ERRATA

Pg xx, ln 12 – after “Lastly,” insert “although the study did not prospectively recruit participants, so cannot determine causation,”

Pg 3, ln 15 – after “that” insert “potentially”.

Pg 4, ln 13 – before “The thesis” insert “In order to maximise the statistical power of each study, each participant completed all four studies, so that each study examined the same groups of individuals.”

Pg 7, ln 1 – after “injuries” insert “(which expose different and varied areas of the brain to the external environment)”

Page 7, ln 2 – after “injuries” insert “(which in contrast to open injuries, do not expose areas of the brain to the external environment)”

Pg 8, ln 17 – after “estimates” insert “through a process analogous to regression to the mean – the more measurements taken, the closer to the true severity”

Pg 9, ln – remove “that connect neurons”

Pg 10, ln 17 – replace “may lead” with “may relate to”

Page 13, ln 7 – insert “(Baumeister and Parker, 2012)” after “sub-types”

Page 14, ln 6 – replace “density” with “concentration”.

Pg 14, ln 15 – after “(Ruhe et al., 2007).” insert “Despite this, the effectiveness of anti-depressant medications does indicate that monoamine alterations are at least part of the picture in MDD.”

Page 24, ln 5 – replace “an” with “a”.

Pg 29, ln 23 – after “task” insert “- the oddball task”

Page 30, ln 9 – omit “to” from “to between”.

Pg 30, ln 22 – after “injury.” insert “Despite this, the previous research examining depression following a TBI does seem to indicate a reduction in the amplitude of cognition related EEG measures”

Page 35, ln 5 – insert after the heading: “Because voltage is the potential for electrical current to flow between two points, it is measured as the difference between a grounded electrode and the active electrode, minus the difference between the ground and reference electrode, which gives the difference between the active and reference electrode (Luck, 2005, pg 103)”

Page 35, ln 18 – change “difficult” to “impossible”

Page 35, ln 22 – insert “pg 414” prior to the final parenthesis, and add “The inverse problem is impossible to solve because a single scalp activity pattern may be the result of a number of different cellular activity patterns, with no way of determining which pattern is the ‘true’ pattern (Buzsàki et al, 2012)”

Pg 36, ln 7 – change “0-3Hz” to “<3Hz”

Pg 36, ln 12 – change “event related” to “event-related”

Pg 37, ln 6 – add “and thought to reflect inter-regional communication” before parentheses.

Pg 39, ln 14 – replace “PCS” with “post-concussion syndrome (PCS)”

Pg 40, ln 7 – insert “than” after “more”

Pg 42, ln 13 – replace “only” with “mainly”

Pg 43, ln 6 – omit “been”

Pg 45, ln 15 – replace “simultaneously” with “simultaneous”

Pg 47, ln 9 – insert “,” after “increases”

Pg 48, ln 15 – insert after sentence end “In general the SW is less well studied than the other oddball ERPs, so the functions that this ERP represents are less certain.”

Pg 53, ln 7 – replace “not all P3b changes more chronically post injury were” with “not all chronic post injury changes in the P3b were”

Pg 60, ln 3 – insert “,” after “athletes”

Pg 60, ln 19 – move “Elting et al.” into parentheses

Pg 69, ln 11 – insert “Only two studies have examined the CNV following TBI.” after “(Campbell & de Lugt, 1995).”

Pg 75, ln 18 – insert “(beta bandwidths defined by Thornton, 2003)” after “measured”

Pg 80, ln 8 and 10 – remove “J.M.” from “(J.M. Ford et al., 1994)”

Pg 83, ln 1 – insert “it” before “effectively”

Pg 90, ln 14 – change “similar a” to “a similar”

Pg 99, ln 22 – after “controls,” insert “and has lower signal to noise ratio than the P3b,”

Pg 100, ln 22 – after “amplitude” insert “, low signal to noise ratio,”

Pg 108, ln 4 – insert “in” after “N2”

Pg 109, ln 8 – insert “(Baribeau-Braun and Lesévre, 1983; Knott and Lapierre, 1991)” after “ERP”

Pg 110, ln 9 – change “(Kaiser et al. (2003)” to “(Kaiser et al. 2003)”

Pg 113, ln 7 – insert “(pg 69)” after “Figure 2”

Pg 129, ln 13 – omit “a” after “be”.

Pg 130, ln 4 – insert “in MDD” after tasks

Pg 130, ln 13 – After “simple models” insert “, which, for example, hypothesise general decreases in activity. Differences may be more likely to be specific to processes that underlie the behavioural changes in MDD.” and replace “Differences” with “As such, differences in neural activity between controls and MDD”.

Pg 130, Ln 14 – replace “This is” with “The probability that emotional tasks are more likely to reveal neural changes in MDD is”

Pg 134, ln 13 – Replace “two of them” with “two of the three”

Pg 134, ln 21 – omit “for”

Pg 135, ln 9 – replace “patter” with “pattern”

Pg 135, ln 20 – insert “that” after “suggest”

Pg 136, ln 7 – after “section.” insert “Some research suggests that individuals with MDD may perceive neutral stimuli as negative (Beck, 2008), perhaps suggesting that the neutral face condition did not fulfil the intended purpose for the MDD group”

Pg 137, ln 19 – after “results” insert “of studies focusing specifically on emotional memory processing”.

Pg 139, ln 9 – replace “though” with “thought”

Pg 140, ln 17 – replace “indicates” with “are interpreted as indicating”

Pg 141, ln 8 – insert “ERP” after “each”

Pg 142, ln 1 – insert “(Deldin et al., 2009)” after “collaborators”

Pg 142, ln 12 – insert “(Pg 148)” after “figure 4”

Pg 147, ln 14 – insert “idealised” after “of”

Pg 151, ln 5 – insert “Additionally, none of these studies controlled for anxiety.” after “2012).”

Pg 151, ln 17 – insert “(pg 156)” after “table 10”

Pg 168, ln 20 – insert “EEG” after “related”

Pg 173, ln 4 – replace “cingulated” with “cingulate”

Pg 174, ln 13 – insert “per se” after first “inhibition”

Pg 177, ln 16 – after “(TBI-MDD).” insert “Depression prior to the TBI was an exclusion criterion for the TBI-MDD group.”

Pg 184, ln 1 – after “was” insert “arbitrarily”, and after “groups” insert “, although ANOVAs are generally considered robust to violations of this type (Schmider et al., 2010)”

Pg 184, ln 2, 5, 8, 19 – replace “within and between repeated” with “mixed measures”

Pg 185, ln 10 – replace “($p > 0.05$)” with “($p = 0.94$)”

Pg 187, ln 20 – replace “marginally significant” with “trend”

Pg 191, ln 12-13 – replace “In order to assess whether the P3e was related to motor activity, a” with “A”

Pg 192, ln 12 – replace “(Kaiser et al. 2003)’s” with “Kaiser and colleagues (2003)”

Pg 196, ln 6-7 – replace “,$F = 16.030$, $p < 0.001$” with “($F (1, 67) = 16.030$, $p < 0.001$)”

Pg 199, ln 4 (after table) – remove “individuals with”

Pg 200, ln 6 – after “1992).” insert “The interaction between N2a area and N2b area and group indicated that although the MDD and TBI-MDD groups showed a typical early N2 amplitude (which seems to be related to automatic sensory template mismatch – Ogura et al., 1993), the late N2 amplitude was reduced in these groups (which this study and others indicates is related to response inhibition).”

Pg 201, ln 10 – after “However” insert “one study using”

Pg 203, ln 19 – after “2009).” insert “However, this may be due to a ceiling effect in the behavioural data, with all groups performing at above 90% accuracy.”

Pg 204, ln 5 – replace “result” with “results”

Pg 204, ln 20 – after “extremely low” insert “(MDD groups $p = 0.023$ x TBI-MDD group’s $p = 0.006 = 0.000138$)”

Pg 205, ln 4 – replace “most likely” with “may be”

Pg 205, ln 18 – replace “related processes are” with “related N2 is”

Pg 215, after ln 4 – insert “Schmider, E., Ziegler, M., Danay, E., Beyer, L., Buhner, M., 2010. Is it really robust? Reinvestigating the robustness of ANOVA against violations of the normal distribution assumption. Methodology: European Journal of Research Methods for the Behavioral and Social Sciences 6 (4), 147-151.”

Pg 222, ln 1 – insert “in” after “affect”

Pg 223, ln 10 – After “episode.” insert “Depression prior to the TBI was an exclusion criterion for the TBI-MDD group.”

Pg 223, ln 16 – replace “This” with “The”

Pg 230, ln 4 - after table replace “$p = 0.000$” with “$p < 0.001$”

Pg 234, ln 11 – replace “There were no differences in the second measure of error processing, ERN, across any of the groups” with “There was a trend towards an interaction between group and CRN/ERN amplitude, which seems to be the result of the MDD group showing no differentiation between ERN and CRN amplitude, while other groups showed a larger ERN”

Pg 236, ln 21 – replace “common” with “present”

Pg 237, ln 18 – after “(2009).” insert “It could be that altered ERN amplitudes are related to one of the symptoms that vary in MDD, for example apathy or psychomotor retardation (Schrijvers et al. 2008).”

Pg 237, ln 21 – remove “no”

Pg 262 – the x axis for graphs on this page should be labelled with “s” rather than “ms”

Pg 310, ln 5 – after “regions.” insert “Future research may be able to use this information to develop predictive measures of MDD risk following TBI, and use this information to develop novel treatment techniques.”

Pg 323, ln 7 – replace “altered” with “increased”

Pg 324, ln 15 – after “(Leuchter at al., 2012).” Insert “Although theta band functional connectivity is disrupted for months following a severe TBI (Castellanos et al., 2010), participants in the current study with mild-moderate TBI are likely to recover sooner, in the absence of factors that lead to MDD. Therefore, although the time since injury was shorter for this group than the TBI-MDD group, their theta band functional connectivity may have nonetheless recovered.”

Pg 327, ln 16 – replace “unfortunately” with “unfortunate”

Pg 328, ln 14 – after “(appendix).” insert “We are currently pursuing this line of research.”

Pg 329, ln 9 – after “groups.” insert “These studies are the first to have compared electrophysiological activity during cognition across these four groups.”

Page 343, after line 3 – insert “Baumeister, H., Parker, G., 2012. Meta-review of depressive subtyping models. Journal of Affective Disorders 139 (2), 126-140.”

Page 354, line 7 – insert “Luck, S.J., 2005. An introduction to the event-related potential technique. The MIT Press, London.”

Changes in Neural Activity in Major Depressive Disorder Following a Traumatic Brain Injury

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A thesis submitted for the degree of Doctor of Philosophy

(Neuroscience)

August, 2012

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Appendix A: **Bailey, N.W**., Hoy, K.E., Maller, J.J., Segrave, R.A., Thomson, R., Fitzgerald, P.B. (2011). Response inhibition changes in depression and depression post traumatic brain injury measured with EEG. Australasian Society for Psychiatric Research. 377

Appendix B: Maller, J.J., Thomson, R.H.S., Pannek, K., Rose, S.E., **Bailey, N**., Lewis, P.M., Fitzgerald, P.B. (In Press). The (eigen) value of diffusion tensor imaging to investigate depression after traumatic brain injury. Human Brain Mapping..... 379

List of Prepared Manuscripts and Presentations

Papers Accepted for Publication During Candidature

Maller, J.J., Thomson, R.H.S., Pannek, K., Rose, S.E., **Bailey, N**., Lewis, P.M., Fitzgerald, P.B. (In Press). The (eigen) value of diffusion tensor imaging to investigate depression after traumatic brain injury. Human Brain Mapping.

Papers Submitted During Candidature for Peer-Review:

Bailey N.W., Hoy K.E., Maller J.J., Segrave R., Thomson R., Williams N., Zafiris J. Daskalakis, Fitzgerald P.B. An exploratory analysis of the Go/Nogo N2 in major depression and depression following traumatic brain injury

Bailey, N.W. Hoy K.E. Maller J.J. Upton D.J. Fitzgerald, P.B. Error Positivity is Reduced in Depression and Traumatic Brain Injury Depression

Bailey, N.W., Segrave, R.A., Hoy, K.E., Maller, J.J., Fitzgerald, P.B. Impaired Alpha Synchronization During Working Memory Retention in Depression and Depression Following Traumatic Brain Injury

Bailey, N.W., Hoy, K.E., Maller, J.J., Rogasch, N.C., Segrave, R.A., Fitzgerald, P.B. Functional connectivity alterations during working memory in depression following traumatic brain injury

Conference Posters Presented During Candidature

Bailey, N.W., Hoy, K.E., Maller, J.J., Segrave, R.A., Thomson, R., Fitzgerald, P.B. (2011). Response inhibition changes in depression and depression post traumatic brain injury measured with EEG. Australasian Society for Psychiatric Research.

Bailey, N.W., Hoy, K.E., Maller, J.J., Segrave, R.A., Thomson, R., Fitzgerald, P.B. (2011). Response inhibition changes in depression and depression post traumatic brain injury measured with EEG. Biological Psychiatry Australia.

Declarations

General Declaration

In accordance with Monash University Doctorate Regulation 17/ Doctor of Philosophy and Master of Philosophy (MPhil) regulations the following declarations are made:

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes four original papers submitted for publication in peer reviewed journals. The core theme of the thesis is the use of EEG to investigate changes in neural activity in depression following a traumatic brain injury. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the candidate, working within the Monash Alfred Psychiatry Research Centre, under the supervision of Professor Paul Fitzgerald and Dr Kate Hoy.

The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research.

In the case of Chapters 7, 8, 9, and 10 my contribution to the work involved the following:

Thesis chapter	Publication title	Publication status	Nature and extent of candidate's contribution
7	An exploratory analysis of the Go/Nogo N2 in major depression and depression following traumatic brain injury	Revision submitted	Project design and construction; hypothesis formulation; ethics applications; recruitment and testing; data analysis; manuscript writing and preparation
8	Error positivity is reduced in depression and depression following traumatic brain injury	Submitted	As above
9	Impaired Alpha Synchronization During Working Memory Retention in Depression and Depression Following Traumatic Brain Injury	Submitted	As above
10	Functional connectivity alterations during working memory in depression following traumatic brain injury	Submitted	As above

I have renumbered sections of submitted papers in order to generate a consistent presentation within the thesis.

Signed:

Date:

Declaration for Thesis Chapter 7

Declaration by candidate

In the case of Chapter 7, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Researched a suitable task and conceived of the details of the study. Researched and programmed the cognitive EEG task, and piloted. Formulated hypotheses. Recruited participants and ran the testing sessions. Analysed the data, and compared the groups and conditions with statistical tests. Wrote the first draft of the paper. Re-wrote the paper after advice and comments from co-authors.	85%

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Dr Kate Hoy	Advised on study set up, recruitment, and testing procedure. Assisted with study piloting and a number of EEG preparations. Advised on draft manuscript.	
Dr Jerome Maller	Assisted with recruitment. Advised about study set up and analysis. Commented on draft manuscript.	
Dr Rebecca Segrave	Assisted with study set up and task programming. Assisted with a number of EEG preparations. Advised on analysis and draft manuscript.	
Dr Richard Thomson	Assisted with task design, a number of EEG preparations, and analysis. Commented on draft manuscript.	
Mr Nick Williams	Assisted with analysis and advised on draft manuscript.	
Associate Professor Zafiris Daskalakis	Advised on draft manuscript.	
Professor Paul Fitzgerald	Helped conceive and plan details of the study. Advised on study set up, hypothesis generation, and recruitment. Commented on draft manuscript.	

Candidate's Signature	[redacted]	Date 3/8/12

Declaration by co-authors

The undersigned hereby certify that:

(1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(4) there are no other authors of the publication according to these criteria;
(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
(6) the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

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Signature 5		7/8/12
Signature 6		2012/04/22
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Declaration for Thesis Chapter 8

Declaration by candidate

In the case of Chapter 8, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Researched a suitable task and conceived of the details of the study. Researched and programmed the cognitive EEG task, and piloted. Formulated hypotheses. Recruited participants and ran the testing sessions. Analysed the data, and compared the groups and conditions with statistical tests. Wrote the first draft of the paper. Re-wrote the paper after advice and comments from co-authors.	90%

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Dr Kate Hoy	Advised on study set up, recruitment, and testing procedure. Assisted with study piloting and a number of EEG preparations. Advised on draft manuscript.	
Dr Jerome Maller	Assisted with recruitment. Advised about study set up and analysis. Commented on draft manuscript.	
Dr Daniel Upton	Advised on study set up and testing procedure. Advised on draft manuscript.	
Professor Paul Fitzgerald	Helped conceive and plan details of the study. Advised on study set up, hypothesis generation, and recruitment. Commented on draft manuscript.	

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(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
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Declaration for Thesis Chapter 9

Declaration by candidate

In the case of Chapter 9, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Researched a suitable task and conceived of the details of the study. Researched and programmed the cognitive EEG task, and piloted. Formulated hypotheses. Recruited participants and ran the testing sessions. Analysed the data, and compared the groups and conditions with statistical tests. Wrote the first draft of the paper. Re-wrote the paper after advice and comments from co-authors.	85%

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Dr Rebecca Segrave	Assisted with study set up and task programming. Assisted with a number of EEG preparations. Advised on analysis and draft manuscript.	
Dr Kate Hoy	Advised on study set up, recruitment, and testing procedure. Assisted with study piloting and a number of EEG preparations. Advised on draft manuscript.	
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Candidate's Signature	[redacted]	Date 6/8/12

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Declaration for Thesis Chapter 10

Declaration by candidate

In the case of Chapter 10, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Researched a suitable task and conceived of the details of the study. Researched and programmed the cognitive EEG task, and piloted. Formulated hypotheses. Recruited participants and ran the testing sessions. Analysed the data, and compared the groups and conditions with statistical tests. Wrote the first draft of the paper. Re-wrote the paper after advice and comments from co-authors.	90%

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Dr Kate Hoy	Advised on study set up, recruitment, and testing procedure. Assisted with study piloting and a number of EEG preparations. Advised on draft manuscript.	
Dr Jerome Maller	Assisted with recruitment. Advised about study set up and analysis. Advised on draft manuscript.	
Mr Nigel Rogasch	Assisted with analysis and advised on draft manuscript.	2%
Dr Rebecca Segrave	Assisted with study set up and task programming. Assisted with a number of EEG preparations. Advised on analysis and draft manuscript.	
Professor Paul Fitzgerald	Helped conceive and plan details of the study. Advised on study set up, hypothesis generation, and recruitment. Commented on draft manuscript.	

Candidate's Signature [redacted] 6/8/12

Declaration by co-authors

The undersigned hereby certify that:

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Signature 5		3/8/12

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Glossary of Abbreviations

µv	Microvolts
5-HT	Serotonin
ACC	Anterior Cingulate Cortex
ANOVA	Analysis of Variance
BDI	Beck Depression Inventory
BP	Bereitshaftspotential
CNV	Contingent Negative Variation
CRN	Correct Response Negativity
CT	Computerised Tomography
DA	Dopamine
DAI	Diffuse Axonal Injury
dB	Decibel
DLPFC	Dorso-Lateral Prefrontal Cortex
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders Edition IV
DTI	Diffusion Tensor Imaging
EEG	Electroencephalography
EHI	Edinburgh Handedness Inventory

ERD/ERS	Event-Related Desynchronisation/Event-Related Synchronisation
ERN	Error Related Negativity
ERP	Event-Related Potential
FA	Fractional Anisotropy
fMRI	Functional Magnetic Resonance Imaging
FN	Feedback Negativity
GCS	Glasgow Coma Scale
GABA	Gamma-Aminobutyric Acid
HAM-D	The Hamilton Rating Scale for Depression
Hz	Hertz
IQ	Intelligence Quotent
kΩ	Kilo-Ohms
LOC	Loss of Consciousness
LORETA	Low Resolution Brain Electromagnetic Tomography
LTD	Long-Term Depression
LPC	Late Positive Component
LTP	Long-Term Potentiation
MADRS	Montgomery-Asberg Depression Rating Scale

MDD	Major Depressive Disorder
MDE	Major Depressive Episode
MEG	Magneto-Encephalography
MFN	Medial Frontal Negativity
MINI	Mini International Neuropsychiatric Interview for DSM-IV
MMP	Movement Monitoring Potential
MP	Motor Potential
MRCP	Movement Related Cortical Potential
MRI	Magnetic Resonance Imaging
mTBI	Mild Traumatic Brain Injury
Nχ	Negative Voltage Deflection (at time or ordinal position χ following stimulus)
NA	Noradrenaline
Pχ	Positive Voltage Deflection (at time or ordinal position χ following stimulus)
PCS	Post-Concussion Syndrome
Pe	Error Positivity
PFC	Pre-Frontal Cortex

PINV	Post-Imperative Negative Variation
PTA	Post-traumatic Amnesia
PTSD	Post-Traumatic Stress Disorder
RT	Reaction Time
S1	First Stimulus in a Trial
S2	Second Stimulus in a Trial
SD	Standard Deviation
SPSS	Statistical Package for the Social Sciences
SSRI	Selective Serotonin Reuptake Inhibitor
sTBI	Severe Traumatic Brain Injury
SWN	Slow Wave Negativity
TBI	Traumatic Brain Injury
TBI-MDD	Major Depressive Disorder following a Traumatic Brain Injury
TMS	Transcranial Magnetic Stimulation
WM	Working Memory
WTAR	Weschler Test of Adult Reading

Abstract

Rates of major depressive disorder (MDD) are significantly higher following a traumatic brain injury (TBI) than in the general population. Major Depression following a TBI (TBI-MDD) results in significant personal suffering, and poorer recovery outcomes. Although there are a number of psychosocial factors that can contribute to the development of TBI-MDD, evidence suggests that neural changes are also involved. However, very little research has directly examined changes in brain function in TBI-MDD. Understanding the composition and mechanisms of such changes may lead to methods to identify, treat, and possibly even prevent TBI-MDD. This thesis constitutes the first comprehensive exploration of neural changes associated with TBI-MDD. There are a number of areas of cognition which are impacted by both TBI and MDD; these changes are considered integral to both the sequalae of TBI and the development/maintenance of MDD. These cognitive changes are associated with changes in neural activity and as such are an ideal target for investigation of neural changes associated with TBI-MDD. In this thesis a series of studies were undertaken comparing electroencephalographic (EEG) measures of neural activity underlying a number of relevant cognitive processes across four different groups: a TBI group, an MDD group, an MDD following TBI group (TBI-MDD), and a healthy control group. The comparisons of neural activity between groups allowed characterisation of which processes were affected by TBI and MDD, and how this was modulated by the combination of both. Comparisons also permitted inferences to be drawn with regard to which affliction may be responsible for the lingering symptoms experienced by those with TBI-MDD. The between group differences also provided indirect evidence about the aetiology of TBI-MDD. In order to control for the heterogeneity that focal lesions would introduce to neural activity measures, only individuals with closed injuries of mild to moderate TBI severity were included. The

four different groups were compared across response inhibition event related EEG potentials, and error related processes. Band activity and connectivity was also measured during working memory and at rest in these groups. The results revealed a reduction in neural activity in the MDD and TBI-MDD groups during response inhibition, error processing, and working memory. The TBI only group did not differ from healthy controls on these measures. The results also suggested that individuals with TBI-MDD show a maladaptive increase in inter-hemispheric connectivity during working memory, a finding specific to TBI-MDD. This pattern of results suggests that it is the occurrence of MDD more than the TBI that is responsible for the lingering cognitive symptoms that individuals with TBI-MDD experience. The lack of differences between individuals with TBI only and healthy controls also suggests that in the absence of MDD, full recovery might be the expected outcome in the majority of mild to moderate TBIs. Lastly, in combination with previous literature, the results provide evidence of potential causal mechanisms leading to TBI-MDD, involving aberrant functional connectivity.

Chapter One

General Introduction and Thesis Overview

"You are only coming through in waves"

- Pink Floyd

“If a rat is a good model for your emotional life, you’re in big trouble”

- Robert Sapolsky

A traumatic brain injury (TBI), as its name suggests, is a traumatic event that a surprisingly high proportion of the population experience at least once in their lifetime. Some research suggests that by as early as young adulthood, a quarter of us will have experienced a TBI of at least mild severity (McKinlay et al., 2008). These injuries impact directly on the brain; the matter that comprises *who we are*, and as such, they can lead to ongoing issues that can impact an individual’s life for months, years, and in some cases for a lifetime. One of the most common issues following a TBI is depression; rates of Major Depressive Disorder (MDD) are significantly elevated following a TBI in comparison to the general population. Estimates of these rates most commonly range from 20-45% (Jorge et al., 1993; Kaponen et al., 2002; Olver et al., 1996; Rapoport et al., 2006; Rapoport et al., 2005).

Unfortunately, it seems that the development of MDD following TBI has an effect not only on an individual’s emotional state, but also their recovery outcomes (Rapoport et al., 2006; Ruff et al., 1996). The treatment of the MDD component of TBI-MDD can improve these poorer outcomes (Fann et al., 2001). However, there is very little research to guide

the treatment of MDD following a TBI, and clinicians acknowledge that treatment of this disorder is complicated (Fleminger et al., 2003). Therefore, an understanding of the mechanisms involved in TBI-MDD is important, as this may assist with treatments, leading to a reduction in the suffering of affected individuals, and improved outcomes.

A number of psychosocial factors are associated with the development of TBI-MDD. These include poor coping strategies, negative beliefs about symptoms and recovery, stress, and functional impairment. However, research has shown that individuals who have suffered a TBI show higher rates of depression than orthopaedic patients with similar injury severity and functional impairments (Levin et al., 2001; McCleary et al., 1998; Varney et al., 1987). This suggests the involvement of neural changes in addition to the psychosocial factors. While the psychosocial factors that are associated with TBI-MDD are well researched, very little research has examined potential neural factors.

Neuroimaging techniques such as computerised tomography (CT), magnetic resonance imaging (MRI), functional MRI (fMRI), and electroencephalography (EEG) are common methods used to inform researchers about brain changes in psychiatric disorders. These techniques allow researchers to gather information about potential neural mechanisms involved in these disorders. Thus far, methods used to examine neural changes in TBI-MDD have been largely restricted to CT and MRI. These methods allow measurement of structural changes as a result of lesions following a TBI. However, these techniques have more difficulty in measuring the microscopic changes that take place following TBI that are a result of diffuse axonal injuries (DAI), and are also unable to inform us about dynamic changes in neural activity.

EEG, on the other hand, is an ideal method for measuring neural activity with detailed temporal resolution. While there has been almost no research examining changes in neural activity in TBI-MDD with EEG, a number of studies have demonstrated brain activity changes in both TBI alone, and in MDD alone. The alterations in brain activity in TBI and MDD have been associated with specific aspects of cognition, for example memory, attention, response inhibition, error awareness, and emotional processing (impairments which are common to both disorders).

This information provides a tractable background for the exploration of neural activity changes in TBI-MDD, particularly with respect to these specific cognitive processes. The examination of these changes may enable the development of predictive tests of MDD following TBI, and potential treatments for individuals suffering from TBI-MDD.

Aims of the Thesis

This thesis aimed to identify the differences in neural activity between people who develop MDD after even a mild to moderate TBI, and those who do not. The broad aim was to offer insight into the neural factors that contribute to the higher rates of MDD following a TBI, compared to both the general population and individuals who have suffered a comparable injury to another part of the body.

The following studies compare individuals who have had a TBI with and without the subsequent development of MDD to individuals who develop MDD without having first suffered a head injury. This was done to determine if the MDD following TBI is similar to non-injury related MDD, or whether it is due to injury specific factors, and as such needs to be treated as a separate disorder.

To achieve these aims, four different empirical studies were performed. These studies used electroencephalography (EEG) to compare brain activity between groups with a traumatic brain injury (TBI), a traumatic brain injury and also depression (TBI-MDD), depression alone (MDD), and healthy controls:

1) A study to determine whether electrophysiological processes related to response inhibition are reduced in amplitude as a result of TBI-MDD;
2) A study investigating whether response error related electrophysiological processes are reduced in individuals with TBI-MDD;
3) A study examining whether brain activity related to inhibition and attention during a working memory task is altered in TBI-MDD;
4) A study that examining whether functional connectivity between brain regions during a working memory task and at rest is altered in TBI-MDD.

The thesis is formatted so that the reader is initially introduced to the concepts of TBI and MDD, then the characteristics of MDD following a TBI are discussed. This provides the background and rational for the current research. Following this, a brief introduction to EEG is provided, outlining the information that can be obtained with this technique. Chapters 4 and 5 review the previous research that has used EEG to separately examine neural changes in MDD and in TBI. These reviews discuss the current state of knowledge in each field. Chapter 6 uses these reviews to extrapolate the specific aspects that are likely to provide the most knowledge in the study of neural changes in TBI-MDD.

Chapters 7 through 10 are comprised of the four experimental papers (previously outlined) that were submitted for publication in peer-reviewed journals during my doctoral

candidature. The final chapter (11) provides an integrated discussion of the results of these studies, and the conclusions that can be drawn from these results about the neural changes that take place in TBI-MDD.

Chapter Two

Traumatic Brain Injury, Major Depressive Disorder, and Depression Following a Traumatic Brain Injury

This chapter will provide a general introduction to traumatic brain injury (TBI), major depressive disorder (MDD) and depression following a TBI (TBI-MDD). It will also provide a focussed review on the mechanisms that might affect the neural processes of individuals affected by TBI and MDD; and finally speculate as to the neural changes that might cause MDD following a TBI.

Traumatic Brain Injury

A traumatic brain injury is an insult to the brain that is caused by either a collision between the head and another object, or rapid acceleration/deceleration of head movement (Fortune and Wen, 1999). Both of these actions can cause the brain to impact against the inside of the skull, which, if occurring with sufficient force, disrupts brain function. The acute disruption in brain function can cause a loss of consciousness (LOC). It is also likely to cause confusion and disrupted memory formation, a state known as post traumatic amnesia (PTA). The presence of either LOC or PTA is the criteria that differentiates a TBI from a blow to the head that does not cause brain injury (Kay et al., 1993). The term concussion is often used to describe these states (LOC and PTA) following more mild injuries, and as such the term concussion also refers to a TBI. TBI refers to both open injuries (where the skull is penetrated) and closed injuries (where the skull remains intact). To avoid

the significant heterogeneity introduced by the focal effects of open injuries, this thesis (and thus the following review) focuses specifically on closed injuries.

Prevalence

Estimates of TBI prevalence suggest 1.4 million people experience a TBI in the United States each year (Langlois et al., 2011). International estimates of the rates of hospitalisation as a result of TBI over the course of one year vary between 108 and 332 per 100,000 (Abelson-Mitchell, 2006), with an Australian estimate putting the figure at 149 per 100,000 (Fortune and Wen, 1999). However, the total number of TBIs each year may in fact be significantly higher than this, as the majority of head injuries do not result in a hospital admission (McKinlay et al., 2008). Indeed, one study reported that 24% of undergraduate students self report a head injury with some degree of LOC (Sawchyn et al., 2000). Similarly, a recent cohort study in New Zealand found that by the age of 25, over 30% of people had sought medical treatment for a concussion, with 12% having experienced an injury severe enough to be admitted to hospital overnight (McKinlay et al., 2008).

The majority of TBIs are due to traffic related incidents (Kreutzer et al., 2001), and affect people of working age, with the highest rate of injury experienced by young people aged 15 to 19 years (Fortune and Wen, 1999). TBIs affect males at a much higher rate than females – almost 70% of hospital admissions as a result of TBI are males (Fortune and Wen, 1999). Following a TBI the individual may continue to struggle with employment, social relationships, and recreation. Since TBI does not necessarily reduce life expectancy, long term support is often necessary, so as well as the significant personal suffering, these injuries are associated with a significant economic cost (Fortune and Wen, 1999).

Severity

TBIs can be divided into three main categories of severity; mild, moderate, and severe. The division is most commonly based on three different measures. The first measure taken is known as the Glasgow Coma Scale (GCS). This scale is administered by medical staff, and estimates an individual's level of consciousness by assessing motor responses to instruction or pain, verbal responses to questions, and eye opening (Teasdale and Jennett, 1974). This scale gives a score from 3-15, with higher scores reflecting less severe injuries. Typically, 13-15 is defined as a mild injury, 9-12 as a moderate injury, and below 8 as severe. The second measure used to define injury severity is the length of LOC. Typically, LOC of less than 30 minutes is defined as a mild injury, and less than 24 hours as a moderate injury (Kay et al., 1993; Malec et al., 2006; Rao and Lyketsos, 2000). Lastly, length of PTA is used to measure of injury severity, with duration shorter than 24 hours indicating mild injuries, moderate injuries between one and seven days, and longer PTA indicating severe injuries (Department of Defense and Department of Veterans Affairs, 2008; Kay et al., 1993; Malec et al., 2006). It should be noted that the different measures of TBI severity are not always consistent with one another, so studies often use a combination of measures to obtain more accurate estimates. Previous research using each different method to assess TBI severity indicates that more severe injuries result in poorer recovery (Dikmen et al., 1990; Ross et al., 1994; Williams et al., 1984). This is because during more severe injuries the brain suffers injury mechanisms to a larger degree.

Mechanisms of Damage

There are two immediate mechanisms by which a TBI injures the brain. The first is through focal contusions, which directly inflict mechanical damage on neurons, and damage

capillaries which releases blood into the surrounding tissue. Blood is neurotoxic, so this results in neuron death, leading to hematomas and focal lesions that affect the brain area they develop in (Levin et al., 1987). Focal lesions are the only macroscopic impact of a TBI and can be commonly visualised using CT or MRI scans.

The second immediate mechanism of injury is known as diffuse axonal injury (DAI), which involves damage to the axons that connect neurons, as the stable structure surrounding the axon shifts during cranial acceleration or deceleration (Fork et al., 2005). Unfortunately, this mechanism of injury is difficult to image due to it's microscopic nature, and difficult to localise to any specific area due to the distributed nature of the injury (Silver et al., 1991). The results of DAI are thought to impair long range white matter communication between brain regions, resulting in a less efficient processing network, the result of which is thought to be the most important factor contributing to the outcomes following TBI (Adams et al., 1982). Both focal lesions and DAI are thought to impact the frontal and temporal lobes in particular (Fork et al., 2005).

The delayed effects of a TBI include hypoxia and brain swelling. Hypoxia results from impeded blood supply to specific neurons, which causes cell death, upon which chemicals that are toxic to other cells are released. Brain swelling leads to mechanical compression of different brain regions, resulting in further cell death (Adams et al., 1982). Additionally, TBI results in a 'neurometabolic cascade', during which excessive amounts of glutamate (an excitatory neurotransmitter which is excitotoxic when over-abundant) is released, causing further neuron death (Giza and Hovda, 2001). Research has suggested that the excess glutamate not only causes short term neuron death, but also may result in a longer term increase in gamma-aminobutyric acid ($GABA_b$), an inhibitory neurotransmitter, possibly as a

defence mechanism in order to prevent further glutamatergic excitotoxicity (Perez-Pinzon, 2007). These $GABA_b$ increases may result in impaired synaptic plasticity. Recent research using transcranial magnetic stimulation (TMS) has shown that more than nine months following mTBI, measures of neural plasticity, ie. long-term potentiation (LTP) and long-term depression (LTD), are suppressed, and that these changes are related to impairments in learning (De Beaumont et al., 2012).

Symptoms following a TBI

Following a TBI, individuals can experience a number of changes, which vary widely from person to person, and may occur in a number of different domains, collectively termed 'post concussive syndrome' (PCS). Physical symptoms may occur following a TBI, the most common of which are headaches, fatigue, insomnia, and dizziness, but can also include a number of specific impairments in areas like hearing, vision, balance and coordination (Rutherford et al., 1977). Since a TBI frequently affects the frontal lobes, relevant for emotion and cognition (Bigler, 1999), a number of emotional changes can also occur. These include increased anxiety and depressed mood, as well as impairment in memory, attention, and information processing (Olver et al., 1996). These changes in emotion and cognition may lead to behavioural changes, such as increased irritability, impulsivity, self-centredness, aggression and disinhibition (Fortune and Wen, 1999; Olver et al., 1996). Of these, the most commonly reported symptoms following TBI are memory problems, increases in irritability, more fatigue, headaches, and reduced ability to concentrate (Tennant et al., 1995).

Mechanisms of recovery

There are two methods by which the brain recovers following a TBI. Firstly, although plasticity may be suppressed following TBI (De Beaumont et al., 2012), neuroplastic changes can still replace neurons, and form new connections to compensate for damaged areas (Castellanos et al., 2010). This can result in adaptive recovery following a mild TBI, but may lead to maladaptive reorganisation in more severe injuries (Povlishock and Christman, 1995). The second method of recovery is through more macroscopic nervous system adaptations, where brain regions that previously did not perform a function are adapted to perform a function lost due to damage (Muñoz-Céspedes et al., 2005). Both of these recovery methods depend upon optimal metabolic and chemical function for optimal results. However, higher stress levels are often experienced following a TBI, (Ponsford et al., 2000), and long term exposure to stress related neurotransmitters is known to cause neuronal atrophy, and may hinder neuronal recovery (Watanabe et al., 1992).

Outcomes following TBI

As a result of lingering symptoms, a large proportion of individuals who suffer a TBI (approximately 40%) are classified as not having a good recovery (Jennet and Bond, 1975). Estimates of the lifetime prevalence of permanent sequalae resulting from a TBI are 269 per 100,000 by the age of 34 years (Winqvist et al., 2007). Research indicates that approximately 30% of individuals who suffer a TBI are diagnosed with a mental illness 1 year following their injury (Deb et al., 1999). Unfortunately, in some individuals, outcomes may not improve over time, with some research indicating that more neurological and cognitive problems are reported five years following the injury than at two years, as well as lower employment (Olver et al., 1996). In particular, depression is highly prevalent following TBI.

Major Depressive Disorder

Prevalence

MDD is common not only following a TBI, but also in the general population. The World Health Organisation (2001) estimates that in one year 5.8% of males and 9.5% of females worldwide will experience a depressive episode. Similar rates are found in the Australian population (Goldney et al., 2000), with over one million people in Australia estimated to suffer from mood or affective problems (Australian Bureau of Statistics, 2006). The disorder is associated with significant cost, with depression and anxiety combined accounting for 8.2% of all disability adjusted life years (a measure of the number of healthy years of life lost to disability) in Australia (Begg et al., 2007). Individuals with MDD suffer significantly reduced quality of life, reduced physical health, and more reliance on health services (Goldney et al., 2000). Worldwide, approximately 850,000 people commit suicide every year as a result of depression (World Health Organisation, 2003). In addition to the significant personal cost of depression, it is the fourth largest cause of burden to society as a result of disease, and is projected to become the second largest cause by 2020 (World Health Organisation, 2001). It has been estimated that if the cost of depression in terms of days off work could be alleviated in Australia, approximately $1 billion worth of productivity would be regained by the community (Goldney et al., 2000).

Symptoms and Course of MDD

The symptoms of MDD fall into three main categories; a mood category, which includes depressed mood, reduced interest, and feelings of worthlessness; a somatic category, which includes weight changes, motor agitation or slowing, sleep disturbance, and

decreased energy; and a cognitive category which includes diminished thinking ability, and negative ruminations (Kreutzer et al., 2001). If five or more of these symptoms are present in sufficient severity for two or more weeks, a major depressive episode is diagnosed. Because MDD is comprised of such a variety of symptoms, and because each of these symptoms can be expressed in a variety of manners, two individuals with MDD can express the illness with considerable differences. As such, researchers have suggested MDD can be further divided into a number of sub-types. These include melancholic depression, MDD with psychotic features, and atypical depression. Depression is also viewed as an episodic disorder, with sometimes long periods of euthymia followed by eventual relapses in the majority of cases (Kuyken et al., 2008). It also seems that each additional relapse increases the risk of further episodes (Bocktin et al., 2006), and that sub-threshold depressive symptoms often remain between episodes, increasing the risk of relapse further (Judd et al., 2000).

While mood symptoms are in the most widely recognised symptoms of MDD, the disorder is also consistently associated with cognitive impairments (Austin et al., 1992). These include deficits in attention, memory, executive functioning deficits, and the presence of a mood congruent bias (a focus on negative information). In a meta-analysis of neuropsychological testing in MDD, Veiel (1997) suggests the lower performances seen in MDD indicate a “global diffuse impairment of brain function”, which is comparable to that found in TBI.

Aetiology of MDD

There are a number of different models that attempt to explain the development of MDD. Probably the most well known is the monoamine neurotransmitter deficit model.

The monoamine neurotransmitter deficit model

This model proposes that depression is the result of impairment in the monoamine neurotransmitter function in the brain. In particular, deficits in the function of serotonin (5-HT), dopamine (DA), and noradrenaline (NA, also known as norepinephrine) are suggested. The Monoamine Theory is based on the effectiveness of anti-depressant treatments, most of which block monoamine re-uptake from the synaptic cleft. This increases the density of the targeted monoamine in the synaptic cleft, upregulating the monoamine's action (Elhwuegi, 2004). While monoamine levels do seem to be altered in MDD, the current view is that depression is more complex than simply reduced monoamine levels - not all patients respond to re-uptake inhibitors, and drugs that increase monoamine activity (for example cocaine and amphetamines) do not work as anti-depressants (Elhwuegi, 2004). In addition to this, re-uptake inhibitors block monoamine re-uptake from the synaptic cleft within hours, but the anti-depressant effect takes weeks to occur (Baldessarini, 1989). Lastly, while monoamine depletion does lead to a reduced mood in individuals in remission from MDD, it has no significant effect on the mood of healthy controls (Ruhe et al., 2007).

Genetics

Related to the monoamine hypothesis is the genetic model of MDD. Meta-analysis of family and twin studies of depression found that while a large proportion of the variability in depression was explained by an individual's environment, 31% to 42% of the variability was explained by additive genetic effects (Sullivan et al., 2000). A number of genes have been found to relate to higher or lower levels of specific monoamines. One gene in particular; the 5-HTTLPR allele, is well studied. This gene is responsible for serotonin transport, and has two polymorphisms. The short version of this gene is thought to result in lower

transcriptional activity (Laksy-Su et al., 2005) which results in lower production of a transport protein responsible for 5-HT re-uptake from the synapse (Furlong et al., 1998). The short version of the 5-HTTLPR gene has been associated with more severe depression and more lifetime episodes of depression than the long version of the same gene (Zalsman et al., 2006). Although gene variations may explain much of the variation in the development of MDD, the model is closely linked to the monoamine hypothesis, and therefore is not complex enough to be a full explanation.

