.4.2.2. Neuropsychological: For descriptive purposes, premorbid intellectual ability was estimated using the Wechsler Test of Adult Reading (WTAR; Wechsler, 2001) and global cognition was measured using the MMSE. Also for descriptive purposes, we used Petersen's criteria (Petersen et al., 2001; Petersen & Morris, 2005) to document those having either amnestic or non-amnestic forms of mild cognitive impairment. That is, decrements of at least 1.5 standard deviations in comparison to normative data on a memory task (amnestic) or within a non-memory domain (non-amnestic). Furthermore, individuals could meet these criteria for mild cognitive impairment based on a deficit within a single cognitive domain, or multiple cognitive domains. Based on our prior research in LLD (Naismith et al., 2003; Naismith, et al., 2006), we specifically examined the following domains in relation to MMN:

- a) Visuomotor speed: The *Trailmaking Test* (Reitan, 1979) Part A was used as a measure of visuomotor speed (*TMT-A*, seconds). Z-scores were computed from age-adjusted normative data (see Tombaugh et al, in Spreen & Strauss, 1998).
- b) Working memory: The total digit span score from the Wechsler Adult Intelligence Scale – III *Digit Span* (Wechsler, 1997) subtest was used as a measure of auditory working memory, and scores were scored according to normative data (age-scaled score).
- c) Verbal memory: The *Rey Auditory Verbal Learning Test* (RAVLT) (Spreen & Strauss, 1998) was administered (n = 30) to measure unstructured verbal learning. Total learning over the five trials was examined (*RAVLT1-5*, maximum score = 75) as well as delayed recall raw score (*RAVLT-7*, maximum = 15). Age and education z-scores were calculated from Australian-specific normative data (Senior, 1999).
- d) Language: Language generativity was assessed using *phonemic* (letters F,A,S) and *semantic* (animal names, total words in 1-minute) verbal fluency. Age and education adjusted normative data were used (see Tombaugh et al, in Spreen & Strauss, 1998).
- e) Executive functioning: This encompassed the *Trailmaking Test* Part B (*TMT-B*, seconds) (Reitan, 1979) to assess mental flexibility. Z-scores were computed from age-adjusted normative data (see Tombaugh et al, in Spreen & Strauss, 1998).

4.4.2.3. *Disability*: The 36-item self-administered World Health Organization Disability Assessment Schedule (WHO-DAS) (World Health Organisation, 1999) was used to assess disability. Domains of functioning included understanding and communicating, getting along with others, participation in society, self-care, getting around, and life activities. A standardized summary score was also calculated to reflect a total disability score. Higher scores indicate greater disability.

4.4.2.4. *Neurophysiological:* As described previously (Hermens, et al., 2010; Kaur, et al., 2011), after being fitted with a cap for EEG recording, participants were seated comfortably in a light and sound attenuated room, set at an ambient temperature. The entire duration of the neurophysiological test (including set-up time) was approximately one hour. Participants were presented, via headphones, with 2,500 binaural pure tones (1,000 Hz, 75 dB SPL, 10 ms rise/fall) at a 500 ms stimulus onset asynchrony; following a pseudo-random sequence of 2,300 (92%) 50 ms standard (Hermens, et al., 2010) tones and 200 (8%) 100 ms deviant (long) tones. Tones were presented while participants watched a silent video of a comedy movie (and were asked to report back the gist of the movie at the end of the task). A 64-channel Quik-cap (Neuroscan) acquired EEG data from sites according to the standard 10-10 International system (including mastoids). Data was referenced to a nose electrode. Vertical and horizontal electro-oculogram (EOG) was monitored for eye-blink artefact; correction was based on established methods (Semlitsch, Anderer, Schuster, & Presslich, 1986). Scalp and EOG potentials were amplified and digitised continuously by a system (SynAmps2, SCAN 4.3.1 software) having a frequency response from .01 to 100 Hz (and a gain of 20,000). The digitisation rate for the ERP component was 200 Hz per channel. Segments of the EEG record contaminated by other artefacts ($\pm 100 \mu V$) were rejected. Mismatch difference waveforms were obtained by subtracting ERP waveforms elicited by the deviant stimuli from those of the standard stimuli. The mean amplitude, peak amplitude and peak latency for MMN was determined according to a 100-250 msec epoch. This epoch was selected according to previous MMN studies in older adult samples (Cooper, Todd, McGill, & Michie, 2006; Gaeta, Friedman, Ritter, & Cheng, 1998; Pekkonen, Jousmaki, Partanen, & Karhu, 1993). MMN variables were processed at four sites: frontal (Fz), central (Cz) and temporal (left and right mastoid: M1 and M2, respectively).

4.4.3. Statistical analysis

All analyses were conducted on SPSS for Macintosh, Rel. 18.0.0 Chicago: SPSS Inc. Pearson correlation coefficients were used for all correlations unless otherwise stated. Partial correlations were used to covary for age. Between group analyses utilised independent samples t-tests with assumption of unequal variance, where warranted. All analyses were two-tailed and employed an alpha level of 0.05.

4.5. Results

Demographic, psychiatric, and neuropsychological data are included in Table 6. This data shows that there were no differences in age, sex, medical burden or premorbid intellectual functioning between patients and controls. While largely euthymic, patients continued to have higher rates of depressive symptoms than controls, poorer social and occupational functioning and greater disability. They also had decrements in the areas of memory and mental flexibility in comparison to controls. Using formal MCI criteria, 82% (18/22) of the sample met criteria for MCI, indicating a high degree of residual cognitive dysfunction. Of these, seven patients had amnesic MCI and 12 showed deficits in multiple domains of functioning. Control participants did not manifest cognitive deficits.

Figure 5a and 5b illustrate the MMN waveforms of the patient and control samples and Table 7 displays descriptive data for mean MMN amplitude and peak latency. Since mean amplitude findings were comparable to those obtained using peak amplitude, we report only the former. Significant differences in mean MMN amplitude were evident between patients and controls at the left (M1) and right (M2) temporal sites. However, there were no differences between groups in frontal or central sites. Across all sites, there were no differences between patients and controls in terms of peak latency (M1: $F = 0.08$, ns; M2: $F = 1.00$, ns; Fz: $F = 0.00$, ns; Cz: $F = 0.03$, ns).

Table 6:

Demographic, psychiatric and neuropsychological data (mean \pm SD) for control participants and patients with lifetime depression.

	Controls n = 12	Patients n = 22	t-value (df)	p-value
Age, years [‡]	65.2 \pm 4.2	64.6 \pm 8.4	0.29 (32)	0.777
Sex, male:female [#]	4:8	6:16	0.1 (1)	0.711
Cumulative Illness Rating Scale	1.4 \pm 0.6	1.4 \pm 0.6	-0.2 (32)	0.844
Hamilton Depression Rating Scale [‡]	1.1 \pm 2.0	6.5 \pm 3.9	-5.2 (31)	0.003
SOFAS	81.8 \pm 10.1	67.1 \pm 13.3	3.2 (31)	0.000
Alcohol use, units per week [‡]	3.4 \pm 2.2	6.8 \pm 10.8	-1.5 (32)	0.142
WHO-DAS, summary score	10.3 \pm 8.9	27.9 \pm 13.8	4.0 (32)	0.000
Education, years	13.1 \pm 2.9	13.8 \pm 3.8	-0.6 (32)	0.552
Mini-Mental State Examination	29.1 \pm 1.1	28.2 \pm 1.4	1.8 (32)	0.078
WTAR, predicted IQ	106.8 \pm 7.3	104.8 \pm 9.3	0.6 (32)	0.529
Trailmaking, Part A, z-score	0.3 \pm 0.7	-0.1 \pm 1.1	1.1 (32)	0.280
Digit span, age-scaled score	11.7 \pm 1.8	10.1 \pm 2.7	0.8 (32)	0.399
RAVLT 1-5, z-score [‡]	0.3 \pm 0.5	-0.6 \pm 1.1	3.3 (32)	0.002
RAVLT-7, z-score	0.2 \pm 0.5	-0.7 \pm 0.9	3.9 (32)	0.000
Phonemic fluency, z-score	0.2 \pm 0.9	-0.1 \pm 0.8	1.2 (32)	0.252
Semantic fluency, z-score [‡]	0.1 \pm 0.5	-0.1 \pm 1.2	0.5 (32)	0.636
Trailmaking, Part B, z-score [‡]	0.1 \pm 0.6	-0.6 \pm 1.1	2.4 (32)	0.024

SOFAS, Social and Occupational Functioning Scale; WHO-DAS, World Health Organisation Disability Assessment Scale; WTAR, Wechsler Test of Adult Reading; RAVLT, Rey Auditory Verbal Learning Test. Significant values are represented in bold; All test statistics are students t-test unless otherwise specified; [‡] students t-test with unequal variances assumed; [#]Chi-square.

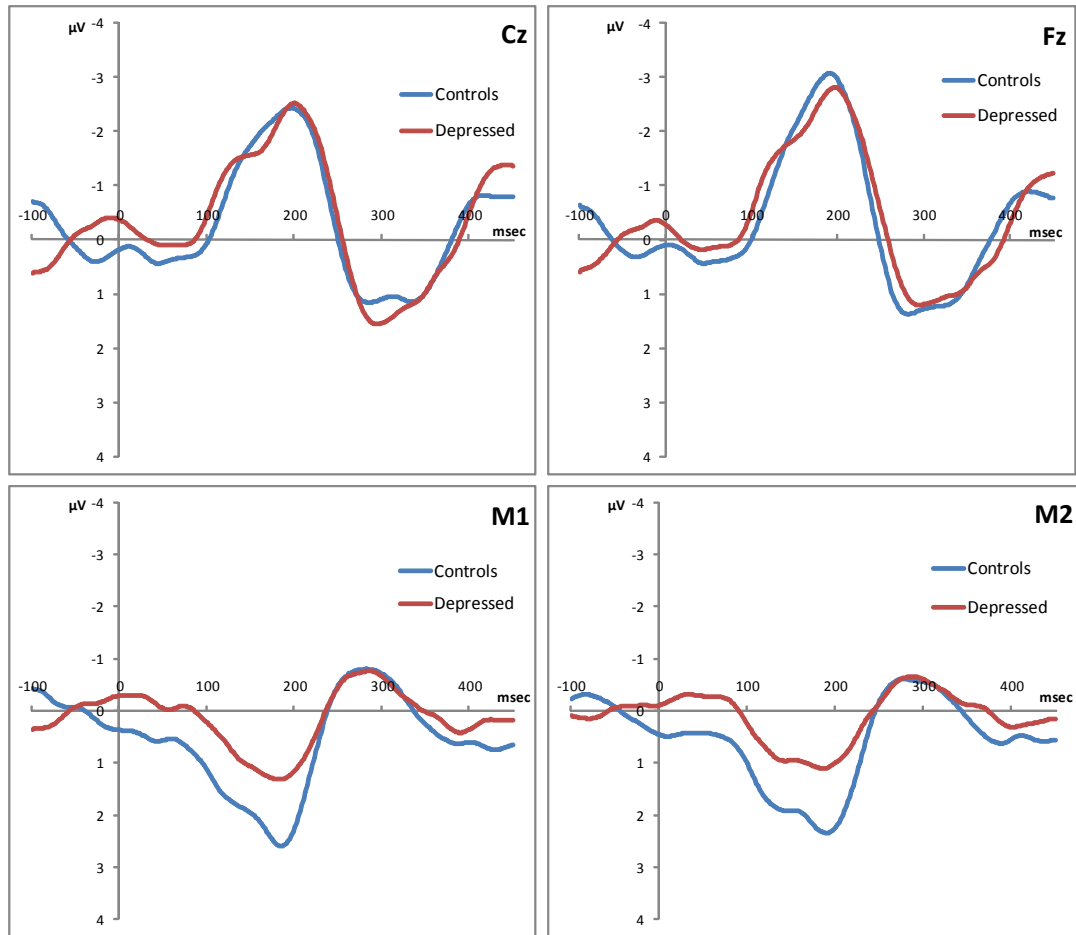


Figure 5a: Grand average event-related potentials for lifetime depression (red; $n = 22$) and control (blue; $n = 12$) groups at (clockwise, from top left) central (Cz), frontal (Fz), right temporal (M2) and left temporal (M1) sites. The lifetime depression group (red) showed reduced MMN (100-250 ms) amplitudes (μV) at both temporal sites (M1, M2) compared to controls (blue). Note: M1 & M2 waveforms are reversed in polarity due to the nose-referenced recording.

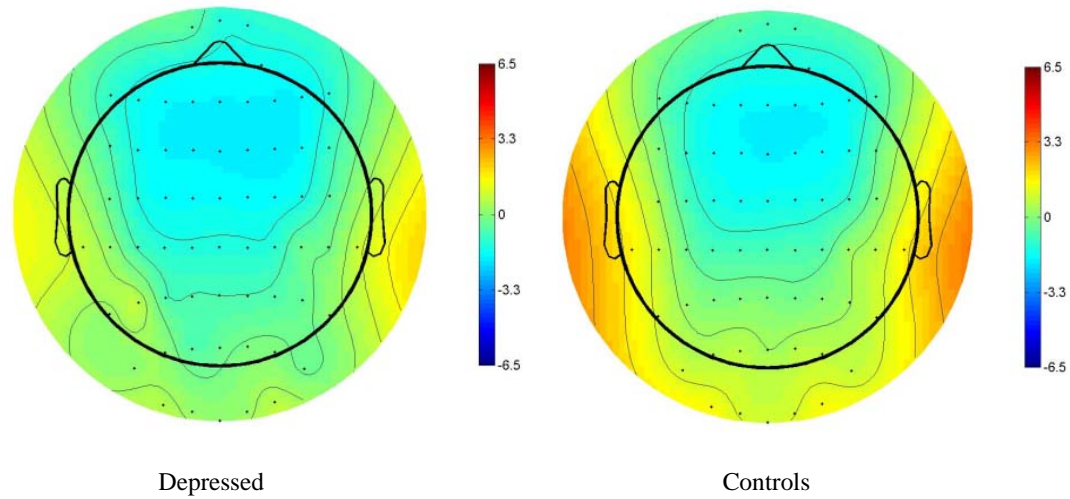


Figure 5b: Head maps depicting the mean amplitudes for MMN recorded across scalp sites for lifetime depressed and control groups. The scale in microvolts (μV) ranges from the greatest negativity at $-6.5 \mu\text{V}$ (darkest blue colour) to the greatest positivity at $6.5 \mu\text{V}$ (darkest red colour).

Table 7:

Mean amplitude and peak latency MMN data (mean \pm SD) for healthy controls and patients with a history of depression.

	Controls n = 12	Patients n = 22	t-value (df)	p-value
Mean amplitude Cz	-1.5 ± 1.7	-1.6 ± 1.7	0.2 (32)	0.842
Mean amplitude Fz	-1.8 ± 2.0	-1.9 ± 1.6	0.1 (32)	0.906
Mean amplitude M1	1.6 ± 0.8	0.8 ± 0.7	3.1 (32)	0.004
Mean amplitude M2	1.6 ± 0.5	0.7 ± 0.7	3.8 (32)	0.000
Peak latency Cz	188.5 ± 25.7	194.6 ± 34.0	-0.5 (32)	0.590
Peak latency Fz	186.2 ± 14.3	185.9 ± 31.6	0.0 (32)	0.979
Peak latency M1	166.2 ± 33.5	169.4 ± 31.6	-0.3 (32)	0.784
Peak latency M2	168.7 ± 34.5	164.5 ± 38.5	0.3 (32)	0.754

Significant values are represented in bold.

4.5.1. Correlations between MMN and clinical characteristics

There was no significant difference between males and females with regard to MMN amplitudes, nor was there any association with age. For the depressed sample, neither left nor right mastoid MMN reductions were associated with depressive symptom severity (M1, $r = -0.19$, ns; M2, $r = -0.04$, ns), number of depressive episodes (M1, $r = -0.19$, ns; M2, $r = 0.12$, ns), age of depression onset (M1, $r = -0.06$, ns; M2, $r = -0.11$, ns), alcohol use (M1, $r = -0.25$, ns; M2, $r = -0.03$, ns) or clinician-rated social and occupational functioning (M1, $r = 0.27$, ns; M2, $r = 0.29$, ns).

4.5.2. Correlations between MMN and neuropsychological functioning and disability

Although age was not associated with MMN, when comparing the association between MMN, cognition and disability, we controlled for age using partial correlations since age is usually related to each of these variables. For control participants, there was no significant association between MMN amplitudes and performance on neuropsychological tests or disability. As shown in Table 8, for patients with depression, reduced right temporal (M2) amplitude was associated with poorer semantic verbal fluency. However, there was no association between MMN mean amplitude at M2 and performance on tests of visuomotor speed, working memory, verbal learning and memory consolidation, phonemic fluency or mental flexibility. There were no significant associations between MMN mean amplitude at M1 and neuropsychological performance. However, as shown in Figure 6, there was a strong relationship between both M1 and M2 mean amplitude and self-rated disability, with lower amplitudes being associated with greater disability (Table 8).

Table 8:

Partial correlations (controlling for age) between temporal MMN data for mean amplitude in patients with lifetime depression (n = 22).

	Mean amplitude			
	M1		M2	
	Partial r	p-value	Partial r	p-value
Disability, WHO-DAS	-0.56	0.008	-0.60	0.004
Trailmaking, Part A, raw score	-.011	0.962	-.009	0.970
Digit span, raw score	.013	0.582	-.032	0.894
RAVLT1-5, raw score	.010	0.967	.129	0.578
RAVLT-7, raw score	.166	0.471	.117	0.614
Phonemic fluency, raw score	.398	0.074	.304	0.304
Semantic fluency, raw score	.407	0.067	.445	0.043
Trailmaking, Part B, raw score	.066	0.777	-.139	0.548

WHO-DAS, World Health Organisation Disability Assessment Scale; WTAR, Wechsler Test of Adult Reading; RAVLT, Rey Auditory Verbal Learning Test. Significant values are represented in bold.

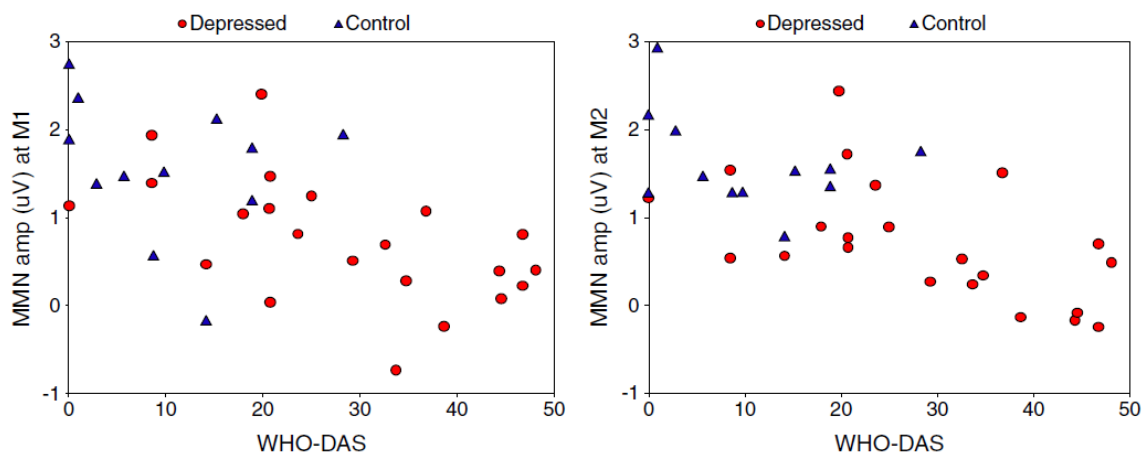


Figure 6: Scatterplot demonstrating the correlation between decreased mean amplitude at M1 and M2 and greater levels of disability for patients with depression (in red) compared to the controls (in blue).

