

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

Loren Mowszowski

Bachelor of Psychology (Hons)

Department of Psychology, Faculty of Human Sciences

Macquarie University, NSW, Australia

Research conducted at the Ageing Brain Centre, Brain and Mind Research Institute,

University of Sydney, NSW, Australia

March 2013

Empirical thesis submitted in partial fulfilment of the requirements of the degree of

Doctorate of Psychology (Clinical Neuropsychology)

Table of Contents

Thesis Abstract.....	vi
Candidate’s Declaration.....	vii
Publications and Conference Presentations.....	viii
Acknowledgements.....	ix
Explanation of Thesis Format.....	xi
List of Tables.....	xiii
List of Figures.....	xiv
List of Commonly Used Abbreviations.....	xv
Chapter 1: General Introduction.....	1
1.1. Research question.....	2
1.2. The ageing population.....	3
1.3. Targeting ‘at risk’ groups.....	4
1.3.1. Mild Cognitive Impairment.....	4
1.3.2. Late-life depression.....	6
1.3.3. Subjective cognitive impairment.....	8
1.4. Identification of true prodromal cases within ‘at risk’ groups.....	11
1.5. Early intervention strategies.....	12
1.6. Cognitive Training as an early intervention technique.....	13
1.7. Efficacy of CT in ‘at risk’ groups.....	14
1.8. Neuroplasticity as the underlying mechanism of CT.....	14
1.9. Neural changes associated with CT.....	16
1.10. The use of event-related potentials in research of ‘at risk’ groups.....	17
1.11. The Mismatch Negativity paradigm.....	18
1.12. Research aims.....	19
1.13. Hypotheses.....	19
Chapter 2: Early intervention for cognitive decline: can cognitive training be used as a selective prevention technique?	21
2.1. Abstract.....	22
2.2. Introduction.....	23
2.2.1. Cognitive Remediation and Cognitive Training.....	23
2.2.2. CT as a preventive technique.....	25
2.3. Methods.....	26
2.4. Results and Discussion.....	27
2.4.1. Effectiveness of CT as a primary prevention tool.....	27
2.4.2. Evidence for CT as a secondary prevention tool.....	29

2.4.3. Opportunity to develop CT in other ‘at risk’ groups: late-life depression.....	33
2.4.4. Effectiveness of CT as a tertiary prevention tool.....	35
2.4.5. Limitations of Cognitive Training research.....	37
2.4.6. Cognitive activity protects against decline.....	39
2.4.7. Mechanisms of neuroplasticity.....	40
2.4.8. CT as a promoter of neuroplasticity.....	41
2.5. Summary and conclusions: CT as a preventive technique for cognitive decline.....	42
2.6. Addendum to methods.....	44
2.6.1. Search strategy.....	44
2.6.2. Criteria for inclusion.....	44
2.6.3. Criteria for exclusion.....	44
2.7. Literature update since publication of this review.....	45
2.7.1. CT in ‘at risk’ groups.....	45
2.7.2. Neural changes associated with CT.....	48
2.8. Additional considerations following publication of this review.....	51
2.8.1. Terminology of neuroplasticity / CT mechanisms.....	51
2.8.2. CT and other indicated prevention programs.....	51
Chapter 3: Reduced Mismatch Negativity in Mild Cognitive Impairment: associations with neuropsychological performance.....	52
3.1. Abstract.....	53
3.2. Introduction.....	54
3.3. Materials and methods.....	58
3.3.1. Participants.....	58
3.3.2. Psychiatric and medical assessment.....	58
3.3.3. Neuropsychological assessment.....	60
3.3.4. Neurophysiological testing.....	61
3.3.5. Statistical analyses.....	62
3.4. Results.....	62
3.4.1. Sample descriptive, clinical and social functioning data.....	62
3.4.2. Neurophysiological data.....	64
3.4.3. Neuropsychological data.....	66
3.4.4. Correlations between neurophysiological and neuropsychological data.....	66
3.5. Discussion.....	69
3.6. Addendum: Additional considerations following publication.....	75
3.6.1. Diabetes.....	75
3.6.2. Use of ‘Digit Span’ subtest for measurement of working memory.....	75

3.6.3. Measurement of cognitive flexibility.....	76
3.6.4. Visual inspection of data for normality.....	76
3.6.5. Statistical power.....	76
Chapter 4: Reduced temporal mismatch negativity in late-life depression: An event-related potential index of cognitive deficit and functional disability?.....	77
4.1. Candidate’s contribution to the present paper.....	78
4.2. Abstract.....	79
4.3. Introduction.....	80
4.4. Methods.....	83
4.4.1. Sample.....	83
4.4.2. Measures.....	83
4.4.2.1. Psychiatric.....	83
4.4.2.2. Neuropsychological.....	84
4.4.2.3. Disability.....	85
4.4.2.4. Neurophysiological.....	86
4.4.3. Statistical analysis.....	87
4.5. Results.....	87
4.5.1. Correlations between MMN and clinical characteristics.....	91
4.5.2. Correlations between MMN and neuropsychological functioning and disability	91
4.6. Discussion.....	93
Chapter 5: A Healthy Brain Ageing Cognitive Training program enhances neurophysiological responses in older ‘at risk’ adults: an event-related potential study.....	96
5.1. Abstract.....	97
5.2. Introduction.....	98
5.2.1. Targeting ‘at risk’ groups.....	98
5.2.2. Mild Cognitive Impairment.....	99
5.2.3. Late-life depression.....	101
5.2.4. Subjective cognitive impairment.....	103
5.2.5. Early intervention strategies.....	105
5.2.6. Cognitive training as an early intervention technique.....	106
5.2.7. Efficacy of CT in ‘at risk’ groups.....	106
5.2.8. Neuroplasticity as the underlying mechanism of CT.....	108
5.2.9. Neural changes associated with CT.....	109
5.2.10. The use of event-related potentials in CT research with ‘at risk’ groups.....	111
5.2.11. The Mismatch Negativity paradigm.....	113