Brain Structure and Function Changes

There have been a number of structural and functional brain changes identified in MDD. Research using electroencephalography (EEG) to measure electrophysiological reflections of brain activity indicates two main changes in MDD. The first is that variations in cognition related scalp recorded voltages are reduced in amplitude. These findings will be reviewed in detail in Chapter 5. The second is that individuals with MDD may show asymmetrical resting activity, with more activity in the right hemisphere than the left, in contrast to the left > right asymmetry shown by healthy controls. The right > left asymmetry is related to a proposed specialisation of the right hemisphere for withdrawal behaviour and negative emotion, and the left hemisphere for approach behaviour and positive emotion (Davidson, 1992). This research focuses on alpha band power, which is activity oscillating at 8-13Hz. More activity in this band has been conceptualised as representing a decrease in brain activity (Pfurtscheller et al., 1996). A recent meta-analysis of this hypothesis showed a significant relationship between MDD and left > right resting frontal alpha power, indicating right > left activity (Thibodeau et al., 2006). Other research, however, indicates that the right hemisphere bias is not predictive of MDD – individuals with lower left frontal activity

do not have a more depressed mood, do not respond more to a negative mood induction, and do not score higher on a measure of dysfunctional attitudes, and when individuals are grouped based on their hemispheric asymmetry those with a right hemisphere bias are not more depressed (Gotlib et al., 1998; Mathersul et al., 2008). Additionally, more recent conceptualisations of alpha activity suggest that the picture is more complex than simply that alpha activity reflects less brain activation (Klimesch et al., 2007).

Research into brain structure and functional changes in MDD has often used Magnetic Resonance Imaging (MRI) to obtain images of the brain, enabling researchers to measure volumes of different areas, and blood flow activity. This technique has revealed a number of differences in the brain structure and activity of individuals with MDD (Sheline, 2000). In particular, changes are found in the hippocampus (Campbell et al., 2004), amygdala (Abler et al., 2007; Lee et al., 2007; Siegle et al., 2002), prefrontal cortical areas including the dorso-lateral prefrontal cortex (DLPFC) (Siegle et al., 2007), and anterior cingulate cortex (ACC) (Mitterschiffthaler et al., 2008; Tang et al., 2007). These areas are components of the limbic-cortical-striatal-pallidal-thalamic tract, which appears to be altered in MDD (Sheline, 2000). Alterations in this circuit are thought to relate to changes in emotional expression (Drevets and Furey, 2009). The limbic-thalamo-cortical circuit, which includes the amaygdala, hippocampus, medial thalamus, and orbitomedial prefrontal cortex also appears to be altered in MDD (Drevets and Furey, 2009). Alterations to this circuit are thought to result in the cognitive changes in MDD (Mayberg, 1997). Researchers into brain structure and activity emphasize that the functional connectivity between different areas may be altered in MDD, proposing a dysfunctional network approach to explain MDD (Drevets, 2000; Gotlib and Hamilton, 2008; Mayberg, 1997). In particular, MDD is thought to

be the result of impaired regulation of the activity related to emotional, cognitive, and physical stress on these circuits (Mayberg, 2006). Evidence suggests that altered glutamatergic and glucocorticoid activity in MDD may lead to altered neural plasticity, which may be partially responsible for the network dysregulation (Maletic et al., 2007).

Stress

As suggested above, the changes in neural activity and structure may be caused by the effects of chronic stress. Animal studies have indicated that long term high exposure to stress results in decreased hippocampal size (Uno et al., 1989), with decreased dendrite length and less dendritic branching (Watanabe et al., 1992). Stressful events result in disruption to the physical homeostasis, so the body reacts to regulate the change and return to a state of balance (Sheline, 2000), through a feedback loop involving the hypothalamic-pituitary-adrenal (HPA) axis releasing a sequence of hormones, which ends in the release of glucocorticoids by the adrenal gland (Sheline, 2000). Following a stressful event, the feedback loop is regulated by the hippocampus, which suppresses the release of each of the hormones in the sequence (Sheline, 2000). In long term stress, however, the hippocampus may fail to sufficiently regulate the feedback loop, resulting in excessive glucocorticoid levels, which can be neurotoxic (Sapolsky, 2000). The increased glucocorticoid levels can increase the level of glutamate, a neurotransmitter that is also neurotoxic at high levels (Moghaddam et al., 1994), and may result in reduced blood flow to the hippocampus (Sapolsky, 2000). It is not surprising then that stressful life events are significant risk factors for the development of MDD (Risch et al., 2009).

The Cognitive Model of MDD and the Coping Styles Model of MDD

The cognitive model proposes that negative thought patterns and belief systems about one's self are responsible for the symptoms of MDD (Beck, 2008). These dysfunctional attitudes are negative cognitive schemas that influence memory and attention, increasing memory for, and attention to, negative events (Scher et al., 2005). They are proposed to be overactive in MDD, with lower thresholds of activation than in individuals without MDD (Beck, 2008). As these negative schemas are the cause of the negative mood bias found in MDD the cognitive model tends to view the negative bias not only as a symptom, but as a cause of the disorder. These negative schemas may be activated in response to stress - individuals with more active dysfunctional attitudes are thought to fall into a major depressive episode (MDE) following lower amounts of stress than those with less active dysfunctional attitudes (Scher et al., 2005). Similarly, high levels of stress can increase the likelihood of a depressive episode (Scher et al., 2005).

Although the cognitive model examines mental processes rather than physical, it is not necessarily separate from other models of MDD. Beck (2008) proposes that the over-active negative schemas found in MDD are analogous to the over-active amygdala and impaired inhibitory control by the prefrontal cortex found in imaging studies of MDD. Similarly, stressors used in the cognitive sense in this model are reflected by the physiological increases in glucocorticoids described in the stress model.

Similar to the cognitive model of MDD, the coping model describes subjective states that are associated with MDD. This approach generally divides coping methods into emotional coping, which attempts to alter the feelings elicited by the stressor, and problem solving coping, which attempts to alter the situation to make it less stressful (Lazarus, 1993).

Research into coping styles indicates that avoidant coping, which involves retreating from a stressor, is associated with more depressive symptoms (Penland et al., 2000), while problem solving coping is associated with fewer depressive symptoms (Billings and Moos, 1984). Similar to coping styles, emotional attribution styles are related to MDD as they provide an interpretation of a negative event. This involves judgements on whether the cause of a negative event is internal or external, and whether the personal characteristics that caused the event are stable or fundamental to the person (Bruder-Mattson and Hovanitz, 1990). Negative events that are attributed to internal and fundamental characteristics of the person are associated with increased vulnerability to MDD.

An Integrated Model

Although the explanatory models of MDD have been presented here separately, they are likely to be part of an integrated model – each piece reflecting a different perspective of the same image. Neurotransmitter function alterations are detected as blood flow changes when imaging techniques are used, and as negative schemas when subjective measures are taken. Brain and behaviour are interwoven to the point they are indistinguishable – it is only the tool we use that seems to separate them. As such, while one technique may be used to measure a specific aspect of MDD, the results have implications for knowledge about other aspects. In particular, evidence suggests that the cortico-limbic dysregulation model of MDD is the neural representation of the impaired cognitive appraisal of negative schemas proposed by the cognitive model of MDD (Beck, 2008). The cognitive control impairments are the behavioural expression of prefrontal dysfunction, and the emotional symptoms are the expression of limbic overactivity.

Similarly, treatment interventions at one level can have significant effects on measures taken at other levels, for example antidepressant medication has been associated with structural neuronal remodelling and hippocampal recovery (Bessa et al., 2009; Kempermann and Kronenberg, 2003). And finally, negative impacts at the neuronal, structural, and functional network level (like the impact that occurs in a TBI) can result in changes that on a behavioural level are expressed as MDD.

Major Depressive Disorder Following a Traumatic Brain Injury

As discussed previously, a significant proportion of individuals who have suffered a TBI do not have a good recovery. One way in particular that a poor outcome following a TBI can be expressed is the occurrence of major depression.

Prevalence

Although it is accepted that MDD is a common negative after effect of a TBI, the reported rates vary widely. This is perhaps due to the use of a number of different methods to assess MDD, varied inclusion criteria for severity of TBI, and a range of times between injury and measurement of rates of MDD.

The First Year Following Injury

Estimates of the rate of MDD in the first year after TBI vary from 15-45%. Three months following a mild to moderate injury, the proportion of individuals suffering from MDD was 17% in one study (Levin et al., 2001). Two months after injury, MDD has been found in 15.6% of mildly injured adults over 50 years of age (Rapoport et al., 2006). Similar rates have been found in a sample of mild/moderate TBI after an average of 200 days following injury, with 28.4% diagnosed with MDD by a psychiatrist (Rapoport et al., 2005).

Longitudinal studies indicate that these rates are high for the course of the first year. Jorge, Robinson and Arndt (1993a) found that out of 66 TBI sufferers (the majority of mild to moderate severity), 29% reported having a depressed mood at their initial evaluation using the Present State Exam psychiatric interview. This rate continued to vary between 26% and 31% in quarterly follow up assessments lasting one year, with 42% meeting criteria for MDD at some stage over the year (Jorge et al., 1993a). Another more recent longitudinal study of mostly mild injuries using a self report measure found an initial rate of MDD in 44%, decreasing gradually to 36% at six months following injury, and 29% at one year after (Pagulayan et al., 2008).

Years Following Injury

At around one year following injury, rates of MDD following a TBI are still higher than in the general population. At the lower end of the estimates, Deb et al. (1999) found 13.9% of a sample of 164 TBI sufferers of varied severity had a psychiatric diagnosis of MDE one year following their injury. Other estimates are higher – in another study of 43 patients one year following their injury, 25% had a diagnosis of major or subclinical depression (Jorge et al., 1993b). As well as studies combining a range of severities, high rates of depression are found a year after mild TBI. For example, Schoenhuber and Gentilini (1988) found that 35 mild TBI patients were significantly more depressed than their age, education, and case matched controls, despite the fact none required more than three days of hospitalisation. Another study comparing depression symptoms in the general population to symptoms in individuals with a history of mild TBI (more than one year prior) found significantly higher BDI scores in TBI individuals (Trahan et al., 2001).

The rates of MDD tend to remain high for years following a TBI. In an extensive study of 722 TBI sufferers with a variety of severities but a median LOC of less than one hour (indicating the majority were mild injuries) Kreutzer, et al. (2001) found that 42% fit the criteria for MDD using the Neurobehaviour Functioning Inventory (NFI) self report an average of 2.5 years following their injury. Rates as high as 77% have even been reported in a group of 120 TBI sufferers who were injured over two years prior (Varney et al., 1987). Even five years following a TBI, 56% of 103 individuals reported that they were more depressed than prior to the TBI (Olver et al., 1996). These elevated rates may even persist across the lifetime. In a very long term follow-up of 60 patients, with an average of 30 years since a TBI of a wide range of severities, 26.7% had suffered from MDD, and 10% were currently depressed (Kaponen et al., 2002), indicating MDD may be a long lasting rather than transient sequalae of TBI. Even more than 50 years following an injury experienced in World War II, both lifetime prevalence and current episodes were increased compared to those who had not suffered a head injury (Holsinger et al., 2002).

Although the results are mostly consistent, not all studies have found high rates of depression following a TBI. Sawchyn et al. (2000) found no difference in BDI scores between those who reported having suffered a head injury with a loss of consciousness an average of 5.7 years previously, and those who did not in a sample of 326 undergraduates. The researchers separated the groups on the basis of self reported injury occurrence only though, rather than through any medical confirmation or measure of severity so this may not accurately represent a TBI sample.

An explanation for the wide variety of estimates of MDD following a TBI has been offered by Jorge, Robinson, Arndt, et al. (1993c). These authors suggest that the reason

estimates vary so widely may be due to the use of rating scales rather than structured interviews and diagnostic criteria. A review of rates of MDD following TBI indicates that research using rating scales generally obtain higher rates of around 30-35%, while structured diagnostic interviews obtain rates of around 25% (Satz et al., 1998). However, regardless of the measure used, the review showed a link between TBI and MDD (Satz et al., 1998), and generally it seems rates of MDD following a TBI are higher than the 5-10% found per year for the general population (World Health Organisation, 2001). Unfortunately, these high rates do appear to persist, with the majority of individuals who develop MDD soon after their TBI remaining depressed one year following their injury (Rapoport et al., 2006), and assessments years after injury of the rate of TBI-MDD indicate that a high rates are present even when symptoms have subsided, potentially for the remainder of their life. It also seems that the fact most injuries are mild is no relief - increased rates of MDD are reported for all TBI severities.

The Impact of TBI-MDD

In addition to the personal distress associated with MDD, emotional changes can also influence the outcome of TBI itself (Ruff et al., 1996). Older adults who develop depression following a TBI report more psychosocial dysfunction and distress, and more symptoms of PCS six months following the injury, and worse scores on measures of function activities one year following the injury (Rapoport et al., 2006). In addition to the poorer outcome of TBI-MDD, individuals who develop MDD following a TBI also show more impaired cognitive performance. Research by Rapoport et al. (2005) revealed that 85% of the patients who developed MDD following TBI were cognitively impaired, compared to only 47% of those who do not develop MDD. This impairment was apparent in measures of

working memory, processing speed, executive function, and visual memory as compared to participants with TBI alone. These cognitive difficulties are similar those seen in MDD itself, and are also consistent with what is generally seen following a TBI (Rapoport et al., 2005), so it appears that the combination of MDD and TBI may enhance the cognitive effect of either disorder alone. When the MDD is treated with an selective serotonin reuptake inhibitor (SSRI) in TBI-MDD patients over an eight week period, not only did depression scores improve, but also most of the cognitive impairments were improved (Fann et al., 2001). These results suggest that MDD may be the cause of the cognitive impairments found in TBI-MDD; research has even indicated that MDD may be a larger contributory factor than the TBI. When a TBI group was compared to a general trauma group in measures of cognition, no difference was detected. However, patients with MDD from both TBI and general trauma groups performed worse in measures of memory, processing speed, and executive functions than those without MDD (Levin et al., 2001). Unfortunately, sufferers of a TBI are often unaware of the impact of MDD on cognition, so attribute these impairments to irreversible effects of the TBI (Fann et al., 2001). Some individuals may not even be aware that they have developed MDD following TBI, and may attribute their mood symptoms to the TBI as well (Jorge and Robinson, 2003). As a result, they may not seek treatment for the factor may be the most significant cause of impairment and suffering following the injury.

Potential Aetiology of TBI-MDD

Although currently there are no models to explain the development of MDD following a TBI, a number of factors have been proposed, which fall into two main categories. The first and more extensively researched category offers psychosocial explanations. These explain what might be termed a “reactive” depression – an emotional

reaction to the stressors and limitations resulting from the injury (Moldover et al., 2004). These accounts focus on coping styles, personality, psychiatric history, and stress as risk factors for TBI-MDD. The second category focuses on changes in neural structure and function resulting from a TBI which may lead to MDD. Less is understood, however, about how changes in neural structure and function relate to MDD following a TBI.

Psychosocial Explanations

The psychosocial explanations for TBI-MDD are easy to imagine. After a TBI, life may be changed for the worse, with limitations on previously taken for granted abilities, social isolation, and a potentially painful recovery. More than half of TBI sufferers report having lost friends and feeling more socially isolated than prior to the injury (Olver et al., 1996). A large amount of the research into the cause of TBI-MDD has focused on how individuals cope with these changes. Coping styles following a TBI are similar to those used by non-injured persons, and are reasonably stable post-injury (Malia et al., 1995). Similar to non-injury related MDD, the use of emotion focused coping, avoidance coping, and wishful thinking are associated with lower psychosocial functioning, negative affect, and depression (Anson and Ponsford, 2006; Kendell et al., 2001; Kortte et al., 2003; Malia et al., 1995). In addition to coping styles, some research has indicated that the cognitive model of MDD may help explain TBI-MDD. Mildly injured individuals are found to underestimate the number symptoms that non-injured people experience (Ferguson et al., 1999) suggesting that following a TBI people attribute feelings of fatigue, irritation, and poor concentration to their injury (an internal irreversible feature of themselves), even though the same symptoms are experienced by non-injured people. Similarly, mild TBI sufferers are found to hold negative beliefs about their memory function, and place more importance on memory

success than non-injured controls (Kit et al., 2007). These negative beliefs were found to contribute to depressive symptoms (Kit et al., 2007). General changes in self attitude have been found to be the main factor that distinguished between those who developed MDD and those who did not (Jorge et al., 1993a). Other factors that are likely to contribute to TBI-MDD include higher anxiety, self-reported psychosocial dysfunction, and low self esteem (Anson and Ponsford, 2006). Younger patients, individuals with pre-injury alcohol consumption, and individuals with lower cognitive scores are also more at risk (Deb et al., 1999). Perceived stress, subjective pain, and involvement in litigation explain a significant amount of the variance in depressive symptoms following a mild to moderate TBI (Bay and Donders, 2008).

Although poor coping styles, negative beliefs, and other psychosocial factors seem likely explanations for TBI-MDD, it is also unknown the extent to which these factors are prior vulnerabilities, leading to MDD in some individuals following a TBI but not others, or whether they are a result of changes in brain function that result from the TBI.

Similarly, although previous history of mental illness is linked to the development of MDD (Jorge et al., 1993a), research indicates that previous vulnerability only explains some cases of TBI-MDD – one study found that out of the 15.6% who developed MDD two months following a TBI, none had a history of MDD, even though 18.2% of the total sample had a history of MDD (Rapoport et al., 2006).

Other research indicates that depressive symptoms correlate with functional impairment, and functional impairment at one month is predictive of MDD at six and twelve months (Pagulayan et al., 2008). However, level of functional impairment cannot completely explain the high rates of TBI-MDD. Research comparing rates of MDD in general trauma to

TBI indicates the rate is twice as high after TBI, even when no differences are found in functional outcome or social support (Levin et al., 2001; McCleary et al., 1998; Varney et al., 1987).

It has also been suggested that the elevated rates of MDD following a TBI are an artefact of the overlap between symptoms that follow a TBI and the symptoms of MDD (Trahan et al., 2001). This does not fully explain the high rates however, as four symptoms consistently differ between those who develop MDD following a TBI and those who do not; lack of energy, depressed mood, feelings of worthlessness, and suicidal ideation, all of which are more typical of MDD than TBI (Jorge et al., 1993a).

Despite the logic of the psychosocial explanations for elevated rates of MDD following a TBI, these factors do not seem to completely explain the elevated rates. Therefore, research has begun to examine whether there are neural factors that also contribute.

Neural Factors

As previously mentioned, neural structure and activity changes are found in non-injury MDD which may offer a possible explanation for the symptoms of the disorder. Despite this, very little research has looked at whether these changes also take place in individuals who develop TBI-MDD.

Some research has used imaging techniques have examined the relationship between lesion location and TBI-MDD. This research has found associations between left anterior lesions and MDD using computed tomography scans (CT) (Robinson et al., 1988; Robinson and Szetela, 1981). In particular, an association has been found between lesions in

the DLPFC and basal ganglia (Federoff et al., 1992). However, this is not consistent, as other research showing no difference between depressed participants and non-depressed participants in the frequency of frontal lobe injury (Reza et al., 2007).

The variability in lesion studies may be due to differences in time since injury. To test this, Jorge, Robinson, Arndt, Forrester, et al. (1993c) compared patients who developed MDD in the acute period following their TBI to those who had a delayed onset of MDD. CT scans indicated that those with acute onset were more likely to have a left anterior lesion, and were more likely to show subcortical lesions, than individuals who did not develop MDD and those who had delayed onset MDD. Delayed onset MDD, on the other hand, was not associated with lesion location, but was associated with poorer social functioning scores. The authors suggest that depression in the acute phase following a TBI may be a result of the neurotransmitter interruption following the injury, while delayed onset depression is a psychological response to changes that the injured person perceives in their life (Jorge et al., 1993c). However, this explanation does not take into account the disruption to brain activity from DAI. If an injury that results in short term neurotransmitter pathway impairments leads to early onset MDD, perhaps permanent DAI impairment would lead to non-transient MDD. Also in contradiction to the 'early onset MDD results from lesions, late onset MDD results from psychosocial factors' explanation, lesions in the DLPFC have been found to confer vulnerability to severe depression long after the injury occurred (Koenigs et al., 2008).

A recent review of the causes of TBI-MDD suggests that lesion studies of TBI-MDD seem to show an association between location and MDD soon after the injury (Moldover et al., 2004). However, this association tends to disappear over time, perhaps because TBIs often involve diffuse damage that is difficult to measure using neuroimaging techniques.

Moldover, et al. (2004) emphasize that MDD following a TBI should be viewed as a heterogeneous group, with neural damage from the injury and psychosocial factors varying in influence between individuals. However, they suggest there is little evidence as yet of permanent physical changes in the brain leading to MDD following a TBI. It is possible that this is due to the previous difficulty in measuring the microscopic effects of DAI with CT or MRI, so Rosenthal, Christensen, and Ross (1998) suggest that measures of functional activity may help explain the aetiology of MDD following a TBI.

So far, only three pieces of research have examined the issue of depression following a TBI on measures of *functional activity*.

The first compared blood flow changes using fMRI in the brains of injured athletes with and without depressive symptoms during a working memory task (Chen et al., 2008). Their results indicated that the depressed TBI athletes had differences in activity of the DLPFC and the dorsal and rostral ACC compared to non-depressed TBI athletes and controls. It also indicated that activity in the DLPFC was negatively correlated with scores on the BDI (Chen et al., 2008). They suggest this indicates individuals who develop depressive symptoms following a TBI have impaired cortico-striatal-thalamic network function (Chen et al., 2008). While this research confirms that there are activity differences between individuals who develop depressive symptoms following a TBI and those who do not, blood flow changes are measured over the course of seconds, so cannot offer information about how moment to moment brain activity is affected, nor how the functional connectivity between different regions might be affected by injuries such as DAI.

The second study used EEG measures of electrophysiological activity recorded during a simple cognitive task (Reza et al., 2007). Individuals who had experienced a TBI and had

high depression scores had delayed voltage peak latencies in response to stimuli, and lower voltage amplitudes compared to the control and non-depressed TBI groups. These authors suggest this implies a reduced information processing capacity in these participants (Reza et al., 2007). Although this study indicates brain function changes with high temporal resolution, it focused on individuals with severe injuries, so the results may be affected by the presence of focal lesions. Additionally, while their results reflect an impairment in the TBI-MDD groups ability to synchronise neural populations, their between group comparisons were only taken from one electrode position, so cannot inform us about disruptions to between region connections as a result of DAI. Lastly, the cognitive task they used only measured aspects of attention and memory updating so cannot fully characterise the processes that are disrupted in TBI-MDD.

The final study to examine the issue again used EEG to compare severe TBI individuals with and without negative affect in measures of error processing. This study found that following an error, a voltage deflection representing response evaluation and error detection was more reduced in individuals with TBI and negative affect (Larson et al., 2009). Similar to Reza et al. (2007), the results may have been affected by focal lesions, and did not compare groups on measures of communication between areas, so again cannot inform us about network connectivity. Also, neither Reza et al. (2007) nor Larson et al. (2009) examined MDD, but rather negative affect and high depression scores. Additionally, neither study included a non-injured MDD group to assess whether the effect of TBI-MDD is more severe than that of MDD alone (due to the combination of both), or whether the changes in brain activity might be attributable to the MDD rather than the injury.

Summary of TBI-MDD and Rationale for the Current Study

Following TBI, rates of depression are elevated compared to the general population. Unfortunately, TBI-MDD leads to poorer outcomes, in terms of personal distress, functional living, and cognitive capacity. There are a number of psychosocial factors that may explain some of the higher rates of MDD after TBI, but do not explain the full extent of the increase. While other potential explanations are highly likely to relate to changes in brain activity, very little research has examined this issue. The majority has attempted to infer how changes in brain activity might have taken place from structural imaging of lesion locations. This method only indirectly approaches the issue, and can only visualise macroscopic changes. Microscopic changes, in the form of DAI are thought to be more important following a TBI. Only three studies have directly examined functional activity in TBI-MDD and none have be able to provide information about potential effects of DAI, which leaves a significant gap in our understanding of this issue.

The literature on both TBI and on MDD suggests that examining a number of different brain processes may hold promise for explaining how neural activity is altered in TBI-MDD. Firstly, both TBI and MDD affect a number of different areas of cognition. In particular, inhibition impairments and working memory impairments are common to both, while negative mood biases are found in MDD but not TBI. Both TBI and MDD are also thought to affect the network function of brain activity. Comparing groups with TBI-MDD to groups with TBI only, MDD only, and healthy controls on electrophysiological measures of brain activity and brain connectivity related to inhibition, working memory, and mood congruent bias is likely to provide information on how the brain processes of these groups

differ. This will address whether changes are more related to the TBI or MDD, ultimately allowing for increased knowledge regarding the potential neural aetiology of TBI-MDD.

Chapter Three

Introduction to Encephalography

As suggested in the previous chapter, electroencephalography (EEG) is a technique that can be used to compare functional brain activity between different groups. In this chapter I will provide a brief introduction to EEG, with a particular focus on the origin of the recorded signal. This information provides an understanding of the significance of the results presented in later chapters.

The Origin of EEG signal

Brain activity is constructed from networks of communicating neurons. These communications take place through two methods; between and within neurons. Between neuron signalling occurs via the transmission of neurotransmitters through synapses between neurons. Within neuron communication transmits information along each individual neuron through electrical field variations. These electrical variations take two main forms – the first and most well known is the action potential, which is the rapidly moving depolarisation of a neuron's axon. Action potentials reaching the synapse are the cause of neurotransmitter release. Although these action potentials cause relatively large changes in voltage amplitude, they alter the electrical field for less than two milliseconds (for the most part, recent research has suggested Ca+ spikes may last longer), which is too brief to sum with the surrounding neuron's action potentials (Buzsàki et al., 2012). As a result, action potentials do not generate enough of a combined voltage shift to be detected at the scalp. However, when neurotransmitters bind to receptors on the dendrite of a second neuron, ion channels on the membrane of the second neuron are opened. This

allows the movement of electrically charged ions across the membrane, resulting in the synaptic potential. The synaptic potential lasts 10-30 times as long as the action potential (Schaul, 1998), which is enough time for the change in field to synchronise with synaptic potentials in millions of surrounding neurons. When this occurs in neurons that are aligned with each other and towards the scalp and are sitting relatively near the scalp, the potential changes are strong enough (around 10-100μv) to be conducted to the scalp and detected as a voltage difference between an active and reference EEG electrode (Buzsàki et al., 2012). If approximately 1cm² of cortical surface is activated simultaneously, the signal generated can be detected by scalp EEG electrodes (Lopes da Silva, 1991). Therefore, the EEG signal is measuring the synaptic potential changes that occur simultaneously in millions of closely spaced cortical neurons. This signal appears to 'wave' as it oscillates from positive to negative voltage over time. These waves can be divided into different frequencies of oscillations based on the number of peaks and troughs that occur per second. The different frequency bands that EEG researchers generally divide the signal into are described below.

Pyramidal neurons in the cortex are asymmetrically shaped, with thick dendrites on one side only, so that the electrical potentials they generate are directional, are aligned with each other towards the scalp, and are close to the scalp. As such, and because they are the most common neuron in the cortex, these neurons are generally thought to be the origin of these EEG signals (Buzsàki et al., 2012; Schaul, 1998). Negative potentials detected at the scalp represent depolarization of the dendrites of these neurons (Birbaumer et al., 1990). Positive potentials on the other hand may reflect a lowering in cortical excitability (Rockstroh et al., 1992). Dendrites conduct high frequency oscillations much less than the low frequency oscillations (Gold et al., 2006). Additionally, fewer neurons can fire in the

brief window allowed by the higher frequencies, while more can be recruited during the longer window of the slow frequencies (Buzsàki et al., 2012). As a result, low frequencies generated in the brain are more reliably detected at the scalp than high frequencies.

Advantages of EEG

The difference between the reference and active electrode is amplified and digitised with millisecond resolution. The fine grain temporal resolution of EEG offers advantages over fMRI, which has much lower temporal resolution, and is a less direct measure of current brain activity (blood flow changes only reflect metabolic requirements of a region, as opposed to EEG which directly measures neuron signalling). Comparing this signal between different experimenter manipulated conditions, and between different groups, allows for an understanding of the electrophysiological alterations that are associated with specific cognitive processes and specific pathologies (Buzsàki et al., 2012).

Although EEG has a superior temporal resolution to fMRI, it gives inferior spatial resolution. This is because each electrode records the spatiotemporal summation of the synaptic potential variation from around $10cm^2$ of the cortex, which is dependent on the volume conduction of that signal (Buzsàki et al., 2012). While electrodes record from a single location on the scalp, and hundreds of electrodes may be used, determining the exact source of the signal is difficult as alterations in electrical potentials are conducted throughout the volume of the scalp. This is known as the inverse problem – which "arises when attempting to infer the microscopic variables from the macroscopic ones" – in other words, trying to use scalp recorded voltage variation to obtain knowledge about underlying neural activity (Buzsàki et al., 2012).

Methods of EEG Analysis

EEG data can be analysed in a number of different ways. One method is to divide the different scalp recorded wavelengths based on the frequency of oscillation per second. This can be achieved by using Fourier analysis or Wavelet analysis calculations, which give a measure of the amplitude of a signal within a defined frequency band (rather than the amplitude at all frequencies at one specific point in time, which is given by the raw EEG data). EEG researchers generally categorise these bands as: Delta (0-3Hz), Theta (4-7Hz), Alpha (8-13Hz), Beta (13-25Hz), and Gamma (26Hz and above). Each of these bands is thought to represent a specific underlying process. As well as calculating overall band amplitudes from resting EEG recordings, average band analyses can be calculated during specific periods of cognitive tasks over a number of repeated trials, and compared to a non-active reference period, a process known as event related synchronisation/desyncronisation (ERS/ERD). The alpha and theta bands will be discussed in more detail in chapters 9 and 10.

A second method of analysing EEG data is to average the activity that occurs with temporal consistency preceding or following an event (either a stimulus presentation or participant response). The process of averaging eliminates the random fluctuations from trial to trial which are large in amplitude, but vary between positive or negative from trial to trial, and so average to zero. This leaves only the positive and negative variations that consistently occur in each trial, which are much smaller in amplitude, but do not average to zero. When this activity is recorded from cognition related processes it is known as an event related potential (ERP). ERPs represent activity related to specific cognitive processes. These are discussed in greater detail in Chapters 4 and 5.

Another method of analysing EEG data that is used in the current thesis is with coherence. Coherence measures the extent to which variations in band amplitude at one electrode are related to variations in band amplitude at another. This is thought to reflect functional connectivity, which is defined as temporal correlation between activity in separate brain regions (Friston et al., 1993). The functional connectivity between different regions is thought to be mediated by white matter conduits (Thatcher et al., 2007). Coherence is discussed further in chapter 10.

The Application of EEG Analysis to TBI and MDD

The following two chapters review the literature investigating brain activity changes in both TBI and MDD, measured with EEG analyses techniques. In particular, the chapters focus on research that has examined brain activity associated with cognitive processes.

Chapter Four

EEG analyses of cognitive processing following mild traumatic brain injury - a review

Electroencephalography (EEG) has been used extensively to examine processes related to cognition following a traumatic brain injury. Although this thesis is focused on MDD following a mild to moderate TBI, previous research using EEG has commonly examined participants with mild traumatic brain injury (mTBI), or has examined individuals with moderate to severe TBI as a single group. In order to avoid the confounding influence of focal injuries, this chapter does not include research with participants with severe TBI, and as a result focuses only on mTBI. Alterations in neurophysiological activity, as measured using EEG, may reflect subtle cognitive and behavioural changes, and may indicate impairment in neural connectivity as a result of diffuse axonal injury (DAI). Although a review of neuropsychological testing studies suggests patients fully recover cognitive function within months, cognitive related EEG changes have been found even decades post injury, suggesting underlying neural changes may not fully recover. This type of research is well suited for studying minor neural processing changes that may take place in mild TBI (mTBI), and may offer answers as to the source of the ongoing difficulties some mTBI sufferers face. This is particularly true if more recent innovative and in-depth EEG analyses are used, and more theoretically guided studies are conducted.

This chapter will particularly focus on the cognitive event related potentials (ERPs) and active task related bandwidth research, as resting bandwidth analysis post mTBI has been recently reviewed and early evoked potential recordings only provide mixed results

(Gaetz & Berstein, 2001; Nuwer, Hovda, Schrader, & Vespa, 2005). Cognition is also more likely to be affected than sensory processing post mTBI (Gevins et al., 1992). This is perhaps because damage is commonly found in frontal and temporal areas post mTBI (Metting et al., 2007). Since cognitive tasks are more demanding on neural resources than resting or sensory processing tasks, it makes theoretical sense that cognitive ERPs would offer more information about subtle changes resulting from mTBI.

Traumatic Brain Injury

Mild TBI

Mild TBI is commonly defined as an injury which results in a loss of consciousness (LOC) of less than half an hour, a Glasgow Coma Scale (GCS) score of 13+, and post traumatic amnesia (PTA) of less than 24 hours (Kay et al., 1993). The vast majority (> 70%) of TBIs are mild (Fortune and Wen, 1999). Although patients experiencing mTBI are often assumed to make a complete recovery within weeks, mTBI sufferers often report ongoing symptoms, which are collectively referred to as PCS. Of the self-reported symptoms following mTBI, headache is most prevalent, but anxiety, insomnia, dizziness, irritability, and fatigue are also common, as well as concentration and memory difficulties (Ponsford et al., 2000; Rutherford, Merret, & McDonald, 1977). In addition to this, risk of psychopathology is elevated. Similar to more severe injuries, the most significant psychiatric issue is depression. Estimates of the rate of depression post mTBI generally fall between 15% and 35% (Atteberry-Bennet, Barth, Loyd, & Lawrence, 1986; Rapoport, Kiss, & Feinstein, 2006; Schoenhuber & Gentilini, 1988).

Cognitive changes following mTBI

The cognitive changes following a mTBI are amongst the most debilitating, and are associated with poorer outcome so an understanding of the aetiology and magnitude of these issues is important (Atteberry-Bennet et al., 1986; Jorge et al., 2004). Subjective reports indicate mTBI sufferers have increased concentration difficulty three months after the injury, when compared to non-head injury controls (Ponsford et al., 2000). Even one to five years following mTBI, sufferers self-report cognitive complaints more the general population (Bohnen et al., 1994; Ponsford et al., 2000). However, because they are subtle and not physically apparent, relatives of patients are often not aware of them (Seel, Kreutzer, & Sander, 1997). This can be a source of extra frustration for the patient. Also, despite the prevalence of persistent subjective cognitive impairment, meta-analytic studies have shown only mild impairments, that are resolved by 3 months post injury (Binder, Rohling, & Larrabee, 1997; Schretlen & Shapiro, 2003). This discrepancy may be because the cognitive testing measures that have been generally used are not sensitive enough to detect minor changes (Binder et al., 1997). Research with fMRI suggests that mTBI sufferers may be compensating for their cognitive difficulties by recruiting more resources or a different pattern of resources in order to perform at a similar level to controls (McAllister et al., 2001). This suggests that while mTBI groups may show similar performances, the task is more effortful and fatiguing to them than non-mTBI groups.

Causes of cognitive changes following mTBI

Changes in cognitive functioning post injury are likely to be the result of changes in brain function, either due to psychogenic causes (such as mood, stress, and coping factors) or neuropathological causes (for example diffuse axonal injury). The current view is that it is

most likely due to a combination of both (Ryan & Warden, 2003). Despite the reported prevalence of ongoing symptoms, structural imaging techniques seldom show pathology post mTBI (Ryan & Warden, 2003). Even when structural neuroimaging shows abnormal results, only weak correlations with neuropsychological testing is found (Hofman et al., 2001). Both CT and MRI lack the sensitivity to detect abnormalities that cause functional impairment following mTBI (Metting, Rodiger, De Keyser, & Van der Naalt, 2007). This is perhaps because the mechanism of injury in mTBI is commonly microscopic in the form of DAI rather than macroscopic in the form of lesions (Gaetz, 2004). DAI refers to damage to white matter axons spread across the brain. They result from mechanical forces stretching axons, leading to axon swelling that causes disruption in usual metabolic processes, and can lead to connection impairments or disconnection (Povlishock & Christman, 1995). As the mechanical force causing the injury increases, deeper brain structures are affected by DAI, more axons are affected and they are affected more severely, with a larger and larger proportion suffering irreparable damage (Gennarelli, 1996). The extent to which this reduces widespread axonal functioning, i.e. network communication and efficiency, is likely to be a significant factor contributing to lingering symptoms following a mTBI.

Individual neuron changes are not well distinguished with CT and MRI imaging, and diffusion tensor MRI is only in the early stages of being able to assess overall axon integrity (Gaetz, Goodman, & Weinberg, 2000; Metting et al., 2007). EEG however can inform about network communication, so may be a useful measure of functional communication that is mediated by axon connections and impaired by DAI. EEG allows analysis of the processes that lead to overt behavioural responses by measuring the underlying electrophysiological function, and also the processes associated with covert behaviour (for example response

inhibition). This allows researchers to study underlying brain activity that relates to behavioural responses, as well as allowing the study of covert processes that cannot be studied with simple response measurements. It also has excellent temporal precision, so is a suitable method to measure subtle changes in neural communication and efficiency that are difficult to measure with structural neuroimaging techniques.

Definition of Cognitive ERPs

Event related potentials (ERP) are endogenously generated electrical variations in EEG signal which follow the presentation of a stimulus. Detection of a stimulus induces alterations in distribution of neural activity as specific areas of neurons process the new information (Gevins et al., 1992). The properties of ERPs are dependent on internal factors such as attention and task goals, and represent cognitive processes (Campbell & de Lugt, 1995). As such they are referred to as endogenous potentials – generated internally. This differs from the earlier evoked potentials (EPs), which are generated by and dependent only upon external sensory factors, and are referred to as exogenous potentials. There is no distinct demarcation point between endogenous and exogenous brain potentials, so those in between can be thought of as mesogenous ERPs – influenced by both internal and external factors. ERPs are measured by recording the EEG signal from a short epoch (approximately 1 second) time locked around a stimulus presentation, averaged over a number of trials. This averaging eliminates the random noise that is not relevant to processing that stimulus, leaving only the signal that commonly follows a particular stimulus (Campbell, Deacon-Elliott, & Proulx, 1986; Gaetz & Berstein, 2001). Because EEG has a excellent temporal resolution, ERP differences can be measured on the scale of milliseconds, which make them excellent candidates for measuring minor differences in

neural processing (Reinvang, 1999). The advantage of ERPs over cognitive tasks alone is that ERPs provide a measure of the processing that leads to a response, and can be measured even when no response is made (Reinvang, 1999). This allows researchers to determine if brain activity is changed even when behavioural responses are not, and allows for the analysis of processes involved in non-responses in error or in response inhibition tasks. Group level analyses have been shown ERPs to be stable and reliable enough for comparison over time (Segalowitz & Barnes, 1993).

Unfortunately, there is no consistent and accepted naming practice for ERPs. As a result, two wave peaks with very similar characteristics may be labelled differently by different researchers. This can make it difficult for non-experts to understand the mTBI and ERP literature. There are two common naming methods used. The first is to use the letter N for a negative peak or P for positive peak, followed by a number representing the order in which the peak occurs. For example the two most commonly compared ERPs in mTBI research are the P3b, which is the third positive peak following stimuli presentation (at parietal electrodes, in contrast to the P3a which peaks at frontal electrodes), and the N2, which is the second negative peak. The second labelling method also uses a letter to represent positive or negative deflections, but labels the time in milliseconds at which the peak occurs after the stimulus. This is less easily understood, as the latency of the same apparent peak can vary by up to half a second depending on individual and group differences, and task parameters. Using this method, the P3b is referred to as the P300 (positive peak occurring 300ms post stimulus), but can vary from 275ms to 875ms (Campbell et al., 1986). Labelling ERPs by their sequence is perhaps a preferable method, as differences in latency are often the dependent measure differentiating two groups,

referring to peaks by their timing is potentially confusing. The ordinal method of labelling peaks will be used in this thesis.

ERP Measures post TBI

The Oddball Task

The most commonly used method used to measure changes in ERPs following a TBI is the oddball paradigm. This task records electrophysiological activity while participants are presented a large number of two types of stimuli. The 'Distracter' or 'Frequent' stimulus is presented often, and the participant is instructed to ignore it. This stimulus establishes an expectation in the participant of stimuli timing and characteristics. The 'Oddball' stimulus is presented infrequently, and has different characteristics to the frequent stimuli, defying the expectation. The participant is instructed to silently count its occurrence, or respond to it with a button press. Both visual and auditory modalities have been used in the oddball task, although auditory stimuli are more common. It is the only EEG task with the history and application to be considered standardised, and has similar test-retest reliability to behavioural tests (Reinvang, 1999). More recently researchers have used oddball tasks that include three different stimuli - a frequently ignored stimulus, a rare target oddball stimulus, and a rare distracter oddball stimulus that is also ignored. Another variation on the standard auditory oddball task is the dichotic listening task, which presents tones separately to each ear, with the instruction to only attend to stimuli through one ear. This version allows analysis of the process of actively ignoring a tone (Campbell & de Lugt, 1995).

The N2

Oddball tasks elicit early potentials to both the standard and target tones, but late cognitive potentials including the N2 and P3b only following target tones (Reinvang, Nordby, & Nielsen, 2000). Both auditory and visual stimuli are used to elicit the N2 and P3b. Pure tones are most commonly used as auditory stimuli, but environmental sounds are also used, and both are usually presented through headphones. Visual stimuli usually consist of images presented on a computer screen. Figure 1 shows a typical ERP waveform with the N2 and P3b component indicated.

The N2 ERP is thought to be made up of three subcomponents. The first is found in anterior electrodes, and is related to novelty detection (Patel & Azzam, 2005). It is sometimes referred to as the N2a and is generated regardless of attention (Patel & Azzam, 2005). Because of this it is thought to represent pre-attentive processing (Polo, Newton, Rogers, Escera, & Butler, 2002). This is followed by another anterior subcomponent, the N2b, related to cognitive control (including inhibition and monitoring response conflict) (Patel & Azzam, 2005). Simultaneously with the anterior N2 components, the N2c is associated with attention and found in posterior electrodes when responding to visual stimuli, and in anterior electrodes for auditory stimuli (Folstein & Van Petten, 2008). The N2 component divisions are clearer in response to visual stimuli than auditory (Folstein & Van Petten, 2008). The posterior N2 is larger in response to infrequent targets (Folstein & Van Petten, 2008). When combined with fMRI research, the N2 complex is associated with BOLD activation in the medial frontal brain areas, and the dorsolateral prefrontal cortex (DLPFC) (Karch et al., 2010). Studies using EEG source localisation suggest that it is generated in the anterior cingulate cortex (ACC) (van Veen & Carter, 2002).