4.6. Discussion

This study demonstrates that older patients with lifetime depression and only mild residual symptoms show significantly reduced MMN at temporal/mastoid electrodes. This result is consistent with prior neurobiological data showing alterations in frontotemporal circuitry in patients with depression (Hickie, et al., 2005). In this sample, the MMN deficit was linked to poorer semantic fluency; a neuropsychological task that is considered to recruit frontotemporal and particularly temporal-lobe neural circuits (Gourovitch et al., 2000; Rascovsky, Salmon, Hansen, Thal, & Galasko, 2007). However, it was not clearly associated with other neuropsychological functions that probe frontotemporal circuits, namely learning and memory. Nor was it related to depressive symptom severity. This data overall suggests that MMN dysfunction may exist as a relatively distinct marker of underlying brain change. Of considerable significance, MMN deficits in this sample were strongly associated with higher levels of disability, suggesting that this biomarker has relevance for daily functioning.

The current finding of normal MMN amplitudes at fronto-central sites is consistent with some (Umbricht, et al., 2003) but not all studies (He, et al., 2010; Kahkonen, et al., 2007) conducted in younger symptomatic samples (Umbricht, et al., 2003). Our finding of decreased temporal MMN is also consistent with studies using magnetoencephalography (Takei, et al., 2009) and visual MMN paradigms (Chang, et al., 2010). However, it is contrary to the findings of Umbricht et al (Umbricht, et al., 2003), who reported *increased* MMN amplitudes at mastoid electrodes. Although the reasons for these discrepancies are unclear, some differences in samples did exist. Notably, our sample was older, less symptomatic and over 80% of our older sample met established criteria (Petersen & Morris, 2005) for the diagnosis of mild cognitive impairment. Indeed, they demonstrated reduced performance on tasks of memory encoding and storage, that typically reflect underlying alterations in fronto-temporal circuitry (Hickie, et al., 2005). Such changes, may, in turn,

render the temporal MMN generators less efficient. It has been postulated that while both systems interact with each other, the temporal MMN generators relate to sensory memory mechanisms, whereby the frontal generators are postulated to have a cognitive role, namely attentional switching (Giard, et al., 1990). Thus, the current findings of decreased temporal (i.e. mastoid) MMN would suggest altered sensory memory mechanisms in older patients with lifetime depression, possibly reflective of underlying changes in temporal regions.

Since MMN is a ‘pre-attentive’ process, these findings suggest that fundamental neurobiological changes do exist even in patients with largely remitted symptoms, and that these deficits do not merely reflect suboptimal effort. Interestingly, however, while reduced MMN in those with depression relates to the ability to retrieve information from semantic memory, these reductions did not directly correlate with other neuropsychological measures that were compromised in this sample. Specifically, MMN deficits did not correlate with performance on tasks of memory encoding or consolidation, or mental flexibility. Collectively, these findings suggest that the MMN deficits observed in this sample occur relatively independently of commonly observed cognitive deficits in older people with depression (Naismith, et al., 2003; Naismith, et al., 2006).

In this study, the magnitude of the MMN response rather than its timing, best differentiated patients with lifetime depression from their healthy peers. It is believed that the MMN is driven by excitatory postsynaptic potentials from apical dendrites (Frodl-Bauch, Bottlender, & Hegerl, 1999) and its amplitude has been linked to the activity of the excitatory neurotransmitter, glutamate. In keeping with this assertion, the acute administration of drugs (including alcohol) that block glutamate’s N-methyl-d-aspartate receptor (NMDAr) has been shown to reduce MMN in humans and animals (Javitt, Steinschneider, Schroeder, & Arezzo, 1996; Umbricht, Koller, Vollenweider, & Schmid, 2002; Umbricht et al., 2000). Therefore

MMN is thought to be a marker of post-synaptic glutamatergic activity and thus a reduced response may reflect a reduction in glutamatergic/excitatory output.

The unique findings of this study highlight the utility of MMN for understanding the neurobiological basis of affective disorders, even in the remitted state. They also indicate the considerable overlap between this marker of subconscious brain activity and phenotypic markers of cognitive functioning and disability. Further studies exploring the relationship between temporal MMN changes and underlying brain changes, such as those observed via neuroimaging, are now required. Furthermore, the relationship between MMN deficits and fundamental neuropharmacological changes would assist in determining future treatment targets. For example, treatments targeting the glutamatergic system, which is increasingly postulated to play a role in depressive disorders, might offer promise in this regard. Indeed, such treatment options would be particularly appealing if the disability associated with cognitive decline and depression could be averted (Naismith, Longley, Scott, & Hickie, 2007).

This study is not without limitations. While the MMN deficits did not appear to relate to depressive symptom severity, the contribution of depressive symptom ‘state’ on MMN cannot be concluded with certainty, thus precluding interpretations that MMN is a ‘trait’ biomarker. Additionally, the majority of this small sample was taking antidepressant medications and some were also taking mood stabilisers and antipsychotics. However, recent data suggests that MMN is not modulated by either the serotonergic or dopaminergic system (Leung et al., 2010), thus it is unlikely that the observed effect in this study is due to psychotropic medication use. Finally, longitudinal analysis of this sample would be helpful in order to determine the predictive utility of MMN as a biomarker of ongoing cognitive decline, symptom relapse or dementia (Naismith et al., 2009).

CHAPTER FIVE:

A Healthy Brain Ageing Cognitive Training program enhances neurophysiological responses in older ‘at risk’ adults: an event-related potential study

This chapter is currently under preparation for submission to *Biological Psychiatry*.

5.1. Abstract

Background: The expanding ageing population and associated predictions of increased dementia incidence have instigated a focus on secondary prevention. This involves early identification of individuals ‘at risk’ of developing dementia and development of intervention strategies targeting the underlying pathophysiology at prodromal stages. Such ‘at risk’ groups include those with mild cognitive impairment, late-life depression and subjective cognitive impairment. Cognitive Training (CT) is an appropriate selective intervention strategy as it improves memory and psychosocial outcomes, possibly by increasing cognitive reserve and/or promoting neuroplasticity. However, limited research has utilised neurobiological outcomes to clarify underlying neuroplastic processes. A neurophysiological event-related potential, Mismatch Negativity (MMN), is a non-invasive measure of pre-attentive information processes underpinning higher-order cognitive/psychosocial outcomes which may provide new insight into the neural mechanisms underlying CT efficacy.

Methods: Twenty-five treatment and fifteen control participants underwent neurophysiological, neuropsychological and medical/psychiatric assessment before and after a multi-faceted seven-week “Healthy Brain Ageing” Cognitive Training program or a ‘treatment-as-usual’ seven-week waitlist period.

Results: The treatment group demonstrated enhanced fronto-central MMN responses following CT compared to decreased responses in the control group ($p < 0.05$). The treatment group also demonstrated improved phonemic verbal fluency ($p < 0.05$) and decreased self-rated memory difficulties ($p < 0.05$) following CT; however, there were no significant correlations between enhanced MMN and cognitive/psychosocial outcomes.

Conclusions: We are not aware of any other study applying the MMN paradigm to CT in health-seeking ‘at risk’ individuals. The enhanced MMN response supports the notion of neuroplasticity and indicates increased efficiency of fundamental, pre-attentive processing in relation to the multi-faceted CT intervention. Limitations include the lack of an active control group and combination of the ‘at risk’ subgroups; further research is warranted to replicate and extend these findings as well as longitudinally investigate the utility of CT in preventing or delaying progression to dementia.

5.2. Introduction

The rapidly expanding ageing population is becoming an internationally recognised dilemma. With such expansion comes the increased risk of emerging neurodegenerative disease, with prevalence rates for Alzheimer's disease (AD) alone doubling every five years after the age of 60 (Lobo et al., 2000; National Institute on Aging, 1999). Worldwide, dementia prevalence is expected to rise to 81 million people in 2040 (Ferri et al., 2005). The healthcare, psychosocial and financial burden associated with dementia are well-documented, with worldwide costs estimated at US\$604 billion dollars in 2010, representing more than 1% of the global gross domestic product (Prince, Bryce, & Ferri, 2011).

In the context of these projections, advances in the understanding of the pathophysiological progression of AD and other dementia syndromes have prompted a re-evaluation of diagnostic criteria (e.g. McKhann, 2011), taking into account earlier stages of these disease processes, as well as investigation of various clinical and experimental treatment paradigms. Since current treatments merely target symptoms in the absence of any known cure, the focus on secondary prevention strategies (see Thal, 2006) has become paramount. This involves early identification of individuals 'at risk' of developing dementia, with a view to developing and implementing intervention strategies which may ultimately be able to reduce dementia incidence by targeting the underlying pathophysiology at a prodromal stage (Mowszowski, Batchelor, & Naismith, 2010; Naismith et al., 2009) (see Chapter Two).

5.2.1. Targeting 'at risk' groups

In terms of possible candidates for secondary prevention, it is clear that some individuals are more likely to progress to dementia syndromes. For example, epidemiological research has demonstrated strong associations between ageing, genotype (e.g. apolipoprotein in AD),

lifestyle and vascular risk factors (including diabetes, hypertension and obesity) and the development of dementia (Barnes & Yaffe, 2011; Fratiglioni & Qiu, 2011). Importantly, the emergence of mood and/or cognitive symptoms has also been shown, in many cases, to reflect the earlier stages of underlying neurodegeneration (Cummings, Doody, & Clark, 2007; Emery, 2011). As such, those individuals with depression, subjective cognitive complaints and mild cognitive impairment are widely considered to be ‘at risk’ for developing dementia longitudinally, and are therefore important candidates for targeted prevention strategies.

5.2.2. Mild Cognitive Impairment

In characterising ‘at risk’ groups, the literature has focused on the clinical syndrome of Mild Cognitive Impairment (MCI) (Gauthier et al., 2006; Petersen et al., 2009). By definition, individuals with MCI remain ‘functional’ and independent in everyday activities; however they subjectively report cognitive decline which is corroborated by a close informant and evident on objective neuropsychological testing (Petersen et al., 2001). The significance of MCI as an ‘at risk’ or transitional state to dementia, particularly AD, is highlighted by the data suggesting transition rates of around 10-15% per year in clinical samples and approximately 45% over a five year period, a much higher rate than that observed in the general healthy elderly population (i.e. 1-2%) (Gauthier, et al., 2006; Petersen, et al., 2001). Community-based epidemiological samples of individuals with MCI also demonstrate a transition rate of 6-10% per year – lower than the clinical samples, but still much higher than the 1-2% base incidence rates of dementia per year (Petersen, et al., 2009). Importantly, dementia may not be a definitive outcome of MCI, as approximately 40-50% of individuals diagnosed with MCI have been shown to stabilise or revert to normal functioning (Ganguli, 2006; Gauthier, et al., 2006; Mitchell & Shiri-Feshki, 2009).

Over time, the concept of MCI has been developed further and two subtypes are now widely acknowledged, differentiating those individuals with specific deficits in memory (amnesic, or aMCI) from those with deficits in other cognitive domains such as language, visuospatial skills or executive functions (non-amnesic, or naMCI) (Petersen, 2004). Furthermore, individuals may demonstrate deficits within a single cognitive domain or within multiple cognitive domains. These subtypes are not only clinically useful but may also provide more specific prognostic information. Multiple-domain MCI (particularly when memory impairment is evident) is more likely to result in conversion to dementia and therefore appears to represent a more advanced disease state, while single-domain MCI is thought to represent a more benign condition, and data have shown that a large number of this subgroup may revert to normal functioning over follow-up periods of two to three years (Forlenza et al., 2009; Hughes, Snits, & Ganguli, 2011; Mitchell & Shiri-Feshki, 2009; Nordlund et al., 2010). Furthermore, it appears that clinical subtypes may have some significance with respect to aetiology and disease trajectory: aMCI has been associated with increased conversion to AD. While naMCI has been associated with increased conversion to vascular dementia, frontotemporal dementia or dementia with Lewy bodies (Gauthier, et al., 2006; Hughes, et al., 2011; Petersen, 2004; Yaffe, Petersen, Lindquist, Kramer, & Miller, 2006), recent studies have demonstrated that a high proportion of these individuals may also go on to develop AD (Duara et al., 2011; Fischer et al., 2007).

Advances in the identification of pathophysiological biomarkers associated with the presence or progression of underlying neurodegenerative disease processes, particularly AD, have recently been extended to MCI (see Dubois et al., 2007; Winblad et al., 2004). For example, a seminal study by Rowe et al. (2007) demonstrated two differential patterns of amyloid burden using [¹¹C] Pittsburgh Compound B (PIB) PET scanning in individuals with MCI: one pattern was indistinguishable from that seen in an AD group, while the other

pattern more closely resembled healthy controls. Such advances may also provide further clarification regarding the aetiological significance of MCI subtypes (McKhann, 2011; Petersen, et al., 2009; Vemuri, 2010).

5.2.3. Late-life depression

In recent years, depression has been recognised internationally as a prodromal feature and independent risk factor for cognitive decline (Alexopoulos, 2005; Emery, 2011; Panza et al., 2010; Steffens et al., 2007). Indeed, two large community-based studies recently demonstrated that increasing levels of depressive symptoms are associated with increasing risk for dementia (Saczynski et al., 2010), particularly for those with recurrent depression (Dotson, Beydoun, & Zonderman, 2010). In a recent systematic review of potentially modifiable risk factors associated with cognitive decline and dementia, Barnes and Yaffe (2011) calculated that more than 10% of AD cases worldwide are potentially attributable to depression. It was estimated that a 10% reduction in depression prevalence could potentially result in a worldwide reduction of dementia incidence by approximately 326 000 cases. Similarly, a prospective seven-year cohort study of modifiable risk factors for dementia (Ritchie et al., 2010) suggested that eliminating the impact of late-life depression (LLD) would lead to an estimated 10.3% reduction in the incidence of dementia.

While depression is widely known to affect cognitive functioning at any age, in those over the age of 60 years and/or those with late-onset depression (i.e. first episode after age 50 or 60) it is associated with even greater deficits in processing speed, executive functions (i.e. ‘frontal’ or higher-order functions) as well as aspects of learning and memory (Herrmann, Goodwin, & Ebmeier, 2007; Kohler, Thomas, Barnett, & O'Brien, 2010; Naismith et al., 2003; Naismith, Hickie, Ward, Scott, & Little, 2006; Sheline et al., 2006). According to a recent five-year follow-up study of depressed older adults, memory deficits and executive

dysfunction best predict conversion to dementia (Potter et al., 2012). These cognitive deficits appear to be underpinned by structural and functional brain changes, particularly within frontosubcortical and frontotemporal networks (Ballmaier et al., 2004; Hickie et al., 2005; Hickie et al., 2007; Taylor et al., 2004). Currently, it is unclear to what extent such changes reflect comorbidities such as underlying cerebrovascular disease or early neurodegenerative pathology, or whether they reflect the specific effects of depressive illness on neuronal, particularly hippocampal, integrity (Duman & Monteggia, 2006; Naismith, Norrie, Mowszowski, & Hickie, in review). Possible mechanisms mediating this relationship may include down-regulation of the hypothalamic-pituitary-adrenocortical axis, neurotoxic effects of glucocorticoids and reduced expression of brain-derived neurotrophic factor (BDNF) which promotes neuronal differentiation, growth and survival (Duman & Monteggia, 2006; Hickie, et al., 2005). Importantly, it is now understood that cognitive deficits in LLD are not merely reflective of depressive 'state' and tend to persist despite adequate symptom resolution (Butters et al., 2000; Devanand et al., 2003).

There is also a great deal of overlap between depression and MCI. It appears that more severe depressive symptoms represent a greater risk for MCI, with 55% of individuals with LLD meeting criteria for MCI (Lee, Potter, Wagner, Welsh-Bohmer, & Steffens, 2007). Within the MCI population, rates of depression vary, with recent reviews suggesting a median depression prevalence of 44.3% in hospital-based studies and 15.7% in population-based studies (see Panza, et al., 2010 for a review). This combination of depression and MCI is associated with a twofold risk of developing AD with an earlier age of onset (Modrego & Ferrandez, 2004). Other studies suggest that those with LLD tend to progress predominantly to vascular forms of dementia (Baldwin, Gallagley, Gourlay, Jackson, & Burns, 2006; Hickie, Scott, Wilhelm, & Brodaty, 1997), likely due to the increased white matter lesion burden associated with LLD (Alexopoulos, 2005; Blazer, 2003; Santos et al., 2009).

5.2.4. Subjective cognitive impairment

While MCI and LLD have been well-established as likely prodromal phases of dementia, interest is now turning towards identifying ‘at risk’ individuals at even earlier stages of the clinical continuum. This continuum has been operationalised in the widely-used Global Deterioration Scale (Reisberg, Ferris, de Leon, & Crook, 1982), a clinician-rated scale comprising seven clinically identifiable stages ranging from “No Cognitive Decline” (stage one) through to “Very Severe Cognitive Decline (i.e. late dementia; stage seven). Stage three is most analogous to the current and widely-used criteria for MCI outlined above (see Petersen, 2004). However, Reisberg’s group have recently argued that the earlier stage two, which identifies individuals with subjective cognitive complaints only (in the absence of objective evidence on testing), is also important in terms of prognostic value (Reisberg & Gauthier, 2008; Reisberg & Shulman, 2009).

This syndrome of ‘subjective cognitive impairment’ (SCI) or, similarly, ‘subjective memory complaints’ has met with some scepticism regarding its validity as a marker of increased risk for dementia, given the frequency of subjective cognitive complaints in ageing, and the fact that some degree of cognitive decline is expected as part of the normal ageing process or as a symptom of other common comorbidities in ageing (e.g. depression, anxiety) (Paradise, Glozier, Naismith, Davenport, & Hickie, 2011). However, proponents of the SCI construct have generally acknowledged such limitations but maintain that there is great utility in identifying those individuals whose subjective complaints represent the very early clinical manifestation of an underlying neurodegenerative process; particularly those who are health-seeking. Indeed, longitudinal studies have suggested that the SCI stage may last approximately 15 years and may precede the emergence of objective evidence of cognitive decline or later functional impairment (Pritchep et al., 2006; Reisberg, 1986; Reisberg et al.,

2008). Furthermore, over a seven-year observation period, individuals with SCI (categorised as Global Deterioration Scale stage two at baseline) were shown to have a 4.5 risk increase of decline to either MCI or AD compared to individuals with no cognitive complaints (i.e. stage one at baseline) (Reisberg, Shulman, Torossian, Leng, & Zhu, 2010). Similar findings have been reported by groups utilising measures other than the Global Deterioration Scale to identify SCI (i.e. combination of self-report questionnaires and neuropsychological tests). For example, Duara and colleagues (2011) reported that 28.6% of individuals with SCI (termed 'pre-MCI' in this study) declined to MCI or dementia over a two- to three-year follow-up period compared to just 4.1% of individuals without cognitive complaints at baseline.