5.2.12. Aims and hypotheses.....	114
5.3. Methods.....	115
5.3.1. Participants.....	115
5.3.2. Design.....	116
5.3.3. Intervention.....	117
5.3.4. Measures.....	119
5.3.4.1. Psychiatric and medical assessment.....	119
5.3.4.2. Primary outcome: neurophysiological functioning.....	121
5.3.4.3. Secondary outcomes: a) neuropsychological assessment.....	122
5.3.4.4. Secondary outcomes: b) self-reported functioning.....	123
5.3.5. Statistical analyses.....	124
5.4. Results.....	125
5.4.1. Sample characteristics.....	125
5.4.2. Baseline group differences.....	128
5.4.3. Effects of treatment.....	130
5.5. Discussion.....	133
Chapter 6: General discussion.....	140
6.1. Contribution of this research to the literature.....	141
6.2. Review of research aims.....	141
6.3. Utility of CT as an early intervention technique: efficacy in ‘at risk’ older adults.....	143
6.4. Application of the MMN paradigm as a novel neurophysiological biomarker of ‘at risk’ status.....	146
6.5. MMN as an outcome measure of CT efficacy and index of neuroplasticity in ‘at risk’ older adults.....	150
6.6. Limitations of the research.....	154
6.7. Directions for future research.....	156
6.8. Concluding remarks.....	157
Chapter 7: References.....	159
Appendices.....	xvi
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

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).

Loren Mowszowski

Student ID: 41410076

March 2013

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*

Acknowledgements

I would like to thank my supervisors at Macquarie University, Dr Jennifer Batchelor and Dr Sue Meares, for guiding me through the research project and preparation of this thesis. I would also like to thank Alan Taylor for his assistance with planning the statistical analyses.

I would also like to extend my thanks and appreciation to my ‘on-site’ supervisors at the Brain and Mind Research Institute, Associate Professor Sharon Naismith and Dr Daniel Hermens, for their time and effort in assisting me with many aspects of the research project including training in neurophysiological assessment, statistical guidance and preparation of scientific journal articles. In particular, I would like to thank Sharon Naismith most sincerely for her encouragement and dedication, and for showing me the value and enjoyment of clinical research.

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, Chania 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).

List of Tables

Table 1.	Stages of a prevention hierarchy for dementia	p.26
Table 2.	Mean (SD) scores for sample demographic, clinical and social functioning variables in MCI and control groups, with corresponding between-group test statistics	p.63
Table 3.	Mean (SD) scores for neurophysiological (MMN) variables in MCI and control groups, with corresponding between-group test statistics	p.65
Table 4.	Mean (SD) scores for neuropsychological variables in MCI and control groups, with corresponding results for between-group test statistics	p.66
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	p.68
Table 6.	Demographic, psychiatric and neuropsychological data (mean \pm SD) for control participants and patients with lifetime depression	p.88
Table 7.	Mean amplitude and peak latency MMN data (mean \pm SD) for healthy controls and patients with a history of depression	p.90
Table 8.	Partial correlations (controlling for age) between temporal MMN data for mean amplitude in patients with lifetime depression	p.92
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	p.120
Table 10.	Individuals meeting criteria for ‘at risk’ status within the treatment and control conditions	p.127
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	p.128
Table 12.	Baseline mean (SD) scores for neurophysiological (MMN) variables in treatment and control groups, with corresponding between-group test statistics	p.129
Table 13.	Baseline and follow-up neurophysiological, neuropsychological and psychosocial data (mean [SD])	p.132
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	Appendix 5

List of Figures

Figure 1.	Cognitive Remediation terminology	p.25
Figure 2.	Grand Average MMN waveforms for MCI and control groups	p.64
Figure 3.	Scatter plot for mean amplitude at M1 versus self-reported disability for control subjects and patients with MCI	p.67
Figure 4.	Scatter plot for mean amplitude at M2 versus verbal learning for control subjects and patients with MCI	p.69
Figure 5a.	Grand average event-related potentials for lifetime depression and control groups	p.89
Figure 5b.	Head maps depicting the mean amplitudes for MMN recorded across scalp sites for lifetime depressed and control groups	p.90
Figure 6.	Scatterplot demonstrating the correlation between decreased mean amplitude at M1 and M2 and greater levels of disability for patients with depression compared to the controls	p.92
Figure 7.	Participant flow through the study	p.117
Figure 8.	Grand average waveforms for treatment and control groups at baseline and follow-up	p.130
Figure 9a.	(Supplementary) Grand average standard and deviant ERPs for control and depression groups	Appendix 1
Figure 9b.	(Supplementary) Grand average standard and deviant ERPs for control and MCI groups	Appendix 1

List of Commonly Used Abbreviations

AD	Alzheimer's disease
aMCI	Amnesic 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-amnesic 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