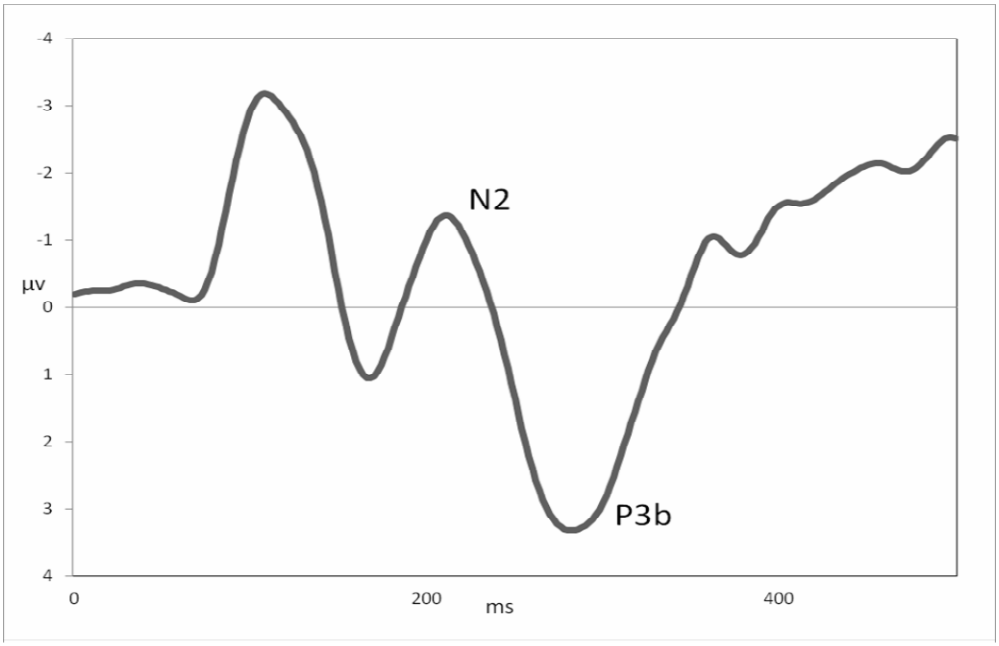


Figure 1. A model example of an ERP waveform following an oddball stimulus presentation (at time point 0).

The P3b, P3a, and SW

There are two main variations on the oddball P3. The dichotic oddball task elicits the same ERPs as those measured by typical oddballs, but the task allows for separate analysis and comparison of tones that are attended to and tones that are ignored through constructing difference curves (P3d). This allows for an electrophysiological test of sustained auditory attention, as ERPs can be compared between the attended and non-attended ear (Knight, 1991). Secondly, the three stimuli oddball tasks elicit a P3a frontal response to the rare distracter stimuli, and a P3b parietal response to the target which is similar to the typical P3b. The P3a is largest in the frontal electrodes (Campbell & de Lugt, 1995). The P3b is the most heavily researched ERP, due to the ease of detection (Patel & Azzam, 2005). There are two theories about the underlying process that generates the P3b. The first proposes that it is related to memory updating (Donchin & Coles, 1988). More recently it

has been proposed to be related to attention to stimulus (Nieuwenhuis, Aston-Jones, & Cohen, 2005). The latency of the P3b ERP relates to the duration of stimulus identification and categorisation, but not response selection (McCarthy & Donchin, 1981). Longer P3b latency is found when more processing is required (Kramer & Strayer, 1988; Reinvang, 1999). P3b amplitude indicates the amount of neural processing devoted to the stimuli (Wickens, Kramer, Vanasse, & Donchin, 1983). According to Johnson's (1986) information theory perspective, the amplitude of the P3b is determined by three properties. The first is the subjective probability of a stimulus. This can be controlled by the experimenter, and as it increases the P3b amplitude decreases. The second is the information conveyed by the stimulus (the complexity of the stimuli/task, and instruction associated with stimuli). The more meaningful the stimulus is, the larger the P3b amplitude. The effects of both are modulated by the amount of information a person receives (due to their level of attention and uncertainty about accuracy of perception). The more information received, the greater the amplitude. This is demonstrated in research showing greater P3b amplitude for recognition memory targets compared to non-targets (Kramer & Strayer, 1988). The P3b is associated with fMRI BOLD response in the DLPFC, temporo-parietal junction and superior temporal gyrus (Karch et al., 2010). Because the P3b has a number of widespread neural generators, and electrical signals are conducted in a spreading manner through the brain, the P3b amplitude at any electrode results from the sum of activity from each neural generator (Johnson, 1993). Some aspects of the distribution of the P3b can be manipulated independently, suggesting different P3b generators are related to different aspects of processing (Johnson, 1993). The P3b has a central-parietal maximum in response to the target, and similar activity is found in the ventral temporofrontal areas in intracranial recordings (Campbell & de Lugt, 1995; Halgren, Marinkovic, & Chauvel, 1998). It represents

voluntary attention (Knight, 1991). P3b amplitude correlates with recognition accuracy in the Rey complex figure task which measures visual memory (De Beaumont et al., 2009).

Research has not subdivided the P3b into it's component parts in the same manner as the N2. However, in addition to the P3b, a frontal positive deflection can be elicited in the same time window when novel unexpected stimuli are presented. This deflection is termed the P3a, and thought to reflect automatic attention allocation to that novel stimuli (Knight, 1991). Intracranial recordings show activity similar to the P3a is generated in paralimbic and frontoparietocingular cortices (Lamarche, Louvel, Buser, & Rektor, 1995). It is thought to represent susceptibility to distraction, or alternatively involuntary allocation of attentional resources to potentially important events (Knight, 1991; Theriault, De Beaumont, Gosselin, Filipinni, & Lassonde, 2009). P3a amplitude has been found to be positively correlated with performance on the Erickson Flanker task, which measures distractibility (De Beaumont et al., 2009). One final ERP that is sometimes measured is the slow wave (SW) - a negative wave following the P3b (between 400ms and 800ms post stimuli), which may represent re-orientation to prepare for the next stimuli (Potter, Bassett, Jory, & Barrett, 2001).

Summary of Oddball ERPs

A brief summary of the N2 component would describe it as relating to novelty detection, cognitive control, and attention in the cognitive domains, and probably generated by medial- and pre-frontal areas as well as the ACC. The P3b ERP latency is related to stimulus identification and categorisation, and the amplitude to attention and how much meaningful information is extracted from the stimulus. It seems to be generated from a number of different brain regions. The P3a may reflect automatic allocation of attention to a potentially important novel stimulus.

The following sections review the research using the oddball task to look at electrophysiological changes post mTBI. Because there is suggestion that visual and auditory modalities differ in their ability to discriminate between the two groups, each modality will be reviewed separately, and the two modalities will be compared in a summary of the oddball research.

Auditory Oddball Research in TBI

Research using the auditory oddball task varies in sample size, severity of injury, stimuli used, and difficulty of task. Perhaps because of this, results also vary. Table 1 provides a brief summary of this research.

The N2 following a TBI

The majority of research that focuses on changes in the N2 following a head injury analyse it as a complex rather than dividing it into its sub-components. Because analysing it in this manner includes the N2a subcomponent, it is a measure of pre-attentive processing as well as cognitive processes so should be regarded as a mesogenous ERP. Results focusing on the N2 vary widely between studies. The studies that have shown N2 changes generally show either a reduction in amplitude or latency delays post mTBI, and have generally used samples of participants who report cognitive or neuropsychological symptoms ongoing for more than a year in some cases (Reinvang et al., 2000; Solbakk, Reinvang, & Nielsen, 2000; Solbakk, Reinvang, Nielsen, & Sundet, 1999). A sample that included athletes who have a number of mTBIs and were most recently injured only a matter of weeks earlier also showed N2 changes, both in an asymptomatic and symptomatic group (Gosselin, Theriault, Leclerc, & Montplaisir, 2006). However, the change found in N2 studies is not consistent, with some

studies of participants with ongoing PCS symptoms showing reduced amplitude in simple or dichotic oddball tasks (Gosselin et al., 2006; Solbakk et al., 2000; Solbakk et al., 1999), while others showed delayed latency without amplitude changes in simple two tone oddballs with sample sizes of over 20 mTBI participants (Alberti, Sarchielli, Mazzotta, & Gallai, 2001; Gaetz & Weinberg, 2000). One study showed both latency delays and amplitude reductions in participants referred for a neuropsychological assessment one to ten years following their injury (Reinvang et al., 2000). Confusingly, Ford and Khalil (1996) found larger N2 amplitudes as well as a latency delay in a large sample of 54 mTBI with PCS symptoms within a year of their injury. The N2 changes in these symptomatic samples may indicate an electrophysiological basis for the difficulties with attention and cognitive control that individuals with lingering cognitive symptoms exhibit, although not all studies that used samples with reduced cognitive performance showed changes (Potter et al., 2001). Only two studies have focused on fully recovered mTBI participants. One study found no differences between mild head injured participants and control participants three to seven months after the injury (Sivak et al., 2008). However, the mTBI sample used consisted of very mild injuries in the majority of cases – only 9 of 31 had a confirmed LOC. The other showed a trend towards reduced N2 amplitude in ten asymptomatic athletes; their participants were tested five weeks post injury. Studies using participants injured years earlier have also found no differences in a three stimuli oddball task or two stimuli oddball task with increasing levels of difficulty, even when cognitive performance was reduced in the mTBI group on an attention shifting task (Potter et al., 2001; Segalowitz, Bernstein, & Lawson, 2001). Table 1 shows that of the nine studies focusing on a simple amplitude comparison of the whole N2 complex post mTBI, three showed a lower amplitude (although two of these used the same mTBI participants), one showed a trend towards lower amplitude, four studies found no

difference, and one study found larger amplitude in the mTBI group. Of the eight studies that have compared mTBI and control groups in N2 latency four have shown delay in N2 latency. The majority of these studies have used samples with ongoing cognitive and PCS symptoms. Of the two that did not, only one showed a trend towards N2 reduction in a sample tested soon after their injury. The majority of these studies have used simple two tone oddball tasks with average mastoid reference montages. Some have used more complex tasks with a distracter tone as well as the rare and frequent tones, and some have used nose or average reference montages. However, these differences do not seem to explain the variability in study results, as the results do not vary consistently with these changes.

If mTBI resulted in alterations to aspects of processing measured by the auditory N2, we would expect that the type of difference would be consistent between studies. Not only do more studies show no difference, even in samples with ongoing symptoms, but when a difference is found it is not consistent. It seems unlikely that there is a simple relationship between mTBI and N2 changes. It is possible that changes to processes that contribute to the N2 are present in individuals with lingering symptoms post mTBI.

P3b and Slow Wave

Most researchers studying neural activity post mTBI focus more on the oddball P3b than the oddball N2. Similar to the N2 research, the results vary between studies. Table 1 provides a summary of the auditory oddball research and P3 results divided by amplitude and latency. Some researchers have not found differences in P3b amplitude or latency between mTBI and control groups using typical oddballs, and using three stimuli oddball tasks in typically fully recovered, mildly injured participants (Papanicolaou et al., 1984;

Potter & Barrett, 1999; Sivak et al., 2008). In a sample of 15 mTBI participants who made a full recovery, tested at one, three, and eight weeks post injury von Bierbrauer and Weissenborn (1998) found P3b abnormalities only in the three patients with neuropsychological pathology. Although initial testing at four days post injury showed reduced and delayed P3b amplitudes and latencies, Pratap-Chand, Sinniah, and Salem, (1988) found fully recovered participants' ERP characteristics significantly improved so that between 30-240 days post injury their results did not differ from that of controls. The results of a study by Rousseff et al. (2006) showed that although there was a positive correlation between severity of head injury and P3b changes, and that 80% of participants with brain contusions had abnormal P3b's, participants with mTBI did not differ from controls when tested between one and 28 months post injury. However, no mention was made as to whether these participants suffered from PCS or cognitive changes. Another three stimuli oddball study with a sample of mTBI with up to five years having elapsed since injury showed no P3b differences following novel or target stimuli, but instead increased negativity in the slow wave compared to controls (Potter et al., 2001).

Similar to the N2, some researchers focusing on samples with ongoing symptoms have found P3b changes. A smaller P3b and slow wave amplitude but no latency differences post-mTBI in auditory oddball tasks, smaller P3 and delayed latency, or only delayed latency (Alberti et al., 2001; M. R. Ford & Khalil, 1996; Reinvang et al., 2000; Solbakk et al., 1999). Gaetz and Weinberg (2000) studied younger adult mTBI sufferers with PCS, and found they had a delayed P3b (they did not compare amplitudes) compared to healthy controls, but older adult mTBI sufferers with PCS symptoms showed no difference. The results of research by Packard and Ham (1996) indicated the majority of mTBI participants with ongoing

headache symptoms had abnormalities in latency, amplitude, or P3b distribution compared to the age and gender matched controls. Not all studies examining the P3b in patients with ongoing cognitive impairment showed differences however – Sangal and Sangal (1996) failed to find a difference in P3b amplitude or latencies using a simple auditory oddball task with participants who complained of cognitive difficulties, but this may have been due to their small sample size (N = 8).

Conversely, not all P3b changes more chronically post injury were associated with ongoing symptoms – Bernstein et al. (1998) found lower P3 amplitude in well functioning university students on average 8 years following self reported mild TBI. Studies with participants injured more than once tended to show P3b changes as well – Theriault et al. (2009) studied athletes 5-12 months following a mTBI, in asymptomatic athletes with at least 2 prior concussions, both P3a and P3b amplitudes were reduced (but not delayed) compared to controls. P3a amplitudes also trended towards being lower in participants who were injured between 22 and 60 months prior, indicating some, but not complete recovery. Results of a study by Gosselin et al. (2006) indicated that although asymptomatic athletes showed smaller and delayed P3 as well as symptomatic athletes with multiple concussions, headaches and concentration difficulty were negatively correlated with P3b amplitude, so those with ongoing symptoms had larger ERP changes.

Segalowitz et al. (2001) had 10 well functioning mTBI participants (on average 6.4 years post injury) perform four different auditory oddball tasks of increasing level of task difficulty. They found that P3b amplitude was lower in all four tasks compared to controls, but there were no latency differences. Their results also indicated that amplitude differences were smallest in the hardest tasks. P3b reductions/delays may even last decades

as De Beaumont et al. (2009) showed in a sample of ex-athletes aged 50-65 years, even though three decades or more had passed since their mTBI. They suggest that minor brain changes may be masked by cognitive reserve (possibly recruiting other neural resources to perform the same task) in early adulthood, but become more apparent with age.

As with the N2 literature, studies examining the P3b vary in their reference montages and number of stimuli. Again, these variations do not seem to relate to systematic differences between studies, so do not explain the results. In sum, it seems P3b changes in auditory oddball tasks are present in mTBI groups with lingering symptoms, and may be detectable in non-symptomatic groups as well, even years to decades following a mTBI (Berstein et al., 1998; Segalowitz et al., 2001). P3b changes may be found even in the absence of neuropsychological differences to controls, indicating that ERPs may detect brain changes that are not apparent using other methods (Gosselin et al., 2006; Segalowitz et al., 2001).

Generally following mTBI auditory oddball ERP amplitudes are reduced in both positive and negative ERPs, suggesting the brain's capacity for differential processing is reduced, rather than simply a general shift towards one polarity (Reinvang et al., 2000). Recent research with moderate to severe TBI participants who have a good recovery found that although the test-retest reliability of auditory oddball ERPs is good for control participants, it is poor for TBI populations (Lew, Gray, & Poole, 2007). This may help explain the lack of consistent findings in the studies discussed above, and suggests that TBI related impairments may vary from day to day rather than show a consistent picture. Although the auditory oddball task appears to have some ability to discriminate TBI from controls,

particularly when lingering symptoms are present, it is at present too inconsistent to be useful in a diagnostic or treatment setting.

Table 1 – Auditory oddball mTBI research

Authors	mTBI (N)	Time Since Injury	Sample Characteristics	Task Complexity	Sig. N2 Differences?		Sig. P3 Differences?	
					Amplitude	Latency	Amplitude	Latency
Papanicolaou et al. (1984)	10	Up to 3 months	Some tested days after PTA, moderate injuries	Simple - 2 tones	Not analysed		Not analysed	No differences
Potter and Barrett (1999)	12	Up to 3.5 years	No persistent symptoms but lower performance on cognitive tasks	3 stimuli oddball with tones and novel distracter	Not analysed		No differences in P3a or P3b	
von Bierbrauer and Weissenborn (1998)	15	8 weeks	No persistent symptoms or cognitive changes	Simple - 2 tones	Not analysed		No differences	
Pratap-Chand et al. (1988)	20	4 days, then again 30 to 230 days later	No persistent symptoms	Simple - 2 tones	Not analysed		Reduction at initial testing improved at re-testing to be same as controls	Delay at initial testing improved at re-testing to be same as controls
Reinvang et al. (2000)	52	1 to 10 years (mean = 3)	Referred for neuropsyc assessment	Simple - 2 tones	Reduced at Cz but only trend when covaried for age	Delayed at Cz	Reduced at Pz. Highly significant	Delayed at Pz, highly significant.
Bernstein et al. (1998)	N/A	8 years	University students self reporting injury	Simple tones	Not analysed		Reduced	Not analysed
Rousseff et al. (2006)	40	0.5 to 28 months post injury	Half with CT identified contusions, half without	Simple - 2 tones	Not analysed		Not analysed	Delayed in participants with contusions, but not in those without
Packard and Ham (1996)	50	14 months on average	Headaches or cognitive difficulties	Simple - 2 tones	Not analysed		16/50 reduced by more than 2SD from mean	20/50 delayed by more than 2SD from mean
Sivak et al. (2008)	31	3 to 7 months	23% with MRI contusions	Simple - 2 tones	No differences		No differences	

Authors	mTBI (N)	Time Since Injury	Sample Characteristics	Task Complexity	Sig. N2 Differences?		Sig. P3 Differences?	
					Amplitude	Latency	Amplitude	Latency
Solbakk et al. (2000)	20	More than 1 year	Referred for cognitive complaints – No impairment in 14/20	Simple - 2 tones	Reduced at Fz, Cz, Pz	No difference	Reduced at Cz and Pz. Negatively correlated with hypochondria and hysteria	No difference
Potter et al. (2001)	24	Less than 5 years (median 1 year)	mTBI group reduced performance on neuropsyc testing	3 stimuli oddball with tones and novel distracter	No difference	No difference	No difference	No difference
Gosselin et al. (2006)	20	Mean = 15 weeks for symptomatic athletes, 5 weeks for asymptomatic	Athletes with multiple mTBI. Half still symptomatic.	Simple - 2 tones	Nd trended towards reduced		Reduced for both symptomatic and asymptomatic mTBI. Correlated with symptoms	Delayed for both symptomatic and asymptomatic mTBI
Theriault et al. (2005)	20	5-12 months for 10, 22-60 months for 10	Athletes with 2+ mTBI. No lingering symptoms	3 simple tones	Not analysed		Reduced P3a in recent injury group. P3b reduced in both groups.	No differences
De Beaumont et al. (2009)	19	27 to 41 years	Ex-athletes aged 50-65 with 1+ mTBI. Showed reduced cognitive performance.	3 simple tones	Not analysed		P3a reduced (correlated with Erikson Flanker accuracy). P3b trended towards reduced	P3a delayed at Fz and P3b delayed at Cz and Pz.
Alberti et al. (2001)	25	3 to 6 months	PCS headache/ attention/ memory complaints. No cognitive impairment	Simple 2 tones	No differences	Delayed at Cz, Pz	No differences	Delayed at Cz, Pz. Correlated with anxiety and depression.
Solbakk et al. (1999)	20	More than 1 year	Same sample as Solbakk et al. (2000)	Dichotic oddball (attend one ear, ignore other)	N2 Reduced for attended ear, and Nd reduced.	No N2 differences, delayed Nd.	Reduced in ignored channel	No differences
Segalowitz et al. (2001)	10	On average 6.4 years	Well functioning university students	4 auditory with increasing levels of difficulty	No differences		Reduced peak amplitude and area under curve in all tasks. Difference largest in easiest tasks.	No differences

Visual Oddball Research

Auditory oddball tasks are not generally considered very demanding, so may not be taxing enough to consistently detect the subtle processing and activity changes that may be present post mTBI. In order to increase task demands, oddball tasks with visual stimuli have been used, as they allow for more varied stimuli, and may be more demanding on participant attention (as participants must focus their eyes, as opposed to auditory stimuli which are heard regardless of attention). Table 2 summarises the visual oddball research, along with research that has used both visual and auditory modalities.

The N2

Only five studies have compared the N2 between mTBI and control participants using visual oddball tasks. De Beaumont et al. (2007) used a complex visual oddball with stimuli presented to only one visual hemisphere at a time. This allowed them to calculate the N2pc – the difference in N2 amplitude between hemispheres, measuring the increase in processing in the hemisphere that is attending to the stimuli, which represents visuo-spatial attention. Using this method they found no difference between groups of asymptomatic athletes with one or more concussions and controls. Gaetz et al. (2000) also reported no N2 differences between controls and participants who had experienced between one and three mTBI in a visual oddball with simple written words as stimuli. Broglio et al. (2009) tested a larger sample of 46 athletes on average 3.4 years since post injury. Their results indicated that N2 was smaller post mTBI (but not delayed) compared to controls for novel stimuli in a 3 stimulus oddball (with differently orientated triangles as frequent and rare-target stimuli, and novel line drawings of objects as novel stimuli). Contrary to Broglio et al. (2009), Ford

and Khalil (1996) showed a marginally larger N2 amplitude and significant delay using varied checkerboard pattern size as stimuli in a sample of 54 mTBI with PCS symptoms tested within a year of their injury. Lastly, Gaetz and Weinberg (2000) had groups of mTBI participants with PCS symptoms perform three visual oddballs (with simple geometric shapes, three digit numbers, or three letter strings as stimuli) and only analysed latency. N2 latency was delayed for the task that used numbers as stimuli only.

Although not many mTBI studies have measured the visual N2, the sum of the research that has indicates it seems unlikely that this ERP is consistently affected.

The P3b

The P3b is more commonly analysed in visual oddballs than the N2. Findings comparing the visual P3 between mTBI and controls tend to be more consistent, with only two studies showing no amplitude differences although both did find prolonged latencies in a sample with cognitive difficulties and in athletes with multiple mTBI (Gaetz et al., 2000; Sangal & Sangal, 1996). Dupuis et al. (2000) reported that although asymptomatic athletes within 6 months of a concussion did not differ from controls, symptomatic athletes had smaller P3b amplitudes (but no latency changes) using simple geometric shapes for stimuli. Using the same sample, Lavoie et al. (2004) showed that with a more demanding oddball task, asymptomatic subjects also displayed reduced P3 amplitudes. Number of concussions, severity, and time since injury did not correlate with P3b amplitude, but number of symptoms did. A study by De Beaumont et al. (2007) found reduced P3b amplitude but no latency delay in a group of asymptomatic athletes with more than one concussion (on average 56 months post injury), compared to controls and a group with only one concussion (who did not differ from controls). In a larger sample of mTBI athletes Broglio et al. (2009)

showed a smaller P3b (but not delayed) for rare-target stimuli, but no changes were found in the P3a in response to novel stimuli.

Although many visual oddball studies have focused on athletes Lachapelle et al. (2008) found smaller and delayed P3bs in non-athlete mTBI in outpatient rehabilitation with differently sized checks in a checkerboard as stimuli, as did Ford and Khalil (1996). Gaetz and Weinberg (2000) thoroughly assessed P3b latency changes post mTBI with three different types of visual stimuli and dividing participants into an older and younger group. They found that both groups showed delayed latencies in all task types. Sangal and Sangal (1996) also found 8 mTBI with cognitive impairment on average 3.1 years post injury showed delayed P3b latency (but no amplitude differences) with letters as stimuli. In addition to neural processing changes, visual oddballs can be adapted to assess emotional processing. Using traffic accident related and neutral words as stimuli, Granovsky et al. (1998) tested participants with traffic related mTBI. They showed no general P3b differences, but had a much larger difference between P3b amplitude to traffic related words compared to neutral words than the control group. This difference correlated with their score on the Zung Anxiety scale.

Overall, it seems that visual P3b changes take place post mTBI. Some studies have shown latency delays, but amplitude reductions are more common. It may be that latency delays are due to a reduced P3a rather than actual processing delays Elting et al. (2005). Similar to the auditory P3b, studies including participants with lingering symptoms find visual P3b changes in the year following injury (Dupuis et al., 2000; Gaetz et al., 2000; Lachapelle et al., 2008). In this first year, changes do not correlate with time since injury (Dupuis et al., 2000). Multiple injuries appear to lead to ERP changes (Gaetz et al., 2000)

even without lingering symptoms Although these ERP changes may be somewhat resolved over the longer term, can still be present years later (Broglio et al., 2009). This is the case even when neuropsychological batteries detect no differences (De Beaumont et al., 2007). Differences in the P3b may be related to distress, and the visual oddball may be adapted to measure post-traumatic stress disorder (PTSD) (Granovsky et al., 1998). Unlike the auditory tasks, visual oddball tasks using a variety of stimuli seem more consistent at detecting changes post mTBI. Three studies have used both auditory and visual oddball tasks, allowing direct comparison of the two different types of task. Ford and Khalil (1996) using both stimuli modalities have found similar ERP differences between mTBI and controls with both, but other researchers found that visual stimuli detect more significant differences, or that only visual stimuli detected differences (Gaetz & Weinberg, 2000; Sangal & Sangal, 1996).

Summary of Oddball Research

Oddball research has revealed inconsistent changes in ERPs post mTBI. Similar to Gaetz and Berstein (2001) and reviews including more severe injuries (for example Campbell and de Lugt [1995] and Reinvang [1999]), many studies show differences, but the ERP characteristic that differentiates mTBI from control groups varies between studies. Reductions in N2 amplitude have been demonstrated, more often in participants with ongoing PCS or cognitive impairments. This fits with research in other populations, which report that N2 changes are related to reduced cognitive performance both in clinical populations with brain changes and in healthy populations (Podemski et al., 2008; Pokryszko-Dragan et al., 2009; Portin et al., 2000; Tachibana, Aragane, & Sugita, 1995; van Harten et al., 2006).

Table 2 – Visual and combined visual and auditory oddball mTBI research

Authors	mTBI (N)	Time Since Injury	Sample Characteristics	Oddball Modality	Task Complexity	Sig. N2 Differences?		Sig. P3 Differences?	
						Amplitude	Latency	Amplitude	Latency
Dupuis et al. (2000)	20	Up to 2 years	Sports related. Half still symptomatic.	Visual	Simple - typical oddball with shapes for stimuli	Not analysed		Reduced for symptomatic subjects	No differences
Lavoie et al. (2004)	20	Up to 2 years	Sports related. Half still symptomatic. Same participants as Dupuis et al. (2000)	Visual	Difficult – differential response to second consecutive rare target only.	Not analysed		Reduced in both asymptomatic and symptomatic. Correlated with PCS scores but not time since injury.	No differences
Lachapelle et al. (2008)	17	Up to 28 months	MVA related. Symptomatic – in outpatient rehabilitation.	Visual	Simple – typical oddball with different sized checkerboards as stimuli	Not analysed		Reduced. Those with ERP abnormality less likely to return to work.	Delayed.
Gaetz et al. (2000)	45	More than 6 months (mean = 13 months)	Sports related. Divided into groups of 1, 2, or more than 2 concussions.	Visual	Moderate – written words as stimuli	No differences		No differences	Delayed for group with 3+ mTBI only. Correlated with self-reported cognitive difficulties.
De Beaumont et al. (2007)	30	More than 9 months	Sports related. Asymptomatic, divided into groups of 1 mTBI or 2+.	Visual	Difficult – green square in array of 3 red squares. Respond unless a gap appears at the bottom of the green square.	Not analysed		Reduced in subjects with 2+ mTBI. Trend towards correlation with time since injury.	No differences.
Broglio et al. (2009)	46	3.4 years on average	Athletes aged 18-25 with on average 1.7 mTBIs, and no differences to controls in symptoms or cognition.	Visual	Complex – shapes for frequent and target stimuli, and novel line drawings as distracters.	Reduced for novel distracters.	No differences	No difference in P3a for novel stimuli. Reduced P3b at Pz.	No differences.

Authors	mTBI (N)	Time Since Injury	Sample Characteristics	Oddball Modality	Task Complexity	Sig. N2 Differences?		Sig. P3 Differences?	
						Amplitude	Latency	Amplitude	Latency
Granovsky et al. (1998)	13	Between 2 weeks and 1 year	MVA related, 18-22yo with PCS.	Visual	Complex – written words as stimuli, responding to different colour.	Not analysed		No overall differences. Patients showed increased P3 to MVA related words. Correlated with anxiety.	No differences
Sangal and Sangal (1996)	8	6 months to 9 years	Cognitive difficulties	Visual and Auditory	Simple – 2 auditory tones and visual letters	Not analysed		No differences	Delayed for visual task only, in an average of all 31 electrodes
Gaetz and Weinberg (2000)	20	19 to 53 months	Ongoing PCS. Divided into young and old group and compared to matched control groups.	Visual and Auditory	Simple - 2 auditory tones. Moderate visual with shapes, words, or numbers as stimuli.	Not analysed	Delayed for visual numbers in both groups, and in auditory for older groups only.	Not analysed	Delayed at Cz and Pz for all visual tasks in both younger and older group. Delayed for auditory in younger group only.
Ford and Khalil (1996)	54	Less than 1 year	Majority from MVA. Recruited from rehabilitation service	Visual and Auditory	Simple - 2 auditory tones and visual checkerboards	Increased in anterior electrodes for auditory task, and for frequent visual stimuli only.	Delayed in anterior electrodes for auditory stimuli, and for frequent visual stimuli.	Reduced in both visual (in parietal electrodes) and auditory (in frontal electrodes) modalities.	No differences

Reductions in N2 amplitude would suggest that some aspect of processing related to novelty detection, attention, or cognitive control behaviours are impaired post mTBI, since these processes are related to the ERP. However, changes are not consistently found in all patients with ongoing symptoms, and are generally not found in fully recovered patients. Because none of the studies that compare the N2 between mTBI participants and controls have separated the different components of the N2, it is unclear whether any changes found are related to pre-attentive processing or cognitive control aspects of the N2, attentional aspects, or a combination of all three (Folstein & Van Petten, 2008; Patel & Azzam, 2005). Taking all the oddball research into account the N2 does not seem to be consistently altered post mTBI in visual or auditory modality oddball tasks.

P3b changes are more commonly found following mTBI. Similar to the N2 results, P3b changes are found more commonly in mTBI participants with lingering PCS or cognitive symptoms, which may represent an electrophysiological basis for attention or memory encoding impairments. Similar results are apparent in non-TBI samples, where P3b delays and smaller amplitudes are related to lower cognitive performance both in clinical populations and in healthy controls (Podemski et al., 2008; Pokryszko-Dragan et al., 2009; Portin et al., 2000; Tachibana et al., 1995; van Harten et al., 2006). However, in contrast to the N2, P3b changes are also found in fully recovered mTBI. These changes may be result in cognitive decline in old age (De Beaumont et al., 2009), so although they may be unrelated to cognitive impairment in some mTBI sufferers, they may indicate risk as the individual ages. It also suggests that the P3b may be a marker of processing changes that are too subtle to detect with neuropsychological testing. These changes in P3b amplitude and latency may indicate that mTBI groups have subtle alterations in neural processes that

underlie the obtaining of information and meaning from a stimulus, mentally categorising stimuli, and attention to ongoing events. While the effect of these changes in processing on behaviour may be too subtle to detect with neuropsychological testing, the mTBI sufferer may notice subjective changes, and may report them as problems with concentration or memory – which are common PCS symptoms.

For mTBI groups it seems that visual oddball tasks are more likely than auditory oddball tasks to show significant differences in comparison to control groups. Two of the three studies that use both visual and auditory stimuli show that visual stimuli are superior at discriminating the two groups and a higher proportion of visual studies show significant differences (Gaetz & Weinberg, 2000; Sangal & Sangal, 1996). This supports Gaetz and Berstein's (2001) suggestion that ERPs measured from visual stimuli are more sensitive to the effect of a mTBI than those taken from auditory stimuli. Counter to another suggestion of those authors, the inclusion of more recent research in this review indicates that amplitude measures are more likely than latency measures to reveal differences. However, this contradicts a review of all severities of TBI by Duncan et al. (2005), who advise that auditory stimuli are more likely to differentiate these groups from control groups. This may be because severe injuries are more likely to affect sensory processing, and the auditory system is affected by ischemia and anoxia more than the visual system (Duncan et al., 2005). This altered auditory processing in more severe injuries will have a carry-on effect on later ERPs, resulting in altered auditory ERPs more often than visual ERPs. MTBI is less likely to affect sensory processing, so ERP results are not influenced by auditory system impairments. A comparison of the 'task/stimuli complexity' column of Table 1 and Table 2 may reveal another explanation as to why visual tasks are more likely to differentiate the

groups – auditory tasks tend to use simple tones as stimuli, while visual tasks use more complex stimuli such as shapes, letters, checkerboards and words. It would make more theoretical sense for changed ERPs post mTBI to be related to stimulus complexity, as more complex stimuli have more meaning available to be extracted (a factor which modulates P3 amplitude) which is a function that mTBI sufferers may not perform as well due to reduced connectivity.

Other ERP research

Although the Oddball task has been the most common way to research the electrophysiological effects of mTBI, a number of other tasks also appear to be useful. These include response preparation and motor control tasks, which may offer insight into attention and planning changes that may be present post mTBI. Simple decision and arithmetic tasks have also been studied, which also inform mTBI researchers about attention, as well as numerical manipulation (requiring working memory) and stimulus discrimination. Table 3 presents the important details and results of the studies that have used tasks other than the oddball task.

Table 3 – Other cognitive EEG measures comparing mTBI participants to controls

Authors	mTBI (N)	Time Since Injury	Sample Characteristics	Task	Findings
Gaetz and Weinberg (2000)	20	19-53 months	Ongoing PCS. Divided into older and younger group for comparison with controls.	Visual and auditory CNV with tones, shapes, numbers or words as stimuli	Shape CNV showed reduced CNV amplitude at Fz, Pz. Word CNV showed reduced amplitude at Oz, and auditory CNV reduced at FPz.
Gaetz et al. (2000)	45	More than 6 months	Divided into groups of 1 mTBI, 2 mTBI or 3+ mTBI	Visual CNV with shapes	No differences
Potter and Barrett (1999)	12	Within 3.5 years	No persistent symptoms	Auditory PASAT (adding number to previously heard number)	Control N130 amplitude increased as task difficulty increased, but no change for mTBI. Control P230 amplitude reduced as task difficulty increased, but no change for mTBI. Control N500 amplitude increased in frontal electrodes as task difficulty increased, but no change in mTBI.
Polo et al. (2002)	11	More than 1 year	Good recovery but ongoing cognitive complaints	Visual reaction task (while ignoring auditory tones)	Reduced amplitude P3b at Pz
Solbakk et al. (2005)	32	More than 1 year	12 with frontal lesions (analysed separately)	Visual response to emotional valence of images	No differential response to different emotional valence. Lesion group showed increased occipital amplitude after 300ms. mTBI without lesion showed reduced amplitude after 500ms in frontal/central/parietal regions
Slobounov et al. (2002)	6	10 to 20 months	Athletes with single mTBI	Voluntary finger contraction to controlled intensity with feedback	Reduced BP, MP, and MMP negativity in more pressure condition. Gamma band activity absent in mTBI, but present in controls.
Wiese et al. (2004)	22	12, 26, and 52 weeks	mTBI with MRI prefrontal contusions	Self initiated finger taps	BP reduced 8 weeks post injury, did not differ at 12 or 26 weeks, then enhanced at 52 weeks.
Slobounov et al. (2005)	8	Baseline, 3, 10 and 30 days	Athletes without lingering symptoms or neuropsyc findings	Whole body anterior-posterior movements from waist	All movement related cortical potential amplitude reduced compared to baseline at all time points. Effect larger in frontal electrodes.
Cudmore et al. (2000)	38	7 years on average	Normal functioning university Students. Split into <20min LOC and >30min LOC.	Dual task with auditory oddball and concurrent working memory task.	No overall bandwidth differences. mTBI group showed increased beta (13-30Hz) bandwidth coherence between fronto-parietal regions in the dual-task compared to single task. Controls showed no difference between the dual and single task.

Authors	mTBI (N)	Time Since Injury	Sample Characteristics	Task	Findings
Thornton (2003)	85	17 days to 27 years, 3.1 years on average	Referred for neuropsyc examination. mTBI lower in neuropsyc measures than controls	EEG recording during silent mental retrieval of behavioural memory test story	mTBI group had decreased coherence and phase synchronisation in upper beta (32-63.5Hz) bandwidths between frontal and posterior regions, but increase in power. These changes negatively correlated with memory function.
Kumar (2009)	30	2 months on average	Recruited from post-trauma clinic. 12 with positive CT findings	Sequentially presented Sternberg memory task using digits (verbal memory) or circle location (visuo-spatial memory) as stimuli	In verbal memory mTBI group showed reduced alpha (8-14Hz) and beta (14-35Hz) fronto-temporal and fronto-parietal coherence, and no increase in temporo-parietal coherence during retrieval (unlike controls). In visuo-spatial memory mTBI showed lower interhemispheric frontal alpha coherence, and no temporo-parietal lower beta coherence increase in retrieval (unlike controls).

The CNV

The contingent negative variation (CNV) represents response preparation. Tasks measuring the CNV present subjects with a warning signal to prepare for response, and the imperative signal to respond (Reinvang, 1999). The CNV is the electrophysiological potential change in the time between these two signals. Figure 2 depicts a typical CNV waveform.

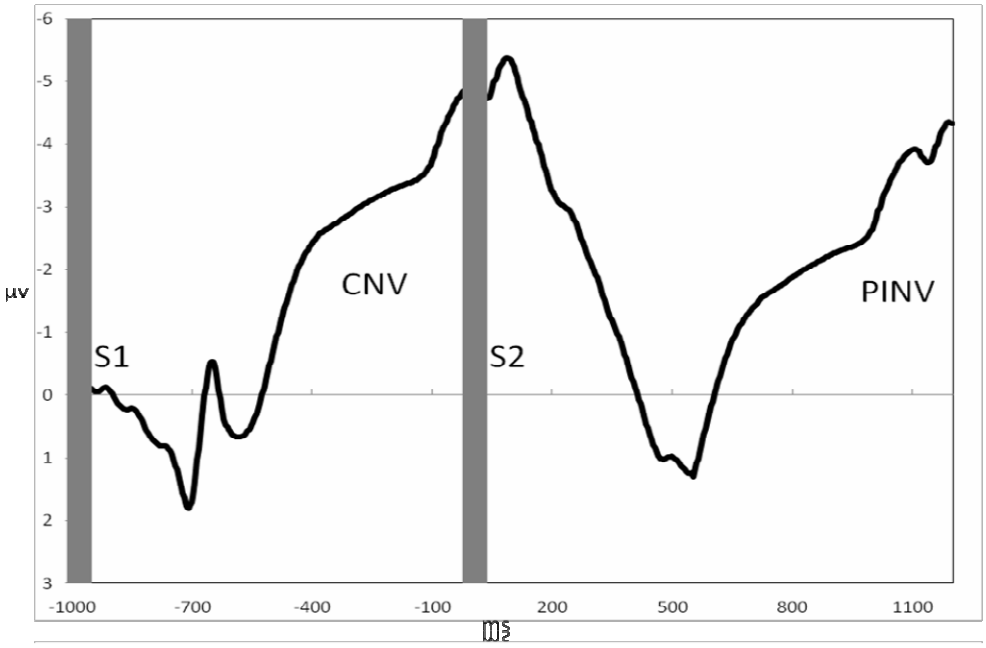


Figure 2. A model example of the response preparation CNV generated following the warning stimulus S1, in anticipation of the imperative stimulus S2.

Intracerebral recording indicates the CNV complex originates from frontal, temporal, and motor cortex regions (Lamarche et al., 1995). Changes in the CNV may reflect slowed processing as neural networks do not adequately orient to stimuli, and as a result are inefficient (Campbell & de Lugt, 1995). In addition to their oddball task, Gaetz and Weinberg (2000) tested their mTBI participants (who still showed PCS) with three visual and one

auditory CNV tasks. Although more mTBI participants than controls had abnormal peak amplitudes that were more than 2.5SD from the mean, only two of the visual CNV tasks significantly differentiated the mTBI group from controls in frontal and only one task differentiated parietal electrode peak amplitude. The lack of clear effects was in spite of differences in the oddball ERPs. Similarly, Gaetz et al. (2000) found no differences in CNV amplitude between a group of individuals who had experienced three or more mTBIs and controls, even though there were differences in the same participants in the oddball ERPs. These results suggest that oddball tasks may be more sensitive to differences between mTBI and control groups than CNV tasks.

Movement Related Cortical Potentials (MRCP)

Since balance and motor control can also be affected by mTBI (Goldberg, 1998), some research has looked at EEG during controlled movements. This research focuses on negativity 500-600ms prior to movement (known as the Bereitshaftspotential [BP] early movement preparation), negativity 100ms prior to the beginning of movement up till the beginning of movement (motor potential [MP] late stage movement potentials), and the movement monitoring potentials (MMP) which occur during movement (Slobounov, Sebastianelli, & Simon, 2002). Movement related potentials offer valuable information about the processes leading up to behavioural responses, which may include planning and mental readiness. If impairments in motor control are present it may explain impaired performance in neuropsychological testing that requires button presses for electronic tasks or fine motor control in pen and paper tasks. Impairments in areas processing motor control may also be compensated for by recruiting other neural resources, which may cause task relevant attention to suffer.

Slobounov et al. (2002) compared a group of six mTBI participants (10-20 months after injury) to controls on measures of EEG negativity during controlled fine motor movement with the dominant index finger. They found significantly reduced EEG negativity when at 50% of maximum strength (but not when up to 25%) in the MP, and MMP in fronto-central electrodes. Their results also showed that mTBI participants completely lacked a BP. This suggests a potentially large effect size of mTBI on movement related potentials and that more difficult tasks may be better at illuminating between group differences. However, the authors did not report whether their participants suffered any persistent symptoms. The results of Slobounov et al. (2002) are in direct opposition to those reported by Wiese et al. (2004), who used a self initiated finger tapping task. Their results show a reduction in BP amplitude at 8 weeks post injury, but found no difference to controls at 12 and 26 weeks, and enhanced BP amplitude compared to controls at 56 weeks. However, the different results could be due to differences in task difficulty (self-initiated finger tapping is easier than maintaining a constant pressure at 50% of maximum strength). Also, Wiese et al. (2004) used participants who all had prefrontal contusions, even though they only included mTBI. They suggest that the shift from reduced BP to enhanced BP reflects two stages of recovery. The first where mTBI patients cannot perform as well as controls due to impaired function, then later the network has re-organised to perform the task, but cannot perform it as efficiently – leading to increased BP amplitude (Wiese et al., 2004). Perhaps when a contusion is present, signal from all other areas has to increase in order to compensate for the lack of signal from that area, resulting in larger movement potentials. On the other hand, without a contusion, all areas function as they would previously, but due to DAI are not able to synchronise their activity as well, resulting in smaller movement potentials.

Other research looking at MRCPs has used whole body postural movement, since acute mTBI often report balance problems, but very little research has directly examined the reason for this (Slobounov, Sebastianelli, & Moss, 2005). In addition to post injury data, Slobounov et al. (2005) managed to obtain baseline (pre-injury) data on the BP, MP and MMP during postural movement by recruiting athletes at high risk of head injury, and compared between baseline and data taken 3, 10, and 30 days post injury. Although posture abnormalities mostly recovered by 10 days post injury and completely recovered by 30, and no lingering symptoms or neuropsychological assessment changes were detected, the BP, MP, and MMP, improved compared to day 3, still did not recover to baseline by day 30 (Slobounov et al., 2005). This effect was larger at anterior and central areas than posterior, supporting the idea that frontal areas are more affected by mTBI (Slobounov et al., 2005). The authors argue that their research suggests return to play measures for athletes need to be reassessed, and time-off periods extended.