As with MCI, investigation of pathophysiological biomarkers identifying individuals with SCI will provide further elucidation of the underlying disease processes driving these subjective complaints. Thus far, neuroimaging markers such as Pittsburgh compound B have shown promise as potential markers of this early stage (see Dubois, et al., 2007) and one recent study has demonstrated 90% predictive accuracy of quantitative electroencephalogram features (such as mean frequency and absolute power) in predicting cognitive and clinical decline in SCI (Pritchep, et al., 2006).

Overall, while SCI has not been as well investigated as MCI or LLD to-date, evidence from this emerging body of research suggests that it does robustly capture an early stage of the dementia process, prior to the emergence of MCI (Reisberg & Gauthier, 2008). As such, SCI represents a 'widening of the net' in terms of secondary prevention and should be included as a target for early intervention strategies (Reid & MacLulich, 2006; Reisberg & Shulman, 2009). Moreover, these findings have important implications for population sampling in designing targeted secondary prevention studies. Clearly those individuals seeking contact with healthcare services are aiming to address their cognitive concerns (i.e.

individuals with SCI). Thus, health-seeking behaviour itself may be an early indicator of underlying disease in many cases where “the patient knows, but [presently] the doctor doesn’t know” (Reisberg, et al., 2008, p. S98). Thus, health-seeking groups may better represent those individuals who are truly ‘at risk’ for cognitive decline. Practically, it is frequently more difficult to recruit healthy older adults *without* cognitive complaints to participate in studies investigating cognition (Reisberg, et al., 2010); this too suggests the utility in sampling health-seeking participants rather than community-based samples generally.

5.2.5. Early intervention strategies

It is clear that identification of therapeutic targets for improving cognitive functioning in ‘at risk’ groups such as MCI, LLD and SCI is warranted, both for symptomatic improvement as well as for potential disease modification (Cummings, et al., 2007; Naismith, et al., 2009). Advances in knowledge of the underlying pathophysiology of neurodegenerative diseases have led to investigations of pharmacotherapy as an early intervention strategy in MCI. However, large-scale clinical trials of acetylcholinesterase inhibitors such as donepezil, galantamine and rivastigmine for aMCI, and other drugs including vitamin E and ginkgo biloba have demonstrated only modest symptomatic effects and limited delay of conversion to AD beyond 12-18 months (Ames, 2011; Gauthier, 2004; Gauthier, et al., 2006; Winblad, et al., 2004). Furthermore, these drugs have been associated with side-effects including gastrointestinal symptoms, haemorrhaging or other toxicities, such that the risk-benefit ratio has been questioned (Ames, 2011; Winblad, et al., 2004).

Overall, in the absence of convincing evidence for the efficacy of pharmacological interventions, recommendations for early intervention for dementia generally point towards management of modifiable (i.e. vascular) risk factors, increased cognitive activity, and management of mood and psychosocial functioning (Emery, 2011; Naismith, et al., 2009).

Furthermore, it has been suggested that these approaches may be most efficacious when implemented in combination, and that systematic evaluation of such multifaceted intervention programs is now required (Barnes & Yaffe, 2011; Emery, 2011; Naismith, et al., 2009).

5.2.6. Cognitive Training as an early intervention technique

Recently, Cognitive Training (CT) has been identified as a viable secondary preventive tool in ‘at risk’ groups such as MCI and LLD (Gates, Sachdev, Fiatarone Singh, & Valenzuela, 2011; Jean, Bergeron, Thivierge, & Simard, 2010; Mowszowski, et al., 2010; Naismith et al., 2011) (see Chapter Two). CT refers to a specific approach within the broader field of Cognitive Remediation, a cognitive/behavioural intervention which also includes cognitive stimulation and cognitive rehabilitation (see Figure 1 in Mowszowski, et al., 2010) (Figure contained in Chapter Two). The CT approach refers to programs which enhance cognition by providing theoretically-driven strategies and skills, usually involving ‘guided practice’ on tasks reflecting various cognitive functions. CT may be strategy-based; i.e. following a compensatory approach incorporating both internal (e.g. visual imagery, categorising information) and external (e.g. using calendars or environmental cues) techniques to strengthen intact cognitive functions and adapt to areas of weakness or decline. CT may also be computer-based; that is, following a restorative approach to improve functioning in specific domains via repeated exercises which typically incorporate multiple cognitive skills and allow for graded difficulty and independence on learning tasks (e.g. *CogPack* (Sartory, Zorn, Groetzinger, & Windgassen, 2005) and *NEAR* (Medalia & Freilich, 2008)).

5.2.7. Efficacy of CT in ‘at risk’ groups

Over the last decade, a body of literature has emerged documenting the promising effects of CT in ‘at risk’ groups, predominantly focusing on MCI. A review by this group

(Mowszowski, et al., 2010) (see Chapter Two), also included the only known study to-date which has investigated the efficacy of CT in LLD (Naismith, et al., 2011), and there are no known trials evaluating CT in health-seeking individuals or those with SCI. This review indicated generally positive findings, suggesting that CT programs can improve cognitive functioning (particularly learning and memory) in ‘at risk’ groups and may represent a viable non-pharmacological early intervention strategy, particularly since they are easy to implement, enjoyable and offer the potential for social engagement. Two systematic reviews published over the last two years have focused on participants specifically diagnosed with aMCI (Jean, et al., 2010) or have attempted to delineate the efficacy of specific CT approaches in MCI by comparing the efficacy of trials using applied memory strategy training vs. trials using repetitive multi-domain cognitive exercises (Gates, et al., 2011). Both systematic reviews reported generally beneficial effects on memory performance, global cognitive measures and some measures of psychosocial functioning (i.e. quality of life and mood). Stronger effect sizes and generalizability of benefits were more frequently seen in those trials using a computer-based, cognitive exercise approach, perhaps because these multi-domain exercises offer a broader range of cognitive challenges to stimulate neuroplastic processes (Gates et al., 2011). In the past, it has been argued that multi-faceted approaches to CT may be optimal (Naismith, et al., 2009; Rebok, Carlson, & Langbaum, 2007). In this regard, for both participant satisfaction as well as longer term efficacy, it has been argued that such programs should also incorporate practical memory strategies as well as general psychoeducation targeting those factors associated with healthy brain ageing (Naismith, et al., 2009; Norrie et al., 2011).

Overall, the balance of evidence suggests that CT is effective in improving cognitive functioning in ‘at risk’ groups, especially MCI which has been most widely studied. Further research is needed to elucidate the efficacy of CT in other ‘at risk’ groups such as LLD and

SCI. However, a major limitation within the literature has been the lack of focus on concomitant effects on brain physiology to delineate the underlying neural mechanisms of CT.

5.2.8. Neuroplasticity as the underlying mechanism of CT

The underlying mechanism of CT is thought to be related to increasing cognitive activity, with a central component of promoting neuroplasticity. The concept of increasing cognitive activity as a protective measure against cognitive decline stems from a large body of research demonstrating the impact of ‘cognitive reserve’, a model which postulates that individuals with higher levels of lifetime complex cognitive activity (stemming from level of education, occupational attainment and cognitively-demanding leisure activities) are more resilient to pathological brain changes, such as those resulting from neurodegenerative processes (Stern, 2011). Cognitive or neuronal reserve is thought to mediate the point at which clinical symptoms emerge, as well as their trajectory over time, in spite of the process of underlying neurodegeneration which may have been operating for many years previously (Stern, 2002). Indeed, a meta-analysis of 22 studies involving 29 000 participants overall and investigating the link between complex lifetime cognitive activity and dementia risk, reported an overall risk reduction of 46% for those individuals with high levels of lifetime complex mental activity (Valenzuela & Sachdev, 2006).

This protective effect appears to be underpinned by the promotion and/or maintenance of brain structures. At a cellular level, cognitive activity likely influences spine density, synaptogenesis and vascular supply to the brain. It is also likely to promote glial and metabolic activity, trophic factors (e.g. BDNF) and hippocampal neurogenesis (Stern, 2011; Valenzuela, 2008). These processes represent the mechanisms of neuroplasticity, a concept which has been well-established in animal literature (Turkstra, Holland, & Bays, 2003) and

which has recently received renewed interest in human healthy and clinical populations (Kelly, Foxe, & Garavan, 2006; Mahncke, Bronstone, & Merzenich, 2006). The traditional view of the brain as a ‘static’ structure has been revised on the basis of numerous studies which show that neuronal connections and circuits undergo continual modification and reorganization (Fuchs, Czeh, Kole, Michaelis, & Lucassen, 2004). Neuroplasticity is also believed to be bi-directional; i.e. the same plasticity processes can either degrade (i.e. negative plasticity) or strengthen (i.e. positive plasticity) cognitive functioning. Such ‘negative’ plasticity may be involved in age-related cognitive decline (Mahncke, et al., 2006) and depression (Fuchs, et al., 2004). By contrast, processes that strengthen brain function can be conceptualized as ‘positive’ plasticity and can provide a foundation for therapy. From the cognitive standpoint, it is possible that the efficacy of CT lies in its facilitation of ‘positive plasticity’. Using terminology conceptualized independently of CT, the mechanisms of neuroplasticity for rehabilitation may be either restorative (i.e. reorganization of existing networks) or compensatory (engagement of other cognitive abilities or networks) (Strangman et al., 2005). Importantly, evidence suggests that neuroplasticity and enhancing cognitive reserve through life experiences and/or behavioural interventions can still occur in later life and that substantial restoration is possible even in the ageing brain, to delay or reverse the effects of normal ageing or neurodegenerative pathology (Greenwood, 2007; Mahncke, et al., 2006; Stern, 2011).

5.2.9. Neural changes associated with CT

It is thought that the mechanism of CT lies in its facilitation of neuroplastic processes as well as enhancement of cognitive reserve, to slow down the trajectory of cognitive decline and protect against further impairment. However, as noted above, a significant limitation within CT literature has been the lack of focus on concomitant CT effects on brain physiology (see

Mowszowski, et al., 2010) (Chapter Two). The use of standardised, objective neurobiological outcome measures provides insight into neurophysiological changes which may underlie the cognitive/psychosocial effects of CT, and may also clarify whether specific CT programs influence the neurodegenerative process or whether they merely enhance cognition without impacting on underlying pathology. Such measures can also complement or even anticipate clinical outcomes, for example when the cognitive/ functional effects of CT may be delayed: in these cases, the use of clinical outcomes alone would likely result in dismissal of the program as ineffective (Cummings, et al., 2007; Mueller et al., 2005). In fact, it is plausible that the underlying neurobiological changes may occur first, *followed by* changes to higher-order cognitive functions. In addition to investigating the nature of these neurobiological changes, it is therefore also important to delineate the time course of various CT effects.

Within the ageing literature, the few earlier CT studies which investigated neurobiological correlates of CT demonstrated increased activation in parieto-occipital cortex on positron emission tomography (PET) scanning (Nyberg et al., 2003), as well as elevated neurochemical signals in the hippocampus on magnetic resonance spectroscopy (MRS) (Valenzuela et al., 2003), in healthy older adults following memory strategy training. Fortunately, neuroimaging outcomes have received renewed interest in recent years, with a growing body of CT studies targeting healthy older adults adding to these earlier findings. According to a recent systematic review of CT studies utilising MRI outcomes, five studies have included older adult samples and each has reported at least one significant brain-imaging outcome, most commonly reflecting training-related changes in the frontal lobes (Suo & Valenzuela, in press). For example, Lovden and colleagues (2010) reported increased white matter connectivity evident on diffuse tensor imaging (DTI) in the anterior region of the corpus callosum in older adults who received training in working memory, episodic

memory and processing speed compared to untrained controls. This increase in white matter connectivity following memory training was recently confirmed by Engvig and colleagues (2011), who also demonstrated a positive relationship between the increase in fractional anisotropy and improvements on a memory task following CT. In an earlier study, this group also reported regional increases in cortical thickness in the right insular, fusiform and orbitofrontal cortices on post-CT MRI in healthy older adults who underwent eight weeks of intensive memory strategy training (Engvig et al., 2010). Again, these increases were positively correlated with improvement in performance on a memory task. Furthermore, increases in resting cerebral blood flow in the prefrontal cortex have recently been reported in healthy older adults following an eight-week training program targeting attention and distractibility (Mozolic, Hayasaka, & Laurienti, 2010). These increases in blood flow were larger than those seen for an active control group, and were also positively associated with reduced susceptibility to distraction on a cognitive task at follow-up.

To-date, only one known study has investigated neuroimaging outcomes following CT in MCI. Forster et al. (2011) recently reported improved global cognitive scores and attenuated decline in cerebral metabolism on PET scanning in a group of aMCI participants who received a six-month cognitive intervention focusing on cognitive training, compared to an active control group. The authors suggested that these findings represent evidence of cognitive stabilization following cognitive intervention. However, it should be noted that the active control condition followed a cognitive stimulation approach but also contained elements of CT. Thus, the validity of the control group is uncertain.

5.2.10. The use of event-related potentials in CT research with ‘at risk’ groups

Due to the heterogeneity in progression to dementia within ‘at risk’ groups, increasing attention has been directed towards utilising pathophysiological biomarkers within a research

context, aiming to ‘purify’ samples in clinical intervention trials testing potential disease-modifying therapies (Cummings, et al., 2007; Dubois, et al., 2007; Winblad, et al., 2004). Furthermore, such biomarkers may also have utility as outcome measures of treatment efficacy and/or indicators of underlying mechanisms of neural change.

Recently, several biomarkers of underlying neurodegenerative disease have been extended to preclinical groups, particularly MCI but also SCI and LLD. Most investigations have focussed on those biomarkers which have already been identified in established dementia, particularly AD: cerebrospinal fluid markers of tau and beta-amyloid, genetic markers of mutations in amyloid precursor protein, presenilin or apolipoprotein, and neuroimaging markers of mesial temporal lobe (hippocampal and/or entorhinal) atrophy, white matter lesions, deficits in regional cerebral blood flow or glucose metabolism or cholinergic abnormalities (Gauthier, et al., 2006; Petersen & Morris, 2005; Winblad, et al., 2004). However, these investigations often involve costly, invasive and time-consuming measures and can therefore be difficult to implement for added diagnostic clarity in screening large pools of potential research participants. Accordingly, other techniques such as neurophysiological event-related potential responses (ERPs) have been recommended for their wide availability, time efficiency and non-invasiveness and are also emerging as viable biomarkers in these ‘at risk’ groups (Mowszowski et al., 2012; Naismith et al., 2012; Winblad, et al., 2004) (see Chapter Three and Chapter Four). ERPs are practical and objective indices of fundamental sensory and cognitive processes (Jackson & Snyder, 2008; Rossini, Rossi, Babiloni, & Polich, 2007) that have shown great utility in detecting neurobiological changes in a range of psychiatric and neurological conditions. ERPs are time-locked to specific stimuli, and are used to assess the speed and efficiency of information processing by examining the magnitude and latency of the waveform. While numerous ERP paradigms have been used to examine the integrity of various cognitive pathways and neural

regions in MCI (Liddell et al., 2007; Papaliagkas, Kimiskidis, Tsolaki, & Anogianakis, 2008), studies have been characterized by two major limitations: firstly, cognitive paradigms are typically dependent on conscious awareness, attention and engagement with the eliciting stimuli, thus indexing later stages of information processing. This issue is important to address since neuropsychological deficits observed in ‘at risk’ groups (particularly SCI and MCI) may be partially attributable to dysfunction or inefficiency in earlier stages of information processing. Secondly, there has been a tendency to focus on midline scalp electrodes which reflect fronto-central brain functioning. Therefore, ERP studies that employ a passive paradigm and that assess other brain regions implicated in the pathophysiology of prodromal dementia, particularly AD (e.g. the temporal lobes) are required.

5.2.11. The Mismatch Negativity paradigm

Recent findings from this group have suggested that the Mismatch Negativity (MMN) ERP may be a viable neurophysiological biomarker of underlying disease in ‘at risk’ groups. Specifically, the auditory MMN paradigm represents an excitatory response to novel or deviant auditory stimuli within a stream of homogenous sounds, elicited even in the absence of directed attention (see review by Naatanen, Paavilainen, Rinne, & Alho, 2007). Deviant stimuli may differ from the homogenous sound in pitch, duration or loudness. As such, MMN reflects an automatic change detection system operating at the initial stages of information processing. The strongest generators of MMN are the temporal and frontal regions of the brain (Giard, Perrin, Pernier, & Bouchet, 1990; Kujala, Tervaniemi, & Schroger, 2007). The temporal lobes (auditory cortex) process the auditory stimulus and maintain an echoic memory trace for the homogenous sounds, which allows for discrimination of the deviant sound as incongruent. The prefrontal cortex then triggers an involuntary switching of attention to the novel stimulus. Regarding cognitive correlates,

auditory MMN has been associated with verbal memory deficits, poor executive functioning and reduced psychosocial functioning in schizophrenia (Hermens et al., 2010). The integrity of these lower-level sensory processes is thought to be essential for efficient functioning of higher-level processes (Light, Swerdlow, & Braff, 2007), which may be somewhat compromised in SCI, MCI and LLD.

Indeed, relative to controls, an MCI group demonstrated reduced temporal MMN amplitude, which was significantly associated with poorer verbal learning and increased self-reported disability (Mowszowski, et al., 2012; see Chapter Three). Similarly, a group of participants with LLD demonstrated reduced MMN amplitude at temporal sites, which was associated with reduced semantic fluency and greater self-rated functional disability (Naismith, et al., 2012; see Chapter Four). While longitudinal studies are required to further clarify the predictive value of MMN as a biomarker of prodromal dementia, these observed reductions in those ‘at risk’ relative to their age-matched controls, suggests that impaired MMN illustrates fundamental alterations in pre-attentive information processing that appear to underpin higher-order cognitive and psychosocial impairments. Importantly, given its cognitive and psychosocial implications, MMN may also have utility as an outcome measure for individually-tailored cognitive interventions such as CT.

5.2.12. Aims and hypotheses

This randomized controlled study aimed to investigate underlying neurophysiological changes following a multifaceted CT intervention for ‘at risk’ individuals with SCI, MCI or LLD using the auditory MMN ERP. If MMN is a valid index of the neuroplastic mechanisms underlying CT, the MMN response should increase in amplitude for the trained group at post-CT follow-up, reflecting enhanced efficiency of pre-attentive processing in relation to the CT intervention. A secondary aim was to examine the relationship between

neurophysiological and cognitive/psychosocial changes following CT. If the CT program produces cognitive/psychosocial gains on neuropsychological testing or clinical measures at follow-up, these gains should be positively correlated with increased MMN amplitude.

