Neurophysiological changes associated with Cognitive Training in older adults 'at risk' for dementia: application of the Mismatch Negativity event-related potential

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Thesis Abstract

Background: The prevalence of dementia worldwide is expected to increase dramatically with the rapidly expanding ageing population. Research has identified sub-groups of older people with increased risk of dementia, including those with subjective cognitive impairment, depression and mild cognitive impairment. With the current lack of effective treatments for dementia, secondary prevention approaches targeting 'at risk' older individuals are warranted. It has been suggested that cognitive training may have the capacity to delay or slow cognitive decline in these 'at risk' groups. However, the extent to which such interventions also have the capacity to alter underlying brain functioning is largely unknown.

Aims: This body of research aimed to: 1) examine whether cognitive training may be a viable early intervention strategy for 'at risk' older adults; 2) determine whether utilisation of neurophysiological paradigms may be a viable way to probe underlying brain dysfunction in 'at risk' groups; and 3) investigate the extent to which cognitive training may be associated with altered neurophysiological responses.

Methods: The first aim of this thesis was achieved with the publication of a literature review exploring evidence for the efficacy of cognitive training. The second aim of this research employed an event-related potential Mismatch Negativity (MMN) paradigm to determine the capacity to detect changes in 'pre-attentive' cognitive processes in 'at risk' groups, which in turn, are thought to recruit distinct neurobiological circuits. Finally, using a randomised controlled trial in 40 'at risk' older people, this research examined the capacity for cognitive training to alter the MMN response.

Results: The findings of this research confirmed that cognitive training does offer promise as a secondary prevention tool for cognitive decline in 'at risk' cohorts. It also showed that the MMN response is reduced in 'at risk' groups relative to healthy older controls and is also associated with neuropsychological and psychosocial functioning, suggesting its utility as a neural marker of brain dysfunction. Finally, results showed that this marker is enhanced following cognitive training, supporting the notion that neuroplastic changes do occur in relation to this non-pharmacological intervention.

Implications: Further research exploring the relationship between the MMN marker and underlying pathophysiological brain changes associated with dementia is now warranted, as well as research exploring the capacity of this marker to predict cognitive decline longitudinally.

Candidate's Declaration

I hereby certify that the work presented in this thesis entitled, "Neurophysiological changes associated with Cognitive Training in older adults 'at risk' for dementia: application of the Mismatch Negativity event-related potential" has not previously been submitted for a higher degree to any other university or institution.

I also certify that this thesis is an original piece of research and that it has been written by me. Where appropriate, I have acknowledged any assistance in undertaking the research project and in preparing this thesis. I also certify that all sources of information and literature used in the preparation of this thesis have been indicated within the thesis and cited appropriately.

The research presented in this thesis was approved by the Macquarie University HREC (Reference: HE26FEB2010-D00214, 19th November 2009) and also by the Sydney University HREC (Reference: 11962, 12th August 2009).

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Publications and Conference Presentations

Components of this thesis have been published in peer-reviewed, scientific journals. The citations for specific chapters have been provided with each relevant chapter heading; however the citations are also provided here for convenience.

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

Components of this thesis were also accepted for presentation in poster or paper format at various professional conferences. Presentations included:

1) Mismatch Negativity in 'at risk' older adults: associations with cognitive performance (poster format). *APS College of Clinical Neuropsychologists 16th Annual Conference, September 30 – October 2, 2010, Fremantle, Australia*
2) Mismatch Negativity in 'at risk' older adults: associations with cognitive performance (paper format). *Australasian Society for Psychiatric Research (ASPR) Conference, December 5-8, 2010, Sydney, Australia*

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I would like to acknowledge the funding support for the larger research trial from which these data were obtained. This trial was funded by an NHMRC Fellowship awarded to Professor Ian Hickie (Executive Director, Brain & Mind Research Institute) and an NHMRC Clinical Research Fellowship awarded to A/Prof Sharon Naismith.

It is also important for me to acknowledge and thank the various clinicians who assisted with clinical assessments as part of this Cognitive Training study, including Dr Louisa Norrie, Dr Matthew Paradise, Ms Donna McCade and Dr Zoe Terpening. In particular, thank you to Dr Keri Diamond, coordinator of the Cognitive Training trial, for her time, encouragement and assistance with general research procedures and for conducting the enormously rewarding Cognitive Training sessions with me. Thank you also to the wonderful older adults who devoted their time and energy to participating in this study.

Finally, thank you to my family for your unwavering support. I am extremely grateful to my parents, Chanania and Shelly, and siblings, Dani and Barry, for their enormous

encouragement and generosity throughout my studies. My husband Shaun has also been a constant source of encouragement, advice and enthusiasm throughout this project. I thank him and Frankie dearly for their support, as I could not have completed this project without them.

Explanation of Thesis Format

The current thesis comprises a collection of four empirical research papers, three of which have been published in peer-reviewed journals with the fourth currently in preparation to be submitted for publication. Given the independent nature of these papers, some repetition of ideas or phrases throughout the thesis was unavoidable. Whilst the structure of each paper remains in accordance with the specific journal requirements, the mechanical and referencing style has been reformatted in accordance with the American Psychological Association (6th Ed) style. Additionally, tables and figures contained within each chapter have been re-numbered in consecutive order throughout the thesis. Each paper has also been included in its original, published format in the appendices. For ease of reading, reference lists have not been included at the end of each chapter but have rather been combined into one comprehensive reference list which appears as Chapter Seven at the end of the thesis.

The thesis also includes a general introductory chapter in which the existing literature is reviewed, the justification for the current research is established, and the general aims and hypotheses of the research are detailed. Similarly, a general discussion chapter has been included following the fourth paper in order to bring together the findings from each paper and to provide a conclusion to the overarching research aims and hypotheses.

The candidate's role in this research project comprised primary responsibility for neurophysiological assessments (administering baseline assessments and arranging/overseeing follow-up assessments which I could not complete due to being unblinded to treatment condition), analysis of neurophysiological and neuropsychological data and writing of three journal articles (two of which are published; Chapters 2, 3 and 5). The candidate also shared responsibility for and took an active involvement in patient recruitment (including eligibility screening and booking of appointments),

neuropsychological assessments, delivery of psychoeducation, facilitation of Cognitive Training sessions, neuropsychological analysis and writing of a third empirical journal article (also published; Chapter 4).

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List of Commonly Used Abbreviations

AD	Alzheimer's disease
aMCI	Amnestic mild cognitive impairment
BDNF	Brain-derived neurotrophic factor
CT	Cognitive Training
Cz	Central recording site for event-related potentials
DTI	Diffusion Tensor Imaging
EEG	Electroencephalography
ERP	Event-related potential
fMRI	Functional Magnetic Resonance Imaging
Fz	Frontal recording site for event-related potentials
HDRS	Hamilton Depression Rating Scale, 17-Item
LLD	Late-life depression
M1	Left temporal recording site for event-related potentials
M2	Right temporal recording site for event-related potentials
MCI	Mild cognitive impairment
MMN	Mismatch Negativity
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Spectroscopy
naMCI	Non-amnestic mild cognitive impairment
NEAR	Neuropsychological Educational Approach to Remediation
NMDA	N-methyl-d-aspartate
PET	Positron Emission Tomography
RAVLT	Rey Auditory Verbal Learning Test
SCI	Subjective cognitive impairment
WHO-DAS	World Health Organisation Disability Assessment Schedule