Research has also focused on changes post mTBI in EEG bandwidth power during movements. This has been applied to the same time periods as movement related potentials (BP, MP and MMP). For example, wavelet analysis by Slobounov et al. (2002) focused on potentials at fronto-central electrodes in response to a gradual increase of finger strength to 25 and 50% of maximum. This revealed that in a small sample mTBI participants (N = 6), no gamma band activity occurred. In contrast, six controls showed a large gamma response, with highly significant differences when compared to the mTBI group. The authors suggest that post mTBI the frontal and posterior areas of the brain have impaired high frequency gamma communication (Slobounov et al., 2002). Simpler analyses comparing peak amplitude showed less significant differences only in the 50% strength condition,

suggesting Morlet wavelet analyses may be a much more effective measure of movement processing changes post mTBI.

As well as offering information about readiness and motor planning electrophysiological processes post mTBI, movement and motor control related studies may offer answers as to what is changing at a neural connectivity level post mTBI, particularly if these changes are similar to those shown in tasks testing other aspects of cognition.

Other ERP Tasks

Potter and Barrett (1999) utilised a sustained complex attentional task in their ERP study. They presented their mTBI participants with sequential digits, with the instruction to add it to the previous digit and answer out loud. The mTBI group showed no increase in a frontal N500 amplitude (as well as N130 and P230) as task difficulty increased with quicker stimulus presentation, while controls showed a large increase. This is in contrast to their auditory oddball results with the same sample, which showed no difference between the groups. The authors suggest the lack of amplitude increase in harder tasks might represent impaired attentional resource allocation in mTBI – as tasks increase in difficulty they are not able to adjust by allocating more neural resources to the task. This is perhaps because they are already 'at capacity'. Polo et al. (2002) performed a study measuring attentional allocation. They used visual letters and numbers as stimuli, and had participants respond with one finger to letters and another to numbers, while concurrently ignoring tones related another EEG task. This is a good measure of attention allocation, as participants must allocate resources to the digits, while ignoring the tones. Mild to moderate TBI participants with good outcome one year or more post injury showed a significantly reduced P3b,

perhaps indicating impaired attention allocation to task relevant stimuli and as a result a reduction in meaningful information obtained from those stimuli.

Research presenting emotional images has shown that post mTBI, ERPs are not differentially changed for different emotional valences (Solbakk, Reinvang, Svebak, Nielsen, & Sundet, 2005). However, using these more complex stimuli they did find reduced slow wave amplitude in the mTBI participants in the 500-700ms window. This suggests a general processing impairment following mTBI, but not an emotion specific impairment.

Non-Oddball EEG Task Summary

Other EEG tasks are not used as often as oddball research in mTBI, and as a result very little can be concluded from this research. CNV research may indicate impaired attention orientation post mTBI, but with only one of two studies currently showing differences considerably more research is required before any firm conclusions can be made (Gaetz et al., 2000; Gaetz & Weinberg, 2000). Movement preparation related ERPs, and movement related bandwidth in particular does seem to be affected, but again a lack of research means conclusions are limited (Slobounov et al., 2005; Slobounov et al., 2002; Wiese et al., 2004). Both mental addition and complex affective image related ERPs showed significantly smaller amplitudes post mTBI (Polo et al., 2002; Potter & Barrett, 1999; Solbakk et al., 2005). Of the total eight studies of mTBI that use tasks other than the oddball, seven show differences between mTBI and control groups. It is therefore recommended that research should branch out from the typical oddball type task and testing other forms of task. Perhaps tasks that are related to specific functions, such as inhibition and memory (both of which may be affected by mTBI), would offer valuable information about the neural

changes related to these functions that take place post mTBI. Suggestions for future research are provided at the conclusion of this chapter.

Bandwidth Coherence Measures

More recently, measures of coherence of signal between different areas have been used during cognitive tasks. Coherence measures the correlation in time of different bandwidths of the EEG spectrum between two electrodes, which is thought to reflect the effectiveness of the communication between the areas underlying those electrodes (Thatcher, Walker, & Giudice, 1987). As such, measures of coherence are indicative of the strength of axonal connections between both close and distant brain regions (Thatcher et al., 1987). Coherence between areas and between different bandwidths is a possible explanation of memory function in healthy controls, and resting coherence has been found to be related to MRI indicators of brain tissue integrity in more severe TBIs (Klimesch, Freunberger, Sauseng, & Gruber, 2008; Thatcher et al., 2001; Thatcher, Biver, McAlaster, & Salazar, 1998). Three studies have used measures of EEG bandwidth coherence between different regions to study the impact of a mTBI on memory. Thornton (2003) tested 85 mTBI participants with lower neuropsychological test scores on their memory for a short story. During a silent recall period, coherence between lower (13-31.5Hz) and upper (32-63.5Hz) Beta bandwidths was measured. The mTBI group exhibited lower coherence in the upper Beta band between frontal and both parietal and temporal regions, which were related to reduced memory performance. The authors suggest this indicates impaired frontal signal generation in the mTBI group, resulting in impaired information transfer. Although the study tested a vast multitude of analyses without correcting for multiple comparisons, significant findings were only reported if they were also found in adjacent electrodes, and were found

using two different measures of coherence. The study may be worth replicating, but analyses would be better performed in a more hypothesis driven manner. In a similar study of coherence and memory, Kumar et al. (2009) recorded EEG from a mTBI group which included individuals with minor contusions shown by CT scans, while they performed a verbal and visuo-spatial Sternberg working memory task. Correcting for multiple comparisons, they found reduced alpha (8-14Hz) and beta (14-35Hz) coherence between frontal and both parietal and temporal regions in their mTBI group during the verbal task compared to controls, supporting the findings of Thornton (2003). Their visuo-spatial results showed a different pattern, with lower interhemispheric frontal alpha coherence in the mTBI group. They also found that although controls showed increased temporo-parietal coherence during retrieval in both tasks, the mTBI group showed no change. No differences were found in a resting condition, suggesting coherence measures are better at distinguishing mTBI from controls during cognitive tasks. The upper bandwidth coherence reductions post mTBI shown by Kumar et al. (2009) and Thornton (2003) may reflect impaired connectivity between regions. However, upper bandwidth coherence has been shown to be unaffected following a severe head injury in both verbal and visuo-spatial memory tasks similar to those previously described (Randolph & Miller, 1988). If TBI does result in changes to bandwidth coherence, we would expect more severe TBI to result in larger changes than mild. More research is necessary to clarify this issue. The only study to measure coherence during active processing in a sample without cognitive impairment found no overall differences (Cudmore, Segalowitz, & Dywan, 2000). However, they tested participants with a dual attention task memory and oddball task, as well as a memory task alone, and found their mTBI group showed an increase in beta coherence between fronto-parietal regions when performing both tasks together compared to just the memory task (a

result not found in the control group). The authors suggest this implies increased processing cost required by the mTBI group to perform the same as controls. Their results seemingly contradict those of Kumar et al. (2009), but in fact the two studies are not directly comparable. Cudmore et al. (2000) used a continuous memory task, so measured the combined encoding, retention, and recall processes, as well as the oddball task related processes. Their results indicate that mTBI show increased coherence when focusing attention on two tasks simultaneously overall the simultaneous memory processes. Kumar et al. (2009) on the other hand found coherence increases in controls during the retention period of the memory task, but not by the mTBI group. So their results suggest coherence increases specifically during retention are impaired in the mTBI group, and unlike Cudmore et al. (2000) do not inform about split attention processes.

While Nuwer et al. (2005) may be correct that resting measures of coherence between electrodes are not useful, and do not provide a way to discriminate mTBI from healthy controls, cognitive mediated coherence does seem a promising method to measure impaired connectivity following a mTBI, and the effect this has on cognitive processing. However, more studies are required. Studies of coherence are also rather dense with analyses, since each measure can be calculated between every combination of electrode pairs. This makes the results difficult to interpret. Methods to avoid type I errors due to multiple comparisons are vital, and care should be taken when relating new findings to those of previous researchers, as seemingly similar results may not in fact support one another, and seeming contradictory studies may not be comparable. Lastly, future researchers could use coherence measures to determine the functional effect on the

processes underlying cognition of MRI findings of DAI, similar to the relationship tested in resting EEG by (Thatcher et al., 1998).

Factors Relating to EEG Differences Post mTBI

Changes in cognitive EEG measures are usually found in participants with ongoing neuropsychological testing impairments or PCS symptoms. Studies have shown correlations both between subjective symptoms and ERPs and neuropsychological testing performance and ERPs (De Beaumont et al., 2009; Gaetz et al., 2000; Gosselin et al., 2006; Lavoie et al., 2004). This suggests that persistent symptoms are due to actual neural changes, rather than just malingering or psychogenic changes. However, ERP changes are also found in fully recovered mTBI groups (Berstein et al., 1998; Broglio et al., 2009; De Beaumont et al., 2007; Gosselin et al., 2006; Segalowitz et al., 2001; Theriault et al., 2009). The differences do not appear to be related to the time between injuries and testing. This is perhaps unexpected, as studies focusing on neuropsychological testing suggest full recovery after a matter of months after mTBI (Schretlen & Shapiro, 2003). However, differences in EEG measures have been found more than one year post injury in fully recovered groups (De Beaumont et al., 2007; Potter & Barrett, 1999; Slobounov et al., 2002). They have also been detected in groups with ongoing symptoms (Dupuis et al., 2000; Gaetz & Weinberg, 2000; Lachapelle et al., 2008; Lavoie et al., 2004; Polo et al., 2002). Cognitive related EEG measures have even shown differences between mTBI and control groups up to eight years later, even using groups that have made complete recoveries, and in one study even after two to four decades had passed (Berstein et al., 1998; Broglio et al., 2009; De Beaumont et al., 2009; Reinvang et al., 2000; Segalowitz et al., 2001; Theriault et al., 2009). Over the first few months post injury, ERP characteristics have not correlated with time since injury, nor do

they for up to two years (Dupuis et al., 2000; Gosselin et al., 2006; Lavoie et al., 2004). Only one study has found a trend towards a correlation between smaller P3b amplitude and time since injury with participants injured on average 31 months prior (De Beaumont et al., 2007). No significant differences have been found between individuals injured less than a year prior and those injured between two and five years earlier (Theriault et al., 2009). This suggests that perhaps mTBI leads to longer lasting neural changes than the complete recovery after a month that has been traditionally supposed, even when neuropsychological testing shows a full recovery. This is perhaps because ERP measures are more effective at detecting subtle processing changes than neuropsychological testing.

Another factor that appears to relate to ERP changes post mTBI is number of injuries. All studies that have compared athletes with multiple mTBI to controls have found altered ERPs (Broglio et al., 2009; De Beaumont et al., 2007; De Beaumont et al., 2009; Dupuis et al., 2000; Gaetz et al., 2000; Gosselin et al., 2006; Lavoie et al., 2004; Theriault et al., 2009). Studies that have analysed groups with multiple injuries separately from groups with single injuries have also found that multiple injury groups significantly differ from controls while single injury groups do not (De Beaumont et al., 2007; Gaetz et al., 2000). This fits with large scale research into recovery rates post mTBI, which show slowed recovery in those previously injured (Guskiewicz et al., 2003). This suggests that there is a cumulative effect of mTBI, and that perhaps more care should be taken with return to play guidelines for concussed athletes. However, the issue requires more research, as out of the three studies that tested correlations between number of injuries and ERP changes two found no relationship (Dupuis et al., 2000; Theriault et al., 2009). Gosselin et al. (2006) found that

number of mTBIs was only related to changes in the P2, an exogenous ERP that occurs earlier than those discussed in this chapter and is related more to sensory processing.

Possible electrophysiological explanations of P3b amplitude changes post TBI were analysed by Unsal and Segalowitz (1995) who showed that smaller single trial amplitude is the reason for reduced P3b, rather than overall EEG power changes or peak latency jitter. In moderate to severe TBI, source analysis indicates that P3b delays are due to amplitude reduction in the earlier frontal P3a component (Elting et al., 2005). The P3a is related to frontal gray matter, suggesting that the frontal damage that is commonly shown in structural neuroimaging studies following a TBI results in a change in electrophysiology as well (J. M. Ford et al., 1994; Metting et al., 2007). However, some of the mTBI research shows P3b changes only, which are related to parietal gray matter volumes, suggesting that perhaps focusing on a single impaired area is too simplistic (J. M. Ford et al., 1994). Functional network approaches may offer a more comprehensive explanation, as might connecting findings to the injury type or the area of brain presumed to be injured.

In addition to potential neural changes, P3b changes post mTBI may be related to psychological distress. Solbakk et al. (2000) found P3b amplitude was negatively associated with hypochondria in TBI sufferers. Similarly, a study of mTBI found higher depression and anxiety scores correlated with P3b latency (Alberti et al., 2001). In moderate to severe TBI, depression scores have been found to correlate with P3b latency and negatively correlate with P3b amplitude, and to negative affect has been found to effect electrophysiological measures of error processing (Larson, Kaufman, Kellison, Schmalfuss, & Perlstein, 2009; Reza, Ikoma, Ito, Ogawa, & Mano, 2007). P3b changes are commonly found in depressed non-head injured populations as well (Karaaslan, Gonul, Oguz, Erdinc, & Esel, 2003). In order

to determine if changes in ERPs can be attributed to the injury, researchers using EEG should measure or control for mood changes. It is likely that ERP changes post mTBI are the result of a combination of mood and injury effects, but they may in fact only be related to mood effects.

Lastly, it appears that research using visual stimuli is more likely to differentiate mTBI groups from controls. However, because most research using auditory stimuli uses simple tones and most visual task research uses more complex stimuli it is not clear whether this is due to a difference in response to the different modalities, or to differences in processing more complex stimuli.

Discussion and Recommendations for Future Research

A review of the current literature suggests that although reviews of neuropsychological testing by Binder et al. (1997) and Schretlen and Shapiro (2003) indicate that full recovery takes place following mTBI, it is likely that neural changes do persist, and can be detected by testing with cognitive related EEG measures. These changes occur particularly in groups with continuing subjective symptoms, but also in people who have fully recovered, with no lingering symptoms or neuropsychological testing impairments. They do not appear to recover over time, and may be related to employment difficulties and cognitive decline in old age (De Beaumont et al., 2009; Lachapelle et al., 2008). The majority of studies have used the oddball task. The oddball literature suggests that the visual modality may be better for detecting changes, and that the later P3b ERP is more often affected than the N2. The P3b has been shown to be related to the function of a number of different neurotransmitters, including serotonin, acetylcholine, dopamine, GABA, and norepinephrine (Hammond, Meador, Aung-Din, & Wilder, 1987; Hansenne & Ansseau, 1999;

Hansenne, Pitchot, Papart, & Ansseau, 1998; Jonkman et al., 1997; Meador et al., 1989; Pineda & Westerfield, 1993; Potter, Pickles, Roberts, & Rugg, 2000; Semlitsch, Anderer, & Saletu, 1995; Swick, Pineda, & Foote, 1994). A theoretical explanation of the neural generators of the P3b proposed by Nieuwenhuis et al. (2005) suggests that it is generated by neuromodulatory activity in the locus coeruleus, which projects widespread frontal and posterior norepinephrine connections throughout areas including the cortex, thalamus, midbrain and cerebellum. The locus coeruleus appears to respond to task relevant stimuli, with its response mediated by arousal levels, in the same manner as the P3b. This area may generate the activity that synchronises activity in widespread areas. The overlapping signal from all these regions conducts to become the scalp recorded P3b, potentially mediated by cholinergic connections (Nieuwenhuis et al., 2005). This aligns with mTBI research indicating neurotransmitter changes may take place in the cholinergic system (Giza & Hovda, 2001). If this theory of P3b generation is accurate, it implies that ERP research would be a useful method to measure the widespread network connectivity changes, so may be useful for measuring DAI. Lowered amplitude may suggest a reduction in synchronised activity, reducing simultaneously activated processing resources, perhaps as a result of reduced connectivity through DAI. This may explain why the complaints of mTBI patients are often similar to the symptoms of mental fatigue, and relates to fMRI findings of altered cerebral metabolism post mTBI (Gevins et al., 1992; McAllister et al., 2001). Reduced synchronisation of activity (which results in reduced P3b amplitude) may also explain the common concentration and memory complaints of mTBI sufferers, as fewer neural resources are activated in response to a stimulus (due to poorer arousal modulation), reducing the meaning extracted from the stimulus, which results in a smaller number of connections available for reactivation and memory retrieval. If the function of the brain is to form a

model of reality in order to interact with effectively, post mTBI its ability to do so may be reduced due to impaired ability to synchronise resources and energy inefficiency.

Future research could attempt to relate P3b and other ERP changes to underlying neural changes using a similar conceptual framework. In conjunction with diffusion tensor MRI which can be used to assess DAI, the P3b could be used to assess functional communication between brain regions. Correlations between the P3b and degree of DAI detected with MRI should be tested to determine the impact of DAI on electrophysiology. However, because ERP amplitude reductions and latency delays are found in other clinical populations and are not unique to TBI, they have more than one potential explanation (Nuwer et al., 2005). As such, we cannot assume any changes found are the result of DAI. This means that at present, although ERPs are a useful research tool for between group comparisons, EEG is not diagnostically useful, as differences cannot discriminate mTBI from other neurological or psychiatric groups (Nuwer et al., 2005).

In addition to simple ERP analyses, future research should pursue more complex EEG analyses such as bandwidth coherence analysis, which may provide a better indication of the ability of neural regions to synchronise (Slobounov et al., 2002). It is likely that bandwidth analyses may provide more direct information on neural activity underlying cognitive function as well, as functions such as memory are mediated by bandwidth changes (Klimesch et al., 2008). The few studies that have used bandwidth to compare mTBI to controls have found differences in fronto-parietal coherence, suggesting coherence may be a good indicator of reduced connectivity as a result of DAI (Cudmore et al., 2000; Kumar et al., 2009; Thornton, 2003). More complex bandwidth measures such as that used by Slobounov and colleagues to measure signal complexity and information entropy may also

be useful to assess neural network function post mTBI (Slobounov, Cheng, & Sebastianelli, 2009).

Future research should endeavour to use tasks that relate to specific cognitive processes, in order to determine which are affected following mTBI. Research by Segalowitz et al. (2001) indicates that in the auditory modality, simple task demands are better at discriminating mTBI from control groups. They suggest this may be because tasks requiring more processing elicit more complex activity, so create more overlapping peaks and troughs which cancel each other out and reduce the scalp signal. Conversely, simple tasks produce less complex activity, providing larger amplitude recordings. This suggests that care should be taken to test only one aspect of processing, which will offer larger amplitude differences and more specific information on processing impairment. One way to avoid stimulus complexity (which might reduce the absolute ERP peak through an increase in overlapping peaks and troughs) may be to use area under curve analyses, which takes into account overall amplitude for the entire ERP. On the other hand, stimulus complexity (rather than task complexity) may result in larger between group differences. Studies using visual tasks tend to use more complex stimuli than studies using auditory tasks, and seem to differentiate mTBI groups from controls more effectively. It would be useful for a study to vary stimuli complexity with both auditory and visual stimuli, in order to determine whether it is the modality or the complexity that is responsible for the differences. This will inform as to whether mTBI sufferers struggle with increased stimulus complexity, or whether they have a visual modality specific impairment. Either answer may be useful in guiding rehabilitation methods.

In addition to using a more comprehensive neural and cognitive approach to ERP studies, basic EEG principles should be adhered to. Since we cannot state that a signal is due to brain activity unless artefacts can be ruled out as a factor, a good eye correction algorithm is invaluable, as this allows more confidence that any differences detected are due to brain activity (Campbell et al., 1986). Also, in order to minimise type II errors, one way statistical tests may be more appropriate, as latency delays and amplitude reductions are expected in mTBI, rather than the reverse.

To fully explore the impact of a mTBI on electrophysiological function, studies with large longitudinal samples should compare participants both when still symptomatic and fully recovered to controls, using cognitive tasks that measure specific functions. They should analyse both bandwidth and ERPs, control for potential mood effects, and attempt to relate findings to conceptual frameworks of the generation of the electrophysiological measures, in order to provide a potential meaning for the changes. Future research should also correlate EEG measures with MRI methods of measuring DAI, in order to investigate whether ERP changes are due to DAI, or another yet unknown mechanism. Lastly, future research using the oddball task to look at mTBI may prefer to use visual stimuli, which appear to be more effective at differentiating mTBI groups from controls.

Concluding Remarks

The information presented in the current chapter suggests that cognitive related electrophysiological measures may be useful to measure changes post mTBI, particularly the P3. The research indicates that changes do take place that may not recover, possibly even after decades since injury. These changes are particularly found in those with lingering symptoms or cognitive impairment, and in those who have sustained more than one injury.

This may be related to impairment in processing efficiency, possibly due to DAI, but the causal links are uncertain at this stage. Future studies should be more conceptually guided in order to increase understanding of the underlying reason for the changes. Advances in EEG analysis techniques and understanding of the generators and function of the activity underlying ERPs will help with this. New measures such as coherence that take into account the functional connectivity between areas will become increasingly useful. Research should also endeavour to take advantage of tasks other than the oddball, which may test specific areas of cognitive function such as memory or response inhibition. This could allow for a more detailed knowledge of the nature of impairments post mTBI, helping guide our understanding of the long term effects of mTBI and informing future rehabilitation systems.

Chapter Five

A Review of the Electroencephalographic Perspective on Cognitive and Emotional Neural Activity in MDD

Introduction

Major Depressive Disorder (MDD) is one of the world's leading causes of disability (World Health Organisation, 2001). It is associated with impaired educational attainment, marriage stability, employment, and physical health (Kessler, 2012). An extensive accumulation of research has concentrated on explaining this disorder from a neurophysiological perspective. This review comprehensively synthesizes the research that has used EEG to investigate the neurophysiology of MDD since 1980, focussing in particular on studies of cognitive and emotion related neural activity. This review will weigh the evidence for the presence of neurophysiological changes underlying these processes in MDD, and from this extrapolate any potential conclusions that can be drawn regarding brain function in MDD.

The majority of this research has compared event related potentials (ERPs) between MDD and control groups (refer to chapter 3 for a summary of the mechanisms that are thought to contribute to scalp recorded ERPs). Variations in ERPs are dependent on participant internal characteristics, making them ideal for comparing neural activity between groups. A wide variety of cognitive and emotional processes have been tested using ERPs, across a range of tasks. The benefit of such variety is that each offers different information about the neural processes that may be affected. However, it also makes direct

comparisons across studies problematic. Unfortunately, although some methodologies have been used frequently, meta-analysis of this literature is not possible, as many papers have not fully reported their statistics. In particular, articles with non-significant results are less likely to report the relevant statistical details required for a meta-analysis. Although this limits the strength of the conclusions that can be drawn, the holistic perspective of the literature taken by this review still offers a more complete understanding of the field than has been available previously.

The largest portion of the reviewed literature has focused on the Oddball task, so this task is examined in detail first. The second section of this review amalgamates the rest of the research looking at various tasks by examining the common underlying process that each evaluates. This is done in an attempt to draw stronger conclusions from the larger information pool.

Oddball Task

The most frequently used task has been the oddball task. A detailed description of this task and the ERPs commonly measured can be found in the preceding chapter, so only a brief summary is presented here. This task presents one stimulus frequently, with another infrequent stimulus randomly dispersed. Participants are instructed to respond to the rare stimulus type, and ignore the frequent type. Both auditory and visual stimuli have been used. The oddball task is not commonly used for behavioural measurements like accuracy and reaction time, but instead generates ERPs that give a neural reflection of attention and memory updating processes. The task generates a positive voltage deflection maximal at parietal electrodes, peaking between 300-600ms, around 10-20μv from baseline, following the rare 'oddball' stimulus. Generally known as either the P300 (because of it's latency), or

the P3 (because of it's ordinal position as the third positive deflection post stimulus), different aspects of this ERP reflect different neural processes. The P3 latency is thought to represent the time taken to identify and categorise a stimulus (Kramer and Strayer, 1988; McCarthy and Donchin, 1981). Inter-individual differences in P3 amplitude are thought to indicate variations in the amount of meaning extracted from a stimulus, which is modulated by attention (Johnson, 1986; Nieuwenhuis et al., 2003). For the purposes of this review, the parietal P3 is referred to as the P3b. The P3b is the most heavily researched ERP in MDD groups. Functional MRI research suggests the P3b is related to activity in the dorso-lateral prefrontal cortex (DLPFC), temporo-parietal junction, and superior temporal gyrus (Karch et al., 2010; van Veen and Carter, 2002a). Comparisons of these measures between MDD groups and controls are reviewed in the following section. A summary of the reviewed studies can be viewed in table 4 (page 101).

P3b Amplitude

The most commonly found auditory oddball P3b change in MDD groups is a reduction in P3b amplitude (Ancy et al., 1996; Anderer et al., 2002; Blackwood et al., 1987; Gangadhar et al., 1993; Kawasaki et al., 2004; Kemp et al., 2009; Muir et al., 1991; Murthy et al., 1997; Roschke and Wagner, 2003; Roschke et al., 1996; Tenke et al., 2008; Urretavizcaya et al., 2003; Wagner et al., 1997). Since 1980, a total of 38 studies have compared P3b amplitude between a currently depressed MDD group and a healthy control group. Twenty-five have found reduced amplitude, with three showing this result only for the right hemisphere, and four only for subgroups of MDD participants. Only twelve have shown no significant differences between the groups.

From an information processing perspective, P3b reduction reflects less attention to a stimulus, or less meaning extracted from a stimulus, or both (Johnson, 1986). A neurophysiological approach suggests this is due to a reduction in the quantity of neural resources devoted to updating memory in response to a stimulus (Donchin and Coles, 1988; Wickens et al., 1983). More specifically, it is due to impaired synchronisation of those resources. In terms of neurotransmitter activity, P3b amplitude seems to be modulated by the function of serotonin, acetylcholine, dopamine, GABA, and norepinephrine, some of which are thought to be implicated in mood changes and MDD (Elhwuegi, 2004; Hammond et al., 1987; Hansenne and Ansseau, 1999; Hansenne et al., 1998; Jonkman et al., 1997; Meador et al., 1989; Pineda and Westerfield, 1993; Potter et al., 2000; Ruhe et al., 2007; Semlitsch et al., 1995; Swick et al., 1994). Theoretical models of the origin of the P3b suggests the locus coeruleus may be responsible for synchronising the activity of these resources that appear as the P3b as it has widespread projections capable of synchronising activity across the cortex, and shows similar a activity dependence on arousal and task relevant stimuli to the P3b (Nieuwenhuis et al., 2005). In support of this, drugs that impair the locus coeruleus also reduce the P3, but leave other ERPs intact (Duncan and Kaye, 1987). A modelling approach suggests that this synchronisation relies on excitatory and inhibitory feedback loops between cortical, thalamic, and limbic areas (Rennie et al., 2002). This makes sense, as inhibition of an area is likely to display the opposite voltage at the scalp as the release of that inhibition (allowing excitation) (Kok, 1990). Research in healthy controls that presents a second stimulus during the P3b shows reduced activation to this stimulus. This smaller neural response indicates that the P3b is preventing the typical activity, suggesting that the P3b represents decreased cortical excitability, or inhibition (Rockstroh et al., 1992). Assuming these descriptions of P3b generation are correct, it might

be suggested that a reduced P3b in MDD is due to impaired locus coeruleus function, or impaired corticothalamolimbic network synchronisation, possibly due to poorly functioning inhibitory/excitatory mechanisms. This aligns with models of MDD based on other neuroimaging methodologies, which also suggest weakened corticolimbic coordination (Drevets, 2000; Mayberg, 1997).

However, there is considerable variation in the P3b amplitude results, which may be dependent on a number of different factors.

Explanations for Variation in Results

Firstly, some studies have reported P3b amplitude reductions only for sub-groups with MDD, for example Pfefferbaum et al. (1984) – only for medication free participants, Karaaslan et al. (2003) – only for those with psychotic features, Kemp et al. (2010) – only for melancholic subtype and only in frontal electrodes, Hansenne et al. (1996) – only in suicide attempters, and El Massioui et al. (1996) – only in a more difficult task with tones presented to both ears and participants instructed to ignore one side. Sometimes these reductions are only found in the right hemisphere (Iv et al., 2010). Source analysis with LORETA has indicated the P3b reductions in the MDD group may be due to lower current density in bilateral temporal regions, left frontal regions, medial prefrontal cortex, and the right temporo-parietal region (Anderer et al., 2002; Kawasaki et al., 2004; Tenke et al., 2008).

Conversely, some studies have only shown trends (Bruder et al., 2009), or not shown amplitude reductions in MDD (Bruder et al., 2002; El Massioui and Lesévre, 1988; Giedke et al., 1981; Gordon et al., 1986; Himani et al., 1999; Kaustio et al., 2002; Roth et al., 1981; Sara et al., 1994; Vandoolaeghe et al., 1998; Wang et al., 2003; Xu et al., 2010). One study has

even shown a trend towards higher P3b amplitude in sub-clinically depressed participants (Sumich et al., 2006).

With regards to visual oddball tasks, reductions in P3b amplitude have also been shown (Diner et al., 1985), however the majority of research has demonstrated no change in the visual oddball P3b amplitude (Bange and Bathien, 1998; Pfefferbaum et al., 1984).

Varied sample sizes may be one explanation for the variation in P3b amplitude results. Generally, studies that have not found P3b differences between MDD groups and controls have used sample sizes of fewer than 20 (Bange and Bathien, 1998; Giedke et al., 1981; Gordon et al., 1986; Kahkonen et al., 2008; Wang et al., 2003). The larger studies tend to show amplitude reductions in the MDD group (Anderer et al., 2002; Kemp et al., 2010; Kemp et al., 2009; Muir et al., 1991; Urretavizcaya et al., 2003). This pattern is not complete though - with one study using a sample size in the hundreds and found no significant differences (Xu et al., 2010), and some small studies finding P3b changes (Blackwood et al., 1987; Diner et al., 1985; Gangadhar et al., 1993; Iv et al., 2010; Murthy et al., 1997; Roschke et al., 1996; Torta et al., 1994). Therefore, while it is possible that the smaller studies that do not show amplitude reductions due to a lack of statistical power, or a disproportionate impact of sample heterogeneity, we cannot be certain that small sample size can fully explain the variation in findings.

Another possible difference between studies is the sample characteristics. In particular, many studies have excluded participants taking anti-depressant/anti-anxiety medications. Of the 18 studies to show differences between the MDD and control group in midline P3b amplitude, only two used samples that included medicated participants. On the other hand, of the twelve studies showing no difference, five reported using medicated

participants, and another two did not report whether or not their sample included medicated participants. Table 4 summarises these studies. This aligns with research indicating that neurotransmitter function in depression (particularly serotonin and dopamine) affects P3b amplitude (Hansenne and Ansseau, 1999; Hansenne et al., 1995). Evidence also suggests that P3b amplitude reductions are resolved with anti-depressant medication (Karaaslan et al., 2003; Torta et al., 1994). The hypothesis has also been directly tested, with amplitude reductions only found in unmedicated MDD (Pfefferbaum et al., 1984).

Severity of depression has been proposed as another factor that may influence ERP measurements. Some research has found a negative relationship between severity scores and P3 amplitude (Gangadhar et al., 1993). In addition to this, the P3b has been documented to return to healthy control levels in remission (Gangadhar et al., 1993; Karaaslan et al., 2003). However, other researchers have found no relationship between depression severity and P3b amplitude (Bange and Bathien, 1998; Bruder et al., 2009; Hansenne et al., 1996; Karaaslan et al., 2003; Murthy et al., 1997; Roth et al., 1981; Santosh et al., 1994; Urretavizcaya et al., 2003). While this may be due to a small sample size for some studies (Bange and Bathien, 1998; Hansenne et al., 1996), that is not the case for others. One study that included remitted as well as currently depressed participants, and still found differences between the groups (Muir et al., 1991). While low mood alone does not appear to affect the P3b (Kemp et al., 2009), this is again inconsistent, with Murthy et al. (1997) showing P3b reductions in those scoring in the dysthymic range. Since the relationship between severity and P3b amplitude is so inconsistent, this variable is unlikely to explain the different results between studies.

Another factor that might affect P3b amplitude in MDD groups is anxiety. Some research has indicated that groups with comorbid anxiety and depression show an *increased* late P3b amplitude (Bruder et al., 2002). Therefore, if comorbid anxiety increases P3b amplitude, then including these participants may obscure reductions in P3b amplitude in the MDD alone participants. In support of this idea, both of the two studies that excluded participants with comorbid anxiety found reductions in the P3b (Iv et al., 2010; Kawasaki et al., 2004).

Some studies that divide the MDD groups based on the presence of psychotic features have found reduced P3b amplitude compared to controls only in the group with these symptoms present, and a smaller P3b in a group with psychotic features compared to a group without (Karaaslan et al., 2003; Kaustio et al., 2002; Santosh et al., 1994). Controlling for other factors, correlation has indicated only the psychotic features were related to P3b amplitude, not affective factors or overall severity (Kaustio et al., 2002; Santosh et al., 1994). P3b is also reduced in individuals with a history of drug over-dose suicide attempt (Hansenne et al., 1996). However, while the authors excluded drugs that are known to affect P3b amplitude, the effect of the over-dose itself on P3b amplitude is unknown, and may be similar to the effect of a traumatic brain injury, which does seem to impact on P3b amplitude (Gaetz and Berstein, 2001).

Some authors have argued that tasks with higher levels of difficulty will be more likely to detect differences between the groups. The idea is that more difficult tasks are more taxing on cognition, and therefore on neural resources. These more taxing tasks reveal processing impairments in MDD groups, while control groups maintain their more robust successful neural processes. However, there does not seem to be evidence in support of this

idea - studies have shown lower accuracy or delayed reaction times in MDD without any changes in P3b (Bange and Bathien, 1998; Diner et al., 1985; El Massioui and Lesévre, 1988; Sara et al., 1994). A deliberately difficult task that restricted performance to 70% accuracy showed no P3b amplitude reduction in an MDD group (Bruder et al., 1991). Conversely, simple oddball tasks requiring no response, or with over 95% accuracy, have shown smaller P3b amplitudes in the MDD group (Anderer et al., 2002; Bruder et al., 2002).

Specificity of P3b Reductions to MDD:

One issue with studying ERP generation in response to the oddball task in MDD is that alterations are not specific to MDD – similar changes can also be found in schizophrenia (Wang et al., 2010). This raises the possibility that the differences between healthy and depressed groups are due to general neural/cognitive alterations, rather than being specifically due to the depression disease process. In order to determine if this is the case, Roschke and Fell (1997) looked at spectral changes during an oddball task in each disorder. They found that the alterations were due to changes in different bandwidths in each disorder. The depressed group showed increased pre-stimulus gamma, and reduced alpha and gamma during the P3 window compared to controls, while the schizophrenia group showed delta reductions. In addition to this, single trial analyses have been performed on oddball ERPs, as grand average ERP comparisons do not discriminate between a general amplitude reduction on all trials, and some trials showing no amplitude while others show the usual amplitude. These studies seem to indicate that while both MDD and schizophrenia groups show reduced average P3 amplitude, the reduction is due to P3 being generated on fewer trials in schizophrenia, while in MDD the P3 is smaller but generated on the same amount of trials as controls (Roschke and Wagner, 2003; Roschke et al., 1996; Wagner et al.,

1997). This suggests that while people with schizophrenia show impaired target discrimination, MDD show normal target discrimination but reduced neural response.

P3b Amplitude Summary

To summarise the P3b amplitude results it seems there is significant inter-study variation, possibly due to medication effects, and potentially influenced by sample size/characteristics. There is little evidence that the results vary as a function of task difficulty. We can probably conclude that an amplitude reduction is present in patients prior to treatment with anti-depressants. The difference between MDD and control groups may be obscured by comorbid anxiety, and may be due to the presence of psychotic symptoms more than depression severity. The reduction may reflect fewer attentional resources in MDD, resulting in impaired memory encoding, potentially caused by impaired synchrony of neural populations. This explanation supports an impaired network model of MDD. However, the conclusion that there is a P3b reduction in unmedicated MDD assumes there is no 'file drawer' problem, ie. unreported non-significant studies. A number of studies may have analysed P3b in MDD and found no between group differences, but not been reported. Knowledge of these studies might refute these conclusions, but it is impossible to ascertain whether this is the case.

P3b Latency

P3b peak latency delays are also sometimes found in MDD groups (Himani et al., 1999; Karaaslan et al., 2003; Kemp et al., 2010; Kemp et al., 2009; Torta et al., 1994; Urretavizcaya et al., 2003; Vandoolaeghe et al., 1998; Wang et al., 2003; Xu et al., 2010). The majority of studies, however, show either only a trend towards delayed latency (Weir et

al., 1998), or no changes in latency (Ancy et al., 1996; Anderer et al., 2002; Blackwood et al., 1987; El Massioui et al., 1996; El Massioui and Lesévre, 1988; Gangadhar et al., 1993; Giedke et al., 1981; Gordon et al., 1986; Hansenne et al., 1996; Kaustio et al., 2002; Kawasaki et al., 2004; Muir et al., 1991; Murthy et al., 1997; Roth et al., 1981; Sara et al., 1994). The two studies that have analysed P3b latency using the visual modality have shown no differences between groups (Bange and Bathien, 1998; Diner et al., 1985). In total, eleven studies have shown latency delays in MDD groups compared to controls, with another two only showing delays for a sub-sample of the MDD group. Eighteen however have found no delay.

Factors that vary between studies:

Of the studies showing P3b latency delays, some have used large sample sizes of over 50 participants (Kemp et al., 2009; Urretavizcaya et al., 2003; Xu et al., 2010), while others have used small to medium sample sizes of 10-30 (Himani et al., 1999; Karaaslan et al., 2003; Torta et al., 1994; Wang et al., 2003). Those showing no differences tend to use smaller samples of fewer than 24 participants (Ancy et al., 1996; Blackwood et al., 1987; El Massioui et al., 1996; El Massioui and Lesévre, 1988; Gangadhar et al., 1993; Giedke et al., 1980; Gordon et al., 1986; Hansenne et al., 1996; Kaustio et al., 2002; Kawasaki et al., 2004; Murthy et al., 1997; Roth et al., 1981), but a number have used large samples of almost 50 or more and still found no differences (Anderer et al., 2002; Muir et al., 1991). There seems to be no consistent pattern with regards to sample size and significant latency delays in MDD.

Although medication status has differentiated an MDD group from controls in one study where only unmedicated participants showed a P3b delay (Pfefferbaum et al., 1984), this variable does not appear to be responsible for the differences between studies. Of the

studies that report medication status of the participants, six of seven studies that report a delay used unmedicated participants, while eleven of 17 studies that found no latency differences used unmedicated participants. Similar to amplitude measures, P3 latency is not found to be correlated with depression severity (Schelgel et al., 1991; Urretavizcaya et al., 2003). Some studies showing latency delays have found a return to normal after remission, but this may due to factors other than depression severity (Torta et al., 1994; Wang et al., 2003). Also similar to P3b amplitude, latency delays have been found in a subgroup with psychotic features when they are not found in those without these features (Karaaslan et al., 2003; Kaustio et al., 2002). Melancholic MDD has also shown latency delays while non-melancholic do not (Kemp et al., 2010). A number of studies have suggested that P3b latency delays are related to psychomotor retardation, as well as verbal, intellectual and emotional retardation (Schelgel et al., 1991), but this is not consistent (Urretavizcaya et al., 2003). Latency delays have also correlated strongly with sleep disturbance (Bruder et al., 1991). Specific genotypes may also interact with MDD to alter P3b characteristics. (Xu et al., 2010) found that individuals with both MDD and miR-30e (a gene associated with reduced cell growth) showed a delayed P3 latency compared to those without the gene and healthy controls.

P3b Latency Summary

Overall it seems that there is no consistent evidence of globally delayed P3b peak in MDD. Those studies that do show delays may have inadvertently recruited participants with specific symptoms which do appear to delay P3b latency, such as melancholia, psychotic features, psychomotor retardation, or sleep disturbance. Although latency delays in the P3b

are associated with reduced cognitive function (Polich and Kok, 1995), it seems this process is not responsible for the specific cognitive complaints MDD sufferers exhibit.

The P3a

A smaller number of studies have added a third stimuli type into the typical oddball task – a novel distracter. This generates a frontally maximal positive deflection that occurs slightly prior to the P3b, which is termed the P3a. It is thought to represent an orienting response generated in the frontal cortex, and it's function is thought to be the automatic attendance to a salient stimuli (Knight, 1991). The results of these analyses are inconsistent. Some show amplitude reductions (Bruder et al., 2009; Iv et al., 2010), and source analysis of the P3a indicated reduction in mid-line frontocentral longitudinal fissure amplitude compared to controls (Tenke et al., 2010). Others however have shown no differences (Houston et al., 2004; Kahkonen et al., 2008). Bruder et al. (2009) found anxiety was not related to P3a amplitude in MDD, so this is not a potential explanation for the differences between the studies. Within MDD groups, suicide attempt history has been found to relate to the degree of habituation to novel stimuli, represented by P3a reductions to novel sounds towards the end of a three stimulus oddball task (Jandl et al., 2010). The authors suggest increased habituation may be experienced as a higher degree of desensitisation, potentially leading to increased likelihood of attempting suicide.

Overall the P3a literature is currently too sparse to draw significant conclusions with regards to alterations in MDD. Further research may suggest impairment in this process, which would suggest pre-frontal activity dysfunction in MDD. However, the P3a is consistently resolved only in approximately 20% of healthy controls, so it may be a poor comparison measure for MDD groups (Polich, 1988).

The N2

The N2 is another ERP generated by the oddball task. It is a negative deflection occurring 200-300ms post stimulus, and is smaller and less consistent than the P3b. It is thought to reflect a combination of novelty detection, cognitive control, and attention (Folstein and Van Petten, 2008; Patel and Azzam, 2005). Source localisation and fMRI studies suggest it is related to the DLPFC and anterior cingulate cortex (ACC) (Karch et al., 2010; van Veen and Carter, 2002a). N2 amplitude reductions have been found in MDD groups (El Massioui et al., 1996; El Massioui and Lesévre, 1988; Iv et al., 2010; Tenke et al., 2008). These changes have been localised to the bilateral temporal lobe, precuneus and dorsal ACC (Anderer et al., 2002). Some research has found an N2 reduction only for medicated participants (Pfefferbaum et al., 1984). However, the N2 results are even less consistent than other oddball measures, with other research describing N2 amplitude increases in moderate and severe MDD (Giese-Davis et al., 1993; Muir et al., 1991; Sandman et al., 1992). Not surprisingly, some research has shown no differences (Bruder et al., 2009; Kemp et al., 2010; Kemp et al., 2009; Muir et al., 1991; Sara et al., 1994). N2 latency findings are equally inconsistent, with delays been shown in some studies (Giedke et al., 1981; Sandman et al., 1992; Urretavizcaya et al., 2003), sometimes only for melancholic subtypes (Kemp et al., 2010), but just as often N2 latency is not found to differ (Anderer et al., 2002; Bange and Bathien, 1998; Bruder et al., 2009; El Massioui et al., 1996; El Massioui and Lesévre, 1988; Himani et al., 1999; Pfefferbaum et al., 1984; Sara et al., 1994). It seems unlikely that the N2 is reliably affected by MDD. These inconsistent results may be due to the fact that the N2 is not easily measured in the oddball task, due to small amplitude and inconsistent detection.