5.3. Methods

5.3.1. Participants

Participants were 42 health-seeking older adults aged between 50 and 90 years who were recruited from the “Healthy Brain Ageing” Clinic, a specialist research program at the Brain & Mind Research Institute, which preferentially recruits older adults with new onset mood or cognitive disorders. The clinic receives referrals from psychiatry, psychology and neurology clinics as well as from local geriatricians and general practitioners. Upon initial screening, all participants reported subjectively experiencing cognitive decline (such as memory difficulties, poor concentration or word-finding difficulties), and all sought remediation of their cognitive functioning.

Exclusion criteria comprised a Mini-Mental State Examination (MMSE) score < 24, use of cholinesterase inhibitors and/or established dementia; previous head injury with loss of consciousness \geq 30 minutes; history of schizophrenia or neurological condition; previous stroke or transient ischaemic attack; current substance abuse or history of significant substance misuse; intellectual disability or insufficient English language skills for assessment. The study was approved by the University of Sydney Human Research Ethics Committee and by the Macquarie University Ethics Review Committee (Human Research). Written consent was obtained from all participants.

This sample was derived from a larger study primarily investigating neuropsychological outcomes of CT (the larger trial is registered on the Australian New Zealand Clinical Trials Registry, registry number ACTRN12611000570987; results of this

larger study are in preparation for separate publication). During the initial recruitment phase, all participants were given the option to undergo a neurophysiological assessment (EEG) in addition to the primary neuropsychological and medical assessments. As shown in Figure 7, the sample therefore comprised those individuals from the larger CT study who elected to undergo the additional neurophysiological assessment.

5.3.2. Design

Figure 7 illustrates the study's randomised controlled design and a timeline of the assessment and intervention procedure. Random allocation to either the immediate treatment or the treatment-as-usual (control) condition occurred following recruitment and was carried out by a blinded Clinical Trials Manager within the Healthy Brain Ageing Clinic, who was not involved in any phase of the CT study (including recruitment, assessment, intervention, or data analysis). At the completion of the baseline assessments, all participants received a sealed envelope containing their randomisation outcome. Regardless of the participants' allocated condition, all baseline assessments were conducted within a fortnight of the seven-week intervention (treatment/control) period commencement (i.e. weeks one and two), and all follow-up assessments were conducted within a fortnight of the intervention period cessation (i.e. weeks ten and eleven). All clinicians conducting baseline and follow-up assessments were blinded to the participants' allocated condition. After completion of the follow-up assessments (i.e. after week eleven), all control participants were offered the next available place in a subsequent CT group.

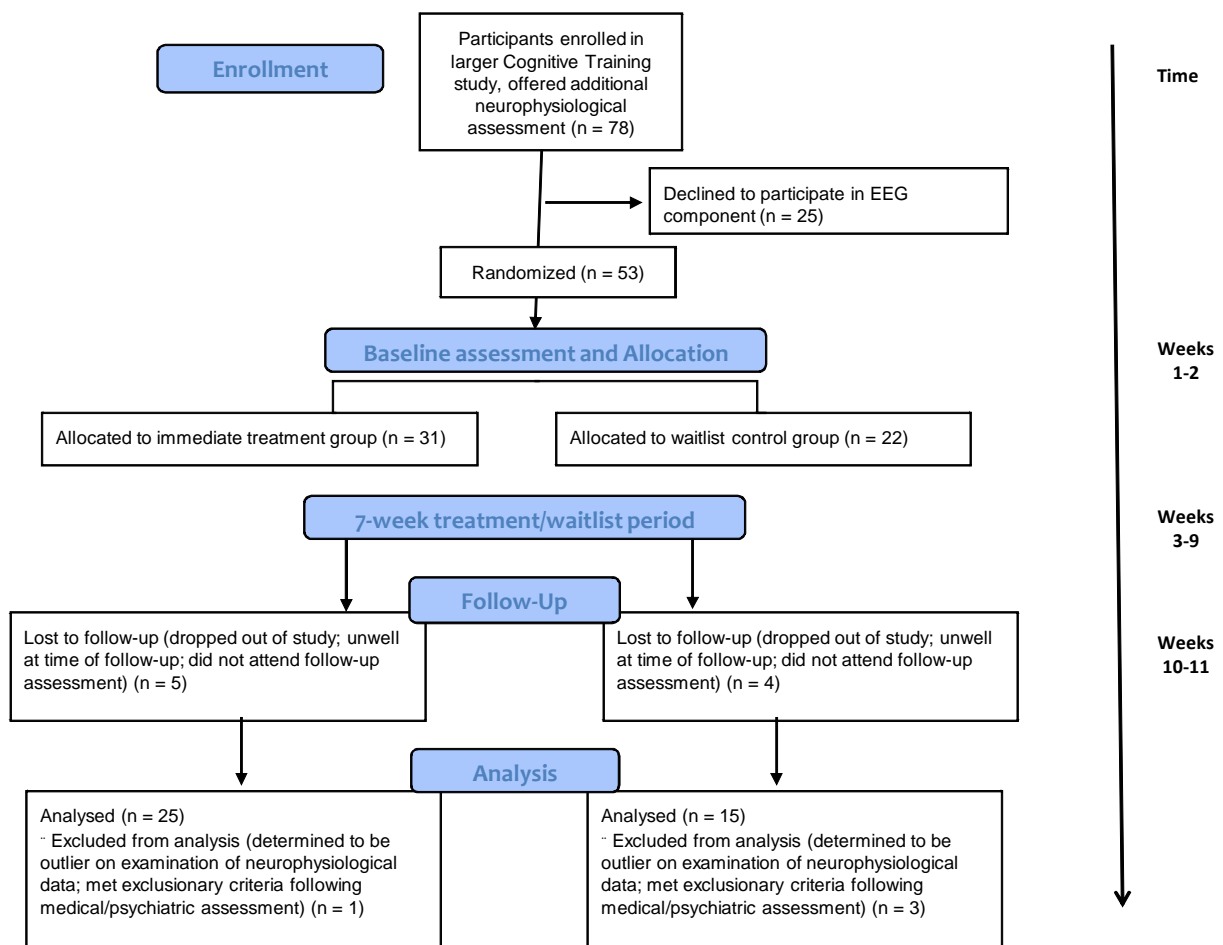


Figure 7. Participant flow through the study

5.3.3. Intervention

The intervention comprised a) a treatment-as-usual control condition or, b) a Healthy Brain Ageing CT program. Both conditions were of seven weeks' duration.

a) Treatment-as-usual: This included a waitlist period of no contact from the researchers.

Participants were able to continue receiving standard clinical care from their usual health-care professionals.

b) Healthy Brain Ageing Intervention: This included twice-weekly sessions, comprising one-hour of Healthy Brain Ageing psychoeducation, followed by one-hour of

computer-based CT. The intervention was conducted in groups with a maximum of 10 participants.

- i) The psychoeducation program has been described previously (Naismith, et al., 2011; Norrie, et al., 2011) but was expanded to 14, rather than 10 sessions to allow more time for practice of memory strategies in class (two extra sessions), diet and exercise (expanded from one to two sessions), and to include a practical session on ‘using the internet’ (one session). As previously reported, all 14 education sessions were delivered by specialists across the disciplines of psychiatry, neurology, clinical psychology, sleep, neuropsychology and exercise physiology and in accordance with scientific literature (see Table 9 for details of each session). Educational material was delivered via PowerPoint presentation and was supplemented with lecture notes and additional handouts, contained within a bound Participant Workbook.
- ii) As employed previously (Naismith, et al., 2011; Naismith, Redoblado-Hodge, Lewis, Scott, & Hickie, 2010), the CT intervention utilised Medalia’s Neuropsychological Educational Approach to Remediation (NEAR) (Medalia & Freilich, 2008). This approach is guided by principles including intrinsic motivation and guided facilitation within a structured environment. Tasks are usually computer-based and are interactive, engaging and contextually relevant to practical activities. Goals include independent learning and increased awareness and improvement of cognitive functioning both within and outside of the training environment. The CT intervention was administered by Clinical Neuropsychologists who had received training in the NEAR technique. Each participant worked on their own computer. The

computer-based CT component included a variety of widely available educational software (e.g. Hoyles Word Games, Sudoku, Zoombinis) as well as more specific ‘brain-training’ packages (e.g. CogPack, Marker Software, 1987-2012). The tasks selected for each participant over the seven-week course were tailored to suit their individual cognitive strengths and weaknesses, based on results from the baseline neuropsychological assessment. In accordance with NEAR principles, participants were asked to rate their performance after each session, and therapists utilised this rating along with the neuropsychological profile and clinical judgement regarding suitability of the session program and choice of future exercises. This component of NEAR is considered to be important for compliance, intrinsic motivation and to encourage graded exposure from simple to more challenging tasks. Prior work utilising this technique has demonstrated high levels of acceptability and compliance, and thus is critical to clinical translation of such programs.

5.3.4. Measures

5.3.4.1. Psychiatric and medical assessment

A semi-structured assessment was conducted by an Old Age Psychiatrist to document history of cognitive decline, psychiatric and medical history. The Structured Clinical Interview for Psychiatric Disorders (First, Spitzer, Gibson, & Williams, 1996) was administered to determine lifetime and current depression diagnoses according to Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV; American Psychiatric Association, 1994) criteria. Current depressive symptom severity was rated using the 17-item Hamilton Depression Rating Scale where scores ≤ 7 indicate normal levels of depressive symptoms

Table 9.

“Healthy Brain Ageing” Psychoeducation Program Designed to Promote Knowledge of Cognition, Teach and Facilitate Practice of Cognitive Strategies and Promote Knowledge of Medical / Lifestyle Factors Affecting the Brain in Later Life.

Session	Topic	Clinician
1	The brain, cognition and ageing	Clinical Neuropsychologist
2	Vascular risk factors	Old Age Psychiatrist
3	Attention: strategies	Clinical Neuropsychologist
4	Memory: Encoding strategies	Clinical Neuropsychologist
5	Memory: Storage problems	Clinical Neuropsychologist
6	Memory: Retrieval strategies	Clinical Neuropsychologist
7	Executive functions: strategies	Clinical Neuropsychologist
8	Depression: pharmacological treatments	Old Age Psychiatrist
9	Depression: CBT and behavioural treatments	Clinical Psychologist
10	Anxiety and stress management	Clinical Psychologist
11	Sleep	Chronobiologist
12	Diet	Nutritionist
13	Exercise	Exercise Physiologist
14	Internet strategies	Clinical Neuropsychologist

(HDRS; Hamilton, 1960). A full medical history was taken and medical burden was rated using the Cumulative Illness Rating Scale – Geriatric version (Miller & Towers, 1991). General functioning was rated using the Global Assessment of Functioning Scale (GAFS;

American Psychiatric Association, 1994), a clinician-rated measure of psychosocial functioning whereby higher scores indicate a higher level of functioning.

MCI was diagnosed using Petersen's criteria (Petersen, 2004), that is, based on decrements of at least 1.5 standard deviations on neuropsychological testing (see below) in comparison to normative data, in at least one neuropsychological domain. Moreover, single domain MCI denoted impairment in only one neuropsychological domain while multiple domain MCI referred to impairment across more than one area of cognitive functioning. The diagnosis was made via consensus of three raters (two neuropsychologists and one psychiatrist). Individuals were further categorised as demonstrating either amnestic or non-amnestic subtypes. A diagnosis of aMCI was made if deficits were of the 'hippocampal-type' (i.e., present on tests of delayed memory recall; Dubois & Albert, 2004). naMCI was diagnosed if deficits were present on tests of other cognitive domains (e.g. executive functioning, processing speed, language, working memory). Additionally, the Global Deterioration Scale (Reisberg, et al., 1982) was used to rate participants along an established continuum of cognitive and functional impairment in older adults.

5.3.4.2. Primary outcome: neurophysiological functioning

As described previously (Hermens, et al., 2010), participants were fitted with a cap for electroencephalography (EEG) recording and presented (via headphones) with 2500 binaural pure tones (1000Hz, 75dB SPL, 10ms rise/fall) at a 500 ms stimulus onset asynchrony; comprising a pseudo-random sequence of 2300 (92%) 50ms standard (short) tones and 200 (8%) 100ms deviant (long) tones. During presentation of the tones, participants watched a silent comedy film and were asked to report the storyline at the end of the task. Two films were used as alternate forms for baseline and follow-up; both films were of the same genre and audience classification. The standard and alternate forms were counter-balanced in

successive order. A 64-channel Quik-Cap (NeuroScan) acquired EEG data from sites according to the standard 10-10 International System (including mastoids). Data were referred to a nose electrode. Vertical and horizontal electro-oculogram (EOG) was monitored for eye-blink artefact with correction based on established methods (Semlitsch, Anderer, Schuster, & Presslich, 1986). Scalp and EOG potentials were amplified and digitized continuously by SynAmps2 via SCAN 4.3.1 software. Offline signal processing and analyses were performed using Neuro-scan Scan 4.3.1 (Compumedics) software. Data were filtered using a bandpass filter (0.15–20 Hz), and epochs of the EEG recordings that were contaminated by movement artifacts ($\pm 100 \mu\text{V}$) were rejected. Mismatch negativity (MMN) difference waveforms were obtained by subtracting ERP waveforms elicited by the deviant stimuli from those of the standard stimuli. The mean amplitude, peak amplitude and peak latency for the MMN component were determined within an epoch of 100-250ms, according to previous studies in older adult populations (see Cooper, Todd, McGill, & Michie, 2006; Gaeta, Friedman, Ritter, & Cheng, 1998; Tales, Haworth, Wilcock, Newton, & Butler, 2008). MMN measures were obtained at four sites: midline fronto-central (Fz and Cz) and temporal (left and right mastoid: M1 and M2, respectively).

5.3.4.3. Secondary outcomes: a) neuropsychological assessment

Clinical Neuropsychologists conducted a semi-structured interview and administered a standardised battery of neuropsychological tests, which were selected on the basis of prior research (Naismith et al., 2010), sensitivity to early dementia and availability of alternative forms. All standard and alternate forms were counter-balanced in successive order. For clinical diagnostic and descriptive purposes, premorbid intellectual functioning was estimated using the Wechsler Test of Adult Reading (WTAR) (Psychological Corporation, 2001) and global cognition was measured using the Mini Mental State Examination (MMSE) (Folstein,

Folstein, & McHugh, 1975). Standardized scores (i.e. z scores or age scaled scores) were calculated for all neuropsychological variables in order to adjust for differences in age (and level of education, where available).

Based on the hypothesised relationship of MMN to frontal and temporal lobe functioning as well as results from a previous CT study in late-life depression (Naismith, et al., 2011), the following cognitive domains were specifically examined:

- a) Verbal learning and memory: The *Rey Auditory Verbal Learning Test* (RAVLT) (Spreen & Strauss, 1998) was administered to measure unstructured verbal learning and recall. Total learning over the five trials (*RAVLT 1-5*; maximum = 60) as well as delayed recall (*RAVLT-7*; maximum = 15) were examined.
- b) Language: Language generativity was assessed using *letter* verbal fluency (F, A, S; also widely identified throughout the literature as *phonemic* fluency – this latter term will be used here) and *semantic* (types of animals) verbal fluency, measuring the total number of words in one minute; see Tombaugh et al., in Spreen & Strauss, 1998).
- c) Working memory: The total digit span score from the Wechsler Adult Intelligence Scale – III *Digit Span* (Wechsler, 1997) subtest was used as a measure of auditory working memory.
- d) Executive functioning: The *Trailmaking Test* Part B (TMT-B, seconds) (Reitan, 1979) was used to assess cognitive flexibility.

5.3.4.4. Secondary outcomes: b) self-reported functioning

In addition to objective neuropsychological tests and clinician-rated measures, participants completed a self-report questionnaire pertaining to their subjective experience of memory decline. The Everyday Memory Questionnaire – revised version (EMQ) (Royle & Lincoln, 2008) is a 13-item questionnaire measuring the frequency of subjective memory difficulties

in everyday life (e.g., “forgetting when it was that something happened; for example, whether it was yesterday or last week”). Participants respond using a five-point scale ranging from zero (once or less in the last month) to four (once or more in a day). These responses are summed, with higher scores indicating higher frequency of subjective memory difficulties. Factor analysis has identified two main factors within the EMQ: seven items identifying retrieval failures load on the ‘Retrieval’ factor and four items identifying disruption to attention/working memory load on the ‘Attentional Tracking’ factor. A third factor, ‘Other’ consists of the remaining two items, which Royle and Lincoln (2008) could not interpret. It is therefore possible to calculate one total score and three factor scores on the EMQ.

Subjective ratings of disability were measured using the 36-item self-administered World Health Organization Disability Assessment Schedule (WHO-DAS) (World Health Organisation, 1999). Domains of functioning included understanding and communicating, getting along with others, participation in society, self-care, getting around, and life activities. A standardized summary score was calculated to reflect a total disability score. Higher scores indicate greater disability.

5.3.5. Statistical analyses

Prior to data analysis, all neurophysiological data were examined for outliers by an expert in neurophysiology and the MMN paradigm (D. Hermens), who was also blinded to treatment condition and diagnosis. Statistical analyses were performed using SPSS for Windows 18.0.0 Chicago: SPSS Inc. Baseline group differences for demographic, clinical and MMN variables were assessed using independent samples t-tests with corrected degrees of freedom and p-values reported when equality of variance was compromised (according to Levene's test), or Mann-Whitney U tests for non-normally distributed variables.

For each of the primary neurophysiological and secondary neuropsychological and clinical outcome measures, a two-way repeated measures ANOVA was constructed with time (baseline, follow-up) as a within-subjects factor and condition (immediate treatment, waitlist control) as a between-subjects factor. Analyses tested for a Condition X Time interaction. For all significant effects, the analysis was repeated after adding clinician-rated depression scores (HDRS) as a covariate, in order to account for any potential impact of a change in mood on performance.

Pearson correlation coefficients were used to measure the relationship between changes in MMN response and cognitive/psychosocial outcomes. All analyses were two-tailed and employed an alpha level of 0.05.

5.4. Results

5.4.1. Sample characteristics

As shown in Figure 7, 78 participants from the larger Cognitive Training study were offered the opportunity to undergo additional neurophysiological assessment. A total of 53 participants elected to have this additional component. Reasons for declining most commonly included the additional time required or scheduling difficulties. There were no significant differences between these participants and those who declined this optional component in age ($t = -0.268$, $df = 76$, $p = 0.79$), gender ($\chi^2 = 2.454$, $df = 1$, $p = 0.12$), global cognitive functioning ($t = -0.536$, $df = 75$, $p = 0.59$) or depressive symptoms ($t = 0.001$, $df = 76$, $p = 0.99$).

Of this sub-group, 31 were randomly allocated to the immediate treatment condition and 22 were randomly allocated to the waitlist control condition. Dropouts included five treatment participants and four control participants (due to illness, disinterest or scheduling difficulties). Three controls and one treatment participant were considered to be outliers on

examination of the neurophysiological data and consequently, were excluded from the final analyses. Therefore, the total sample included 40 individuals comprising 25 treatment and 15 control participants.

In terms of ‘at risk’ status for the whole sample, all 40 participants were health-seeking. 30 of these participants met criteria for MCI (24 with multiple domain MCI; 6 with single domain MCI), predominantly of the non-amnesic subtype (20 with naMCI; 10 with aMCI). Eighteen participants reported a history of depression. Four participants met DSM-IV criteria for a current Major Depressive Episode; all analyses reported below were repeated after excluding these participants, with unchanged results, hence they were retained in the sample. Using the Global Deterioration Scale (Reisberg, et al., 1982), 39 participants were rated as having either SCI (stage two) or MCI (stage three). One participant was rated as having ‘suspected early dementia’ (stage four); however they did not meet the exclusionary cut-off score of 24 on the MMSE and did not have established dementia according to intact general functioning and consensus rating. Furthermore, all analyses reported below were repeated after excluding this participant, with unchanged results; hence, they were retained in the sample. Table 10 displays the number of individuals for each ‘at risk’ group for the treatment and control conditions.

Overall, the sample ranged in age from 51 to 79 years (mean = 66.47 years, SD = 7.84), and included 25 females. Participants were generally secondary educated (mean = 13.40 years, SD = 3.59) with average premorbid general intellectual functioning (mean = 104.82, SD = 8.23) and an average MMSE score of 28.23 (SD = 1.39). Clinician ratings of psychosocial functioning indicated generally mild functional decline (GAFS, mean = 70.33, SD = 12.30) and normal levels of depressive symptoms (HDRS, mean = 4.67, SD = 3.65). In terms of vascular status, four participants reported a history of heart disease, 16 reported hypertension, 16 reported hypercholesterolaemia and two reported a history of diabetes.

Several participants in this sample were taking psychotropic medications as part of standard management of comorbid neuropsychiatric conditions (e.g. depression, anxiety or sleep disturbance), which are often observed in older adults. As such, a detailed medication history was taken. In the treatment group, psychotropic medication usage was evident in a total of ten participants. Of these ten, eight were taking newer-generation antidepressants, including three taking SSRIs and five taking SNRIs. Of these ten participants, four were taking benzodiazepines, one was taking a mood stabiliser and one was taking adjunctive atypical antipsychotics. In the control group, four participants were taking psychotropic medications, which included only antidepressants (two taking SNRIs, one taking a tricyclic antidepressant and one unspecified antidepressant). Importantly, psychotropic medications (including antipsychotics, mood stabilisers and antidepressants) do not appear to modulate the MMN response (Leung et al., 2010; Michie, 2001; Mowszowski, et al., 2012) (see Chapter Three).

Table 10.

Individuals Meeting Criteria for ‘At Risk’ Status Within the Treatment and Control Conditions.

Condition	MCI	aMCI	naMCI	Depression	Current MDE	MCI and depression*	SCI
Treatment (n=25)	18 / 72%	5 / 20%	13 / 52%	12 / 48%	2 / 8%	12 / 48%	10 / 40%
Control (n=15)	12 / 80%	5 / 33%	7 / 46%	6 / 40%	2 / 13%	6 / 40%	5 / 33%

Note: Diagnoses are not mutually exclusive. MCI = Mild Cognitive Impairment, irrespective of comorbid depression history; aMCI = amnesic subtype of MCI; naMCI = non-amnesic subtype of MCI; Depression = history of depression, irrespective of comorbid MCI diagnosis; Current MDE = meets DSM-IV criteria for current Major Depressive Episode; SCI = subjective cognitive impairment only, rated as ‘two’ on the Global Deterioration Scale, does not meet criteria for MCI, does not have a history of depression. * Individuals with comorbid MCI and a history of/current depression.

5.4.2. Baseline group differences

As shown in Table 11, there were no significant treatment vs. control group differences in ‘at risk’ groups, or in demographic, psychosocial (self-rated or clinician-rated) or neuropsychological measures at baseline. The groups also did not differ statistically in MMN response (i.e. in mean amplitudes, peak amplitude or peak latency across fronto-central and temporal sites), at baseline (see Table 12).

Table 11.

Baseline Mean (SD) Scores for Diagnostic, Demographic, Clinical and Social Functioning Variables in Treatment and Control Groups, with Corresponding Between-Group Test Statistics.

Measure	Treatment (n = 25)	Control (n = 15)	Between-group differences (p < 0.05)
MCI	18	12	$U = 172.50, Z = -0.56, p = 0.58$
Depression	12	6	$U = 163.00, Z = -0.74, p = 0.46$
SCI	10	5	$U = 167.50, Z = -0.65, p = 0.51$
Gender, m/f	8/17	7/8	$\chi^2 = 0.860, df = 1, p = 0.35$
Age, years	66.00 (7.42)	67.27 (8.71)	$t = 0.490, df = 38, p = 0.63$
Education, years	14.08 (3.85)	12.27 (2.87)	$t = -1.577, df = 38, p = 0.12$
Premorbid IQ*	105.63 (7.72)	103.53 (9.11)	$U = 159.50, Z = -0.59, p = 0.55$
MMSE, raw score	28.24 (1.23)	28.20 (1.66)	$U = 178.00, Z = -0.27, p = 0.79$
HDRS, score	4.68 (4.01)	4.67 (3.11)	$t = -0.011, df = 38, p = 0.99$
GAFS	72.48 (14.20)	66.73 (7.33)	$U = 122.00, Z = -1.85, p = 0.06$
WHO-DAS [#]	19.05 (13.51)	21.68 (11.51)	$U = 155.50, Z = -0.89, p = 0.37$
Digit Span, age-scaled score	10.76 (3.26)	10.60 (3.11)	$U = 185.50, Z = -0.06, p = 0.96$
RAVLT 1-5, z-score	-0.26 (0.94)	-0.81 (1.19)	$t = -1.633, df = 38, p = 0.11$
RAVLT 7, z-score	-0.33 (0.97)	-0.79 (1.22)	$t = -1.309, df = 38, p = 0.20$
COWAT FAS, z-score	-0.02 (0.86)	-0.02 (1.29)	$t = 0.024, df = 38, p = 0.98$
COWAT Animals, z-score	0.32 (1.29)	-0.19 (0.94)	$t = -1.319, df = 38, p = 0.20$
TMT-B, z-score	-0.71 (1.40)	-0.66 (1.66)	$U = 182.00, Z = -0.15, p = 0.88$

Note: HDRS = Hamilton Depression Rating Scale, 17-item; GAFS = Global Assessment of Functioning Scale; WHO-DAS = self-rated World Health Organization Disability Assessment Schedule, summary score; RAVLT 1-5 = Rey Auditory Verbal Learning Test, total learning over trials 1-5; RAVLT 7 = Rey Auditory Verbal Learning Test, delayed recall of word list; COWAT FAS = Controlled Oral Word Association Test, total for letter trials over F, A, S; COWAT Animals = Controlled Oral Word Association Test, total for animals trial; TMT-B = Trail-Making Test B, completion time. * Premorbid IQ score from the Wechsler Test of Adult Reading was not calculated for one treatment participant due English being her second language. # Two treatment participants did not complete the WHO-DAS questionnaire.

Table 12.

Baseline Mean (SD) Scores for Neurophysiological (MMN) Variables in Treatment and Control Groups, with Corresponding Between-Group Test Statistics.

Site	MMN variable	Treatment (n = 25)	Control (n = 15)	Between-group differences (p < 0.05)
Cz	Peak amp	-2.67 (1.91)	-3.12 (1.50)	$U = 136.00, Z = -1.44, p = 0.15$
	Mean amp	-1.31 (1.58)	-1.95 (1.20)	$U = 128.00, Z = -1.66, p = 0.10$
	Peak lat	189.60 (28.54)	183.33 (40.85)	$t = -0.523, df = 22.28, p = 0.61$
Fz	Peak amp	-3.01 (1.94)	-3.61 (1.68)	$t = -1.000, df = 38, p = 0.32$
	Mean amp	-1.57 (1.68)	-2.28 (1.28)	$U = 134.00, Z = -1.50, p = 0.14$
	Peak lat	183.52 (28.87)	191.33 (28.24)	$U = 170.00, Z = -0.49, p = 0.63$
M1*	Peak amp	2.16 (1.01)	2.15 (1.09)	$t = 0.019, df = 37, p = 0.99$
	Mean amp	0.98 (0.65)	1.19 (0.77)	$t = 0.886, df = 37, p = 0.38$
	Peak lat	167.52 (32.95)	163.86 (28.74)	$U = 140.50, Z = -1.01, p = 0.31$
M2*	Peak amp	1.68 (0.72)	1.85 (1.11)	$U = 142.00, Z = -0.97, p = 0.33$
	Mean amp	0.77 (0.58)	0.92 (0.88)	$U = 125.00, Z = -1.46, p = 0.14$
	Peak lat	169.76 (34.64)	169.43 (35.94)	$t = -0.028, df = 37, p = 0.98$

Note: amp = amplitude (μV); lat = latency (ms). * Data were omitted for one control participant at M1 and M2 due to poor quality of the ERP recording at these sites.

5.4.3. Effects of treatment

1) Primary outcome: neurophysiological (MMN) response

Grand average MMN waveforms for treatment and control groups at baseline and follow-up are shown in Figure 8. Table 13 displays repeated measures ANOVA statistics for MMN and neuropsychological data for treatment and control groups at baseline and follow-up. These results demonstrate a significant interaction effect of Time*Condition at Cz and Fz: i.e. an increase (improvement) in peak and mean amplitude at frontal and central sites for the treatment group following CT compared to the control group, who demonstrated a decrease (decline) in amplitude at these sites over the ‘treatment-as-usual’ waitlist period. These effects remained significant when depression was added as a covariate ($p < 0.05$ for all interactions). There were no significant treatment effects for amplitude at the temporal sites M1 or M2, and no significant treatment effects for peak latency at any of the four sites.

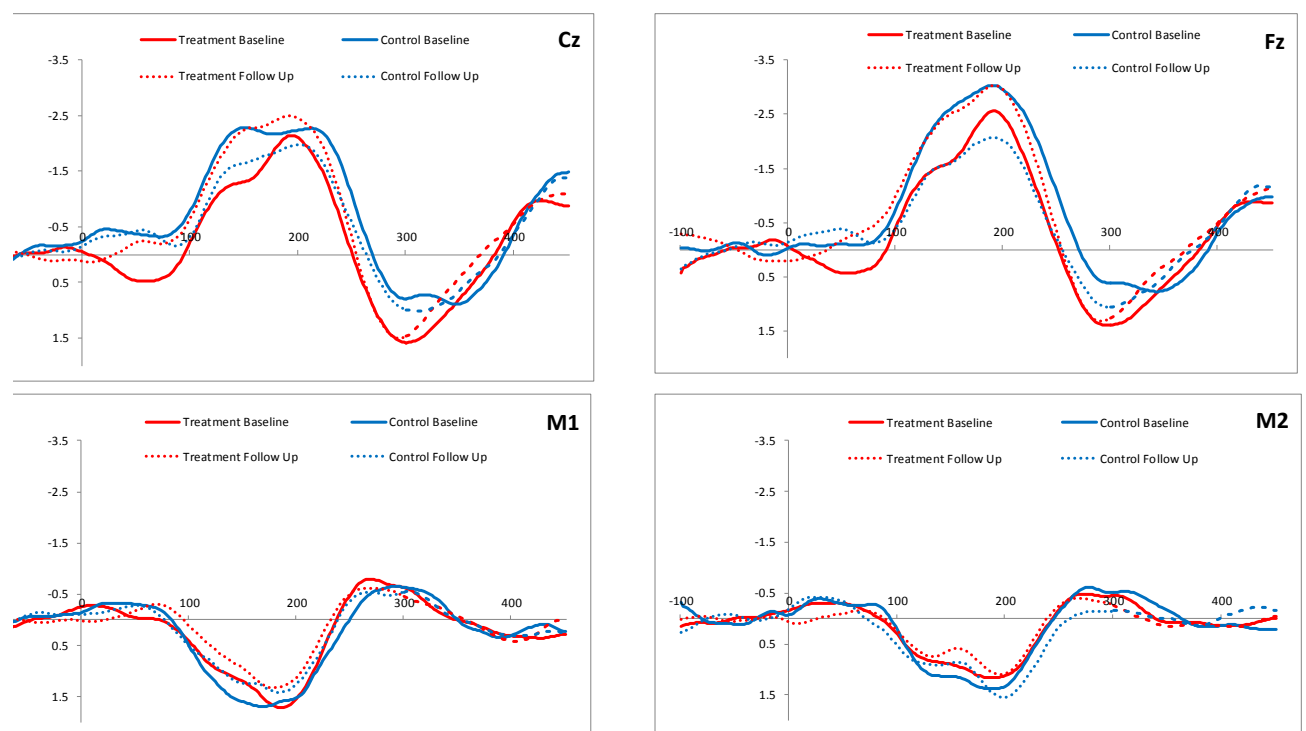


Figure 8. Grand average waveforms for treatment (red) and control (blue) groups at baseline and follow-up. This illustrates the significant effect of treatment in enhancing the MMN amplitude at Cz and Fz at follow-up, while the

amplitude declined for the control group over the treatment-as-usual waitlist period. There were no significant effects for M1 or M2 amplitude, or for latency at any of the four sites. Note: M1 and M2 waveforms are reversed in polarity due to the nose-referenced recording.

2) Secondary outcomes: neuropsychological and psychosocial measures

Regarding secondary neuropsychological outcomes, Table 13 illustrates a significant interaction effect of Time*Condition for phonemic verbal fluency (COWAT FAS test), such that the treatment group improved at post-CT follow-up while the control group declined over the ‘treatment-as-usual’ waitlist period. There were no significant treatment effects on working memory, verbal learning and memory, semantic verbal fluency or cognitive flexibility. In terms of the participants’ subjective ratings of memory functioning, despite four treatment participants failing to complete the EMQ at follow-up, a significant Time*Condition interaction effect for the EMQ Attentional Tracking subgroup, $F [1,36] = 4.76$, $p = 0.036$ indicated that the treatment participants had noticed a significant improvement in their memory difficulties. This effect remained significant when depression was added as a covariate ($p = 0.031$).

Treatment was not significantly associated with a change in psychosocial outcomes including depression, $F [1,38] = 0.00$, $p = 0.948$ and self-rated disability, $F [1,36] = 0.39$, $p = 0.537$ (note: two treatment participants did not complete the WHO-DAS questionnaire).

3) Post-hoc analyses: Correlations between changes in neurophysiological responses and cognitive functioning

In order to examine the relationship between improvements in MMN response and cognitive functioning, absolute change scores were calculated for MMN mean amplitude at Cz and Fz and for phonemic verbal fluency and the EMQ Attentional Tracking subgroup. No significant correlations were found.

Table 13.*Baseline and Follow-Up Neurophysiological and Neuropsychological Data (Mean [SD])*

GROUP						
Measure	Treatment (n = 25)		Control (n = 15)		F (<i>df</i>) (interaction)	P value (< 0.05)
	Baseline	Follow-up	Baseline	Follow-up		
MMN						
Peak amp Cz	-2.67 (1.91)	-3.12 (1.85)	-3.12 (1.50)	-2.59 (1.57)	4.77 (1,38)	0.035^a
Mean amp Cz	-1.31 (1.58)	-1.86 (1.43)	-1.95 (1.20)	-1.47 (1.22)	7.55 (1,38)	0.009^a
Peak lat Cz	189.60 (28.54)	179.76 (28.75)	183.33 (40.85)	185.47 (37.07)	0.61 (1,38)	0.440
Peak amp Fz	-3.01 (1.94)	-3.51 (2.01)	-3.61 (1.68)	-2.77 (1.72)	5.64 (1,38)	0.023^a
Mean amp Fz	-1.57 (1.68)	-2.15 (1.49)	-2.28 (1.28)	-1.40 (1.33)	10.44 (1,38)	0.003^a
Peak lat Fz	183.52 (28.87)	177.68 (34.65)	191.33 (28.24)	184.40 (40.54)	0.01 (1,38)	0.945
Peak amp M1	2.16 (1.01)	1.71 (1.00)	2.15 (1.09)	2.11 (1.15)	0.92 (1,37)	0.345
Mean amp M1	0.98 (0.65)	0.64 (0.76)	1.19 (0.77)	0.99 (1.09)	0.19 (1,37)	0.665
Peak lat M1	167.52 (32.95)	177.92 (26.28)	163.86 (28.74)	162.43 (32.86)	0.78 (1,37)	0.383
Peak amp M2	1.68 (0.72)	1.54 (0.94)	1.85 (1.11)	2.06 (1.20)	0.76 (1,37)	0.389
Mean amp M2	0.77 (0.58)	0.62 (0.78)	0.92 (0.88)	1.04 (1.13)	0.78 (1, 37)	0.384
Peak lat M2	169.76 (34.64)	179.12 (37.88)	169.43 (35.94)	181.14 (31.82)	0.02 (1,37)	0.899
Neuropsychological						
Digit Span	10.76 (3.26)	11.44 (3.51)	10.60 (3.11)	10.53 (3.50)	1.08 (1,38)	0.306
RAVLT 1-5	-0.26 (0.94)	-0.30 (1.00)	-0.81 (1.19)	-0.61 (1.25)	0.73 (1,38)	0.399
RAVLT 7	-0.33 (0.97)	-0.20 (1.04)	-0.79 (1.22)	-0.62 (1.33)	0.02 (1,38)	0.895
COWAT FAS	-0.02 (0.86)	0.20 (1.18)	-0.02 (1.29)	-0.35 (1.00)	4.24 (1,38)	0.047^a
COWAT Animals	0.32 (1.29)	0.41 (0.99)	-0.19 (0.94)	-0.05 (1.46)	0.02 (1,38)	0.903
TMT-B	-0.64 (1.37)	-0.38 (0.95)	-0.12 (0.79)	-0.24 (0.99)	1.23 (1,35)	0.275

Note: Significant values are represented in bold. Note: amp = amplitude (μ V); lat = latency (ms); RAVLT 1-5 = Rey Auditory Verbal Learning Test, total learning over trials 1-5; RAVLT 7 = Rey Auditory Verbal Learning Test, delayed recall; COWAT FAS = Controlled Oral Word Association Test, total for letter trials; COWAT

Animals = Controlled Oral Word Association Test, total for animals trial; TMT-B = Trail-Making Test B, completion time; ^a denotes interaction remained significant ($p < 0.05$) after covarying for depression. * Data were omitted for one control participant at M1 and M2 due to poor quality of the ERP recording at these sites.