Table 4 – Oddball MDD research

Authors	MDD (N)	Sample Characteristics	Task Complexity	Sig. N2 Differences?		Sig. P3 Differences?	
				Amplitude	Latency	Amplitude	Latency
Kemp et al. (2009)	78	Also 127 with sub-clinical depressed mood. Medication free.	Simple tones	No differences		Reduced in MDD group only, not sub-clinical depressed mood.	Delayed in MDD group only, not sub-clinical depressed mood.
Kemp et al (2010)	105	57 melancholic subtype, 48 non-melancholic. Medication free.	Simple tones	No differences	Delayed for melancholic MDD	Reduced in melancholic MDD	Delayed in melancholic MDD
Bruder et al. (2009)	20	Outpatients. Includes 3 bipolar patients.	3 Stimuli: 2 tones and novel distracter	No differences		Reduced for P3a only (not P3b)	No difference.
Iv et al. (2010)	14	First episode. Non-medicated.	3 Stimuli: 2 tones and novel distracter	Reduced in MDD to both targets and novel distracters	No differences	Reduced in MDD to both targets and novel distracters	No differences
Giedke et al. (1981)	13	9 patients medicated.	Simple tones	No differences	Delayed for non-targets only	No differences	
Blackwood et al. (1987)	16	Not medicated	Simple tones	No significant differences		Reduced	No differences
Muir et al. (1991)	48	Majority not medicated. Only 22 currently depressed.	Simple tones	Increased in those with current depression	No difference	Reduced in both current and non-current MDD	No differences.
Himani et al. (1999)	20	Not reported	Simple tones	No differences		No differences.	Delayed
Kahkonen et al. (2008)	13	Unmedicated	Three tone oddball	Not analysed		Only analysed frontal P3a. No differences.	
Weir et al. (1998)	14	Medicated	Simple two tone oddball	Not analysed		Reduced right hemisphere amplitude	Trend towards delay

Authors	MDD (N)	Sample Characteristics	Task Complexity	Sig. N2 Differences?		Sig. P3 Differences?	
				Amplitude	Latency	Amplitude	Latency
Kawasaki (2004)	22	Unmedicated, no comorbidities (including anxiety)	Simple two tone oddball with LORETA source localisation	Not analysed		Reduced, particularly in right hemisphere. Changes localised to bilateral temporal, left frontal, and right temporo-parietal.	No differences
Anderer et al. (2002)	60	Females undergoing menopause aged 45-60yo.	Simple two tone oddball with LORETA source localisation	Reduced, particularly in left parieto-central sites, left and right temporal lobe, precuneus, and dorsal ACC. No latency differences.		Reduced in left and right temporal lobes and medial prefrontal cortex.	No latency differences.
Tenke et al. (2008)	38	Medication free, slightly older than controls	Dichotic oddball using notes or spoken syllables with LORETA	Marginally reduced N2 sink		Posterior and temporal reduction, but only for non-targets when covarying for performance. No hemispheric asymmetry differences.	
Gordon et al. (1986)	17	Medicated, some bipolar included	Simple two tone oddball	Not analysed		No differences	
Roth et al. (1981)	21	Medicated	Simple two tone oddball with varying target frequencies	No differences		No differences. No correlations with HAM-D severity measures.	
Karaaslan et al. (2003)	36	16 with psychotic features, medicated.	Simple two tone oddball	Not analysed		Reduced in those with psychotic features only. Not correlated with HAM-D	Delayed. Not correlated with HAM-D
Urretavizcay et al. (2003)	50	Melancholic subtype, all drug free.	Simple two tone oddball	Not reported	Delayed	Reduced, not correlated with severity	Delayed, not correlated with severity
Vandoolaeghe et al. (1998)	39	Mean age of 53, medication free	Simple two tone oddball	Not analysed		No difference	Delayed, particularly in anti-depressant non-responders.
Kaustio et al. (2002)	22	Medication free, psychotic features measured.	Simple two tone oddball	Not analysed		Reduced for MDD with psychotic features group only.	Delayed at Pz only for group with psychotic features only

Authors	MDD (N)	Sample Characteristics	Task Complexity	Sig. N2 Differences?		Sig. P3 Differences?	
				Amplitude	Latency	Amplitude	Latency
Wang et al. (2003)	15	Unmedicated, then treated with MOA	Simple two tone oddball	Not analysed		No differences	Delayed, but returned to normal after remission
Torta et al. (1994)	10	Not medicated initially, then given neurotransmitter precursor treatment	Simple two tone oddball	Not analysed		Not analysed	Delayed, but returned to normal with treatment
Murthy et al. (1997)	15	Also 15 participants with dysthymia	Simple two tone oddball	Not analysed		Reduced in both MDD and dysthymia	No differences
Ancy et al. (1996)	17	Only 2 medicated, 4 with bipolar. Results compared to ECT response	Simple two tone oddball	Not analysed		Reduced. Smaller in non-responders.	No differences
Bruder et al. (2009)	20	Outpatients without psychotic or melancholic features. Included 5 with dysthymia rather than MDD diagnosis, and 3 bipolar depression.	Three tone oddball	No differences		Reduced P3a, and marginally reduced P3b.	Not measured
Bruder et al. (1998)	40	Medication free. Divided into anhedonia and non-anhedonic	Two complex tone oddball task	Enhanced in MDD. No difference between anhedonia and non.	Not analysed	No amplitude difference. Right hemisphere P3 bias for controls not shown in MDD. Asymmetry correlated with BDI, and anhedonia.	Not analysed.
Iv et al. (2010)	14	First episode with no anxiety or medication	Three tone oddball	Reduced N2 and difference between target and frequent	Not analysed	Reduced P3a and right hemisphere shows reduced P3b	Not analysed
Xu et al. (2010)	354	Compared presence of miR-30e gene to absence in MDD group	Simple two tone oddball	Not analysed		No differences	Delayed in MDD, and delayed even more in MDD with miR-30e
Ogura et al. (1993)	36	Medication free. Tested during episode and during remission	Simple two tone oddball.	No overall N2 difference, reduced difference between target and frequent	No differences	Not analysed	

Authors	MDD (N)	Sample Characteristics	Task Complexity	Sig. N2 Differences?		Sig. P3 Differences?	
				Amplitude	Latency	Amplitude	Latency
Hansenne et al. (1996)	20	Divided into 10 with suicide attempt history and 10 without	Simple two tone oddball	Not analysed		Reduced in those with suicide attempt history	No difference
Gangadhar et al. (1993)	17	Before and after ECT treatment	Simple two tone oddball	No analysed		Reduced before treatment, correlated with HAM-D. Returned to normal in recovery post treatment	Not analysed
Wagner et al. (1997)	11	Compared schizophrenia, MDD, and controls	Single trial analysis of simple two tone oddball	Not analysed		Reduced single trial amplitude in MDD, fewer P3 responses to targets in Schizophrenia	Not analysed
Roschke and Wagner (2003)	21	Compared schizophrenia, MDD, and controls	Single trial analysis of simple two tone oddball	Not analysed		Reduced single trial amplitude in MDD, fewer P3 responses to targets in Schizophrenia	Not analysed
Roschke et al. (1996)	11	Compared to schizophrenia and control	Single trial analysis of simple two tone oddball	Not analysed		Reduced single trial amplitude in MDD, fewer P3 responses to targets in Schizophrenia	Not analysed
Tenke et al. (2010)	49	Outpatients, medication free	Three stimulus auditory oddball	Not analysed		P3a source reduced in MDD group. P3b not analysed.	Not analysed
El Massioui et al. (1996)	8	Inpatients	Two tone dichotic oddball (different tones each ear), attend to one only.	Reduced	No differences	Reduced	No differences
El Massioui et al. (1988)	8	Inpatients 50-65yo.	As above.	Reduced	No differences	No differences	
Sara et al. (1994)	27	Inpatients, medicated patients analysed separately.	Simple two tone oddball task	No differences		No differences	
Sandman et al. (1992)	16	Outpatients	Tones synchronised to heart rate	Enhanced, but no relationship to heart rate	Delayed but no relationship to heart rate	No differences, and no relationship to heart rate	

Authors	MDD (N)	Sample Characteristics	Task Complexity	Sig. N2 Differences?		Sig. P3 Differences?	
				Amplitude	Latency	Amplitude	Latency
Bange, Bathien (1998)	12	Inpatients, medicated, 50yo mean age.	Two simple visual shapes as stimuli.	No differences		No differences	
Diner et al. (1985)	10	Inpatients. Not medicated.	Three stimulus visual oddball.	No differences		Reduced P3 amplitude	No differences
Pfefferbaum et al. (1984)	34	Half were medicated.	Three tone auditory oddball, and simple shape visual oddball	Amplitude reduction in visual task for medicated participants.	No latency changes.	Reduced in auditory task only for drug free participants only.	Delayed in visual task only for drug free participants only.
Totals	43 studies, 1411 participants	Widely heterogenic	A range of task complexity	21 studies in total, 11 showing no differences, 8 showing amplitude reductions, 3 showing increases.	21 studies in total. 16 showing no differences, 5 showing delays.	38 studies in total. 18 studies showing central amplitude reductions. 3 showing right hemisphere changes only, 4 showing reduction in a sub-sample of MDD only. 13 showing no change.	31 studies in total. 11 studies showing latency delays, 2 showing reduction in a sub-sample only. 18 showing no change.
MDD group only (comparisons of within group differences):							
Hansenne and Ansseau (1999)	45	Inpatients, drug free. Tested for serotonin sensitivity.	Simple two tone oddball	Not analysed		Negatively correlated with serotonin sensitivity	Not related to serotonin sensitivity
Hansenne et al. (1995)	20	Inpatients, drug free. Tested for dopamine and noradrenergic function	Simple two tone oddball	Not analysed		Positively correlated with dopamine function, no relationship with noradrenergic function	No relationship to dopamine or noradrenergic function
Hansenne et al. (2000)	54	Medication free.	Simple two tone oddball. Correlations between ERPs and personality.	Correlated with persistence.	Weakly correlated with persistence and harm avoidance.	No correlations	Correlated with self directedness, and negatively with novelty seeking.
Bruder et al. (2002)	76	Split into MDD, MDD /anxiety, and anxiety alone group.	Two stimulus oddball with notes or syllables	Not analysed		Early P3 increased in anxiety, late P3 increased in comorbid anxiety/MDD.	Not analysed

Authors	MDD (N)	Sample Characteristics	Task Complexity	Sig. N2 Differences?		Sig. P3 Differences?	
				Amplitude	Latency	Amplitude	Latency
Chen et al. (2002)	105	Compared different dopamine expression genes.	Simple two tone oddball	Not analysed		No differences between different dopamine alleles within the MDD group	
Jandl et al. (2010)	50	Divided into hard, soft and no suicide attempt groups	Three stimulus auditory oddball	Not analysed		P3a habituated faster (larger reduction) in suicide attempters.	Not analysed
Schlegel et al. (1991)	36	Some medicated. measured psychomotor retardation.	Simple two tone oddball	Not analysed		Not analysed	HAM-D did not correlate with latency, but retardation measures did
Santosh et al. (1994)	40	20 with psychotic features.	Simple two tone oddball	Not analysed		Reduced in psychotic features group.	Not analysed

Non-Oddball Tasks

A number of other tasks have been used to compare the electrophysiological markers of cognitive and emotional processes between MDD and control groups. The following sections review these tasks, grouping them by the process they attempt to measure, in order to gain a more comprehensive understanding of how these processes are affected by MDD. A summary of these studies can be viewed in Table 5 (page 112).

Inhibition Processes – The Go/Nogo and Stroop

The Go/Nogo Task

Another task that is commonly used to measure ERPs is the Go/Nogo task. The Go/Nogo task presents frequent stimuli that require a response, dispersed with infrequent "Nogo" trials, which require responses to be inhibited. Usually the Go trials are presented more frequently, which sets up a pre-potent response habit, so that Nogo trials are demanding on response inhibition processes. The fronto-central Nogo N2 is generated in this task at a similar latency to that found in the oddball N2. It is thought to reflect either response inhibition or conflict monitoring (Azizian et al., 2006; Falkenstein et al., 1999; Geczy et al., 1999; Nieuwenhuis et al., 2003). A frontal 'Nogo P3' is also generated, which has also been proposed to relate to response inhibition by some authors (Geczy et al., 1999; Kropotov et al., 2011; Pfefferbaum et al., 1985), but this is contested by others (Falkenstein et al., 1999; Kopp et al., 1996). Some studies also analyse the posterior P3, which represents similar processes to the oddball P3b - stimulus categorization, meaning extracted from stimuli, and memory updating (Bokura et al., 2001). Go/Nogo study results are exceedingly

variable. This is likely due to sample heterogeneity, as studies focus on the elderly or remitted participants as often as typical MDD.

The Nogo N2

Studies focusing on the Nogo N2 typical MDD have found no between group differences (Baribeau-Braun and Lesévre, 1983; Kaiser et al., 2003; Knott and Lapierre, 1991). However, research into MDD participants in remission has indicated enhanced Nogo N2 amplitudes in MDD (Ruchsow et al., 2008a). However, this enhancement was shown for both Go and Nogo trials, which suggests it was not related to response inhibition. While controls generally show an enhanced Nogo N2 amplitude compared to the Go N2, an elderly group with MDD showed no differentiation (Katz et al., 2010). Their results also indicated that although controls showed an ACC N2 source in controls, this was not the case for MDD, suggesting impaired ACC activity. In direct contradiction, enhanced Nogo N2 (but not Go N2) has also been found in elderly participants with MDD (Zhang et al., 2007). This was found to positively correlate with Hamilton rating scale for depression (HAM-D) scores. As well as the fronto-central Nogo N2, one study has focused on the concurrent temporal positivity as a measure of response inhibition processing. This study found an amplitude reduction for Nogo trials, but an increase for Go trials in the MDD group (Kaiser et al., 2003).

The Nogo P3 and P3b

With regards to the frontal Nogo P3 amplitude, studies in older or partially remitted groups have shown reductions (Ruchsow et al., 2008a; Zhang et al., 2007). One study that found P3 reductions and delays for both rare Go and Nogo trials, suggesting the mechanism for these changes may be similar to the oddball paradigm rather than specific to response inhibition (Baribeau-Braun and Lesévre, 1983). However, Ruchsow et al. (2008a) and Zhang

et al. (2007) analysed the difference between ERPs in response to Go trials and Nogo trials by subtracting Go trial ERP values from Nogo trial ERPs, giving the N2d and P3d. Using this method of analysis, the P3d was smaller in the MDD group, suggesting that although control participants showed an increase in P3 when inhibiting responses, MDD participants did not. The authors suggest these results show response inhibition processing deficits in MDD. Again, the results of some studies show no P3 amplitude differences (Kaiser et al., 2003; Knott and Lapierre, 1991). Fewer studies examine latency in the Go/Nogo task, and in those studies no latency differences between the groups have been discovered for either ERP.

Between Study Variability

One task related variable that differs between studies is the Nogo trial frequency. Fewer Nogo trials makes response inhibition more difficult (as more of a prepotent response tendency is elicited), and this increased difficulty may differentially affect the MDD and control groups. The studies using a 50/50 Go/Nogo ratio vary in result, so it appears this ratio does not consistently differentiate the groups (Katz et al., 2010; Knott and Lapierre, 1991; Ruchsow et al., 2008a; Zhang et al., 2007). Similarly, of the two studies using the more challenging 80/20 Go/Nogo ratio, neither showed Nogo N2 differences (Baribeau-Braun and Lesévre, 1983; Kaiser et al., 2003). Two of the three studies that analysed P3 amplitude showed a reduction however, suggesting that the Nogo P3 may be affected even with equal Go/Nogo ratios (Ruchsow et al., 2008a; Zhang et al., 2007).

Another variable is the modality of stimulus presentation. The three studies that showed altered fronto-central N2 all used visual stimuli (Katz et al., 2010; Ruchsow et al., 2008a; Zhang et al., 2007). The three studies that did not show differences used auditory stimuli (Baribeau-Braun and Lesévre, 1983; Kaiser et al., 2003; Knott and Lapierre, 1991).

However, the direction of N2 amplitude change was not consistent between the visual Go/Nogo studies, so little can be drawn from this information. Studies showing P3 reductions were not consistent in modality of stimulus presentation.

Only one study used unmedicated participants (Knott and Lapierre, 1991), so medication effects on group differences cannot be assessed. The influence of severity is also unclear. Zhang et al. (2007) found P3 amplitudes negatively correlated with HAM-D score within the MDD group. However between study differences suggest this is less clear - Ruchsow et al. (2008a) found P3 reductions in participants during remission, whereas (Kaiser et al. (2003) found no differences in those with current depression.

Overall, there are too few studies with too much sample heterogeneity using the Go/Nogo task alone to adequately assess response inhibition ERPs. It seems unlikely that the Nogo N2 amplitude is consistently affected by MDD. The P3 amplitude may be reduced, although it is unclear whether this is related to response inhibition, or similar processes to those found in the oddball task.

The Stroop Task

Another measure of inhibition is the Stroop task. This task is a measure of cognitive inhibition rather than response inhibition, requiring participants to inhibit conflicting information rather than a conflicting response. The most common example of this is to have participants respond as to the colour of the ink a word is written in, while the word gives the name of another colour. Only two studies have looked at ERPs using the Stroop task. Vanderhasselt and De Raedt (2009) studied a small sample of remitted MDD participants, with either up to two or more than three previous episodes. They found no differences in

the N2. Although the healthy controls showed larger N450 amplitude for infrequent colour word incongruent trials, both MDD groups showed no difference between trials. In a more complicated approach, Stilton et al. (2011) used source localisation in combination with fMRI to compare electrophysiological activity generated in the left DLPFC and dorsal ACC between high depression and low depression scoring unmedicated undergraduates. Using regression analyses they found the activity association between these two areas was less well coupled in MDD, with medium effect size, supporting an impaired neural network model of depression. Depressed individuals who showed low left DLPFC activity exhibited a relationship between dorsal ACC activity and stroop performance, but in individuals with high left DLPFC activity this relationship was lost – suggesting a neural compensatory strategy can overcome dorsal ACC impairments.

The fact that these studies found differences between controls and dysthymic groups in Stroop task related EEG activity suggests differences may be more apparent in cognitive inhibition tasks (such as the Stroop) rather than response inhibition (evidenced by the inconsistent Go/Nogo task results).

Table 5. Inhibition processing studies

Authors	MDD (N)	Sample Characteristics	Task	Findings
Ruchsow et al. (2008)	20	Majority medicated. Examined during partial remission.	Hybrid Flanker Go/No-go task	No-go P3 amplitude reduced in central electrodes for MDD group, N2 amplitude enhanced in MDD for both go and no-go trials.
Stilton et al. (2011)	34	Lifetime history of MDD only. Undergraduates.	Colour word stroop task. Used source analysis.	Current depression score on Mood and Anxiety Symptom Questionnaire interacted with left DLPFC activity 300-440ms post incongruent stimuli to predict dorsal ACC activity at 520-680ms at low depression scores, but not high depression scores.
Vanderhasselt et al. (2009)	23	Females only, examined in remission. Divided into >2 episodes and <3 episodes.	Stroop task. Varied proportion of congruent and incongruent trials.	No differences in N2 between groups. Both MDD groups showed no difference between congruent and incongruent trials for N450, while control group showed larger left frontal N450 in high conflict incongruent condition.
Katz et al. (2010)	11	Geriatric MDD sample	Complex Go/Nogo task. Presented red and purple letter number pairs. If red, respond if letter was a vowel, if purple, respond if number was even.	Healthy controls showed larger Nogo N2 than Go N2, while MDD group did not. Control group's N2 source localised to ACC, but MDD group's did not.
Zhang et al. (2007)	20	Older sample, 60+	Go/Nogo with shapes as stimuli	Enhanced N2, reduced P3.
Kaiser et al. (2003)	23	Inpatients, all medicated	Go/Nogo with tones as stimuli	Reduced fronto-temporal positivity in same window as N2. No fronto-central N2 or P3 changes.
Thier et al. (1986)	11	Medicated	Go/Nogo CNV task	MDD group showed increased PINV, enhanced P3, but no changes in CNV.
Baribeau-Braun et al. (1993)	6	Medicated. All showed psychomotor retardation.	Go/Nogo with frequency of each type varied between 20, 50, and 80%.	Reduced frontal P3 to rare events (both Go and Nogo trials). No N2 changes.
Knott et al. (1991)	14	Medication free	Go/Nogo task with forewarned trials	No differences in N2 or P3

Response Preparation ERPs

Tasks that forewarn participants to prepare to make a response generally present two stimuli, the first a warning (referred to as S1) that the second imperative to respond (referred to as S2) is approaching. These studies measure the contingent negative variation (CNV) preceding S2, which is composed of two sections – an early frontal and a later centro-parietal negativity. They also measure the post-imperative negative variation (PINV) - a prolonged late frontal negativity 800ms – 3500ms following S2. Figure 2 gives an example of how the CNV and PINV waves are shaped. The CNV is thought to represent cognitive processes related to temporal anticipation of an upcoming stimulus, a process which accelerates response times (Leuthold et al., 2004; Macar and Vidal, 2004). The early CNV activity is thought to represent orientation to and processing of the S1, while the later CNV activity reflects anticipation of S2 and motor preparation (Lamarche et al., 1995). Both the early and late CNV are likely to be modulated by attention, and unlike the P3b, seem to represent increased cortical excitability (Rockstroh et al., 1993). Intracranial recordings suggest that CNV like activity is generated in the frontal, temporal, and motor regions of the brain (Lamarche et al., 1995).

In healthy controls, the PINV amplitude is enhanced by stress and unpredictability or lack of control over the outcome of the response contingency, as well as uncertainty about the correct response (Diener et al., 2009b; Kathmann et al., 1990; Klein et al., 1996). As a result, the PINV is thought to reflect evaluation of behaviour-consequence contingencies (Elbert et al., 1982).

The CNV in MDD

Studies examining response preparation ERPs have found reduced CNV in MDD (Claverie et al., 1984; Giedke et al., 1980; Hansenne et al., 1996; Heimberg et al., 1999; Nakamura et al., 1982; Pierson et al., 1996). Reduced CNV amplitude was also found in individuals who have attempted suicide across a variety of disorders including MDD, possibly indicating reduced CNV amplitude is a marker of severely depressed mood (Ashton et al., 1994). CNV amplitude was found to negatively correlate with MADRS score in this sample, and strong negative correlations were found by Papart et al. (1990) between CNV amplitude and both the MADRS and HAM-D. When divided into groups by severity, those with more severe depression scores show even smaller CNV than those with moderate scores (Ashton et al., 1988; Giedke et al., 1980). However, these results are not consistent, with some studies showing no CNV differences between MDD and control groups (Elton, 1984; Knott and Lapierre, 1987, 1991; Thier et al., 1986), or only a trend (Elton, 1984), and no correlation with severity (Knott and Lapierre, 1987). This might be due to a small sample ($N<15$) for Thier et al. (1986) and Knott and Lapierre (1991). One study has even shown an increase in CNV amplitude in MDD (Knott et al., 1991). However, this study measured peak midpoint CNV amplitude, rather than mean amplitude of CNV window as per other studies, and when mean amplitudes were compared no between group differences were found. The result was inconsistent even within the study, only becoming apparent in one of two replications.

The studies have a mix of medicated on non-medicated participants, with no clear pattern related to differences between groups. More severe MDD may decrease CNV amplitude further than moderate, but again this does not seem to explain the different

findings between studies. The CNV task has been combined with the Go/Nogo task to look at impulsiveness in different sub-types of MDD. Anxious-agitated participants showed a larger CNV in Nogo trials than those with blunted affect, suggesting erroneous response preparation due to impulsivity (Pierson et al., 1994). Similarly, Pierson et al. (1996) found CNV amplitude reduced even further in patients with blunted affect. This suggests anxiety and blunted affect have different modulating effects, which may confound the results in MDD groups.

Large CNV amplitude variation is found in MDD groups (Timsit-Berthier et al., 1987), and longitudinal research shows the ERP may not be consistent over time (Elton, 1984). Similar to the oddball ERPs, reductions in CNV amplitude are not specific to MDD – the reductions are even larger in schizophrenia groups (Heimberg et al., 1999). This suggests CNV alterations may be due to general pathology rather than specific to MDD, perhaps reflecting impaired attention (and thus impaired cortical excitability) (Claverie et al., 1984; Heimberg et al., 1999; Rockstroh et al., 1993).

The PINV in MDD

Generally an increased PINV is found in MDD groups (Boltz and Giedke, 1981; Diener et al., 2009a; Hansenne et al., 1996; Knott et al., 1991; Thier et al., 1986). Diener et al. (2009a) measured PINV in a task that warned MDD or control participants about an avoidable or unavoidable mild electrical shock. MDD participants displayed larger PINV when aversive stimuli could not be controlled, suggesting more frontal processing during loss of control. This was related to rumination scores, suggesting that increased PINV may indicate helpless ruminations. Boltz and Giedke (1981) obtained a similar result using loud

sharp tones as aversive stimuli. They suggest the PINV is related to coping mechanisms for external stimuli, indicating that MDD participants find negative events more difficult.

Response Preparation ERP Summary

It seems uncertain at this stage whether response preparation related ERPs are altered in MDD. In general, it appears CNV amplitude may be reduced in MDD. This may reflect impaired anticipation of stimuli in these groups. However, there is considerable variation between studies. Heterogeneity in medication and severity do not seem to explain the differences in results. An increased PINV amplitude seems to be a more consistent result, but this ERP has not been studied enough to draw strong conclusions. PINV may be related to response or contingency uncertainty, with the higher amplitudes found in depression suggesting increased uncertainty. A summary of response preparation ERP research in MDD can be viewed in Table 6.

Table 6. Response preparation studies

Authors	MDD (N)	Sample Characteristics	Task	Findings
Hansenne et al. (1996)	20	Divided into 10 with suicide attempt history and 10 without	Simple CNV task	Reduced CNV in overall MDD group. Increased PINV in suicide attempt history group.
Thier et al. (1986)	11	Medicated	Go/Nogo CNV task	MDD group showed increased PINV, enhanced P3, but no changes in CNV.
Timsit-Berthier et al. (1987)	61	Majority female. Inpatients tested at admission and upon recovery. No control group.	CNV paradigm with S1 tone and S2 light flashes.	CNV amplitude decreased in recovery, and P3 amplitude increased.
Diener et al. (2009)	26	Not medicated.	CNV paradigm varying degree of control over mild aversive electric shock	MDD showed larger frontal PINV than controls, particularly during the loss of control and restitution of control conditions. This correlated with rumination within the MDD group.
Bolz et al. (1981)	18	Medicated	CNV paradigm varying degree of control over mild aversive tone.	MDD group showed smaller CNV and larger PINV amplitude when aversive was difficult/impossible to control.
Nakamura et al. (1982)	13	Split into melancholic and non-melancholic	Standard CNV protocol with auditory tone as S1 and light flashes as S2. Had non-response and response conditions	MDD showed reduced CNV mean amplitude in response condition. No overall difference between melancholic and non-melancholic. Melancholic showed larger CNV recovery from non-response to response condition.
Heimberg et al. (1999)	34	All medicated. Also studied schizophrenia group.	CNV with 3 images as stimuli. If all 3 matched, response was required.	CNV was reduced in MDD group, and reduced even more in schizophrenia group. Smaller difference between response and non-response condition in both MDD and schizophrenia compared to controls.
Giedke et al. (1980)	18	Included 3 bipolar participants. Nine participants medication free.	Standard CNV task with tones for S1 and S2	CNV reduced in MDD group. CNV even smaller in severe depression than moderate depression.
Knott et al. (1991)	50	18 in one study, 32 in another.	CNV with button held down and released upon S2	Midpoint peak CNV amplitude enhanced in one MDD group only, but no overall CNV mean amplitude differences. PINV enhanced in MDD group.

Authors	MDD (N)	Sample Characteristics	Task	Findings
Ashton et al. (1994)	40	Drug overdose suicide attempters. 9 had diagnosis of MDD.	Standard CNV with tone for S1 and S2	CNV reduced and PINV enhanced in suicide attempters. Negatively correlated with MADRS score.
Papart et al. (1990)	59	Inpatients. MDD group only.	Standard CNV with tone for S1 and light for S2	CNV amplitude strongly negatively correlated with HAM-D and MADRS
Elton et al. (1984)	21	Measured on hospital admission and again at discharge	Standard CNV with tone for S1 and S2, and feedback if response was fast enough	No significant differences between MDD and controls. CNV amplitude not very stable over time in MDD group.
Pierson et al. (1994)	21	MDD group only, divided into anxious-agitation and blunted affect subtypes	Go/Nogo CNV with S1 signalling whether response required or not	Anxious-agitated group showed larger CNV in Nogo condition than blunted affect group.
Pierson et al. (1996)	24	Split into anxious agitation and blunted affect subtypes.	Forewarned decision making task	Reduced CNV amplitude in MDD, particularly in patients with blunted affect. Reduced N2b to P3a amplitude, and shorter and earlier P3b in anxious patients
Ashton et al. (1988)	32	MDD group only, divided into severe and moderate groups based on HAM-D	Standard CNV with tones as S1 and S2	Severe group showed lower amplitude CNV than moderate group
Knott et al. (1987)	21	All females, half were inpatients.	Standard CNV with tone for S1 and light for S2	No between group differences in CNV peak amplitude or mean amplitude
Gorsel (1984)	11	“Neurotic” subtype. Inpatients.	CNV style task, but only analysed P3 in response to S1.	No between group differences, and no differences in habituation to repeated trials.
Claverie et al. (1984)	16	Half melancholic, half “neurotic” subtype	Standard CNV protocol with auditory clicks as S1 and light flashes as S2	Reduced CNV amplitude across whole window of CNV in MDD.
Pierson et al. (1996)	24	Inpatients. Divided into anxious agitation and blunted affect groups.	Reaction task. Respond to direction of arrow, or reverse direction of arrow if signalled.	MDD showed reduced CNV amplitude.

Error Processing

Error processing ERPs can be assessed by a range of tasks, as long as they are sufficiently difficult to elicit errors, and that participants are aware of having made an error. Post-error ERPs are the error related negativity (ERN) and error positivity (Pe). Figure 3 depicts the typical shape of these deflections. The ERN occurs between 50ms and 150ms following the response, and is thought to reflect error detection or response evaluation (Falkenstein et al., 2000; Vidal et al., 2000). It is generated by theta activity in the ACC (Cavanagh et al., 2012). The correct response negativity (CRN) occurs in the same window, but is smaller in amplitude, and reflects the same processes. The Pe is found in posterior electrodes, and thought to reflect conscious error awareness or affective appraisal of the error (Falkenstein et al., 2000). Source localisation also indicates that the Pe may be generated by the ACC (van Veen and Carter, 2002b). In addition to these post-error ERPs, feedback negativity (FN) can also be measured. This occurs approximately 300ms after feedback, and is larger in amplitude for negative feedback. It is thought to reflect evaluation of the outcome of actions (Hajcak et al., 2006), and is also thought to be generated by the ACC (van Veen and Carter, 2002a). A summary of the research focusing on error processing in MDD can be viewed in Table 7 (page 123).

The ERN

Some research has found increased ERN amplitude in an MDD group (Chiu and Deldin, 2007; Holmes and Pizzagalli, 2010). This is particularly the case when incorrect trials are punished by a monetary loss, suggesting sensitivity to negative feedback (Chiu and Deldin, 2007). When combined with low resolution brain electromagnetic tomograph

(LORETA) source localisation, the MDD group showed enhanced ERN, due to increased rostral ACC activity 80ms post response (Holmes and Pizzagalli, 2008).

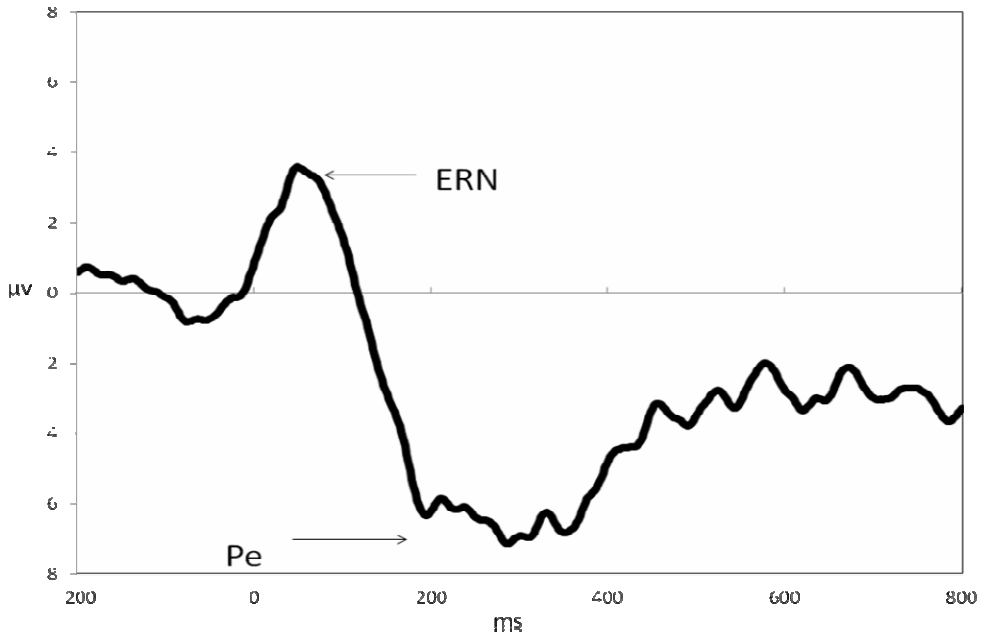


Figure 3. A stylised waveform following a response error, depicting the ERN and Pe deflections.

Other research has found no differences in amplitude, but a delay in latency which correlated with psychomotor retardation (Schrijvers et al., 2008). Yet other research has found no changes in the ERN (Schrijvers et al., 2009), although they did find that increases in ERN amplitude correlated with symptom recovery (which appears in opposition to other results). Olvet et al. (2010) also found no differences in ERN amplitude, but did find that those with more severe MDD showed larger CRN amplitudes. ERN amplitude is not found to correlate with depression severity (Holmes and Pizzagalli, 2010). Schrijvers et al. (2009) and Olvet et al. (2010) hypothesize the difference in ERN findings between studies may be due

to severity effects – groups with moderate MDD show anxiety, which might increase ERN amplitude, while groups with severe MDD may show reduced ERN due to apathy and anhedonia. The former statement appears to be true, with Chiu and Deldin (2007), Holmes and Pizzagalli (2010), and Holmes and Pizzagalli (2008) studying moderate MDD and finding ERN increases. More severe MDD may reduce ERN amplitude back to similar levels as controls, as Schrijvers et al. (2009), Schrijvers et al.(2008) and Olvet et al. (2010) sampled more severe inpatients, and found no difference in ERN amplitude compared to controls. This may reflect a non-linear relationship between severity and ERN amplitude, perhaps related to altering anxiety and anhedonia levels (Olvet et al., 2010; Schrijvers et al., 2009). Alternatively it is perhaps due to increased error sensitivity in MDD which is reflected by increased ERN amplitudes in moderate cases, but disguised by impairments in neural synchrony as cases become more severe.

Support for this second idea may come from a network approach to analysing error related activity, which suggests MDD groups show impaired functional connectivity. In healthy controls, rostral ACC and medial pre-frontal cortex (PFC) activity at 80ms post error predicts left DLPFC activity at 472ms. However, this was not the case for the MDD group (Holmes and Pizzagalli, 2008). These results suggest the increased ERN sometimes found in MDD groups may be a mechanism compensating for the lack of functional coupling. Individuals in the MDD group who showed high left DLPFC activity showed more adaptive behaviour post error than those with lower activity, suggesting the functional coupling is important for learning from mistakes. Also using a source localisation approach, Pizzagalli et al. (2006) compared gamma oscillations generated by the ACC during a resting period to the ability to modify behaviour after making an error in a task. Comparing university students

with moderate to high BDI scores to those with low scores, they found that in the low BDI score group, those with high gamma activity in the ACC showed better post-error performance, while the high BDI group did not show this pattern. Similar to Holmes and Pizzagalli (2008) they suggest that this may be a result of impaired connectivity between the ACC and DLPFC in those with negative affect – so even if the ACC was active it is not able to influence the DLPFC to better control behaviour. This aligns with fMRI research, which also suggests that error processing activates the ACC (Pizzagalli et al., 2006).

The Pe

Research focusing on the Pe has found a reduction in amplitude in MDD (Holmes and Pizzagalli, 2010; Schrijvers et al., 2008; Schrijvers et al., 2009). Other research has found less difference between correct and incorrect trial amplitude in MDD groups, suggesting individuals with MDD are impaired in their ability to differentiate correct from incorrect responses (Olvet et al., 2010). Holmes and Pizzagalli (2010) found Pe amplitude was reduced only when participants were to receive a monetary reward – in other words when the stakes were raised. This was related to anxiety, but not anhedonia. Their results also indicated the lower Pe correlated with BDI measures of severity. Two studies analysing the Pe have shown no differences between groups (Chiu and Deldin, 2007; Holmes and Pizzagalli, 2008). The variation in results from different studies may be related to benzodiazepine medication, as when an MDD group was divided on that basis, only medicated participants showed the reduction (Schrijvers et al., 2008). However, studies have shown Pe reductions using unmedicated MDD groups (Holmes and Pizzagalli, 2010; Olvet et al., 2010), so while medication effect is a possible explanation for the variation in results, it is not fully supported.

Table 7. Error related processing studies

Authors	MDD (N)	Sample Characteristics	Task	Findings
Olvet et al. (2010)	22	Community sample, not medicated.	Ericksen flanker task with arrows as stimuli. Focused on error related ERPs.	MDD group showed less difference between correct and incorrect Pe amplitude. In depression group, CRN amplitude correlated with depression severity.
Schrijvers et al. (2010)	39	Inpatients, MDD group only. Medicated, some with benzodiazepines.	Ericksen flanker task with letters as stimuli. Focused on error related ERPs.	ERN negatively correlated with 'doubt about actions' subscale. Pe correlated with 'perfectionism' and 'concern about mistakes'. No relationship between ERPs and HAM-D score.
Schrijvers et al. (2009)	15	At episode onset and after 7 weeks of treatment. Mostly medicated including benzodiazepines.	Ericksen flanker task with letters as stimuli. Focused on error related ERPs.	No between group ERN differences. Pe amplitude reduced in MDD group. No differences between episode onset and post treatment.
Schrijvers et al. (2008)	26	Medicated, some with benzodiazepines.	Ericksen flanker task with letters as stimuli. Focused on error related ERPs.	MDD showed reduced Pe amplitude, but no differences in ERN amplitude. ERN reduced in benzodiazepine medicated patients only. ERN correlated with psychomotor slowing measure.
Ruchsow et al. (2004)	16	Medicated. Half with first episode, half with multiple episodes.	Ericksen flanker task with letters as stimuli, and feedback about monetary reward. Analysed error related ERPs.	No difference in overall ERN amplitude between MDD and controls. After two errors, healthy controls showed larger ERN, but MDD group showed no change.
Ruchsow et al. (2006)	10	Excluded comorbid anxiety. Analysed during remission. Medicated.	Ericksen flanker task with letters as stimuli, and monetary reward. Analysed error related ERPs.	No difference in overall ERN amplitude between MDD and controls. After two errors, healthy controls showed larger ERN, but MDD group showed no change.
Chiu et al. (2007)	18	Six medicated.	Ericksen flanker task with arrows as stimuli and monetary reward and punishment trials.	MDD showed larger ERN amplitude in all reward conditions, but particularly in the punishment condition. No difference in Pe.
Santesso et al. (2008)	12	Remitted MDD. No medication.	Decision making task. Gave non-contingent monetary punishment feedback.	Feedback ERN larger for remitted MDD. Correlated with BDI scores. No difference in LORETA source localisation of signal between remitted MDD and controls.

Authors	MDD (N)	Sample Characteristics	Task	Findings
Pizzagalli et al. (2006)	17	Compared undergraduates with low vs high BDI score.	Ericksen flanker task with letters, measured gamma and theta activity pre-task.	No theta differences between groups. High BDI group showed higher posterior cingulated gamma, but lower ACC gamma, which predicted behavioural adjustment following errors.
Holmes et al. (2010)	18	Not medicated	Stroop task with monetary reward for some trials. Focused on error related ERPs	MDD showed larger ERN but smaller Pe than controls. BDI negatively correlated with Pe. No interaction with reward.
Holmes et al. (2008)	20	Not medicated	Stroop task with monetary reward for some trials. Focused on error related ERPs and used source localisation	No Pe differences between groups. MDD showed larger ERN, and more rostral ACC activity in this window (80ms post response). MDD group showed reduced rostral ACC and medial PFC connectivity with left DLPFC.
Tucker et al. (2003)	20	Community sample. Medication status not reported.	Decision reaction task with feedback. Measured MFN in response to negative feedback.	MDD show greater MFN to feedback, and bad feedback increased this amplitude more in MDD than controls. Localised to dorsal ACC. Interaction with severity where moderate showed larger MFN while severe showed smaller.
Foti, Hajcak (2009)	42	Undergraduates split into groups based on median point on the depression anxiety stress scale.	Gambling task with feedback on monetary reward. Analysed ERPs to feedback.	Difference in feedback negativity and P3 between reward and non-reward correlated negatively with depression severity.

Feedback Negativity (FN)

As well as response locked ERPs, some research has compared electrophysiological responses to feedback. These studies provide feedback as to the accuracy of responses, and compare a feedback stimulus locked window between groups. Some studies combine this feedback with varied reward/punishment contingencies to also assess sensitivity to tangible consequence.

Tucker et al. (2003) analysed feedback negativity, and found that MDD showed larger medial frontal negativity (MFN) compared to controls. The enhancement divergence from controls was also larger for more negative feedback, suggesting sensitivity to negative feedback. However, when divided by severity, this pattern only held for the moderately depressed – those with severe depression actually showed smaller MFN than controls. In support of the idea that individuals with non-severe MDD show amplitude increases, remitted MDD participants have also been found to show enhanced FN (Santesso et al., 2008). This non-linear relationship is analogous to the apparent relationship between ERN amplitude and severity, and the authors suggest the same explanation - that the enlarged MFN in individuals with moderate depression might reflect anxious arousal, while those with more severe depression have a blunted MFN due to apathy. Again though, an alternative explanation might be that while those with moderate depression are more sensitive to negative valences (so show larger electrophysiological response to these), individuals with severe depression have suffered more neural function impairment, and so cannot synchronise neural populations as well, resulting in reduced amplitude ERPs. However, not all research has found amplitude enhancements in FN (Ruchsow et al., 2006; Ruchsow et al., 2004).

Because feedback can be paired with reward information, FN can also evaluate sensitivity to tangible consequences. Foti and Hajcak (2009) used this idea to examine potential anhedonia in undergraduates with high depression scores. They found that smaller FN amplitude differences between reward and non-reward trials in those with higher depression scores. This perhaps suggests that individuals with MDD show an insensitivity to reward information.

Confounds to Interpretation

One issue with the interpretation of error processing ERPs is that they may be measuring the relationship between a factor which modulates both depression and error processing, rather than a direct relationship between the two. Research indicates that ERN and Pe amplitudes in MDD are not related to HAM-D measured depression severity (Compton et al., 2008; Schrijvers et al., 2010), but rather to doubt about actions and concern over mistakes (Schrijvers et al., 2010), factors potentially related to anxiety (commonly found as a comorbidity with MDD).

Summary of Error Processing ERPs

Because a number of different tasks show altered error related ERPs, it seems this is a process altered in MDD in general (rather than being related to only specific task types). Additionally, enhanced amplitude has been found for both the ERN following errors and for the FN when participants are given feedback about errors. This suggests the enhancements may be related to error processing in general. This may only be the case in moderate MDD, and may be related to error anxiety rather than MDD itself. On the other hand, Pe reductions may only become apparent in more severe MDD, and may reflect reduced

awareness of errors. The error processing differences in MDD may be due to impaired ACC function, resulting in impaired functional connectivity between the ACC and DLPFC, which shows symmetry with the fMRI research.

Language processing

A summary of research into language processing using EEG in MDD can be viewed in Table 8 (page 131). Potential difficulties in language processing in patients with MDD are of relevance for a number of reasons, not the least of which is that they effect participation in psychotherapies (Iakimova et al., 2009). The N400 ERP is the most commonly studied EEG marker of language processing. As the name suggests, it is a negative deflection that peaks about 400ms after the end of a sentence. The N400 amplitude is enhanced when the final word of the sentence is semantically incongruent, thus representing the 'second take' process where an unexpected word that cannot be integrated with the preceding context is re-evaluated (Kutas and Federmeier, 2000; Kutas and Hillyard, 1980).

Few studies have used the N400 to look at language processing in MDD. Deldin et al. (2006) reported the results of three independent studies, including a total of almost 50 MDD participants, none of which demonstrated a difference between control and MDD groups. They suggest that this indicates MDD does not show an all-encompassing impairment in processing, but that impairments are specific to certain functions, and neutral language is not one of those functions. Similar non-significant results with regards to the N400 were obtained in a smaller study with patients in remission (Ruchsow et al., 2008b). These researchers also extended Deldin et al.'s (2006) work, by assessing ERP latencies, and ERPs to syntax violations as well as semantic violations. This involves eliminating one word from the sentence, preventing it from making sense. Typically when this is done control

groups show an increased P600 (thought to be related to syntactical integration). However, the MDD group did not show the increase, suggesting impaired syntactical (but not semantic) processing. However, the authors mention that the P3 may not differ from the P600 – so their results may reflect response to a "syntactic oddball".

Another small inpatient study by Iakimova et al. (2009) showed delayed N400 as well as a delayed late positive component (found in the same time window as the P600) to incongruent semantic sentences. The differences between Iakimova et al. (2009) and Ruchsow et al. (2008b) may be due to severity – although both studies used inpatients, Iakimova's showed more severe HAM-D scores.

Summary

Although there are too few studies focusing on language processing ERPs in MDD to properly assess the matter, it seems unlikely there are neutral language related ERP differences compared to healthy controls. Additionally, because language is a higher order cognitive process, any alterations detected may reflect disrupted lower order processes, for example attention, rather than specific language impairments.

Memory Processing

A summary of research examining EEG measures of memory processing can be viewed in Table 8 (page 131). Despite the fact that memory complaints and impaired memory test results are common in MDD (Veiel, 1997), very few studies have used EEG to look at altered memory processing in MDD (independently of emotion processing). The studies that have examined this issue have focused on a variety of different ERP markers of memory, and have shown a variety of different results. Firstly, a lack of right hemisphere P3

amplitude advantage (in contrast to controls who show a right hemisphere advantage in line with research that indicates this hemisphere is specialised for processing pitch) in a memory for tones task (Bruder et al., 1995). Other research indicates a reduction in both N270 and P3b amplitudes in a task requiring participants to decide whether two sequential visual dot matrices differed, possibly representing impaired conflict monitoring, due to reduced ACC activity (Mao et al., 2005).

Some researchers have compared memory processes with the commonly used Sternberg task. The Sternberg task presents a memory set for participants to retain, followed by a retention period, followed by a single item. Participants are instructed to respond as to whether or not that single item was present in the original memory set. Pelosi et al. (2000) found reduced late positivity beginning 375ms after a probe stimulus in this task. This showed far greater difference than those found in memory performance, suggesting memory ERPs may be a more sensitive than behavioural measures at detecting impairment in MDD. Segrave et al. (2010) also used a Sternberg working memory task, but instead of ERPs they analysed parieto-occipital upper alpha activity in females with MDD. Their MDD group showed more left hemisphere alpha during the retention period. Because alpha is thought to reflect inhibition of non-relevant regions, they suggest this indicates MDD individuals required more inhibition, perhaps of ruminations, in order to exhibit similar performance to the controls. Lastly, Dietrich et al. (2000) used an old/new task, which presents a sequence of stimuli with some repetitions, and compares ERPs between the first and second presentation of a stimulus. These old/new ERPs show more positivity for repeated words beginning 250ms post stimulus. This is the result of alterations to the N400

and P3b in conscious recollection of repeated words. The results of their study indicate a large reduction in the old/new effect in the MDD group.

While there are very few studies that have looked at EEG measures of neural activity changes in memory tasks, all that have showed differences between MDD and control groups. These differences are shown across encoding, retention, and recall processes. This aligns with subjective reports of memory and concentration complaints, and cognitive testing research that suggests memory performance is reduced (Veiel, 1997). However, replication of each different type of analysis should be conducted before strong conclusions are drawn.

Emotion Processing

Table 9 (page 143) summarises EEG research into emotional processing in MDD. Fitzgerald et al. (2008) suggested that alterations in neural function MDD are complex, and not likely to be amenable to simple models. Differences are more likely to be revealed in emotional processing tasks. This is potentially a result of impaired cognitive control of attention, as a consequence of dorsal cognitive and ventral emotional region interactions (Drevets, 2000; Mayberg, 1997). Using this rationale, a number of studies have used ERPs to look at how emotional processing is altered in depression. The majority of these studies have looked at direct electrophysiological responses to simple presentations of emotionally valanced stimuli. These studies are reviewed first. A smaller number of studies have looked at how emotional content influences memory processes, and these are reviewed second.

Table 8 – Memory and Language processing studies

Authors	MDD (N)	Sample Characteristics	Task	Findings
Language Processing Studies				
Ruchsow et al. (2008)	14	Inpatients, medicated, tested during remission.	Sequentially presented words to form sentences. Presented functional sentences, semantic mismatches, or syntactic mismatches.	No differences in N400 for semantic mismatches, or left anterior negativity for syntactic mismatches. Controls showed larger P600 at parietal electrodes for syntactically incorrect sentences compared to correct sentences. MDD did not show this differentiation.
Iakimova et al. (2009)	11	Female inpatients. Medicated.	Presented words sequentially to form sentences. Varied whether final word created semantic violation or not.	No reductions in N400 or late positive component. Delayed N400 and late positive component in MDD.
Deldin et al. (2006)	50	Mixture of inpatient and community sample. Medicated.	Presented one word at a time to form a sentence. Final word varied as to whether it was congruent or incongruent.	No differences between MDD and controls in N400 to incongruent word.
Memory Studies				
Pelosi et al. (2000)	11	Not medicated	Sternberg task with 1, 3, or 5 digit memory set presented in auditory and visual modalities. Analysed ERPs to correctly responded probe.	MDD group showed reduced SW positivity compared to controls, and less positivity as set size increased (opposite to controls).
Bruder et al. (1995)	44	Medication free	Matching to sample with different complex tones presented to each ear, and one probe. Respond if probe matched one ear's tone.	Although controls showed typical right hemisphere P3 advantage to processing complex tones, the MDD group showed no asymmetry.
Mao et al. (2005)	25	Not medicated.	Match to sample task with coloured dots as stimuli.	MDD group showed reduced N270, which was also delayed at parietal sites. P3 reduced in MDD but not delayed.
Segrave et al. (2010)	16	All females	Sternberg task with 8 letter memory set. Analysed Alpha ERD during retention	Increased upper alpha ERD in left posterior regions
Dietrich et al. (2000)	11	Inpatients. Not medicated.	Old/New task	Reduced Old/new effect in MDD participants.

Processing of Emotional Stimuli

Once again, the ERP comparisons between MDD and control groups are variable and inconsistent, with some contradictions. Some studies have presented emotional faces, others emotional words, and very few have presented emotional images of other types. Differences in these late emotional processing ERPs may be influenced by changes in early pre-awareness perceptual emotional processing, as earlier ERPs have been shown to be affected in MDD (Chang et al., 2010).

Some studies find amplitude enhancements to negative stimuli:

Studies using simple presentations in oddball or decision making type tasks have used both words and faces as stimuli, and found increases in P3b amplitudes in MDD groups, including both sub-clinical and typical depression groups (Ilardi et al., 2007; Nandrino et al., 2004; Nikendei et al., 2005). Similar results have been described when the slow wave negativity (SWN) is measured (Nikendei et al., 2005), and also when response related ERPs signal an upcoming negative word to which participants have to respond (Casement et al., 2008). Emotional Stroop tasks have also been used to analyse mood processing in MDD. These tasks present coloured emotional words, and require the emotional information to be ignored so participants can respond to the colour of the word. Using this task, Dai and Feng (2011) found that both remitted and currently depressed groups showed increased N450 amplitudes at lateral parietal electrodes to negatively valanced words. As well as enhanced ERPs to positive stimuli, research has indicated an increase duration and power in gamma activity occurs to negative words in MDD (Siegle et al., 2010). The reverse was found in participants with schizophrenia and depressed mood, indicating that the result is specific to MDD, not just low mood. Gamma activity is thought

to represent feature binding in perceptual research, so the authors suggest this represents increased stimulus elaboration for negative words in the MDD group – implying a potential physiological mechanism for rumination. This perhaps relates to research showing alpha alterations in MDD (Segrave et al., 2010), as alpha is thought to represent a top down inhibitory mechanism that disrupts gamma binding (Jensen and Mazaheri, 2010).

Emotional processing can also be positively and negatively primed. One way to prime emotion is to present two faces simultaneously expressing two different emotions, with the instruction to respond to one face. This positively primes the emotion that is responded to, while negatively priming the other. Dai et al. (2011) tested ERP differences using this paradigm, and found significantly larger P3 amplitudes to positively primed sad faces in an MDD group and a remitted MDD group. Controls on the other hand showed larger amplitude to negatively primed sad faces. Assuming P3 amplitude in negative priming reflects inhibitory processing, these results suggest MDD groups are not as effective at inhibiting sad emotional information, and using more resources to facilitate sad compared to happy information. In a similar methodology, but with words instead of faces, Yao et al. (2010) found that while controls showed delayed late positive component (LPC) latencies for negatively primed stimuli, MDD participants showed shorter LPC latencies for negatively primed negative emotional stimuli. This might suggest preferential processing for negative emotions that resists or "rebounds" from inhibitory processes.

Other studies have found reduced amplitudes to negative stimuli:

Williams et al. (2007) found MDD participants show reduced P3 to fearful facial expressions. This only occurred for consciously perceived faces – when a neutral face mask

followed a very briefly (10ms) presented fearful face no P3 differences were found. This contrasts with anxious individuals, who showed accelerated ERPs even with covert fear.

Similarly Blackburn et al. (1990) found their depressed group showed reduced P3 amplitude for negative words compared to positive words, while controls showed the reverse. Ratio of negative to positive P3 amplitude correlated with BDI and HAM-D score. Kayser et al. (2000) presented images of wounds (negative emotional valence) or healed skin (neutral valence) to the right and left visual field separately to determine whether disgust emotional processing is altered in MDD. They found that their MDD group failed to show the right hemisphere P3 amplitude bias typically found in controls processing emotional images. They also found that MDD patients showed no differences between negative and neutral images, while controls showed increased amplitude for the negative images. While these studies seem to contradict those that show increased amplitude for negative emotions, two of them compare emotions other than sadness (fear in the case of Williams et al. and disgust in the case of Kayser et al.), so may be assessing different aspects of emotional processing.

Some studies show reduced amplitudes to positive stimuli:

Cavanagh and Geisler (2006) tested a group of university students scoring in the mild depression or higher range on the BDI. They showed both lower P3 amplitude and delayed latency when viewing happy faces. P3 latency also positively correlated with BDI score. Similarly, Nandrino et al. (2004) found first episode patients showed reduced P3 amplitudes for when counting positive words compared with the control group, and Dai et al. (2011) found smaller P3 amplitudes to happy faces.

Some have shown enhancement of one ERP but reduction of another:

Inhibition tasks have been combined with emotional processing to see if the inhibition of emotional information is impaired in MDD. One example of this is the Go/Nogo task. In a sample of undergraduates, Krompinger and Simons (2009) found a group with high depression scores showed reduced N2 amplitude to negative stimuli across both trial types, and larger P3 amplitude to negative stimuli compared to positive stimuli. Those with low depression scores showed no differences between emotive stimuli. Yang et al. (2011) used emotionally positive, negative, and neutral written words as oddball stimuli and found the direct opposite patter. The MDD group showed larger N2 amplitudes to negative than positive words, with a smaller N2 to positive words compared to controls. The MDD groups P3 amplitude also trended towards a reduction in negative compared to positive words.

Yet others have found enlarged amplitudes to all emotions:

Rossignol et al. (2008) performed a three stimulus visual oddball with emotional faces as the novel distracter stimuli. They found that a group with subclinical depression and comorbid anxiety showed an *enlarged* P3a to both happy and sad distracters compared to healthy controls, and compared to a group with high anxiety scores but no depression. Similarly McNeely et al. (2008) used an emotional Stroop task and found enhanced N450 for both positive and negative words compared to neutral words, while controls showed no emotional modulation. The extent of this difference in the left frontal region correlated with HAM-D score. The authors of both studies suggest while this does not indicate mood congruent bias, it does represent emphasis on emotive stimuli in neural processing in MDD.

And some have found reduced amplitudes to both positive and negative emotion:

Foti et al. (2010) found that although controls show enhanced late positive potentials to emotional faces compared to neutral faces, an MDD group showed no difference. They suggest their lack of differentiation between emotional and neutral faces in the MDD group indicates reduced reactivity to emotional stimuli in MDD, relating it to blunted affect. However, both the results and interpretations are contradictory to those of the previous section.

Very few studies have shown no differences between MDD and controls:

Only three studies have shown no differences in emotional processing between MDD and control groups: Using the N400 procedure to measure electrophysiological activity to semantic violations, but with emotionally valanced words instead of neutral, Klumpp et al. (2010) found no N400 differences between an MDD and control group. Serfaty et al. (2002) used a response anticipation paradigm, presenting emotional words as S1, and measured the CNV prior to a tone prompting participants to respond if the word was self-referential. They found no interaction between group and emotion in CNV or PINV amplitude. Lastly, using schematic faces in an oddball task Chang et al. (2010) found no interaction between emotion and group.

More complex results:

Poulsen et al. (2009) analysed the medial-frontal negativity (MFN) in response to self referential and non-self referential emotional words. While healthy controls exhibited larger amplitudes to self-referential negative words compared to non-self-referential negative words, MDD participants showed smaller amplitudes to self-referential negative words compared to non-self-referential negative words. The MFN is increased by unexpected

negative feedback, so the results suggest that while controls are surprised by negative words describing them, the MDD group are not. This result seems to indicate that mood-congruent bias is modulated by how applicable the stimulus is to the individual.

Emotional Memory

Perhaps as a result of a mood congruent information processing bias, individuals with MDD tend to also show a mood congruent memory bias (Gotlib and Joormann, 2010). This has also been studied with EEG measures of memory activity. All but one of the studies used either emotional faces (Deldin et al., 2000; Deveney and Deldin, 2004) or emotional words as stimuli (Deldin et al., 2001; Deldin et al., 2009; Dietrich et al., 2000; Shestyuk et al., 2005). Most of these studies measured the SWN after presentation of the 'to be memorised' stimuli (Deldin et al., 2001; Deldin et al., 2009; Deveney and Deldin, 2004; Shestyuk et al., 2005). The SWN is measured from around 800ms post stimulus onwards, and is thought to reflect sustained attention to information held in working memory (Deldin et al., 2009). Some studies have focused on other ERPs, such as the N2 (Deldin et al., 2000), P3 (Deldin et al., 2009), N400 and the old/new ERP (Dietrich et al., 2000). One study has focused on the lower alpha 1 bandwidth activity during the retention period of a working memory task, which is thought to reflect attention (Segrave et al., 2012). This study used emotionally valanced images as stimuli. As with other emotional processing tasks, the results show a mixture of amplitude increases and decreases for emotionally positive and negative stimuli. However, unlike the rest of the emotional processing literature, the memory results show more consistency, with all but one study showing the same direction of change, exhibiting some combination of the following for the MDD group:

- Reduced response to positive stimuli, with amplitude reductions (Deldin et al., 2000; Shestyuk et al., 2005).
- No bias for the MDD group, but a positive stimuli bias for controls, with larger amplitudes to positive stimuli (Deveney and Deldin, 2004).
- Both positive mood congruent bias for healthy controls (with larger amplitudes to positive stimuli) and negative mood congruent bias for the MDD group (with larger amplitudes to negative stimuli) (Deldin et al., 2001; Deldin et al., 2009; Segrave et al., 2012).

The results indicate a combination of reduced positive stimuli response and increased negative stimuli response in MDD. This may imply that MDD participants are not using elaborative memory processing for positive stimuli to the extent that healthy controls do, but are elaborating more for negative stimuli. The amplitude enhancements for negative stimuli have been found to correlate with BDI measurement of depression severity (Deldin et al., 2001). As additional support for this idea, those with dysthymia show no biases in tasks that MDD and controls show negative and positive mood congruent biases respectively, suggesting their mild depression severity is expressed as a midpoint between controls and MDD in mood congruent bias (Deldin et al., 2001).

As with the non-memory related emotional processing tasks, level of arousal of stimuli is potentially confounding. P3b amplitudes are known to be modulated by arousal levels of stimuli (Johnson, 1986), and Deldin et al. (2009) found that controls show larger SWN to high arousal words, and MDD showed larger SWN to low arousal words. This result requires replication, but may add complexity to a picture that is already difficult to interpret.

Another major issue with the emotional memory ERP research is that the majority of the studies only focus on ERPs that are related to encoding of the 'to be remembered' stimulus. They do not analyse EEG activity during retention or recognition periods. This means that memory processes that immediately follow stimulus presentation cannot be separated from other more general stimulus related processing during the same time window. One solution is to focus on memory related processing that occurs during the retention period, for example parieto-occipital alpha (Segrave et al., 2012). The results of this study indicated that during a modified Sternberg task with letters as stimuli and emotive background images, lower alpha 1 showed more desynchronisation (though to reflect attention) for negative background images in MDD and positive background images in controls. Another option is to focus on recall related ERPs. The only study to do this has used the old/new task, which generates larger positivity for consciously recognised stimulus repetitions (Dietrich et al., 2000). Although they reported a smaller old/new effect in the MDD group, there was no interaction with the emotional valence of the words they presented. When looking at both repeated and non-repeated stimulus together however, the MDD group did show a more positive N400 to sad stimuli. This could be interpreted as an amplitude reduction in the N400 to negative stimuli. This would seem to contrast to other studies showing amplitude enhancements for negative stimuli in MDD. However, examination of their grand average graph for the MDD group suggests this might be due to a general positive shift for the whole epoch. Additionally, the N400 occurs earlier than the SWN, so is not directly comparable to the other emotional memory studies.

Summary of Emotional Processing Research

Taken in total, the majority of the electrophysiological emotional processing comparisons indicate some form of a pattern where amplitudes are increased to mood congruent stimuli, and amplitudes are decreased to stimuli of the opposite valance: in MDD groups, happy stimuli are followed by reductions in amplitude and sad stimuli by increased amplitudes. Alternatively, controls show this mood congruent bias with larger amplitudes for happy stimuli and smaller amplitudes for sad stimuli, while the MDD group shows no differences. Most of these studies have measured the P3 amplitude, while some measured the SWN, CNV, N400, N2 or alpha bandwidth desynchronisation.

It appears the weight of evidence leans towards a combination of increased mood congruent P3 amplitude in response to negative stimuli (or reduced P3 amplitude in response to positive stimuli) in MDD. Since P3 amplitude reflects the degree of attention to, and meaning extracted from a stimulus, these studies support the idea that individuals with MDD attend more to negative stimuli, and perform more elaborative processing of negative stimuli compared to positive stimuli. However, it should be noted that stimulus expectation also modulates P3 amplitude. Because of this, studies that find P3 reductions to negative stimuli in MDD indicates that MDD groups have an expectation to see negative stimuli, which also supports a mood congruent bias. As such, results in both directions can be interpreted as supporting the same negative mood bias in MDD. This means that P3 studies of mood congruence in MDD cannot be taken as a test of the hypothesis that there is a negative mood bias in MDD. Perhaps future research will give a more comprehensive understanding of the mechanism by which emotion influences P3 amplitudes in MDD, which may resolve the seeming complexity of the current literature.

The SWN amplitude also seems to show amplitude increases for mood congruent stimuli in MDD. Although fewer studies have focused on the SWN compared to the P3, they consistently show the same direction of amplitude change. SWN amplitude is thought to reflect memory encoding, so this can be interpreted as more neural resources devoted to the encoding of negative stimuli in MDD. At this stage, results for ERPs other than the SWN and P3 seem too inconsistent or not studied enough to draw conclusions. It is also likely that emotions will modulate different ERPs in a different manner, depending on the underlying processes. Lacking knowledge of how these modulations shape each makes a cohesive interpretation of all emotional ERP findings in MDD groups impossible at this stage.

In addition to the fact that ERP research is suggestive of a P3 and SWN amplitude increase for negative emotions in MDD, there is another trend worth noting: Studies that focus on emotional *memory* ERPs seem to show this pattern more consistently (in comparison to those that simply focus on emotional stimuli related ERPs). In a review of the depression mood congruent bias and ERP research, Deldin et al. (2003) hypothesize that tasks that require more elaborate semantic encoding will be more likely to reveal a mood congruent bias. This may be because those tasks activate a wider range of areas resulting in more communication with and activation of areas that relate to emotional processing. Their idea may explain why tasks that have focused on remembering emotional stimuli seem to show a more consistent negative mood congruent bias in depression. It also suggests that self referential tasks or tasks specifically requiring deeper semantic or emotional processing might be more likely to find mood congruent bias differences in ERPs between MDD and control groups. However, all except one of the emotional memory studies (Segrave et al.,

2012) have been performed by one group of collaborators. More independent replication of these studies should be undertaken before strong conclusions can be drawn.

Difficulties and Limitations of Emotional Processing Research

Because different studies reveal different aspects of mood congruent biases in MDD and control groups (with some showing reduced amplitude to positive stimuli in MDD, and others showing increased amplitude to negative stimuli), results can be difficult to compare between studies. To remedy this, future studies could recognise that both amplitude reductions to positive stimuli and amplitude increases to negative stimuli both reflect the same *pattern* of sad mood processing bias. As such, it may be useful to analyse ERPs as difference curves between the positive and negative emotional trials, so the overall direction of amplitude changes towards one emotional valence can be reported. This idea is demonstrated by figure 4. This method will also eliminate the impact of potentially confounding overall amplitude alterations from the emotional processing analyses. As mentioned in regards to the oddball literature, overall amplitude reductions are likely in MDD groups. This can confuse interpretation of emotional ERP results - if amplitudes in response to negative emotional stimuli do not differ between MDD and control groups, it does not necessarily mean no mood congruent bias is present. The MDD group may show reduced amplitudes to neutral stimuli compared to the control group, due to impairments in neural synchrony, in which case the normal amplitudes in response to negative stimuli actually reflect enhanced processing for those stimuli. Given this possibility, neutral emotional conditions are desirable in mood congruent ERP studies.

Table 9 – Emotional EEG measures comparing MDD participants to controls

Authors	MDD (N)	Sample Characteristics	Task	Direction of Emotional Effect on ERP	Findings
Emotional Tasks					
Dai, Feng (2011)	17	Also group of 17 remitted MDD and 17 healthy controls.	Emotional word stroop task – respond to colours, ignore words.	MDD show increased amplitude for sad stimuli	Larger bilateral parietal N450 in response to negative words in both MDD groups compared to controls.
Dai et al. (2011)	17	Also group of 17 remitted MDD and 17 healthy controls.	Negative priming of emotional faces -measures emotional inhibition.	MDD show increased amplitude for sad stimuli	MDD and remitted MDD groups showed larger right parietal P3 to positively primed sad faces than happy faces, and the reverse in the negatively primed condition.
Yao et al. (2010)	18	No medication	Negative affective priming of emotional words	MDD show earlier peak for sad stimuli	Late positivity smaller in MDD group. Controls - delayed late positive peak to negative words. MDD group showed faster peak to negative words.
Cavanagh et al. (2006)	18	Non-diagnosed university students scoring high in BDI	Emotional face visual oddball task with happy face as frequent and fearful face as rare	High depression - reduced amplitude for happy stimuli	MDD showed reduced and delayed P3 to happy faces. No overall changes, and no differences in fearful face processing.
Chang et al. (2010)	15	Single episode only	Oddball task with simple emotional faces – count green coloured, ignore red coloured.	No emotional differences	MDD group showed reduced posterior negativity between 100-350ms compared to controls. Controls showed reduced negativity if faces were inverted compared to upright, but MDD did not. No interaction between group and emotion.
Foti et al. (2010)	22	Not medicated, no comorbidity	Presented emotional face stimuli in sequence.	Controls show larger amplitude for fear	Controls show larger late positive potential for fearful and angry faces compared to neutral faces, but MDD showed no difference.
Williams et al. (2007)	57	Healthy community sample. High and low depression compared	Presented emotional faces overtly or covertly (briefly with neutral face mask following).	High depression scorers show reduced amplitude for fear	High depression group showed reduced late fronto-central P3 to overt fear expressions compared to low depression group.
Ilardi et al. (2007)	16	University students diagnosed with MDD and sub-clinical group.	Oddball with neutral words as frequent and negative words as rare targets.	MDD show larger amplitude for sad stimuli	Enlarged P3 to negative rare word targets in MDD

Authors	MDD (N)	Sample Characteristics	Task	Direction of Emotional Effect on ERP	Findings
Yang et al. (2011)	20	First episode, unmedicated	Emotional word oddball with neutrals as frequent stimuli	MDD show reduced amplitude for sad stimuli	N2 amplitude reduced for positive words compared to controls and negative words, and delayed for all stimuli. P3 trended towards reduction for negative compared to positive words in MDD group. No latency differences
Serfaty et al. (2002)	15	Both inpatients and outpatients.	CNV with emotional words as S1, respond if word is self-referential	No emotional differences	No overall CNV or PINV changes, and no emotional bias effect on CNV or PINV. Increased PINV in MDD for non-responded words
Casement et al. (2008)	12	Dysthymics only	CNV with + or – as S1, predicting positive or negatively valanced words as S2	Dysthymic group - larger amplitude for sad stimuli, controls larger for happy	Controls showed larger CNV to positive warning stimuli, while MDD showed larger CNV to negative warning stimuli.
McNeely et al. (2008)	15	4 in partial remission. Half medicated.	Stroop task with emotional words as distracters	MDD show larger amplitude for both sad and happy emotions	MDD showed larger N450 in response to both negative and positive words compared to neutral words. Controls did not show this pattern.
Kayser et al. (2000)	30	Outpatients, medication free.	Presented images of dermatological disease on faces and neutral faces	No emotional effect	Right hemisphere facial processing P3 bias smaller in MDD than controls, and parietal P3 reduced in MDD. MDD showed reduced P3 to neutral stimuli but no difference for negative
Poulsen et al. (2009)	13	Some medicated.	Presented descriptor of personality trait words (good and bad), respond if relevant to self.	Non-direct relationship	MDD group showed less medial frontal negativity towards endorsed 'bad' words compared to unendorsed, while controls showed greater negativity to endorsed compared to unendorsed bad words. MDD also showed smaller P3.
Klump et al. (2010)	50	Mixture of inpatient and community sample. Most medicated.	Sentences presented, with final word either congruent or incongruent, varied emotional valence of word.	No emotional effect	No differences between MDD group and controls in N400 amplitude and no interaction with emotional valence.
Krompinger et al. (2009)	18	Undergraduates scoring high on the Inventory to Diagnose Depression scale	Go/Nogo task with pleasant and unpleasant images as stimuli	High depression scorers show larger P3 amplitude for sad stimuli, but reduced N2 amplitude	High depression group showed reduced N2 and enlarged P3 to negative images compared to positive. Controls showed no difference.
Nandrino et al. (2004)	26	12 first episode, 14 recurrent. Inpatients.	Presented emotional words – count occurrence of one emotion per condition.	MDD show larger amplitude for sad stimuli that is attended to	Recurrent MDD showed larger P3 for counted negative words and larger P3 for ignored positive words compared to first episode and controls.

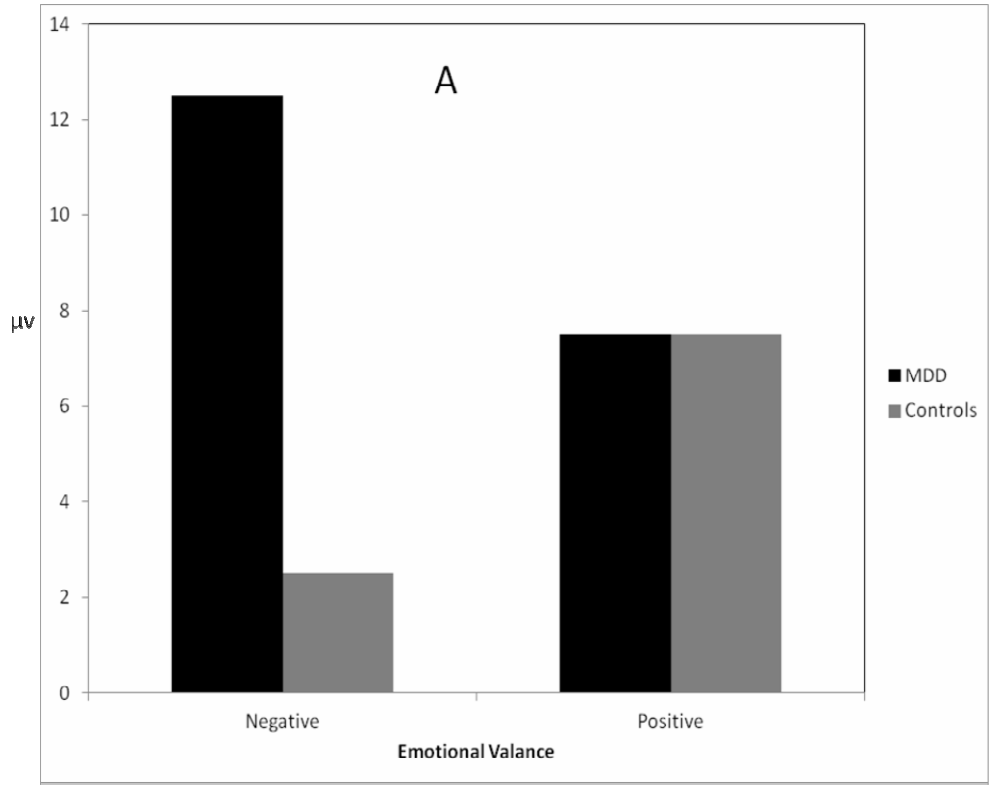
Authors	MDD (N)	Sample Characteristics	Task	Direction of Emotional Effect on ERP	Findings
Rossignol et al. (2008)	12	Subclinical depression & anxiety vs high anxiety & controls	Three stimulus oddball task with emotional faces as distracter	Depressed group show larger amplitude to all emotions	High depression and anxiety group showed enlarged P3a to all emotional distracters compared to other groups.
Authors	MDD (N)	Sample Characteristics	Task	Direction of Emotional Effect on ERP	Findings
Blackburn et al. (1990)	15	Also a remitted depression group	Presented equal frequency of positive and negative emotional words	MDD show larger amplitude to sad stimuli, controls show the reverse	Depressed group showed larger P3 amplitude for negative than positive words, and remitted depression group showed similar pattern. Controls showed the opposite pattern.
Cavanagh et al. (2006)	18	Sub-clinical depressed university students	Emotional face visual oddball task with happy and fearful face as rare stimuli	High depression scorers show reduced amplitude to happy stimuli	Reduced and delayed P3 to happy faces. No overall changes, and no differences in fearful face processing.
Ilardi et al. (2007)	16	University students diagnosed with MDD and sub-clinical depressed students.	Oddball with neutral words as frequent and negative words as rare targets.	MDD show larger amplitude to sad stimuli	Enlarged P3 to negative rare word targets in MDD
Emotional Memory Tasks					
Shestyuk et al. (2005)	15	Medicated	Sternberg task with emotional word as memory stimuli, and letter as probe. Respond as to whether letter was in memory word.	MDD show reduced amplitude to happy stimuli, controls show larger amplitude to happy stimuli	MDD showed reduced SW to positive emotions compared to neutral or negative. Controls showed larger SW to positive words than MDD.
Deldin et al. (2000)	19	Medicated	Memory for emotional faces	MDD show reduced amplitude to sad stimuli	MDD group showed right parietal N2 amplitude reductions, particularly for negative faces.
Ninkendei et al. (2005)	12	Subclinical depression only.	Memory for letters, or if word was noun, using pain related words and neutral words as stimuli.	MDD show larger amplitude to pain stimuli	Words – pain larger P3 and SWN in MDD than controls.
Deveney, Deldin (2004)	17	Six participants medicated.	Memory for emotional faces. Compared negative/positive face ERPs to neutral face ERPs.	Non-direct relationship	Controls showed larger difference between neutral and negative face at left parietal electrode than MDD group. Result driven by ERP to negative faces.

Authors	MDD (N)	Sample Characteristics	Task	Direction of Emotional Effect on ERP	Findings
Dietrich et al. (2000)	11	Inpatients, not medicated.	Presented emotionally valanced words, respond if word is a repeat.	Non-direct relationship	Controls showed reduced N400 for repeated words for both emotions, but MDD did not. MDD also showed less of a reduction for repeated positive words than negative words.
Deldin et al. (2009)	18	Half medicated.	Presented emotional and neutral words with varied arousal levels. Free recall test afterwards.	MDD show smaller amplitude for happy stimuli, controls show larger amplitude for happy stimuli	MDD group showed P3 reductions in left hemisphere for positive stimuli. Controls showed larger SW for positive words compared to negative and neutral words, while MDD showed no such bias. MDD group larger early SW for low arousal compared to high arousal words, while controls showed larger late SW amplitude for high arousal compared to low arousal words.
Segrave et al. (2012)	15	Some medicated, all female, all right handed.	Sternberg task with emotionally valanced background image. Measured lower alpha during retention.	MDD show more activity for sad stimuli, controls show more activity for happy stimuli	Control group showed more lower alpha desynchronisation (perhaps reflecting attention) in parietal electrodes for positive images, while MDD showed more for negative images.
Deldin et al. (2001)	17	With current major depressive episode, but not necessarily diagnosed. Also a dysthymic group.	Emotional word presented to memorise, respond if later probe letter was in word.	MDD show larger amplitude for sad stimuli, controls show larger amplitude for happy stimuli	Major depressive episode group showed larger SW amplitude to negative word (which correlated with BDI score), while controls showed reverse. Dysthymics showed no SW amplitude bias.

Another problem with emotional ERP studies is the question of which factor modulates the ERPs. Using complex stimuli like words and faces means parameters other than simply emotional properties are varied, such as arousal, identity of faces, gender, and semantic/pronunciation properties for words. Future research may benefit from using simpler stimuli and study design in order to reduce the number of potential confounding variables.

One final issue with this analysis of the emotional processing literature is the sample heterogeneity. For example, some of these studies have used samples of participants who score in the depressed range, but do not necessarily have a current diagnosis of MDD (Cavanagh and Geisler, 2006; Ilardi et al., 2007; Nikendei et al., 2005). Despite potentially only testing participants with dysthymia, these three studies support the proposed direction of amplitude alterations in MDD. This may indicate that the effect of mood congruence on ERPs is large, as it is not just restricted to severe or diagnosed MDD samples.

Figure 4 over-leaf. Patterns of mood congruent biases reflected by ERP amplitude measures in MDD and control groups. A – enhanced amplitudes for negative stimuli in the MDD group; B – enhanced amplitudes for positive stimuli in the control group; C – enhanced amplitudes for negative stimuli in the MDD group and positive stimuli in the control group; D – a combination measure taken by subtracting ERP amplitudes from positive stimuli from amplitudes to negative stimuli in each group.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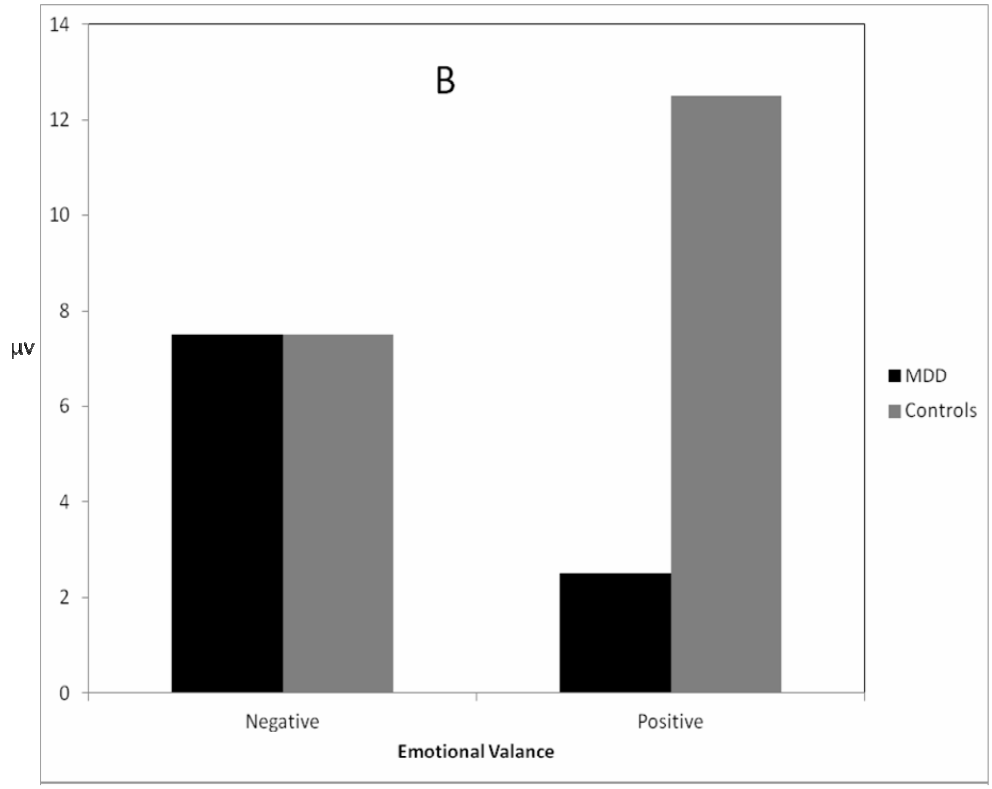
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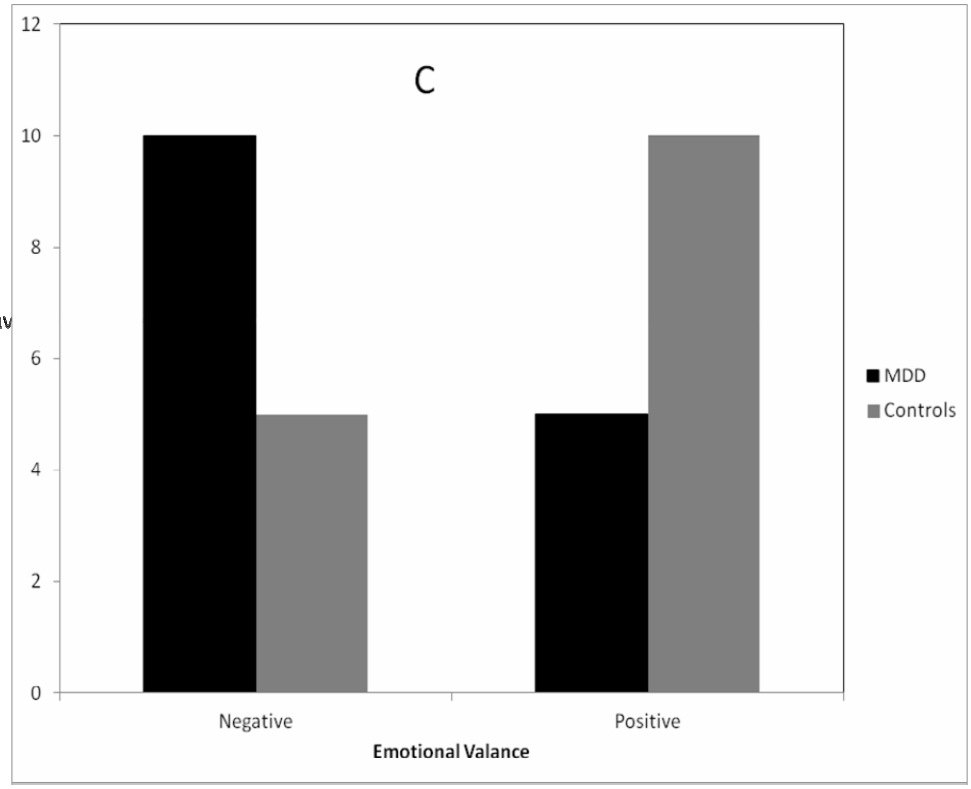
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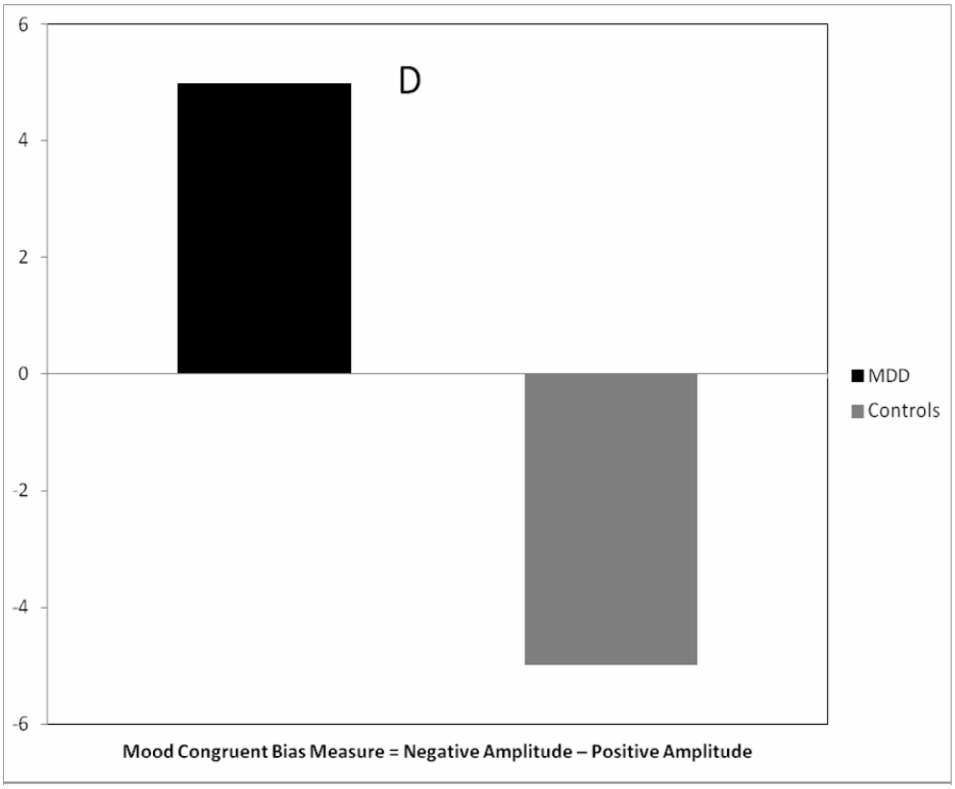
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Bandwidth and Modelling Comparisons

Four studies have used more complex approaches to analyse differences between control and MDD groups. Nandrino et al. (1994) used a non-linear dynamic approach to determine the complexity of the EEG signal across the recording of an oddball task (not time locked to stimuli). They found that both the first episode and multiple episode MDD groups showed more predictability in their pattern of voltage change over very short time periods (4 to 40ms) than healthy controls. This suggests less complexity in the underlying neural activity. Assuming complexity of EEG signal relates to novel generations of thought patterns, this perhaps relates to the repetitive rumination shown in depression. These authors also found that after recovery from depression, the complexity of the first episode group returned to the same level as controls, while the multiple episode group did not. Using a similar approach Sun et al. (2008) compared groups with a measure known as partial directed coherence. This measure uses regression to assess how much the activity in one electrode at one time influences the activity in another electrode at a slightly later time. They found that MDD participants showed lower frontal inter- and intra-hemispheric beta bandwidth connectivity compared to controls both at rest, and during a simple arithmetic task. Strelets et al. (2007) also performed a non-time locked analysis. Their results suggested MDD groups exhibit increased gamma power during arithmetic and spatial imagination, but at the same time reduced inter and intra-hemisphere coherence. This may indicate functional connectivity is impaired, releasing individual brain regions from global control to oscillate of their own accord. Interestingly, they found that exam pressure in their healthy control group reduced group differences, suggesting changes resulting from stress occur in the same direction as those occurring in MDD. These three studies suggest that inter-region

connectivity in MDD is reduced, and predictability of signal in specific regions is increased (perhaps as a result of reduced influence from other regions). More coherence data is required before strong conclusions can be drawn however, as other research has suggested that during resting recordings inter-region coherence is actually *increased* in MDD (Leuchter et al., 2012).