5.5. Discussion

We are not aware of any other study investigating the utility of an ERP paradigm as an outcome measure of CT efficacy and index of underlying neurophysiological change. Furthermore, it is the only known study to apply neurobiological outcomes in a trial of CT in health-seeking ‘at risk’ individuals with SCI, MCI or LLD. Results demonstrate that the MMN response in frontal and central regions is significantly enhanced following CT compared to a treatment-as-usual control condition. This enhancement occurred in conjunction with improvements in phonemic verbal fluency and subjectively-rated memory difficulties in the treatment group; however, the enhanced MMN response was not directly associated with these cognitive improvements.

The finding that the MMN biomarker is altered in response to CT supports the notion that underlying neuroplastic changes have occurred in association with this multi-faceted CT intervention. That is, the enhanced MMN response indicates enhanced efficiency of fundamental, pre-attentive processing in relation to CT. From a neuroanatomical perspective, the enhanced fronto-central MMN response is generally supportive of the few neuroimaging investigations of neurobiological change following CT. As reviewed by Suo and Valenzuela (in press), the most commonly reported training-related changes seen on MRI, DTI and PET scanning have occurred in the frontal lobes.

The finding that MMN latency was not altered by the cognitive intervention may relate to methodological issues such as sampling (e.g. small sample size or lack of statistical power) or measurement (e.g. selection of the epoch in which MMN mean amplitude, peak

amplitude and peak latency were defined – however, as outlined in section 5.3.4.2, the epoch of 100-250ms was selected according to previous MMN studies in older adult populations). Ultimately, since we are not aware of any previous investigations of the MMN paradigm in this specific context, results relating to changes in MMN amplitude and/or lack of change in MMN latency should be replicated for clarification.

An interesting finding is the lack of a direct relationship between cognitive gains and enhanced MMN response in this sample, which is inconsistent with the hypothesised outcome. However, this finding is consistent with the alternative suggestion that the neurophysiological response might anticipate delayed clinical outcomes (Cummings, et al., 2007; Mueller, et al., 2005). Indeed, MMN indexes fundamental, pre-attentive information processing which may be more sensitive to immediate training effects than higher-order clinical outcomes which might develop with a longer training period or over longer follow-up intervals. As part of the larger CT study, these participants may undergo longitudinal follow-up assessment at 12-18 months, which may be helpful in clarifying this alternative hypothesis.

Indeed, this account may relate to the time course proposed by Valenzuela, Breakspear and Sachdev (2007) for the range of processes involved in neuroplasticity. Initial neuroprotective changes occur at a molecular level (e.g. increased neurotrophins or altered synaptic plasticity) and develop rapidly, within days; neuroregenerative processes (e.g. neurogenesis, synaptogenesis and angiogenesis) occur at the cellular level and develop more slowly, over weeks; finally, compensatory network responses develop at a cortical level (involving increased metabolic efficiency and adaptation via functional reorganisation) but take much longer to manifest, in the order of months. According to this timeline, it is plausible that the enhanced MMN response in relation to the seven-week CT program is reflective of the earlier stages of neuroplasticity: therefore a direct association with higher-

order cognitive improvements reflecting a complex compensatory network response might not be expected at this stage. This may also explain the lack of improvement in higher-order psychosocial functioning following CT (i.e. depression or self-rated disability). Again, planned longitudinal follow-up may be helpful in exploring these ideas.

The suggestion of the enhanced MMN response reflecting early molecular or cellular neuroplasticity is further supported by the relationship between MMN and the excitatory neurotransmitter, glutamate, which usually binds to N-methyl-D-aspartate (NMDA) receptors. Acute pharmacological blocking of NMDA receptors has been shown to reduce MMN in humans and animals (Javitt, Steinschneider, Schroeder, & Arezzo, 1996; Umbricht et al., 2000). MMN is therefore thought to be a marker of post-synaptic glutamatergic activity and thus an enhanced response following CT may reflect an increase in glutamatergic/excitatory output. This is significant given the important role of the glutamatergic system in synaptic plasticity processes (i.e. long-term potentiation and depression) supporting learning, memory and attention (Bennett, 2010; Javitt, et al., 1996; Malhotra et al., 1996). Incidentally, this may also explain why only MMN amplitude and not latency was affected by CT. Importantly, the glutamatergic system has also been implicated in the pathogenesis of cognitive impairment in ageing, MCI and AD (Gong, Lippa, Zhu, Lin, & Rosso, 2009; Muller, Scheuer, & Stoll, 1994); therefore, increased glutamatergic functioning in this ‘at risk’ group may facilitate delay or prevention of ongoing cognitive decline.

Nonetheless, there may be an indirect relationship between the concurrent neurophysiological and neuropsychological changes following CT. Phonemic verbal fluency relies on strategic and effortful retrieval processes to generate words according to novel categories; such processes are mediated by frontal lobe networks (Gourovitch et al., 2000; Rascovsky, Salmon, Hansen, Thal, & Galasko, 2007). Similarly, items comprising the

Attentional Tracking factor on the EMQ specifically involve keeping track of information during conversations or reading, confusing details or repeating information; these processes involve attentional control and working memory which are also subserved by the frontal systems (Smith & Jonides, 1995; Stuss & Benson, 1984). Thus, the CT-related enhancement in fronto-central pre-attentive processing may have a more generalised effect on a broader range of executive functions, mediated by frontosubcortical and frontotemporal networks. Accordingly, increased general efficiency of these executive functions (including strategic, effortful retrieval, attentional tracking and working memory) may be more broadly related to the observed improvements in phonemic verbal fluency and decreased self-reported difficulties with ‘attentional-based’ encoding and retrieval. It may also have been interesting to see whether the CT-related improvements in *pre-attentive* information processing are associated with objective tests of attention which typically engage *directed* or *effortful* attentional processes; however, such a measure was not included in this neuropsychological test battery due to time constraints. Future studies may wish to incorporate neuropsychological tests of attention in conjunction with MMN. In MCI and LLD samples to-date, only the temporal MMN response has been shown to relate directly to specific higher-order cognitive functions including memory and semantic verbal fluency (see Mowszowski, et al., 2012; Naismith, et al., 2012) (Chapter Three and Chapter Four); however other samples such as individuals with first-episode psychosis have demonstrated significant associations between the fronto-central MMN response and a range of executive functions including attention, working memory, attentional switching, encoding and verbal fluency (Baldeweg, Klugman, Gruzelier, & Hirsch, 2004; Hermens, et al., 2010; Kaur et al., 2011). The ‘generalised’ influence of enhanced fronto-central processing mediating improvements in executive functions would therefore suggest that, according to CT terminology, the effect of CT has been restorative (i.e. reorganising existing networks).

However, this notion is speculative at present. Further CT studies incorporating neurophysiological and neuroimaging outcomes might help to delineate this further. Additionally, it may be helpful initially to conduct some pre vs. post CT neurobiological analyses on an individual level to further clarify the nature of the CT effect.

Importantly, the cognitive gains resulting from CT have significant implications for the clinical utility of these programs. For health-seeking participants aiming to address cognitive concerns, the opportunity to improve one's cognitive skills is enticing; particularly (according to many of these participants) since word-retrieval problems and memory difficulties are so commonly reported and seem to relate to social withdrawal and anxiety. Therefore, a change in participants' qualitative experience of their memory difficulties is encouraging, as it suggests that the CT program has real-world significance. Furthermore, the program is engaging, is manageable from a time commitment perspective, is informative regarding 'healthy brain ageing' and offers the opportunity for social interaction. This study therefore has a high capacity to be translated into clinical practice.

A somewhat puzzling finding related to the significant decline in MMN response and phonemic verbal fluency in the control group over the seven-week waitlist period. Baseline testing indicated that the treatment and control groups were comparable. While it is possible that the decline was due in part to ongoing underlying neurodegeneration in the absence of CT, it seems unlikely that significant decline would occur over such a short period. Other factors, such as the lack of contact with specialist services (aside from standard medical management) may have contributed. Ultimately, longitudinal replication of these findings will be necessary to clarify the role of CT in preventing ongoing cognitive decline in addition to improving current cognitive functioning.

This study was not without limitations. This was not a double blind study as there was no active control condition. Rather, a waitlist control condition was selected in order to

improve the clinical utility of the study for all participants, i.e. to ensure that control participants would also have access to the CT program at the end of the observation period. Indeed, 11/15 control participants accepted a place in subsequent CT groups. Additionally, a waitlist control condition was thought to be more amenable to adherence. Another potential limitation was the combination of SCI, MCI and LLD groups into one ‘at risk’ sample; some would see this as a potential confound. However, given that we are not aware of any other study of CT in ‘at risk’ older adults, it was important to include the variety of health seeking phenotypes that would usually present to specialist memory clinics. Furthermore, in reviewing the literature on each ‘at risk’ subgroup, it appears that there are many pathophysiological and symptomatic commonalities and as such these groups are all considered to be prodromal syndromes to dementia. One of the overall goals of this research was to raise awareness of the utility of CT as a secondary prevention tool; as such, further research investigating the effects of CT in individual ‘at risk’ populations is warranted. Additionally, in using the *Trail Making Test* Part B as a measure of cognitive flexibility, it is acknowledged that many clinicians/researchers also calculate a derived score which takes into account the unique contribution of cognitive flexibility over and above the contribution of processing speed and perceptual tracking. This may involve calculation of a ratio score (i.e. TMT B / TMT A) or a difference score (i.e. TMT B – TMT A). These derived scores are therefore thought to represent a more ‘pure’ measure of cognitive flexibility (Hester et al., 2005). As such, the omission of a derived score from this study could be considered a potential limitation and it is recommended that future research incorporate these scores when using *Trail Making Test* Part B as a measure of cognitive flexibility.

In conclusion, this study has extended the CT literature by applying a novel neurophysiological outcome measure to investigate the efficacy of a multi-faceted CT program in ‘at risk’ older adults. Results suggest that underlying neuroplasticity has occurred

(as reflected by the enhancement of the fronto-central MMN) in association with this multifaceted CT intervention, alongside higher-order cognitive improvements. These findings further suggest the clinical utility of CT as a secondary prevention tool to delay ongoing neurodegeneration or improve functioning in older adults who may be in the earlier stages of dementia.

CHAPTER SIX:

General discussion

6. General discussion

6.1. Contribution of this research to the literature

The research presented in this thesis represents a contribution to the international clinical and scientific communities' attempts to address the emergent problem of an expanding ageing population. Having discussed the necessity for early detection and secondary prevention tools targeting groups with a higher risk of developing dementia, overall this research has demonstrated the viability of the MMN ERP paradigm as a novel neurophysiological biomarker of 'at risk' status in MCI and LLD; has critically examined the utility of CT as a secondary preventive strategy in 'at risk' groups; and has demonstrated enhanced neurophysiological responses using the MMN paradigm as an outcome measure of treatment efficacy following a multifaceted CT program for 'at risk' older adults (including MCI, LLD and SCI). In doing so, this research has also contributed to knowledge regarding the underlying neural mechanisms associated with CT, thought to reflect neuroplasticity.

6.2. Review of research aims

The overarching goals of this research were to actively contribute to on-going efforts to reduce the impact and elucidate the underlying pathology of cognitive decline in later life. As discussed in Chapter One, the implications of an expanding ageing population include escalating rates of dementia incidence and prevalence, with associated increase in financial and social costs. In light of projected increases in dementia prevalence to 81 million people worldwide in 2040 (Ferri et al., 2005), Chapter One also included an overview of the literature pertaining to early clinical and physiological identification of older adults 'at risk' for cognitive decline and dementia, including individuals with MCI, LLD and/or SCI. Additionally, the literature relating to early intervention strategies aimed at slowing down or

preventing on-going decline in these groups was reviewed, with a focus on CT as a potential secondary preventive technique. A rationale for the investigation of novel neurophysiological biomarkers for ‘at risk’ groups was provided, and the use of such biomarkers as surrogate outcome measures of treatment efficacy and indexes of neuroplastic mechanisms underlying cognitive intervention was discussed. Within this framework of existing knowledge and identified gaps in the literature, three specific research aims were presented:

- 1) To examine existing evidence for the efficacy of CT as a cognitive intervention in older adults, in order to evaluate its utility as a potential selective prevention technique for ‘at risk’ groups. An additional aim was to explore existing knowledge regarding the physiological mechanisms underpinning cognitive and psychosocial gains related to CT, and to extend the understanding of such mechanisms by applying a novel neurophysiological paradigm to this field. This led to the development of the second aim.
- 2) To investigate the viability of the auditory MMN response as a biomarker of ‘at risk’ status in older adults, by characterizing MMN and its relationship to cognitive functioning in ‘at risk’ groups.
- 3) To investigate MMN as a potential outcome measure of treatment efficacy and index of underlying mechanism of neural change following a multifaceted CT program in older adults ‘at risk’ for dementia, including those with SCI, MCI and LLD, using a randomized controlled design. A secondary goal was to examine whether such neurophysiological changes may be associated with broader measures of cognitive and psychosocial functioning.

6.3. Utility of CT as an early intervention technique: efficacy in ‘at risk’ older adults

Chapter Two addressed the first aim of the research and comprised a systematic review and discussion of key findings from studies utilising CT programs in older adult populations, including those ‘at risk’ for dementia. Importantly, the review initially included an operational definition and diagrammatic explanation of CT, as this approach has frequently been confused or combined with other Cognitive Remediation techniques such as cognitive stimulation or cognitive rehabilitation. Thereafter, the purpose of the review was to evaluate the application of a novel framework for CT efficacy, relating to various stages of Thal’s (2006) primary, secondary and tertiary prevention hierarchy for dementia.

It was suggested that CT may act as a primary preventative tool for healthy older adults, reducing the incidence of disease by delaying cognitive decline and/or by building cognitive reserve (Valenzuela, 2008). Indeed, the review showed that generally positive findings are apparent in healthy older adults, suggesting that CT programs may represent a viable primary preventative strategy; however, methodological differences and the need for longer observation periods necessitate further investigation of the preventative capacity of CT in healthy ageing.

It was then proposed that CT may be more appropriate as a secondary preventative technique for individuals ‘at risk’ of developing dementia, in order to improve or slow cognitive decline in pre-selected ‘at risk’ groups or even to delay the conversion of preclinical disease to established dementia. While MCI has been most widely studied within the CT literature, it was suggested that CT may also be appropriate as an early intervention strategy in other ‘at risk’ groups such as LLD, which, as discussed in Chapter Two, is similarly associated with cognitive impairment and increased rates of dementia incidence over time. Evidence from nine CT studies in MCI, one CT study in LLD and three CT

studies in younger samples with a lifetime history of depression was critically reviewed from this ‘early intervention’ perspective. Although a direct comparison of findings was limited by vast methodological and CT program differences and by the lack of other CT studies in LLD, generally positive findings suggested that CT programs can improve cognitive functioning (particularly learning and memory) in these groups. Additionally, preliminary evidence for concurrent neural changes in MCI suggested that CT may promote neuroplasticity. Overall, it was found that CT represents a promising tool that may be effective as a non-pharmacological selective preventative technique in individuals ‘at risk’ for cognitive decline, particularly since they are easy to implement, enjoyable and offer the potential for social engagement. As with healthy older samples, recommendations for further research included tighter methodological control and extension of the observation period; additionally, a major limitation identified within the literature was the lack of focus on concomitant effects on brain physiology to delineate the underlying neural mechanisms of CT.

Since the review presented in Chapter Two was published in 2010, a literature update was included to reflect more recent developments in the CT literature regarding efficacy in ‘at risk’ samples. Two subsequent systematic reviews of ten studies in MCI (Gates et al., 2011) and 15 studies focusing specifically on aMCI (Jean et al., 2010) also reported statistically significant cognitive improvements especially on objective and subjective measures of memory, with some improvement on measures of psychosocial functioning (i.e. quality of life and mood). These reviews also highlighted considerable methodological variability amongst CT studies.

Finally, evidence was examined to substantiate the proposal that CT may act as a tertiary prevention strategy for those individuals with established dementia such as AD, aiming to reduce disability and disease progression. It was suggested that largely disparate

findings indicate that patients with AD may benefit to a lesser extent, or less consistently, than healthy older adults or those with MCI. That is, CT programs as tertiary prevention tools may be implemented ‘too late’ in individuals with established, progressive, dementia. This may be due to the more predictable progressive course and/or higher burden of pathology in AD, resulting in less opportunity for neuroplasticity.

Overall, applying the prevention hierarchy to an evaluation of evidence for CT efficacy was successful, as it provided a logical and pragmatic approach to clarifying the utility of CT in older adults. Indeed, subsequent reviews have also adopted the prevention hierarchy framework in their evaluation of CT in ‘at risk’ older adults (Gates et al., 2011).

This review also highlighted an important limitation which, at the time of publication, was less widely discussed: the dearth of investigation into underlying neural changes occurring with CT by incorporating neuroimaging outcome measures. It was suggested that while advances in physiological and functional imaging techniques such as MRI, PET and ERP readily afford the opportunity to delineate underlying mechanisms of cognitive and/or psychosocial change (Belleville, et al., 2007; Valenzuela, Breakspear, & Sachdev, 2007; Valenzuela & Sachdev, 2006), few studies had utilised these techniques for CT. A subsequent discussion of potential mechanisms of change underlying CT efficacy included the protective effect of increased cognitive activity, as well as the promotion of neuroplasticity. As demonstrated in the literature update following the review, this area has received increasing interest recently and many studies are beginning to incorporate neuroimaging outcomes for this purpose. Indeed, this discussion led to the development of the second and third research aims; that is, to apply a novel ERP paradigm to CT research in ‘at risk’ groups.

A possible limitation of the review itself was the lack of a systematic search strategy. While the primary purpose of the review was to evaluate key findings from the CT literature

within the framework of the prevention hierarchy, a systematic approach would have been optimal and it may have been helpful to include details of the search strategy within the published article. In order to address this limitation, details of the search strategy were included within Chapter Two to clarify the review procedure and reasons for including/excluding various CT studies. However, it is noted that few studies exist in this area, somewhat limiting the opportunity for restrictive searches and meta-analytic techniques.

6.4. Application of the MMN paradigm as a novel neurophysiological biomarker of ‘at risk’ status

As discussed in Chapter One, while ‘at risk’ groups including MCI, LLD and SCI have generally been characterised according to clinical criteria, increasing attention has recently been directed towards incorporating a pathophysiological biomarker approach to identifying true cases of prodromal dementia. Furthermore, as shown in the literature update in Chapter Two, neurobiological outcomes are now emerging as common additions to CT study protocols. However, most of the research investigating physiological biomarkers or neurobiological outcome measures has primarily included neuroimaging techniques (MRI, DTI, PET etc.), which are typically expensive, time-consuming and sometimes invasive. Other neurophysiological responses such as ERPs may also be appropriate and may offer a novel perspective leading to further discovery within ‘at risk’ groups. Therefore, as outlined in the second research aim above, this research investigated the utility of MMN as a biomarker of ‘at risk’ status in older adults in a novel application of this ERP paradigm to the literature.