A more recent modelling approach to oddball task analysis has been conducted by Kerr et al. (2011) to determine which hypothetical neuronal factors in MDD have changed to lead to the ERP alterations. Their model explained 86% of the variation in a subject's ERP to rare targets. Three main factors were altered in MDD subjects: reduced thalamocortical inhibitory signal, decreased cortical excitation, and increased dendritic signal time. However, modelling approaches are only accurate as long as their assumptions are correct. Future developments in neuronal signal modelling will enable more detailed understanding of specific underlying changes.

Summary of MDD-EEG Review

An overall summary of the conclusions that can be drawn from the reviewed EEG research in MDD follows, ordered from strong well supported conclusions, to less certain, weaker conclusions. A summary of these conclusions can be viewed in table 10.

Reductions in the P3b amplitude in the oddball task:

This result is apparent in MDD groups that are not medicated, but potentially not in groups that are medicated. It represents a reduction in synchronised neural response to stimuli, reflected in the cognitive domain as reduced attention/meaning taken from the stimuli. These amplitude differences may be obscured by comorbid anxiety, which may

increase P3b amplitude. Conversely, it may be enhanced by the presence of psychotic features. Average P3b reductions in the MDD group are likely to be due to amplitude reductions in all trials (in contrast to single trial variability in schizophrenia). Results of latency and other ERPs analyses are too inconsistent to suggest they are affected by MDD. In the neurophysiological domain, P3b reductions may reflect impaired inhibitory synchronization of neural resources. Brain areas that may be implicated are the DLPFC, temporo-parietal junction, superior temporal gyrus, and locus coeruleus. The amplitude reduction may represent reduced attention to or meaning extracted from stimuli in the cognitive domain. It is possible that this is a physical manifestation of the distracting negative ruminations that are a typical feature of MDD.

Mood congruent emotional processing amplitude increases in the SWN and P3:

These studies seem to indicate that some combination of amplitude increases for negative stimuli, or decreases for positive stimuli occur in MDD. If a negative bias is not revealed, a lack of the positive bias that healthy controls demonstrate is. This result is more consistent across studies focusing on the SWN, but more well researched using the P3. SWN amplitude bias towards negative stimuli suggests more elaborative encoding of these stimuli in MDD, while the P3 amplitude bias may reflect increased attention to negative stimuli.

Altered error related processing:

ERN and feedback related ERP amplitudes following errors may be increased in moderate MDD, but decreased in severe MDD. This may be a result of higher anxiety in moderate severity (increasing amplitudes), and higher anhedonia in severe MDD (decreasing amplitudes). Alternatively, it may be due to increased sensitivity to error in

MDD, which is disguised by neural synchrony impairment in severe MDD. Error related Pe amplitude seems to be reduced, particularly in more severe MDD. These results suggest that both conscious and automatic error processing is affected by MDD, leading to impaired awareness of errors and ability to use error information to modulate behaviour. The results may also perhaps demonstrate that we cannot expect relationships between electrophysiological measures and clinical characteristics to be directly related to disorder categories, or to be simple linear relationships. Treating them as such may confound our understanding of the issue.

Memory processing impairments:

Although not extensively studied as of yet, all results so far indicate altered neural activity in the encoding, retention, and recall aspects of MDD, which supports the cognitive assessment literature. These impairments may be a result of a reduced ability to allocate neural resources to memory processes.

Possible response preparation CNV and PINV amplitude increases:

With some inconsistency, it seems that CNV amplitudes might be reduced in MDD, perhaps reflecting impaired attention or anticipation of a forewarned imperative stimulus. At a neurophysiological level it potentially suggests impaired cortical excitability in MDD. PINV amplitude increases show consistency, but are not well studied. They may reflect increased response uncertainty in MDD.

No emotionally neutral language impairments:

Although there is a lack of literature focusing on this area, it appears that neutral language processing ERPs are unaffected by MDD. This may suggest that not all domains of cognition are affected by MDD – the disorder may not have a generalised impact.

Possible response/cognitive inhibitory changes:

Results from the Go/Nogo task are too inconsistent to suggest response inhibition ERPs are altered. Two Stroop studies of cognitive inhibition ERPs are suggestive that amplitudes for these processes might be reduced in MDD.

Commonalities across domains:

The MDD and EEG literature suggests there is positive evidence that attentive, memory, and emotional processes are affected. While language processes appear to be unaffected, at this stage the breadth of tasks in the literature is not sufficient to determine for certain whether there are specific higher cognition related neural processes that are unaffected by MDD. It may be that MDD engenders a general impairment across all cognitive process. Across all the different tasks, there do seem to be a few consistent patterns. ERPs seem to show reduced peak amplitude in MDD. This supports the idea that MDD exhibits impairments in neural synchrony, potentially due to poor inhibitory / excitatory function. Additionally source localisation measures across a variety of tasks seem to show reduced ACC and DLPFC activity, and reduced connectivity between these two (Holmes and Pizzagalli, 2008; Pizzagalli et al., 2006; Stilton et al., 2011). This parallels the results of fMRI research (Fitzgerald et al., 2008), and supports a network model approach of MDD (Drevets, 2000; Mayberg, 1997). The exception to the reduced amplitude pattern

regards increased amplitudes to negative stimuli, errors, and uncertainty. This is in harmony with a conception of MDD as a disorder focused on and sensitive to sadness and helplessness.

Table 10 – Conclusions we can draw from the literature studying MDD and EEG measures of cognitive and emotional processes

Conclusion	Certainty of Conclusion	Limitations	Implications for our understanding of MDD
Reduced P3b amplitude in MDD	Strong	Only in unmedicated participants. May be exaggerated by psychotic features. Some inconsistency.	Indicates reduced attention on/meaning extracted from the external environment. May be due to impairments in neural synchrony.
Mood congruent amplitude modulation (enhanced for sad, reduced for happy)	Strong	More likely in memory studies. The valance revealing the effect varies between studies.	Reveals increased attention to negative stimuli, and decreased attention to positive stimuli in MDD.
Altered error processing	Strong-moderate	Non-linear relationship in amplitude modulations. Effect may be due to factors other than depression	Suggests impaired awareness of errors and reduced ability to modulate behaviour as a result.
Impaired memory processes	Moderate	Not many studies have been performed. Methodology varies widely. Few studies focus specifically on retention processes.	Supports literature indicating memory disruptions in MDD. May indicate an inability to allocate neural resources to memory processes.
Impaired response preparation processes	Moderate	Some inconsistency between studies.	Suggests response anticipation processes are impaired, maybe as a result of reduced cortical excitability. Also suggests increased response uncertainty.
No changes in neutral language processing	Moderate-weak	Very few studies performed	May indicate that not all domains of cognition are affected by MDD
Possible cognitive inhibition and response inhibition changes	Weak	Few studies performed on cognitive inhibition, and studies on response inhibition are inconsistent. Varied sample characteristics.	Possible cognitive inhibition impairments. Uncertain as to whether response inhibition is affected.

Issues with these interpretations:

There are a number of potential issues with the aforementioned conclusions and interpretations of those conclusions. Firstly, overall there appears to be no consistent relationship between severity of depression and EEG changes. This seems counterintuitive - a common sense approach would suggest that the mechanism by which depression affects neural activity would affect severe cases more than mild cases, and therefore show larger alterations in EEG measures. It may be that this common sense approach is incorrect. Alternatively, I suggest that point estimates of severity will not accurately reflect the magnitude of effect MDD has had on a person's neurophysiology. A measure that took into account longitudinal severity may more accurately reflect the impact. An area under the curve type approach, with point estimates of severity multiplied by the time experiencing that level of severity could be predicted to correlate with ERP changes. Unfortunately, this prediction is rather difficult to explore. Another possibility is that for more severely depressed participants, testing sessions are often conducted upon temporary improvement (bed-bound patients are unable to attend research studies). This would have the effect of reducing variety in depression severity, without reducing the variety in the effect of severity on neural processes.

In addition to this, there are a number of other variables that are known to affect EEG measures, which may be confounding the reviewed results. For example circadian, menstrual, and seasonal cycles, exercise, arousal/fatigue, sleep, age, interval between previous meal and testing session, and neuroactive drugs (caffeine, nicotine, alcohol), and extroversion/ introversion are factors that appear to affect the P3b (Polich and Kok, 1995). ERPs are so sensitive to subtle differences in neurophysiology that even personality factors

appear to correlate with these measures within depression groups (Hansenne et al., 2000). This suggests the possibility that the relationship between severity and changes in neural activity is less important than the relationship between symptoms and neural activity. For example, error related ERPs seem unrelated to depression severity, but related to response uncertainty and affect (Schrijvers et al., 2010). As well as this, sleep, exercise, and eating habits are all likely to differ between MDD and healthy control groups, so we cannot be certain that differences are not due to these factors instead of the actual disorder. Indeed, insomnia has been found to be related to the P3b changes in MDD (Bruder et al., 1991). Comorbid anxiety is also common in MDD, and may have an opposite effect on ERPs to MDD (Bruder et al., 2002).

Another issue with the interpretation of these results is that differences in analysis techniques may have disproportionate effects on each group, and analysis techniques vary widely between studies. Studies vary their reference montage and the location of comparisons of interest. Eye blink and movement artefact correction procedures are inconsistent. ERP results may be so sensitive that variation in participant instructions may lead to significant differences. The same peak can also be measured in a different manner by different labs – Some studies measure ERP peaks from baseline activity, while others use a peak to peak measure (Mao et al., 2005). Some labs use peak amplitude, while others use mean area under the curve for the ERP window. Neural resources may not be temporally synchronised as effectively in the MDD group, but a quantitatively equal volume to the control group could still be activated during the measured time window. This would create a broad shallow curve in comparison to the control group's sharp condensed peak. In this case, a peak amplitude measure would differentiate the two groups, while an area under

the curve approach would not. The opposite is also possible - equal peak amplitudes, but fewer neural resources synchronizing in the surrounding time in MDD. A peak amplitude measure would indicate equivalence, while an area under the curve would differentiate the groups. This concept is illustrated in figure 5.

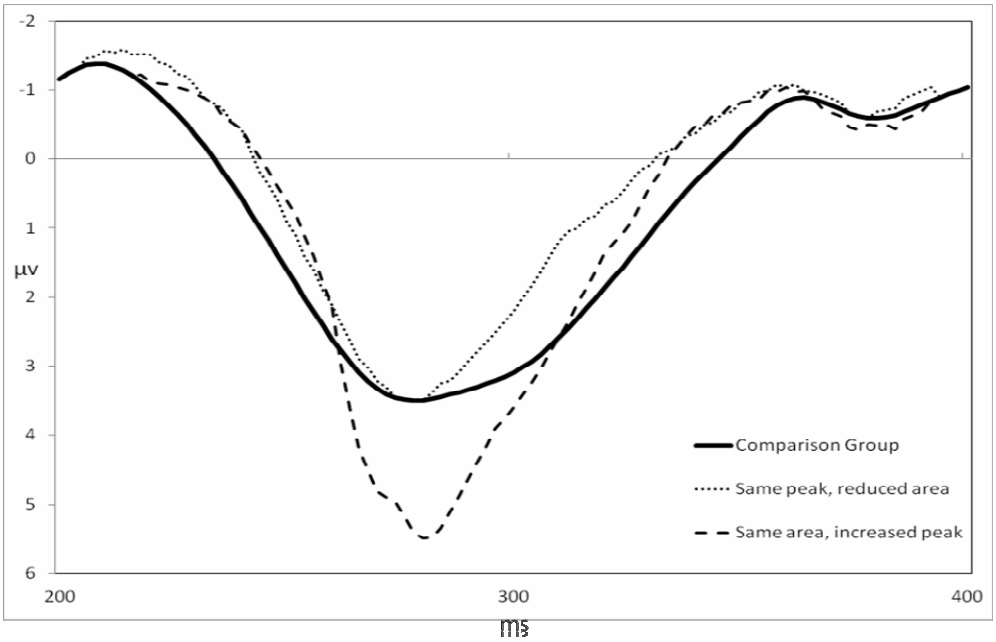

Figure 5. Depiction of the manner in which different measurements can obtain different results in between group comparisons.

Our understanding of the implications of these results is also limited by our lack of knowledge about exactly what processes each ERP represents. The origin and cognitive process related to even the most frequently studied P3b is still debated and uncertain. We cannot be sure that specific ERP activity symbolises the process that it is related to (even though we say for example that the P3b represents meaning extracted from the stimulus). All we can say is that it is associated with it. Indeed, the ERPs may be the outcome or by-

product of the process they are associated with (Meyer et al., 1988). For example, high pre-stimulus alpha has been found to result in larger P3b amplitudes (Jasiukaitis and Hakerem, 1988). This means it is possible that P3b changes in MDD may simply be a result of alpha alterations (which are found in MDD) rather than P3b reductions specifically.

Our expectations also influence our interpretation of the results. An example of this is the emotional processing research, where some studies have shown amplitude increases for mood congruent stimuli, and others have shown amplitude decreases for mood congruent stimuli. Because ERP amplitude changes can be interpreted as reflecting a change in a number of different processes, both result directions were interpreted as supporting a hypothesized mood congruent bias in MDD. If all evidence is interpreted as supportive of the hypothesis, then the hypothesis is not testable with this approach. Related to this, because each stimulus presentation generates a number of different ERPs, researchers can easily analyse more than one measure, and emphasize those that significantly differ. Although good scientific practice suggests this should not be the case, the temptation to highlight positive results may have affected the literature. A positive result bias both in interpretation and reporting would accentuate any potential difference between MDD and control groups, affecting the conclusions of this review.

One last issue with the conclusions drawn by this review is that they are all based on qualitative assessments of results rather than meta-analytic assessments. The number of studies supporting each result has been assessed, but because few studies report all the values involved in their statistical testing, meta-analysis was not possible. This element, in combination with a possible non-reporting of negative results, leaves the possibility that the conclusions drawn do not reflect the reality of neural activity changes in MDD.

How the field could be extended:

Although a simple electrophysiological marker for diagnosing depression would be remarkably useful, ERPs do not have the specificity to depression, sufficient size of difference for this purpose (Gordon et al., 1986; Pfefferbaum et al., 1984), or consistency (as indicated by this review). EEG research into neural changes in MDD has also shared a common fate with other neuroimaging techniques – while it has offered insight into potentially impaired processes and areas, the practical applications stemming from that information have been limited. These studies have emphasized that MDD has a predominant biological aspect rather than simply psychosocial. Some have attempted to predict or test treatment response (Ancy et al., 1996; Vandoolaeghe et al., 1998). Beyond that however, our limited ability to manipulate brain function has meant this area of research has been of limited relevance to the treatment of MDD. With developments in brain stimulation techniques however, the future looks more promising. Source localisation and other analysis techniques are becoming more sophisticated, as is our understanding of the processes associated with these variations in EEG signal, and the areas generating them. These advances will be able to offer valuable information to complement other neuroimaging techniques, advising clinicians as to which areas, processes, and mechanisms will be ideal targets for intervention.

In addition to treatment applications, EEG approaches can help us understand more about the disorder. One approach that is becoming more popular is to determine whether different symptom profiles result in different changes in neural activity within the one disorder. If this is the case, it would suggest MDD is more a collection of variable symptoms that result in similar behavioural profiles, rather than a single disorder. Focusing within

depression as a group, in order to determine whether all cognition related neural activity processes are affected, or just a specific range, future research should endeavour to compare the same groups in two different tasks. This method will enable a dissociation between processes that are and are not affected.

As well as becoming more practical, future research could take steps to increase the certainty and depth of conclusions about neural activity differences in MDD. To increase the certainty of conclusions about neural changes in MDD, there are a number of points to note. When potential differences between groups are so minor (usually on the scale of a few microvolts), are potentially influenced by a suite of other variables (environmental factors, sleep, anxiety, personality etc.), and the previous literature is so inconsistent, increased scientific rigour is required to ascertain a more convincing answer. A few recommendations specific to EEG studies of cognitive processes in MDD can be made.

In terms of recording procedures, environmental factors significantly modify ERPs so care should be taken with these (Polich 1995). Attempts should be made to control for participant cycles, fatigue, and recency of food intake. Anxiety, psychotic symptoms, and exercise should be recorded as covariables. ERPs may even be sensitive to variables like experimenter instructions. Care should be taken to control for these variables – for example a script could be prepared so that task instructions are equivalent for each group.

In terms of analysis, researchers should be cautious of potential expectation effects. Minor unintentional differences in subjective judgements during analysis procedures may influence the study outcome in the 'desired' direction. In order to ensure this does not affect the outcome, future research should use experimenter blinding procedures for processes that are not automated. Secondly, a priori hypotheses that focus on one or two

specific ERPs in only one or two locations or location groups should be adhered to. Post hoc analyses should be reported as such and only tentative conclusions can be drawn from these. The field should emphasize that negative results are as important and valid as positive results. They offer a vital contribution to the field, particularly when (even after a significant amount research) strong conclusions cannot be drawn. Reporting the full statistical values of these negative results is also important, as it allows meta-analytical procedures to be employed when reviewing the field.

To increase our depth of understanding, we should avoid the potential problems with simplifying ERP differences into peak or area analysis (Bruder et al., 2002). For example, while P3b peak amplitude is the most common measurement, if it shows significant differences, then statistically significant differences are likely to be found for the surrounding time windows as well (Kok, 1990). Although we categorise the ERPs into distinct windows and refer to them as distinct entities, the tendency to think of them as such may not be productive. They may alter one another through temporally overlapping voltage changes, and amplitude variations in one may communicate those changes to other ERPs. Similar to focusing on just one bandwidth of activity, focusing on just one part of an ERP is analogous to studying art by looking at the colour red. It can be informative, but we must remember there is a more information available. In order to demonstrate more comprehensively differences between groups, statistical parametric mapping could be used. This method performs a t-test at every point on the curve to determine at which latencies two curves differ. This approach will contain more information than area under the curve or peak amplitude/latency analyses. It uses dynamic causal modelling and Bayesian probabilistic reasoning to model the neural network activity. This method can be critiqued

as not reflecting hypothesis driven reductionist science. However, when a system is as complex as the brain, a simplifying reductionist approach will not allow us to comprehend the whole picture. Exciting new analysis techniques can offer alternative information to simple average ERP analyses, for example partial directed coherence can provide a measure of how much activity in one electrode causes activity in another (Sun et al., 2008). Approaches like this could be incredibly useful for determining the direction of impairment in a whole brain network approach to MDD.

Another way to enhance our degree of understanding is to focus on how differences relate to basic theory. This will offer a broader perspective on the interpretation of between group differences, and what they mean for depression. Collaboration with basic researchers and clinicians will offer a more holistic explanation about how our results can apply to individuals with MDD, and will help the field become less "conceptually fragmented" (Atchley and Ilardi, 2007). EEG perspectives on neural activity can offer one level of understanding, but that level in isolation is not very informative. When associating EEG results with different levels of analysis, it is important to be aware that direct 'one to one' causal relationships are unlikely. Variation in one gene/ protein/ neurotransmitter/ symptom alone will not match variation in neural activity. These simple explanations are tempting as our brains are constructed to appreciate linear relationships. However, complex systems like our brains are not linear, and dysfunction in a complex system is likely to require a complex intervention to solve. EEG research can contribute knowledge that can help, if it uses a complex approach and links with other research streams.

Lastly, there are a number of gaps in the literature, where research lacks replication or generalisation, limiting our ability to draw conclusions. More comprehensively

researching processes that may be affected by MDD, but have not yet sufficiently been examined will help strengthen our confidence in which aspects of processing are affected. For example, inhibition and memory related processes are currently under-researched. In addition to this, expanding research to specific sub-types of depression and depression that is comorbid with other illnesses or disorders (for example depression following a traumatic brain injury) will advise us whether these results are related to depression in general, or only specific sub-types of depression. Solving these issues is of vital importance. By 2020, MDD will be the largest burden of disease in the world (World Health Organisation, 2001). We need the most comprehensive understanding possible to help those who are afflicted.

Chapter Six

Interim Summary and Research Question

This chapter provides a summary of the information presented in the previous chapters, and presents the research question that is answered by this thesis.

As mentioned in Chapter 2, MDD has a high prevalence following a TBI, and results in significant personal suffering and poorer functional and cognitive recovery. While the potential psychosocial causal factors have been reasonably well studied and identified, very little research has examined the changes in brain activity that might alter mood circuits, and as such may be a significant causal factor in the development of TBI-MDD. The majority of studies that have examined neural factors involved in TBI-MDD have used structural imaging to compare lesion location between those with MDD and those without following a TBI. This approach does not offer a direct measure of activity changes, and cannot provide information about the extent of DAI, which is thought to be the most significant impact of TBI. Two studies have examined brain activity in TBI-MDD using EEG measures - Reza et al. (2007) found prolonged N2 latencies and reduced P3 amplitudes in a group with scores in the depression range following a TBI compared to healthy controls. The authors suggest the prolonged N2 latency may be a marker of TBI-MDD, while the reduced P3 amplitude may reflect TBI in general, as it was also found in a TBI only group. The second study, performed by Larson et al. (2009), found that negative affect inversely correlated with error processing ERN amplitudes in a group with TBI. However, neither of these studies compared patients with diagnosed MDD, so their results may characterise the effects of transient negative affect following a TBI rather than MDD. Additionally, neither study included a group with

MDD but no TBI. As a result, we cannot ascertain whether brain changes that occur in TBI-MDD are similar to those that occur in MDD. Finally, both studies included severely injured individuals, and no mild injuries, so the results may reflect the aforementioned impact of lesions on the brain rather than DAI.

Although very little research has examined brain activity in TBI-MDD, a considerable literature is available that details brain activity differences in both TBI and MDD alone when compared to healthy controls. Chapter 4 described areas of cognition that generate brain activity which is altered following a TBI: namely attentional and memory updating processes, as well as measures of functional connectivity (coherence). Similarly, as mentioned in Chapter 5, there are also specific areas of cognition that seem to generate brain activity which differs between individuals with MDD and healthy controls are attentional, working memory, error related processing, emotional processing, and potentially response inhibition processes.

Because some of these processes overlap between the two afflictions, while others may not, measuring the electrophysiological processes related to certain aspects of cognition is likely to characterise how TBI-MDD is similar to TBI and MDD, and the factors that are altered only in the individuals who develop MDD following a TBI, not in the individuals who do not. This provides a rationale for the use of specific cognitive tasks to explore brain activity differences between individuals with TBI-MDD, TBI, MDD, and healthy controls.

Therefore, the goal of the current thesis is to use cognitive related brain activity measures to determine how activity is altered in TBI-MDD compared to TBI, MDD, and healthy controls. This is done in order to enable the generation of ideas about whether TBI-

MDD is caused by brain activity changes that result from the TBI, or if the psychosocial difficulties that follow some injuries may lead to the development of MDD, which in turn cause the brain changes. Knowledge about this issue may be able to guide predictions of which individuals are at risk of TBI-MDD, and the potential development of intervention methods to help these individuals.

As such, specific aims of this thesis are to:

- Investigate whether electrophysiological activity related to response inhibition processes are altered in individuals with TBI-MDD, and whether this is similar to alterations found in individuals with MDD and different to the activity found in individuals with TBI.
- Investigate whether electrophysiological activity related to emotional processing is altered in TBI-MDD, and whether these alterations differentiate those who have developed MDD following a TBI from those who have not.

These aims are addressed by Chapter 7 – an empirical study using an emotional Go/Nogo task.

- Assess whether error processing activity differentiates TBI-MDD groups from TBI and MDD groups.

This aim is addressed by Chapter 8 – an empirical study examining brain activity during response inhibition errors in the Go/Nogo task.

- Determine whether attention and inhibition related bands during working memory are affected in TBI-MDD, MDD, and TBI groups compared to healthy controls.

Chapter 9 accomplishes this goal, comparing alpha and theta activity during the retention period of the Sternberg working memory task between these groups.

- Assess how functional connectivity is affected in TBI-MDD, and whether this might explain why some individuals develop MDD following a TBI while others do not.

This is approached in Chapter 10, which compares the four groups on measures of coherence of these bands between electrodes during working memory processes and while at rest.

Chapter Seven

An exploratory analysis of the Go/Nogo N2 in major depression and depression following traumatic brain injury

The following chapter is comprised of a study that has been reviewed and re-submitted for publication in the International Journal of Psychophysiology. It presents the first ever examination of response inhibition ERPs in individuals with TBI-MDD, as well as the first comparison of how these ERPs differ to simple happy and sad faces in TBI-MDD, TBI, MDD, and control groups. Previous research indicates that both altered response inhibition ERPs and electrophysiological markers of mood congruent biases are present in MDD, so it was expected these differences would also be found in the TBI-MDD group, but not the TBI group.

An exploratory analysis of the Go/Nogo N2 in major depression and depression following traumatic brain injury

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Abstract

Rates of major depressive disorder (MDD) following traumatic brain injury (TBI) are estimated to be between 20% and 45%, a higher prevalence than that seen in the general population. These increased rates may be due to specific changes in brain function following TBI. Event related potentials (ERPs) can measure the electrophysiological differences between groups in areas of cognitive processing impaired in both MDD and TBI, such as response inhibition. The current study presented an emotional Go/Nogo task, with simple emotional faces as stimuli, to participants with TBI, MDD, or both, and compared amplitude and latencies of the Nogo N2, Nogo P3a, P3b and Go SWN between these groups and healthy controls. The results indicated that ERPs were not altered by TBI alone. Both MDD and TBI-MDD groups showed alterations in the later component of the Nogo N2 ERP, which was found to be related to response inhibition. However, the MDD and TBI-MDD groups showed no mood congruent bias in behavioural or ERP measures. The results suggest that TBI-MDD displays similar electrophysiological changes to non-injury MDD.

Keywords: Response inhibition; Event-related potentials; Nogo-N2; Major depressive disorder; Traumatic brain injury

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1. Introduction

Both traumatic brain injury (TBI) and major depressive disorder (MDD) can cause significant suffering to individuals who are affected and their families. The World Health Organisation (2001) estimates that in one year 5.8% of males and 9.5% of females worldwide will experience a depressive episode. Research also suggests that by 25 years of age, almost a third of individuals will have received medical attention for a TBI, with 12% having experienced an injury severe enough to warrant overnight hospitalisation (McKinlay et al., 2008). Following TBI, rates of depression are higher than in the general population, with estimates varying from 13% to 77%, and the majority falling between 20%-45% (Deb et al., 1999; Jorge et al., 1993a; Kaponen et al., 2002; Kreutzer et al., 2001; Levin et al., 2001; Olver et al., 1996; Pagulayan et al., 2008; Rapoport et al., 2006; Rapoport et al., 2005; Satz et al., 1998; Schoenhuber and Gentilini, 1988; Varney et al., 1987). Despite the prevalence of TBI, and the increase in rates of depression post TBI (TBI-MDD), there has been a dearth of research into the pathophysiology of TBI-MDD.

The small amount of research that has focused on TBI-MDD has typically utilised structural Magnetic Resonance Imaging (MRI) to examine the relationship between lesion location and MDD occurrence. Some studies have found lesion location to relate to MDD (Federoff et al., 1992; Jorge et al., 1993b; Koenigs et al., 2008), while other studies do not (Finset and Anderson, 2000; Reza et al., 2007). However, lesion location studies offer no information about functional processing changes that take place. Since MDD is characterised by maladaptive alterations in both emotional and cognitive processing (Harvey et al., 2005; Koster et al., 2005), focusing on functional brain activity related to these constructs may offer more insight into the potential causes of TBI-MDD.

One area of cognition that appears to be affected by both TBI and MDD is inhibition (Erickson et al., 2005; Marco et al., 2011; Westheide et al., 2007). Functional Magnetic Resonance Imaging (fMRI) suggests that inhibition processes are related to activity in the dorso-lateral pre-frontal cortex (DLPFC) and anterior cingulated cortex (ACC) (Hester et al., 2004). These areas have been found to show altered activity in TBI-MDD compared to those with TBI only (Chen et al., 2008) suggesting that cognitive processes related to these areas (such as response inhibition), and activity generated by these areas may be a marker of the development of MDD following a TBI.

An effective method to measure inhibition related neural processing with millisecond precision is to record electrophysiological activity with electroencephalography (EEG) during a Go/Nogo task. This task requires participants to respond as fast as possible to one type of stimuli (Go trials – which set up a prepotent response tendency), but not to the other type of stimuli (Nogo trials – which require the prepotent response tendency to be inhibited). Go/Nogo tasks generate a number of different Event-Related Potentials (ERPs). Visual Go/Nogo tasks generate a negative deflection approximately 200ms to 350ms following the stimuli – the Nogo N2, which is maximal fronto-centrally. The Nogo N2 has been conceptualized as reflecting response inhibition or response conflict monitoring (Azizian et al., 2006; Falkenstein et al., 1999; Geczy et al., 1999; Nieuwenhuis et al., 2003). Folstein and Van Petten (2008) suggest in their review of the N2 that it can be divided into two temporally consecutive sub-components, the N2a and N2b. The N2a is thought to reflect automatic sensory template mis-match processing and the N2b is thought to be related to cognitive control, including response inhibition (Ogura et al., 1993). Both response inhibition and the N2 have been attributed to activity in the orbital/medial

prefrontal area, including the ACC (Bokura et al., 2001; Malloy et al., 1993; Nieuwenhuis et al., 2003).

The Go/Nogo task also generates positive deflections between 250ms and 600ms following the stimulus. Three different types of these have been defined. One of these positive deflections is found in frontal electrodes in response to Nogo trials, and is referred to as the Nogo P3a. The Nogo P3a has been proposed to be related to response inhibition (in addition to the N2), as it tends to be larger in Nogo trials compared to Go trials (Geczy et al., 1999; Kropotov et al., 2011; Pfefferbaum et al., 1985). However, other research suggests it is related to effort required to categorize stimuli (Azizian et al., 2006), occurs too late to be an inhibitory mechanism (Falkenstein et al., 1999), and does not differ between trials where inhibition is likely compared to trials where successful inhibition is unlikely (Kopp et al., 1996). The mixed findings for the Nogo P3a suggest that it does not reflect response inhibition, but is influenced by response inhibition processes.

As well as the frontal ERPs, a posterior P3b is generated by both Go and Nogo trials. This P3b is thought to represent stimulus categorization and meaning extracted from the stimulus, as well as memory updating (Bokura et al., 2001). Lastly, a frontal P3 is generated in Go trials, which is earlier and smaller than the Nogo P3a, and is thought to be related to response production (Bokura et al., 2001).

A number of studies have examined ERPs in the Go/Nogo task in MDD groups. Research comparing MDD groups to controls have found smaller N2 area or peak amplitude in the MDD group (Kaiser et al., 2003; Katz et al., 2010). Source localization has indicated that while the N2 signal is generated in the ACC in controls, the ACC is not the N2's main generator in MDD (Katz et al., 2010). Some research has analysed the Nogo P3a as well as

the N2 - showing a reduced amplitude in MDD compared to controls (Ruchsow et al., 2008; Zhang et al., 2007a).

Despite the fact that impairments in inhibition are found following TBI (Marco et al., 2011), few studies have used the Go/Nogo task with EEG to study this population. Research into severe TBI (sTBI) has indicated that individuals with sTBI do not show the typical ERP pattern, lacking an identifiable N2 and P3 (Nativ et al., 1994) and that alpha power changes related to inhibition found in controls do not occur in individuals with sTBI (Dockree et al., 2004). The only study to include non-severe injuries as well as severe TBI also found reduced Nogo N2 and delayed Go and Nogo P3a (Armilio, 2002). Overall, it seems response inhibition related ERP changes take place post sTBI, but no research has used these ERPs to examine only mild to moderate TBI.

In addition to cognitive impairments, individuals with MDD attend more to negative information, and remember negative information more accurately (Koster et al., 2005; Watkins et al., 1996). The underlying electrophysiological activity related to these mood congruent biases can also be examined using ERPs. Studies that have examined mood congruent biases with ERPs have found that there are differences in the processing of emotive stimuli between controls and MDD subjects. For example, research has demonstrated P3b amplitude enlargements in MDD compared to controls for negative stimuli (Ilardi et al., 2007; Rossignol et al., 2008). Only one study has examined differences in emotional processing following mild TBI (mTBI) with ERPs. Solbakk et al. (2005) found a general amplitude reduction in a mTBI group but the size of this reduction was not different between emotional and neutral images, suggesting that emotional processing may not be affected by mTBI by itself.

Research using a Go/Nogo task with emotional images as stimuli has indicated that a group with high depression scores showed reduced N2 amplitude and larger overall P3 amplitude to negative stimuli compared to positive stimuli in both Go and Nogo trials (Krompinger and Simons, 2009). However, no difference between Go and Nogo N2 was found. The authors noted that the Nogo N2 effect was diminished by frequent switching of emotion-response pairing, perhaps reducing the potential to show differences between groups. The authors were also concerned that stimuli complexity reduced their Nogo N2 effect (Krompinger and Simons, 2009).

Despite the fact that both MDD and TBI groups have shown altered response inhibition ERPs, and altered processing of emotional stimuli is found in MDD, no studies have examined ERPs related to response inhibition or emotional processing in TBI-MDD.

1.1 Aims and Hypotheses

The goal of the current research was to examine neural processes related to response inhibition and emotional processing in TBI-MDD. We hypothesized that individuals with TBI and individuals with MDD would display impairments in neural processes related to response inhibition, reflected by reduced Nogo N2 and Nogo P3a amplitudes. We expected that these reductions would be most apparent in individuals with TBI-MDD, reflecting the combined impact of both disorders. Although we expected controls and participants with TBI alone to show no difference in ERP response between positive and negative emotional stimuli (Chiu et al., 2008; Solbakk et al., 2005), it was hypothesized that ERPs would be modulated dependant on emotional valence in participants with MDD and TBI-MDD.

2. Materials and Methods

2.1 Subjects:

TBI groups were recruited through a number of different avenues including the Alfred Hospital emergency department, the Monash Alfred Psychiatry Research Centre participant database, and community advertising. The depression only group was recruited through community advertising and from the Monash Alfred Psychiatry Research Centre participant database. A healthy control group was recruited from community advertising. Patients with comorbid axis 1 psychiatric disorders as assessed by the MINI were excluded (with the exception of anxiety), as were patients who were taking benzodiazepines or reported a history of neurological illness. In order to avoid the heterogeneity introduced by focal lesions, only closed TBI were included. To ensure the acute effects of TBI did not impact the results, all TBI participants were tested at least 6 weeks post injury. All participants had normal or corrected to normal vision and were between 17 and 65 years of age (three participants were younger than 20). In total, 19 healthy controls, 24 depression alone (MDD), 20 traumatic brain injured (TBI), and 15 TBI-MDD participants were recruited (TBI-MDD). Two MDD participants did not meet severity criteria, one MDD and one TBI-MDD participants were excluded due to probable medication effects (benzodiazepines/oxycontin), and two MDD participants did not complete the EEG session. One healthy control participant's data was lost due to an equipment fault. After exclusions, 18 healthy controls, 19 MDD, 20 TBI only and 14 TBI-MDD participants remained. For the TBI and TBI-MDD participants severity of injury was measured through patient reports and confirmed by hospital records where available. Glasgow Coma Scale score (GCS), length of loss of consciousness (LOC), and length of PTA were recorded (Table 2). All participants in

the MDD and TBI-MDD groups had a pre-existing diagnosis of MDD which was confirmed via diagnostic interview with the MINI International Neuropsychiatric Interview for DSM-IV (Sheehan et al., 1998). Depression severity was assessed with the Beck Depression Inventory-II (BDI-II) (Beck and Steer, 1984) and the Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979), and IQ was estimated with the Weschler Test of Adult Reading (WTAR) (Wechsler, 2001), which has been shown to be a valid measure of pre-morbid IQ post TBI (Green et al., 2008). Handedness was recorded using the Edinburgh Handedness Inventory (EHI) (Oldfield, 1971). Mood and demographic data for each group can be viewed in Table 3. In order to assess current cognitive performance, a computerized cognitive testing battery, the CogState (Maruff et al., 2009), was used to assess verbal memory (short term and long term) with the shopping list recall task, and n-back card tasks. The CogState assessed non-verbal memory with the visual learning task, continuous paired associative learning task and Grotton maze learning task. The CogState also assessed executive function with the set shifting task, and emotional intelligence with the social emotional cognition task. Lastly the CogState assessed motor and reaction speed with the Grotton chase task and card detection task.

In the interests of participant welfare, medications were continued during the study. Twelve of the MDD only and 6 of the TBI-MDD group were taking an antidepressant medication (Table 1). No participant changed medication between the two testing sessions or for the two weeks prior to the study. Written informed consent was obtained from each individual. The study was approved by the Ethics Committee of the Alfred Hospital and Monash University.

Table 1. Current medication for the MDD and TBI-MDD groups

	MDD	*TBI-MDD*
No Medication	7	8
SNRI	7	3
SSRI	4	2
Tricyclic	1	1

2.2 Task and stimuli

Participants performed an emotional Go/Nogo task while 64-channel EEG was recorded. Stimuli were presented via Neuroscan STIM2 software (Compumedics, Melbourne Australia). Either happy or sad simple face representations (Figure 1) were presented on a computer screen situated 75-85cm from the participants' eyes. These images were based on a common method to depict emotion (a yellow circle with upturned or downturned line), but were deliberately kept simple to avoid novelty from stimulus complexity affecting the Nogo N2 amplitude (Krompinger and Simons, 2009). Participants were instructed to respond (Go) to one type of stimuli, and withhold response to the other type (Nogo). The study included four separate blocks, each with 75 happy faces and 75 sad faces (i.e. equal frequency of Go and Nogo trials in each block). Order of presentation was pseudo-random so that no more than four of each type were presented in a row. Two sequential blocks required participants to respond (Go) to the happy face and withhold response (Nogo) to the sad face, while another two sequential blocks required the reverse (for example, the first and second blocks required responses to happy faces, while the second and third blocks required responses to the sad faces). Order of block administration was counterbalanced across the four groups. Responses were made using the index fingers: for a Go trial

participants were instructed to press a button box with their dominant hand and the keyboard spacebar with their non-dominant hand (to control for possible laterality effects) as fast as they could. Participants were instructed to withhold their response for a Nogo trial. Each stimulus was presented for 250ms with an ITI of 900ms (randomly jittered by 50ms to avoid entrainment of activity).

Participants were given a short practice block prior to performing the task. The practice block presented both respond happy and respond sad blocks in the same order that participants would perform these blocks for the EEG recording. Participants also completed another brief practice block immediately prior to the first and third blocks of the EEG task. In these practice blocks, participants responded to the same emotional valance as they would in the following two blocks. The practice blocks were administered in order to avoid the effect of switching response instruction on the Nogo N2 found by Krompinger and Simons (2009). Participants were given a short break after each block to avoid fatigue. The study was performed in a darkened, sound attenuated room.

2.3 Electrophysiological recording and analysis

A Neuroscan 64-channel Ag/AgCl Quick Cap was used to acquire EEG through NeuroScan Acquire Software and a SynAmps 2 amplifier (Compumedics, Melbourne Australia). All electrodes were referenced to a standard QuickCap reference electrode located between Cz and Cpz. Eye movements were recorded with vertical and horizontal EOG electrodes. Electrode impedances were kept below 5kΩ. Scan 4.3 (Compumedics, Melbourne Australia) was used to analyse the EEG data offline. The EEG was digitized at 500 Hz. EEGs were re-referenced offline to linked mastoids and digitally band pass filtered offline at 0.1-30Hz (24dB/octave roll-off).