The MMN paradigm was selected due to its ability to address two limitations within the literature reporting ERP responses in ageing. First, previous studies had typically focused on cognitive paradigms requiring directed attention and conscious engagement with the

eliciting stimuli, thus indexing later stages of information processing. However, it has been consistently suggested here that further information regarding the cognitive decline seen in ‘at risk’ groups might be gained from examining inefficiencies at earlier stages of information processing. The passive MMN paradigm is appropriate in this regard as it indexes fundamental, pre-attentive information processing. Secondly, previous ERP studies have tended to focus on midline scalp electrodes, which reflect fronto-central brain functioning. However, it has been suggested here that ERP paradigms utilised in older groups should also provide some index of functioning in other brain regions which are implicated in the pathophysiology of neurodegenerative disorders and of depression, such as the temporal lobes. Again, the MMN paradigm is an appropriate candidate as the two main generators of the response lie in the temporal and frontal lobes.

Chapters Three and Four report findings from separate examinations of the MMN response in MCI and LLD (respectively), compared to healthy older adults. In terms of the MCI sample, the study was the largest known investigation of MMN in MCI, and demonstrated a significantly reduced temporal MMN response compared to age-matched healthy, cognitively-intact older adults. Furthermore, these findings had functional significance for the MCI group: the right temporal MMN reduction was significantly associated with poorer performance on a task of verbal learning, and the left temporal MMN reduction was significantly associated with increased self-rated disability. Similarly, results from the LLD sample demonstrated that older patients with lifetime depression and only mild residual symptoms showed significantly reduced MMN at temporal sites compared to age-matched healthy controls. Importantly, the MMN deficit in this study was also linked to aspects of higher-order cognitive and psychosocial functioning, that is, poorer semantic fluency and higher levels of self-rated disability. This suggests that the MMN biomarker has some clinical and functional significance.

The findings from both studies were consistent with the hypothesis that cognitive deficits in ‘at risk’ groups are associated with inefficiency of information processing at an early, pre-attentive stage and that MMN is a valid marker of these subtle neurophysiological changes. These findings further substantiated the hypothesis that the attenuation of early information processing mechanisms may underpin aspects of higher-order cognitive and psychosocial functioning in MCI and LLD, specifically those relating to frontotemporal circuitry and particularly temporal lobe functioning. Although the two ‘at risk’ groups demonstrated associations between MMN and differing cognitive functions (i.e. verbal learning in MCI and semantic verbal fluency in LLD), the general pattern of the association is consistent from a neuroanatomical standpoint. That is, both verbal learning and semantic fluency are subserved by frontotemporal circuitry involving the prefrontal cortex as well as medial and lateral temporal lobe regions (Desgranges et al., 1998; Kopelman et al., 1998; Gourovitch et al., 2000; Rascovsky et al., 2007). Moreover, alterations in these frontotemporal networks have been demonstrated in previous neuroimaging studies in both MCI and LLD (Johnson et al., 2006; Machulda et al., 2009; Naismith et al., in review).

Interestingly, both ‘at risk’ groups demonstrated a lateralised association between the right-temporal MMN response and poorer cognitive functioning. This finding is consistent with the lateralized temporal MMN response reported by Borghetti et al. (2006). It has been shown that the MMN to non-linguistic (i.e., tonal) sound changes can be elicited more strongly in the right hemisphere compared to the left, which is more responsive to language-based (i.e., phonemes, syllables and words) changes (see Kujala et al., 2007). Since both of the present studies used a tonal paradigm, it may follow that the resultant MMN was stronger in the right hemisphere and therefore was sufficiently robust at that site to demonstrate a relationship with impaired performance on the higher-level learning and fluency tasks. As

suggested in each study, replication of these findings within other MCI and LLD samples will ultimately help to clarify patterns such as laterality.

An interesting point was raised by a reviewer of the MMN in LLD (i.e. Chapter Four) manuscript prior to publication. The reviewer noted that the difference in MMN between the LLD and healthy control groups may have resulted from differences in response to the heterogeneous standard stimuli, rather than the interspersed deviant stimuli. Supplementary analyses in response to this comment confirmed that the MMN differences between groups were due to differences in the deviant and not the standard ERP. As shown in supplementary Figure 9a (see Appendix 1), there were notable differences between LLD and control groups in their ERPs to deviant stimuli, particularly at the temporal (mastoid; M1 & M2) sites (the greatest differences occurred within the ‘MMN window’ i.e. 100-250 msec). In contrast, the group average ERPs to the standard stimuli were remarkably similar in the depression and control groups. Supplementary analyses of the standard and deviant ERPs for the MCI sample compared to healthy controls revealed the same pattern (see supplementary Figure 9b in Appendix 1). Thus, it appears that the difference in MMN was indeed due to a difference in processing of the deviant stimuli for both ‘at risk’ groups.

As mentioned, both studies were limited by small sample sizes, and the MCI group were heterogeneous with respect to aMCI vs. naMCI subtyping. Ultimately, replication of these findings with other samples, direct comparison to AD and other dementia samples, and longitudinal follow-up of these groups will help to clarify the true predictive validity of MMN as a biomarker for cognitive decline in these ‘at risk’ groups.

Unfortunately, this research did not include a comparison of an SCI sample with healthy controls due to the small SCI sample size at the time of these initial analyses, resulting in insufficient statistical power. It is important for future research to investigate the utility of MMN as a biomarker of ‘at risk’ status in SCI to determine whether the reductions

in fundamental information processing manifest at this earlier ‘at risk’ stage, and if so, whether they relate to subjective cognitive complaints. Given the pattern of association with learning and verbal fluency shown in the LLD and MCI groups, it is plausible that a similar reduction in temporal MMN may relate to self-reported memory and word-finding difficulties. Ongoing research is now required to confirm this hypothesis.

Overall, the findings presented in Chapters Three and Four have shown that MMN may be a viable biomarker of the transitory stage between healthy ageing and dementia, thus representing a practical, time-efficient and non-invasive tool for early identification of ‘at risk’ individuals. These studies have extended the limited understanding of MMN in MCI and LLD through their increased sample size, direct comparison with healthy older adult controls and investigation of the link with higher-order cognitive functions in each group.

6.5. MMN as an outcome measure of CT efficacy and index of neuroplasticity in ‘at risk’ older adults

As discussed in Chapters One and Two, one of the major limitations of the CT literature to-date has been the dearth of focus on neurobiological outcomes to investigate whether well-established cognitive improvements following CT are underpinned by neural changes. This research has included a discussion of the potential mechanisms thought to mediate CT outcomes, namely, increasing cognitive activity and promoting neuroplasticity. In order to fully delineate the utility of CT as a secondary intervention strategy, it is imperative to determine the nature and extent of any neurobiological changes and the impact of such changes on underlying neurodegenerative pathophysiology. As described in Chapter Five, several recent studies have begun to investigate this neurobiological aspect of CT by implementing neuroimaging outcomes in CT trials of healthy older adults. Such trials have reported significant outcomes most commonly reflecting training-related changes in the

frontal lobes (see review by Suo & Valenzuela, in press). Only one known study (Forster et al., 2011) has reported neuroimaging outcomes in MCI; however the validity of these results is questionable since their control group also received a CT-based intervention. Overall, further research is required to investigate underlying neural changes following CT in ‘at risk’ groups: this was addressed by the third research aim, outlined above.

As discussed in relation to the biomarker studies (Chapters Three and Four), the MMN paradigm was considered to be an appropriate outcome measure in this regard due to the time-efficiency, non-invasiveness and cost effectiveness of ERPs in comparison to neuroimaging techniques such as MRI, DTI or PET scans. MMN has also been shown to have satisfactory test-retest reliability over multiple assessments in the range of 0.59-0.78 (Frodl-Bauch et al., 1997; Tervaniemi et al., 1999; Hall et al., 2006). Furthermore, as described above, the MMN response allows for investigation of changes to fundamental, pre-attentive processes, which have been shown to relate directly to higher-order cognitive and psychosocial outcomes, thereby potentially revealing the neural mechanisms of CT-mediated cognitive improvements. In fact, MMN has been utilised in previous investigations of neuroplasticity to determine the effects of language learning, musical expertise, reading-skill training and recovery from stroke (see reviews by Kujala et al., 2007 and Naatanen et al., 2011).

Indeed, the results reported in Chapter Five indicated an enhanced fronto-central MMN response in 25 ‘at risk’ older adults following a multi-faceted CT intervention compared to 15 waitlist control participants, consistent with previous neuroimaging investigations reporting frontal lobe changes following CT (see review by Suo and Valenzuela, in press). The altered MMN response also supported the idea that underlying neuroplastic changes had occurred in association with CT. That is, the enhanced MMN response indicated enhanced efficiency of fundamental, pre-attentive processing in relation to

CT. It was suggested that this enhancement was reflective of the initial stages of neuroplasticity, i.e. rapidly developing (within days) neuroprotective processes at a molecular level (e.g. altered synaptic plasticity or increased neurotrophins) or neuroregenerative processes occurring more slowly (over weeks) at a cellular level (e.g. neurogenesis, synaptogenesis, angiogenesis). This is consistent with the established relationship between MMN and post-synaptic glutamatergic activity and it was suggested that the enhanced MMN response following CT may reflect an increase in glutamatergic/excitatory output. This is significant given the important role of the glutamatergic system in synaptic plasticity processes (i.e. long-term potentiation and depression) supporting learning, memory and attention. Studies utilising spectroscopy may now be ideal to explore these mechanisms further.

Notably, the CT intervention also resulted in cognitive improvements in phonemic verbal fluency and reduced self-reported memory difficulties relating specifically to keeping track of information during encoding or retrieval; however these cognitive improvements were not directly associated with the enhanced MMN response. This may have related to the suggestion that the enhanced MMN response reflected the earlier stages of neuroplasticity, in which case a direct association with higher-order cognitive improvements (reflecting a complex cortical-level compensatory network response, occurring slowly over months) might not be expected immediately after the seven-week training period. Nonetheless, it was suggested that the CT-related enhancement in fronto-central pre-attentive processing may have had a more generalised ‘booster’ effect on executive functions mediated by frontotemporal and frontosubcortical networks. This increase in general efficiency may have related indirectly to the improvements in phonemic verbal fluency and learning/memory difficulties relating to attentional control and working memory, which involve these executive functions that are subserved by frontal lobe networks. According to CT

terminology (proposed independently of the neuroplasticity lexicon), the effect of this CT intervention therefore appeared to have been restorative (i.e. reorganising existing networks). However, this notion was somewhat speculative and further CT studies incorporating neurophysiological and neuroimaging outcomes were recommended, possibly also involving analyses on an individual level, to clarify the nature of the CT effect.

At this stage, it remains unclear as to why the control group declined so significantly over the ‘treatment-as-usual’ waitlist period, particularly as the treatment and control groups were comparable at baseline. It seems unlikely that ongoing neurodegeneration in the absence of CT would result in significant decline over such a short period. It is certainly plausible that other factors may have indirectly contributed, such as a decline in mood, reduced feelings of self-efficacy and empowerment in this health-seeking group (which would have been experienced by the treatment group whilst actively engaged in an intervention targeting their cognitive concerns) or a lack of the socialisation afforded by the group-based treatment. Ultimately, replication of these findings with further research incorporating longer observation periods may help to clarify this issue.

As discussed in Chapter Five, the study was limited by the lack of an active control group; however the ‘treatment-as-usual’ waitlist control condition was deliberately selected in order to increase the likelihood of adherence to the trial and also to be able to offer the control participants a clinically meaningful CT experience at the end of the observation period. Additionally, this study utilised a combined SCI, MCI and LLD ‘at risk’ sample such that it is difficult to tease apart which subgroups might benefit most from CT; however given that we are not aware of any other well-controlled study of CT in ‘at risk’ older adults, it was important to include the variety of health-seeking phenotypes that would usually present to specialist memory clinics. Furthermore, given the pathophysiological and symptomatic commonalities between the three subgroups, all are considered to be possible prodromal

syndromes to dementia and therefore warrant investigation of potential secondary intervention strategies. Further research investigating the neurobiological effects of CT within each ‘at risk’ subgroup is now warranted.

Overall, the study has extended the CT literature by applying a novel neurophysiological outcome measure to investigate the efficacy of a multi-faceted CT program in ‘at risk’ older adults. Results have suggested that underlying neuroplasticity has occurred (as reflected by the enhancement of the fronto-central MMN) in association with this multi-faceted CT intervention, alongside higher-order cognitive improvements. These findings have further suggested the clinical utility of CT as a secondary prevention tool to delay ongoing neurodegeneration or improve functioning in older adults who may be in the earlier stages of dementia.

6.6. Limitations of the research

Several limitations pertaining to specific sections of the research have been addressed within each chapter and have also been discussed above. However, there are some potential limitations, which relate more broadly to the body of research.

In each of the empirical studies comprising this body of research, multiple statistical comparisons were conducted for neurophysiological data and results may therefore be limited by the absence of statistical correction (e.g. use of the Bonferroni statistic). For example, it may have been worthwhile to control the family-wise Type I error rate across MMN components (mean amplitude, peak amplitude and peak latency) for each site. However, it was decided that given the small sample sizes and exploratory nature of this research, a higher probability of Type I errors was preferred over the probability of Type II errors. Nonetheless, future research incorporating multiple comparisons should strongly consider including an appropriate method of statistical correction to control for the probability of

making Type I errors. It is also important to acknowledge that whilst these studies represent the largest known investigations of MMN in this cohort, the small sample sizes may have been limiting with respect to statistical power. Therefore, there may have been insufficient statistical power to detect between-group differences or relationships between neurophysiological and neuropsychological or demographic data. Replication and extension of these results in larger samples (including larger control groups) is now warranted.

Given the age of the sample, it is important to address the potential influence of hearing impairment on the auditory MMN paradigm. While hearing was not specifically assessed as part of this study, all participants were asked about hearing impairments during their medical assessments. Any participant with a hearing aid was requested to wear it for the duration of the neurophysiological assessment. Moreover, it has been reported that while impairments in the central auditory system result in sensory processing deficits which in turn can cause cognitive deficits, these central auditory system impairments are *not* related to peripheral sensory loss (i.e. hearing impairment per se) (Mahncke et al., 2006). As such, it is unlikely that hearing impairment was a confounding factor in this body of research. Nonetheless, for completeness, future research involving auditory paradigms in older samples should include an objective measure of hearing to enable a more definitive analysis of the potential impact of hearing impairment.

Several participants were taking psychotropic medications during the studies, largely for psychological distress (i.e. depressive and anxiety syndromes). In some cases, antipsychotic medications were also used as adjunctive treatments. The potentially confounding effect of these psychotropic medications on MMN response has been addressed within each chapter; however this issue warrants further discussion in relation to the body of research as a whole. Firstly, given that a considerable proportion of community-dwelling older adults have a history of mood disturbance with pharmacological management, it was

considered particularly important to include such individuals in order to improve the ecological validity of the study. Further, evidence was cited from a recent study (Leung et al., 2010) indicating that the MMN response is not modulated by the serotonergic or dopaminergic system. Additional evidence was cited demonstrating that the MMN response is not affected by antipsychotic medication (Michie 2001). Rather, modulation of the MMN response primarily by the glutamatergic system has been emphasised; importantly, this system is relatively unaffected by such psychotropic medications. Thus, it was suggested that it is unlikely that the effects observed in this body of research are due to psychotropic medication use. This suggestion was supported by a post-hoc analysis reported in Chapter Three, which revealed that there was no significant difference in MMN response between those participants taking psychotropic medications and those not taking such medications. Nonetheless, it is recognised that this issue can be difficult to clarify with certainty in small clinical samples which may be underpowered to detect such differences, and for this reason all participant medication use was explicitly detailed within each relevant chapter, and psychotropic medication was specifically identified as a potential confound within the individual discussion sections.

6.7. Directions for future research

Results from these three empirical studies have promising implications for the application of MMN to the ‘at risk’ literature, and for the utility of MMN (and indeed other ERPs) to the CT literature. These neurophysiological measures represent a more practical, time-efficient, non-invasive and cost-effective method of exploring the neurobiological characteristics of prodromal dementia and investigating the underlying neural changes associated with intervention trials.

As mentioned, further research is warranted to replicate these findings. In particular, larger sample sizes and longitudinal follow-up would be helpful in clarifying the predictive

utility of MMN as a biomarker of progression to dementia in ‘at risk’ groups, and in clarifying the longitudinal impact of apparent neuroplastic enhancement of pre-attentive processing following CT. A formal comparison of the MMN response in SCI compared to healthy controls should be undertaken to clarify whether MMN is a viable marker of altered fundamental processing at this earlier ‘at risk’ stage. Furthermore, it would be useful to further delineate the viability of MMN as a biomarker of ‘at risk’ status in more heterogeneous groups, such as separate groups of aMCI and naMCI, and to delineate the extent to which MMN is reflective of underlying neural change within each of the ‘at risk’ subgroups (i.e. SCI, MCI and LLD).

6.8. Concluding remarks

This body of research was designed to explore the neurophysiological profile of ‘at risk’ older adults, and to examine the efficacy and underlying neural mechanisms of CT as an early intervention technique for secondary prevention of dementia.

In reviewing the literature, it was suggested that CT offers promise as a preventive therapeutic technique, particularly as a selective intervention for ‘at risk’ groups; however, further investigation of underlying neural changes is needed to reinforce evidence of improved cognitive outcomes. The research included a novel application of the MMN paradigm to this field in order to investigate its utility as a biomarker of cognitive decline, as well as to examine the MMN response as an outcome measure in a randomised controlled trial of Cognitive Training treatment efficacy.

Results from two empirical investigations have indicated that the MMN response is reduced in ‘at risk’ groups relative to healthy older controls and is also associated with higher-order cognitive and psychosocial functioning. This research has therefore provided preliminary evidence for the utility of a non-invasive, time-efficient neurophysiological

biomarker of 'at risk' status. A third empirical study demonstrated that the MMN response is enhanced following a multi-faceted CT program for 'at risk' older adults, supporting the notion that neuroplastic changes occur in relation to CT. Thus, this research has also extended the somewhat limited knowledge regarding underlying neural changes associated with CT. The latter results are extremely promising given the rapid expansion of the ageing population, as they suggest that in addition to producing cognitive improvements, CT may also be effective in altering the underlying pathophysiological processes associated with prodromal dementia. Ultimately, longitudinal follow-up will aid in clarifying the true utility of CT as a secondary intervention strategy for 'at risk' older adults. Moreover, this CT program was engaging, manageable from a time commitment perspective, informative regarding 'healthy brain ageing' and offered the opportunity for social interaction. This trial therefore has a high capacity to be translated into clinical practice.

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APPENDICES

Appendix 1: Supplementary Figures 9a and 9b

Appendix 2: Publication, “Early intervention for cognitive decline: can cognitive training be used as a selective prevention technique?”

Appendix 3: Publication, “Reduced Mismatch Negativity in Mild Cognitive Impairment: associations with neuropsychological performance

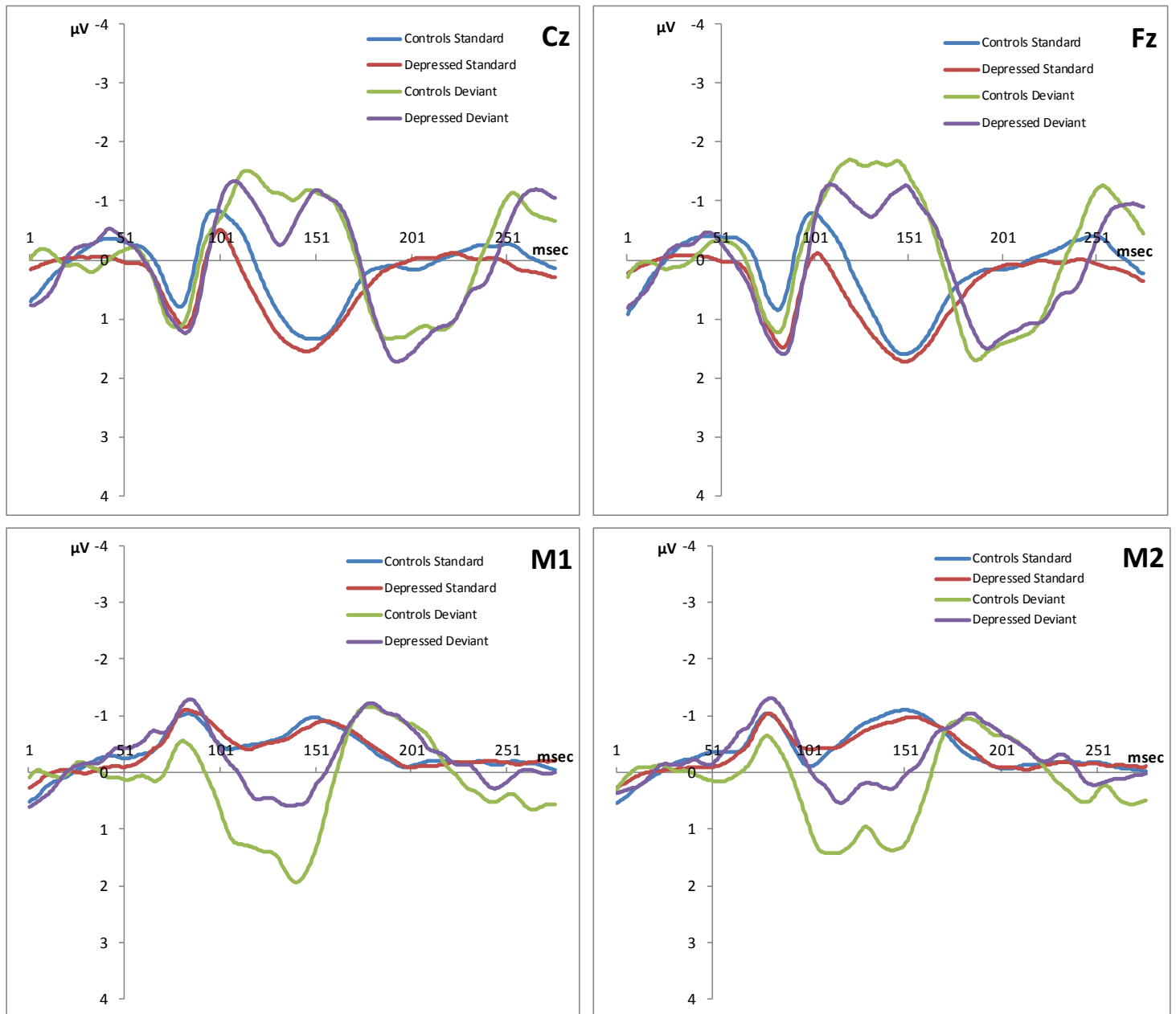
Appendix 4: Publication, “Reduced temporal mismatch negativity in late-life depression: An event-related potential index of cognitive deficit and functional disability?”

Appendix 5: Supplementary data from Chapter 5: “A Healthy Brain Ageing Cognitive Training program enhances neurophysiological responses in older ‘at risk’ adults: an event-related potential study”

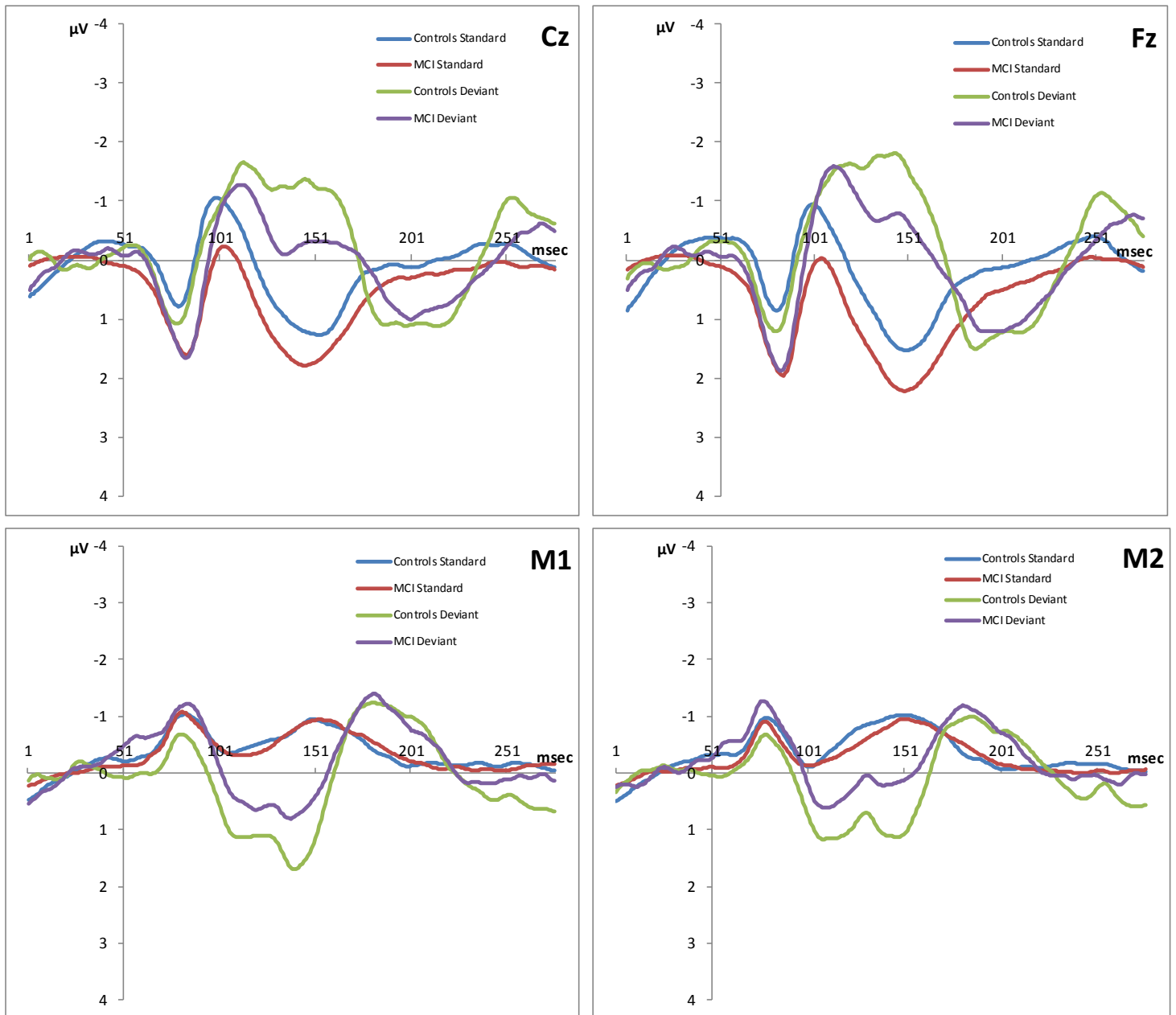
Appendix 6: Macquarie University Human Research Ethics Committee approval letter and University of Sydney Human Research Ethics Committee approval letter

APPENDIX ONE:

Supplementary Figures 9a and 9b



Supplementary Figure 9a: Grand average for (i) the control group's standard ERP (blue); (ii) the depression group's standard ERP (red); (iii) the control group's deviant ERP (green); and (iv) the depression group's deviant ERP (purple) at (clockwise, from top left) central (Cz), frontal (Fz), right temporal (M2) and left temporal (M1) sites. The depression and control groups do not differ in the standard ERPs; whereas they do appear to differ substantially in the deviant ERPs, particularly between 100-250 ms (corresponding to the MMN response). Note: M1 & M2 waveforms are reversed in polarity due to the nose-referenced recording.



Supplementary Figure 9b: Grand average for (i) the control group's standard ERP (blue); (ii) the MCI group's standard ERP (red); (iii) the control group's deviant ERP (green); and (iv) the MCI group's deviant ERP (purple) at (clockwise, from top left) central (Cz), frontal (Fz), right temporal (M2) and left temporal (M1) sites. The MCI and control groups do not differ in the standard ERPs; whereas they do appear to differ substantially in the deviant ERPs, particularly between 100-250 ms (corresponding to the MMN response). Note: M1 & M2 waveforms are reversed in polarity due to the nose-referenced recording.

APPENDIX TWO:

Early intervention for cognitive decline: can cognitive training be used as a selective prevention technique?

(Published journal article)

Due to copyright laws, the following articles have been omitted from this thesis.
Please refer to the following citations for details.

- 1) Mowszowski, L., Batchelor, J. & Naismith, S. (2010). Early intervention for cognitive decline: can cognitive training be used as a selective prevention technique? *International Psychogeriatrics*, 22, 537-548.
DOI: 10.1017/S1041610209991748
- 2) Mowszowski, L., Hermens, D. F., Diamond, K., Norrie, L., Hickie, I. B., Lewis, S. J. G., et al. (2012). Reduced Mismatch Negativity in Mild Cognitive Impairment: associations with neuropsychological performance. *Journal of Alzheimer's Disease*, 30(1), 209-219. DOI: 10.3233/JAD-2012-111868
- 3) Naismith, S. L., Mowszowski, L., Ward, P. B., Diamond, K., Paradise, M., Kaur, M., et al. (2012). Reduced temporal mismatch negativity in late-life depression: An event-related potential index of cognitive deficit and functional disability? *Journal of Affective Disorders*, 138, 71-78.
DOI: 10.1016/j.jad.2011.12.028

APPENDIX FIVE:

Supplementary data from Chapter 5: “A Healthy Brain Ageing Cognitive Training program enhances neurophysiological responses in older ‘at risk’ adults: an event-related potential study”.

a) Blinding

Multiple measures were taken at various time points during the study to ensure that blinding was not broken:

- 1) As stated in section 5.3.2, randomisation outcomes were given to each participant after completion of their baseline assessments to ensure that the clinicians conducting baseline assessments would remain blinded.
- 2) Only one of two clinicians who conducted the intervention actually gave the envelopes containing randomisation outcomes to the participants, to prevent any other clinicians from inadvertently becoming unblinded.
- 3) Prior to giving each participant the envelope containing their randomisation outcome, the clinician reminded the participant that they should not discuss the contents of the envelope with any researchers other than those listed with the outcome (in which they were directed to the Trial Coordinator if they had any questions regarding the group sessions).
- 4) The intervention was conducted on a separate level of the building to where the assessments took place, to avoid the potential for clinicians to see participants coming and going from the intervention.

5) At follow-up, participants were reminded on several occasions (before the clinic commenced and again before each assessment component) not to discuss the intervention period at all with the clinicians.

6) All clinicians were instructed to immediately stop any participant who began to discuss the intervention and to again explain the concept of blinding to them (e.g. 'I'm sorry to interrupt, but in order to reduce the potential for any bias on my part during this assessment, I am not allowed to know which group you were allocated to and therefore it is best that we do not talk about this period at all'). The participant was then directed to the Trial Coordinator to discuss any outstanding issues or queries.

Because of these multiple measures (in particular the last measure), none of the 53 participants broke blinding.

b) Drop out participants

Of the 53 participants who agreed to participate in this study, there were nine dropouts prior to the follow-up period. Dropouts included five treatment participants and four control participants (due to illness, disinterest or scheduling difficulties). For the sake of brevity, baseline differences between these dropout participants and the remaining 44 participants who completed the trial were not reported within Chapter 5. Analysis of these data indicated that there were no significant differences between those participants who dropped out and those who completed the study in age ($t = 1.44$, $df = 51$, $p = 0.16$), gender ($\chi^2 = 0.189$, $df = 1$, $p = 0.77$), global cognitive functioning ($t = -0.32$, $df = 51$, $p = 0.75$) or depressive symptoms ($t = -0.11$, $df = 51$, $p = 0.91$).

c) *Correlations between changes in neurophysiological responses and cognitive functioning*

As stated in Chapter 5, in order to examine the relationship between improvements in MMN response and cognitive functioning following the intervention, absolute change scores were calculated for MMN mean amplitude at Cz and Fz and for phonemic verbal fluency and the EMQ Attentional Tracking subgroup. As shown in Table 14, no significant correlations were found.

Table 14.

Pearson Correlation Coefficients and Corresponding P-Values Between MMN Mean Amplitude at Sites Cz and Fz and Neuropsychological / Self-Report Measures for MCI and Control Groups

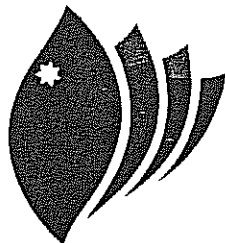
Measure	GROUP							
	MCI				CONTROL			
	Cz		Fz		Cz		Fz	
	r	p-value	r	p-value	r	p-value	r	p-value
COWAT FAS	-0.23	0.274	-0.13	0.531	-0.09	0.755	0.02	0.933
EMQ Attentional Tracking subgroup	-0.02	0.928	-0.02	0.917	0.00	0.995	0.15	0.599

Note: Significant values are represented in bold. COWAT = Controlled Oral Word Association Test; EMQ = Everyday Memory Questionnaire.

APPENDIX SIX:

**Macquarie University Human Research Ethics Committee approval letter and University of
Sydney Human Research Ethics Committee approval letter**

MACQUARIE UNIVERSITY



Research Office
Research Hub, Building C5C East
MACQUARIE UNIVERSITY NSW 2109

Phone +61 (0)2 9850 8612
Fax +61 (0)2 9850 4465

Ethics
Phone +61 (0)2 9850 6848
Email ethics.secretariat@ro.mq.edu.au

19 November 2009

Dr Jenny Batchelor
C3B 421 Psychology Department
Macquarie University

Reference: HE26FEB2010-D00214

Dear Dr Batchelor

Title of project: *Exploring neuroplasticity with cognitive training; A Healthy Brain Ageing program*

The above application was considered by the Executive of the Ethics Review Committee (Human Research). In accordance with section 5.5 of the *National Statement on Ethical Conduct in Human Research (2007)* the Executive noted the final approval from the University of Sydney and your right to proceed under their authority.

Please do not hesitate to contact the Ethics Secretariat if you have any questions or concerns.

Yours sincerely

Dr Karolyn White
Director of Research Ethics
Chair, Ethics Review Committee (Human Research)



Gail Briody

Manager

Office of Ethics Administration

Marietta Coutinho

Deputy Manager

Human Research Ethics Administration

Telephone: +61 2 8627 8175

Facsimile: +61 2 8627 8180

Email: gbriody@usyd.edu.au

Telephone: +61 2 8627 8176

Facsimile: +61 2 8627 8177

Email: mcoutinho@usyd.edu.au

Mailing Address:

Level 6

Jane Foss Russell Building – G02

The University of Sydney

NSW 2006 AUSTRALIA

Ref: DC/JH

17 August 2009

Dr. Sharon Naismith
Brain & Mind Research Institute
Mallett Street – M02G
The University of Sydney
Email: snaismith@med.usyd.edu.au

Dear Dr. Naismith,

Thank you for your correspondence dated 31 July 2009 addressing comments made to you by the Human Research Ethics Committee (HREC). After considering the additional information, the Executive Committee at its meeting on **12 August 2009** approved your protocol entitled **“Exploring neuroplasticity with cognitive training: a healthy brain ageing program”**.

Details of the approval are as follows:

Ref No.: 08-2009/11962

Approval Period: August 2009 to August 2010

Authorised Personnel:

Dr. Sharon Naismith

Miss Loren Mowszowski

Dr. Louise Norrie

Dr. Adam Guastella

Dr. Zoe Terpening

Ms. Donna McCade

Ms. Keri Diamond

Dr. Daniel Hermens

Dr. Matthew Paradise

Ms. Phoebe Carter

The HREC is a fully constituted Ethics Committee in accordance with the *National Statement on Ethical Conduct in Research Involving Humans-March 2007* under Section 5.1.29

The approval of this project is **conditional** upon your continuing compliance with the *National Statement on Ethical Conduct in Research Involving Humans*. We draw to your attention the requirement that a report on this research must be submitted every 12 months from the date of the approval or on completion of the project, whichever occurs first. Failure to submit reports will result in withdrawal of consent for the project to proceed.

Chief Investigator / Supervisor's responsibilities to ensure that:

- (1) All serious and unexpected adverse events should be reported to the HREC as soon as possible.
- (2) All unforeseen events that might affect continued ethical acceptability of the project should be reported to the HREC as soon as possible.
- (3) The HREC must be notified as soon as possible of any changes to the protocol. All changes must be approved by the HREC before continuation of the research project. These include:-
 - If any of the investigators change or leave the University.
 - Any changes to the Participant Information Statement and/or Consent Form.
- (4) All research participants are to be provided with a Participant Information Statement and Consent Form, unless otherwise agreed by the Committee. The Participant Information Statement and Consent Form are to be on University of Sydney letterhead and include the full title of the research project and telephone contacts for the researchers, unless otherwise agreed by the Committee and the following statement must appear on the bottom of the Participant Information Statement. *Any person with concerns or complaints about the conduct of a research study can contact the Manager, Ethics Administration, University of Sydney, on (02) 8627 8175 (Telephone); (02) 8627 8180 (Facsimile) or gbriody@usyd.edu.au (Email).*
- (5) Copies of all signed Consent Forms must be retained and made available to the HREC on request.
- (6) It is your responsibility to provide a copy of this letter to any internal/external granting agencies if requested.
- (7) The HREC approval is valid for four (4) years from the Approval Period stated in this letter. Investigators are requested to submit a progress report annually.
- (8) A report and a copy of any published material should be provided at the completion of the Project.

Yours sincerely



Professor D I Cook
Chairman
Human Research Ethics Committee

cc: Ms. D. McCade, email: dmccade@med.usyd.edu.au
Miss L. Mowszowski, email: lorenm@med.usyd.edu.au

Encl. Approved Participant Information Sheet
Approved Consent Form
Approved Participant Information Sheet for Family Members / Carers
Approved Consent Form for Family Members / Carers
Approved Participant Self-Report Forms
Approved Significant Other / Carer Self-Report Forms
Approved Participation Satisfaction Questionnaire
Approved Recruitment Flyer