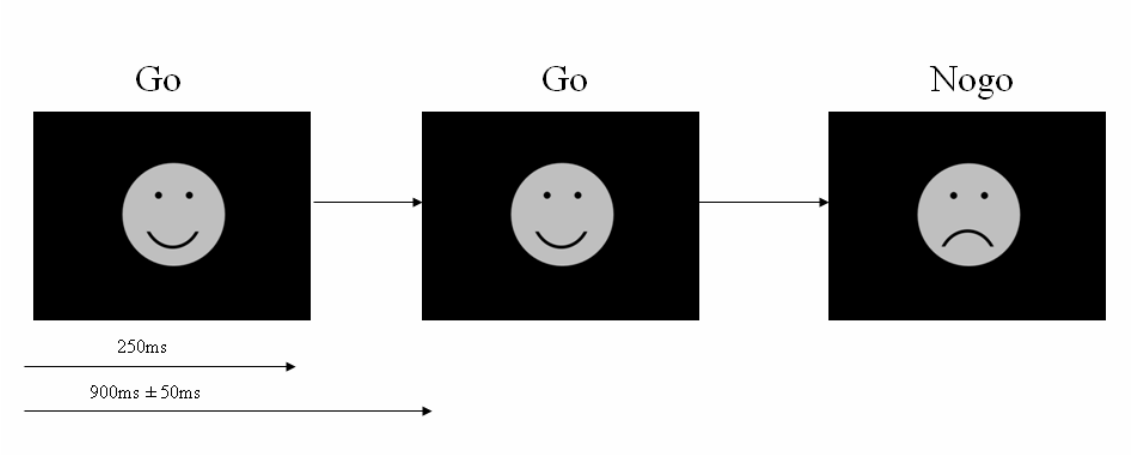

Figure 1. Emotive Go/Nogo task. Only Go and Nogo trials that were preceded by two of the opposite trial type were analysed.

Eye movements were corrected offline using the method designed by Croft and Barry (2000). Stimulus locked epochs were selected for 1000ms following each type of stimulus and each Go or Nogo trial, and baseline corrected to an interval between -100ms and 0ms before the onset of stimulus presentation. Trials contaminated with artifacts greater than ±100μv were rejected prior to averaging, as were trials with responses occurring pre-150ms (assumed to be erroneous). Only trials with correct responses were analysed. A minimum of 18 noise free epochs were required for participant inclusion in analysis. There were no significant differences between groups in number of accepted epochs for each trial type (all $p > 0.05$). Means and standard deviations for the number of accepted epochs for each trial type and group can be viewed in Table 2.

Table 2. Mean number of accepted epochs for each trial type and each group (SD in parentheses)

	Controls	*TBI*	*MDD*	*TBI-MDD*
Happy Go	34.28 (3.41)	34.40 (2.84)	33.11 (4.28)	33.15 (4.38)
Sad Go	35.78 (2.84)	34.60 (3.49)	33.79 (3.43)	33.77 (4.30)
Happy Nogo	34.61 (3.58)	32.70 (5.36)	31.95 (6.46)	31.21 (6.58)
Sad Nogo	34.44 (4.02)	32.65 (5.30)	30.89 (6.21)	30.64 (5.53)

2.4 ERPs of Interest

The averaged ERP peak amplitudes and latencies for Go trials and Nogo trials that followed two or more of the opposite trial type were compared. These more difficult trials required a switch in behavioural response, increasing task demands, as a pre-potent response tendency generated by previous trials must be over-ridden. Both Go and Nogo trial types generated a distinct P3b peak at Pz. Nogo trials show distinct N2 and P3a peaks at Fz. Go trials show an early P3 in frontal electrodes (similar to Bokura et al. 2001, and referred to as P3e), and a later slow wave negativity (SWN) similar to results observed by Kaiser et al. (2003), and suggested by those authors to be related to motor activity.

Visual inspection of grand averages at each electrode determined where each ERP was maximal, and windows for ERP comparisons were determined from these electrodes. Visual inspection by the experimenter of the individual participant averages and grand averages for each trial type determined the window within which each ERP peak was measured, so that the grand average appeared near the midpoint of each window, and the

ERP peaks for each individual fell within the relevant window. After peak measurement, scatter plots of latencies were examined to ensure latencies did not cluster around the window border (which would indicate that amplitude was maximal outside the window). The Nogo N2 component was measured as the difference between the largest negative peak in a window between 170ms-360ms following the stimulus and the preceding positive peak. Visual inspection of grand averages indicated the Nogo N2 appeared maximal at Fz, similar to Krompinger and Simons (2009). The Nogo P3a and P3b component peak was measured between 280-600ms. The P3e component was measured as the most positive peak 220-420ms post stimulus and the SWN was measured as the maximum negative peak between 300 and 650ms post stimulus. Visual inspection of grand averages indicated the Nogo P3a, Go P3e, and Go SWN were maximal at Fz, while the P3b was maximal at Pz. Visual examination of the grand average Nogo ERPs suggested that non-depressed groups showed a prolonged Nogo N2 peak compared to the depressed groups. This prolonged Nogo N2 perhaps reflects larger amplitude in the Nogo N2b window in the non-depressed groups. In order to test this post-hoc hypothesis the Nogo N2 was divided into two equal windows: the Nogo N2a between 170-265ms, and the Nogo N2b between 265-360ms. The amplitude in these two windows was calculated with an area under curve analysis, which sums the difference between each sample point in the defined window and the baseline.

2.5 Statistical evaluation

Electrodes of interest were Fz and Pz as previous research and visual inspection of grand averages indicated ERPs were maximal at these points. Statistical comparisons were made using SPSS version 17.0. The data was normally distributed and assumptions of sphericity were met ($p > 0.05$). Where equality of error variance assumptions were violated

a more stringent alpha value of p = 0.01 was selected to test differences between groups. Two way within and between repeated measures analyses of variance (ANOVA) compared amplitudes and latencies for happy and sad Nogo trials between groups for the Nogo N2, and Nogo P3a, and the happy and sad Go trials between groups for the Go P3e and SWN. A three way within and between repeated measures ANOVA compared the happy and sad Go and Nogo for the P3b between groups. One way ANOVAs with post hoc t-tests were used to assess whether there were differences in mood and cognitive assessment between the groups. A three way within and between repeated measures ANOVA compared the area under the Nogo N2a and Nogo N2b curve in four groups' in both happy and sad Nogo trials.

In order to determine the cognitive process reflected in the N2b, a comparison was run between N2b area in easy and difficult Go and Nogo trials. Easy Go and Nogo trials followed two or more of the same type of trial, and as such, both have low conflict monitoring and low response inhibition processing demands. In the hard Go trials there is more conflict monitoring and response production than in the easy Go trials. Comparing the easy and hard Nogo trials, there is an increase in conflict monitoring and response inhibition demands in the hard trials. Therefore, if the N2b is related to conflict monitoring in this task, the difference between the easy and hard trials will be in the same direction for both Go and Nogo trials. However, if it is related to response inhibition, the difference between the easy and hard trials will be in the opposite direction. A three way within and between repeated measures ANOVA compared the area under the N2b curve for all participants between easy and hard trials. In order to determine whether any of the dependent variables may have been influenced by medication effects, repeated measures ANOVA compared ERP

amplitudes and latencies between those in the MDD groups who were medicated to those who were not, for both happy and sad trials.

3. Results

3.1 Mood and Demographic Assessment

As expected, one-way ANOVAs indicated that MADRS and BDI-II scores significantly differed between groups ($p < 0.05$). Given the significant omnibus ANOVA, post hoc Fischer's LSD tests indicated that both MDD and TBI-MDD groups were significantly more depressed on the MADRS and BDI-II than the TBI and control groups ($p < 0.001$). The TBI and control groups did not differ in MADRS or BDI-II ($p > 0.05$). The TBI-MDD group had a significantly higher BDI-II score ($p = 0.014$), but not MADRS score ($p > 0.05$) than the MDD group. One-way ANOVAs indicated that groups were matched for gender, age, handedness, IQ estimated by the WTAR, and years of formal education (all p-values > 0.05). The TBI-MDD and TBI groups did not differ in injury severity as assessed by the GCS, LOC, and PTA (all p-values > 0.05).

3.2 Cognitive Function

One way ANOVA indicated the Grotton maze chase tasks (GMCT), showed a significant between group effect, $F(3, 60) = 5.826$, $p = 0.001$, as did the Grotton maze learning task, which measured visuo-spatial memory, $F(3, 60) = 4.863$, $p = 0.004$. Given the significant group effect, post hoc Fischer LSD tests were performed. These tests indicated the TBI-MDD group had significantly fewer moves per second than the TBI and control group in the Grotton maze chase task, indicating slower motor movement ($p = 0.002$ and $p = 0.018$

respectively), and significantly more errors than both the TBI and control group in the Grotton maze learning task ($p = 0.003$ and $p = 0.017$ respectively). All other tasks showed non-significant results (all $p > 0.05$).

Table 3. Mean values for demographic, depression rating score, and head injury severity measures for each group (SD in parentheses)

	Controls	*TBI*	*MDD*	*TBI-MDD*
N	18	20	19	14
Gender (F/M)	9/9	5/15	9/10	8/6
Age	42.83 (15.71)	33.15 (13.83)	38.74 (11.29)	43.29 (10.68)
Years of Formal Education	16.17 (2.90)	16.98 (3.41)	15.32 (3.77)	14.77 (3.77)
WTAR IQ	111.50 (3.20)	107.47 (5.66)	106.21 (7.86)	109.69 (5.94)
MADRS	1.06 (1.21)	2.45 (2.44)	25.63 (3.79)	26.50 (8.05)
BDI-II	1.50 (2.01)	3.30 (3.53)	23.05 (7.90)	30.08 (9.75)
EHI	88.61 (27.21)	75.54 (48.32)	88.26 (41.48)	64.08 (65.97)
GCS	N/A	13.00 (1.41)	N/A	13.67 (0.58)
LOC (hours)	N/A	0.42 (0.42)	N/A	3.73 (3.73)
PTA (hours)	N/A	30.8 (70.26)	N/A	33.63 (80.93)

WTAR IQ: Weschler Test of Adult Reading; MADRS: Montgomery-Asberg Depression Rating Scale; BDI-II: Beck Depression Inventory II; EHI: Edinburgh Handedness Inventory; GCS: Glasgow Coma Scale; LOC: Loss of Consciousness; PTA: Post-Traumatic Amnesia.

3.3 Behavioural Data

Participants performed well in the emotional Go/Nogo task, with task accuracy exceeding 90% across all four experimental groups. One way ANOVAs comparing both accuracy and reaction time on the GoNogo task between the four groups showed no

significant differences (all p's > 0.05). Means and standard deviations for behavioural data can be viewed in Table 4.

Table 4. Mean accuracy and reaction time for each trial type for each group (SD in parentheses)

	Controls	*TBI*	*MDD*	*TBI-MDD*
Reaction time				
Happy Go	357.44 (38.95)	361.64 (50.81)	358.97 (50.81)	367.42 (49.45)
Sad Go	354.23 (35.97)	370.62 (38.57)	369.55 (52.15)	368.24 (49.85)
Percentage Correct				
Happy Go	97.44 (6.04)	97.89 (4.91)	96.71 (6.69)	96.13 (9.55)
Happy Nogo	95.36 (5.61)	91.17 (8.55)	91.96 (8.81)	92.43 (9.38)
Sad Go	98.66 (7.20)	96.37 (12.62)	98.92 (9.18)	93.78 (12.45)
Sad Nogo	95.18 (3.36)	92.55 (7.03)	92.09 (8.71)	93.39 (6.91)

3.4 Event Related Potentials

Means and standard deviations for each ERP per group and trial type can be viewed in Table 5.

3.4.1 Nogo N2

A group (4) by emotion (2) repeated measures ANOVA indicated there was a marginally significant effect of group on Nogo N2 amplitude, $F(3, 66) = 2.592$, $p = 0.051$. There was no significant effect of emotion, ($p = 0.405$), nor was there an interaction between group and emotional valence, ($p = 0.195$). Given the marginally significant group effect, post-hoc Fischer LSD tests were performed, which showed overall (including both

happy and sad trials) between group differences: the TBI-MDD and MDD groups showed lower Nogo N2 amplitude compared to controls ($p = 0.021$ and $p = 0.028$ respectively). These differences can be viewed in Figure 2. With regards to Nogo N2 latency, Levene's test of equality of error variances showed that the error variance was not equal between groups, so a more stringent alpha value of $p = 0.01$ was selected to test differences between groups. A group (4) by emotion (2) repeated measures ANOVA indicated there was a marginally significant effect of group, $F(3, 66) = 3.893$, $p = 0.013$. Post hoc Fischer LSD tests were conducted to determine which between group differences were responsible for the omnibus ANOVA differences. Comparisons indicated the TBI-MDD group showed an *earlier* Nogo N2 peak compared to controls ($p = 0.004$) and TBI ($p = 0.003$), but no other groups differed ($p > 0.05$). These differences can be viewed in Figure 3. There was no significant effect of emotion, ($p = 0.561$) or interaction between group and emotional valence ($p = 0.876$). Nogo N2 amplitude and latency did not correlate with behavioural or cognitive data (all p's > 0.05).

3.4.2 Nogo P3a

Group (4) by emotion (2) repeated measures ANOVAs showed no difference in Nogo P3a amplitude or latency between the groups in any condition, or between any conditions, nor any interaction (all p's > 0.05). Nogo P3a amplitude and latency did not correlate with behavioural or cognitive data (all p's > 0.05).

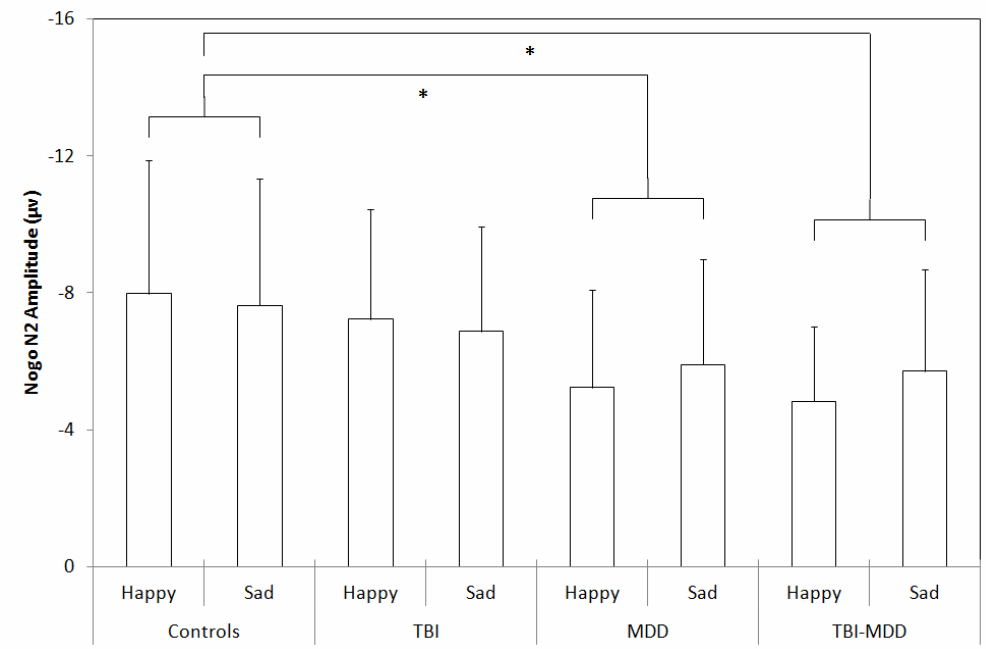

Figure 2. Mean Nogo N2 amplitude for happy and sad trials for each group. Error bars indicate standard errors. * indicates significant differences at $p < 0.05$.

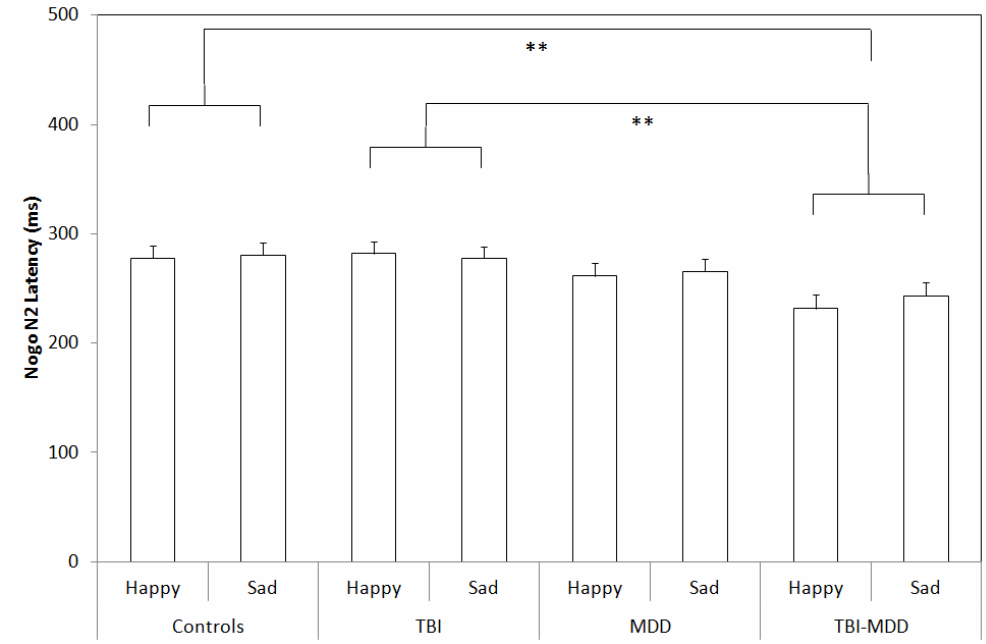

Figure 3. Mean Nogo N2 latency for happy and sad trials for each group. Error bars indicate standard errors. ** indicates significant differences at $p < 0.01$.

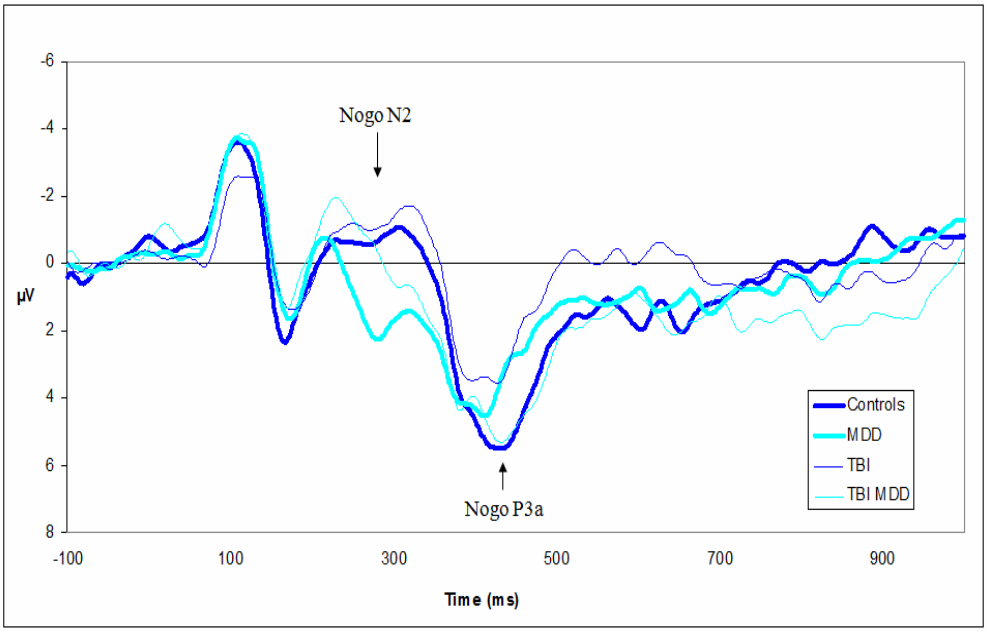

Figure 4. Grand average Happy NoGo trial waveforms for each group at Fz

3.4.3 Go and Nogo P3b

A group (4) by emotion (2) by Go/Nogo trial type (2) repeated measures ANOVA revealed no significant effect of group on P3b amplitude, ($p = 0.268$). There was a significant main effect of emotion, $F = 23.356$, $p < 0.001$, with both Go and Nogo sad trials showing a larger amplitude P3b. There was also a significant main effect of Go/Nogo, $F = 22.572$, $p < 0.001$, demonstrating that both happy and sad Go trials showed a larger P3b amplitude than Nogo trials (Figure 5). No interactions were significant (all $p > 0.05$). With regard to P3b latencies a group (4) by emotion (2) by Go/Nogo trial type (2) repeated measures ANOVA showed no significant effect of group, ($p = 0.500$). Nor was there a significant effect of emotion, ($p = 0.290$). No significant effect of Go/Nogo was found either, ($p = 0.125$), and no interactions were significant. Go and Nogo P3b amplitude and latency did not correlate with behavioural or cognitive data (all p's > 0.05).

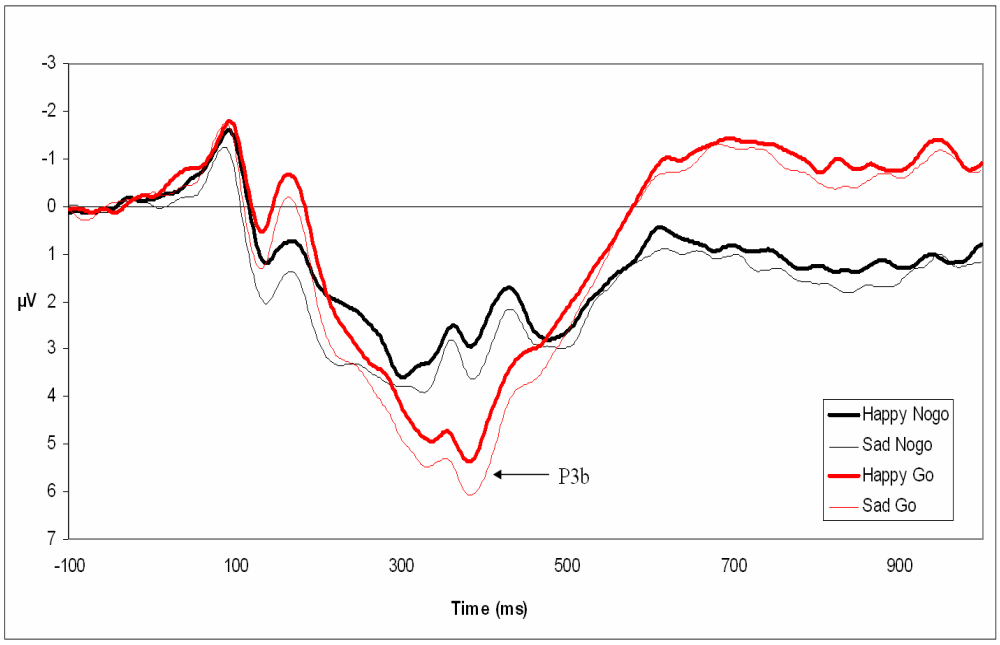

Figure 5. Grand average Happy and Sad Go and Nogo trial waveforms for all participants at Pz

3.4.4 Go P3e

A group (4) by emotion (2) repeated measures ANOVA comparison for P3e amplitude demonstrated a significant effect of group, $F(3, 65) = 3.010$, $p = 0.036$. No significant effect of emotion was revealed ($p = 0.724$), nor interaction between the two ($p = 0.510$). Given the significant group effect post-hoc Fischer LSD analysis were conducted, and showed the depression group had significantly larger Go P3e amplitude than the TBI group for the pooled data for both happy and sad trials ($p=0.004$), but no other groups differed. A group (4) by emotion (2) repeated measures ANOVA showed no significant differences between groups for P3e latency ($p = 0.846$). Nor was there a significant effect of emotion ($p = 0.576$), nor interaction between the two ($p = 0.942$). In order to assess whether the P3e was related to motor activity, a correlation was run between P3e latency and Go RTs. This

was highly significant in both sad trials (r = 0.337, p = 0.005) and happy trials (r = 0.330, p = 0.007).

3.4.5 Go SWN

A group (4) by emotion (2) repeated measures ANOVA showed there was no difference across the groups for SWN amplitude (p = 0.154), or for emotion (p = 0.609), nor interaction between group and emotion (p = 0.905). A group (4) by emotion (2) repeated measures ANOVA showed a significant main effect of group (across both happy and sad trials) was found on SWN latency, F (3, 65) = 3.184, p = 0.030. There was no significant main effect of emotion (p = 0.861), nor interaction between group and emotion (p = 0.115). Given the significant main effect of group Fischer LSD post hoc comparisons were conducted and indicated that MDD and TBI-MDD groups had significantly delayed SWN latencies across both emotions compared to the control group (p = 0.027 and p = 0.007 respectively). These differences can be viewed in Figure 6. In order to assess (Kaiser et al., 2003)'s suggestion that the SWN was related to motor activity, a correlation was run between SWN latency and Go RTs. This was significant in both sad trials (r = 0.274, p = 0.023) and happy trials (r = 0.312, p = 0.009).

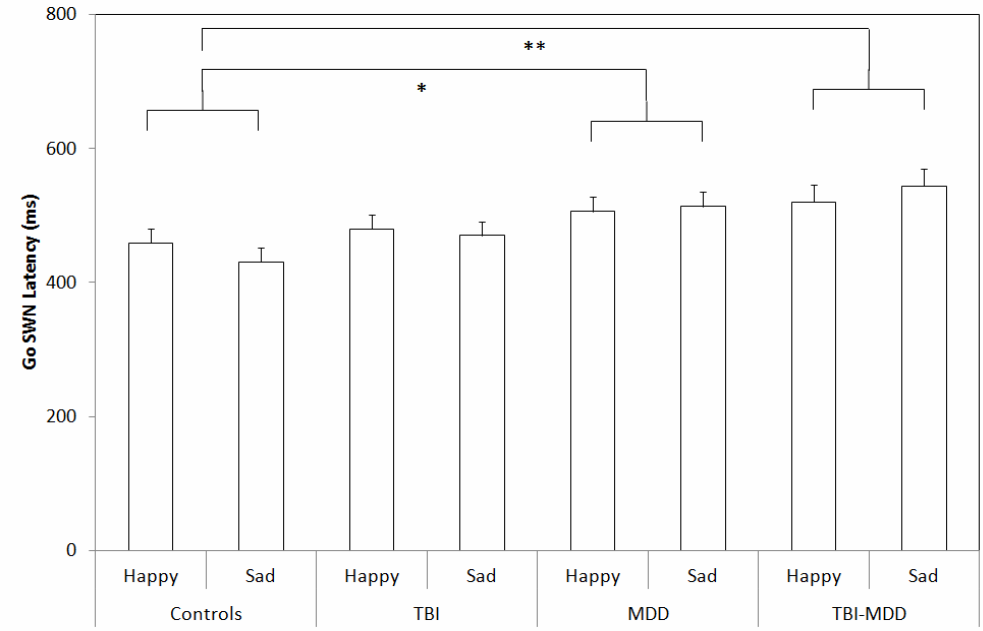

Figure 6. Mean Go SWN latency for happy and sad trials for each group. Error bars indicate standard errors. ** indicates significant differences at $p < 0.01$, while * indicates differences at $p < 0.05$.

3.4.6 Nogo N2a and N2b

A group (4) by N2 area (2) by emotion (2) repeated measures ANOVA indicated there was a significant interaction between group and area of Nogo N2, $F = 3.032$, $p = 0.035$. Given the significant interaction, post hoc N2 area (2) by emotion (2) repeated measures ANOVA comparisons were conducted within each group. These comparisons indicated the significant interaction was due to significantly less negative area in the Nogo N2b compared to the Nogo N2a in the MDD ($p = 0.023$) and TBI-MDD groups ($p = 0.006$), but not in the TBI or control groups (both $p > 0.050$). These interactions can be viewed in Figure 9. No significant main effect of group was detected for mean Nogo N2a and Nogo N2b area ($p = 0.330$). There was no significant effect of emotion ($p = 0.501$), nor interaction between group and emotion ($p = 0.124$). The relationship between Nogo N2b area in happy and sad

trials and MDD rating scale scores in the combined MDD and TBI-MDD groups was investigated with correlations. Nogo N2b for sad trials correlated with MADRS score ($r = 0.307$, $p = 0.044$) so that higher MADRS scorers showed less negative Nogo N2b area in sad Nogo trials. This relationship can be viewed in Figure 10. No other correlations were significant (all $p > 0.05$).

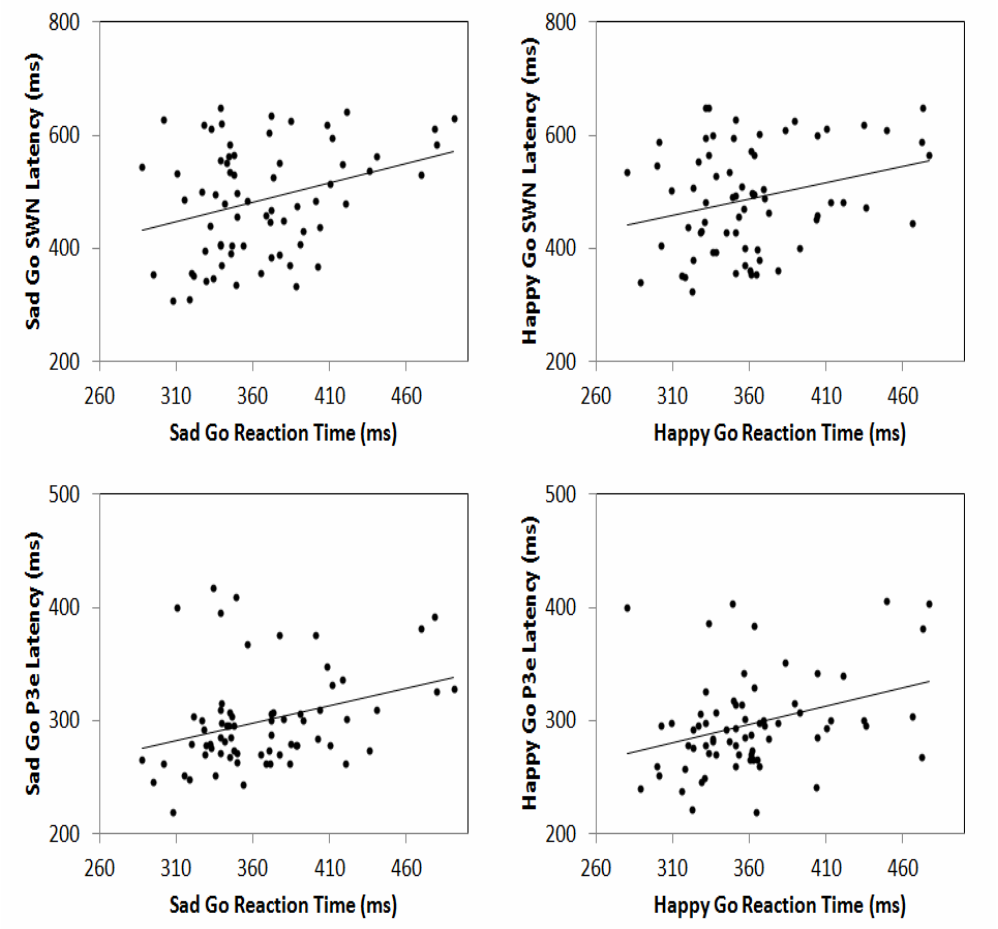

Figure 7. Scatter plots depicting significant relationships between SWN and P3e latencies and reaction times

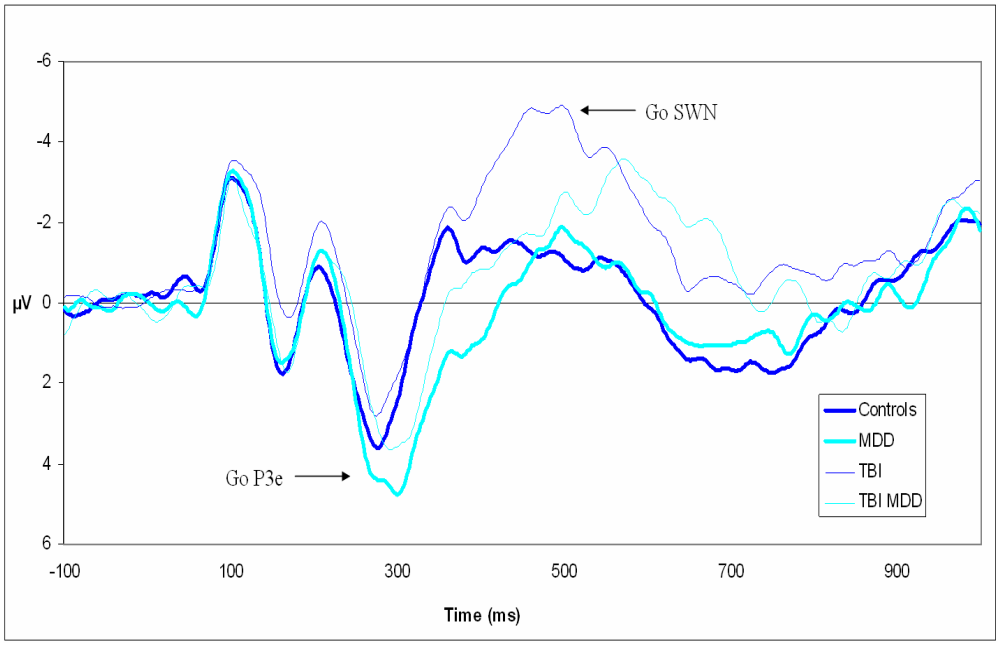

Figure 8. Grand average Sad Go trial waveforms for each group at Fz

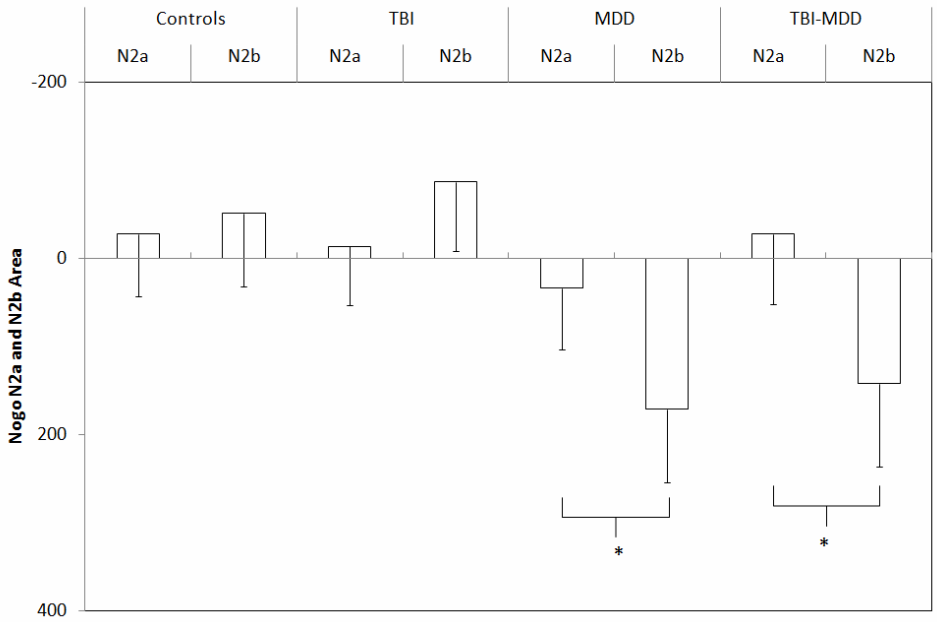

Figure 9. Mean Nogo N2a and N2b area collapsed across happy and sad trials for each group. Error bars indicate standard errors. * indicates significant differences at $p < 0.05$.

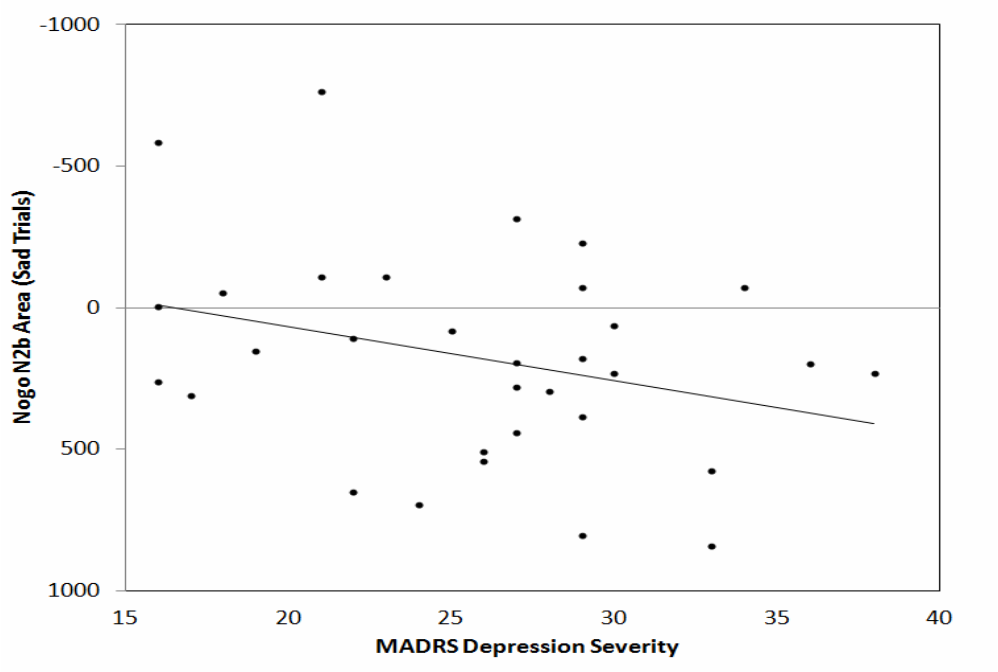

Figure 10. Scatter plot depicting the relationship between Nogo N2b area for sad trials and MADRS score in the MDD and TBI-MDD groups

3.4.7 The N2b and response inhibition

An emotion (2) by Go/Nogo trials type (2) by difficulty (2) repeated measures ANOVA comparing all participants from all groups indicated there were no significant main effects (all $p > 0.05$). There was a significant interaction between difficulty and Go/Nogo trials, $F = 16.030$, $p < 0.001$. To assess this significant interaction, post hoc t-tests were conducted. These comparisons indicated that across all groups Hard Happy Nogo trials show significantly more negative N2b area than Easy Happy Nogo trials ($p = 0.012$), and Hard Sad Nogo trials show marginally significantly more negative N2b area than Easy Sad Nogo trials ($p = 0.053$). On the other hand, post hoc tests indicated that Hard Happy Go trials showed more positive N2b area than Easy Happy Go trials ($p = 0.006$), as did Hard Sad Go trials over Easy Sad Go trials ($p = 0.001$). Figure 11 demonstrates this finding visually. The result

suggests that the Nogo N2b is related to response inhibition rather than conflict monitoring in this task.

3.4.8 Medication effects

No comparisons between medicated participants and unmedicated participants were significant (all $p > 0.05$).

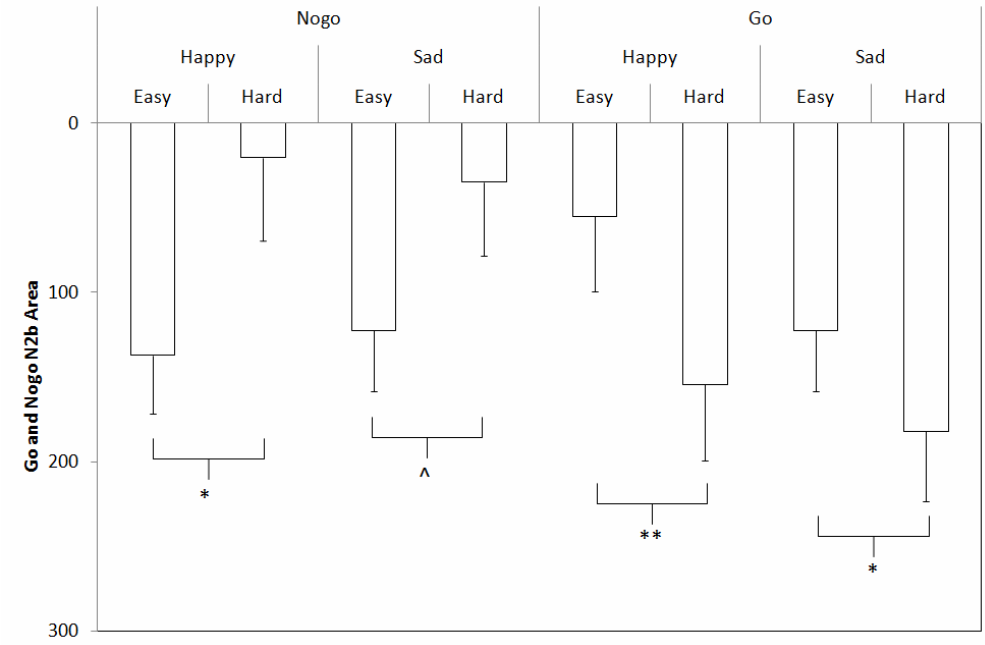

Figure 11. Mean N2b area for happy and sad trials Go and Nogo trials. Error bars indicate standard errors. ** indicates significant differences at $p < 0.01$, while * indicates differences at $p < 0.05$, and ^ indicates trends at $p < 0.10$.

Table 5. Mean amplitude (μv) and latency (ms) for each ERP in each group for each trial type (SD in parentheses)

	Controls	*TBI*	*MDD*	*TBI-MDD*
Nogo N2 Amplitude				
Happy	-7.98 (3.89)	-7.23 (3.22)	-5.23 (2.85)	-4.83 (2.19)
Sad	-7.64 (3.69)	-6.87 (3.08)	-5.90 (3.07)	-5.71 (2.99)
Nogo N2 Latency				
Happy	277.56 (55.56)	281.70 (47.45)	261.44 (59.09)	231.57 (22.62)
Sad	280.56 (52.07)	277.90 (39.69)	265.78 (58.74)	243.43 (26.60)
Nogo P3a Amplitude				
Happy	7.29 (4.66)	5.44 (4.66)	6.81 (4.13)	7.46 (4.22)
Sad	7.64 (4.09)	7.03 (3.99)	6.52 (3.94)	9.00 (5.84)
Nogo P3a Latency				
Happy	452.67 (75.35)	421.60 (53.98)	395.89 (95.45)	409.29 (66.93)
Sad	426.67 (58.90)	407.90 (34.28)	423.78 (99.94)	423.29 (73.68)
Nogo P3b Amplitude				
Happy	6.75 (2.50)	5.83 (2.12)	5.55 (2.61)	4.52 (2.60)
Sad	7.06 (2.35)	6.31 (2.61)	6.12 (2.62)	5.32 (3.02)
Nogo P3b Latency				
Happy	382.67 (93.79)	373.90 (98.24)	431.44 (103.23)	373.08 (89.91)
Sad	385.78 (93.53)	362.20 (64.62)	369.11 (93.58)	404.00 (91.21)
Go P3b Amplitude				
Happy	7.51 (3.09)	7.23 (3.15)	7.22 (3.75)	6.04 (3.16)
Sad	7.06 (2.35)	6.31 (2.61)	6.12 (2.62)	5.32 (3.02)
Go P3b Latency				
Happy	397.89 (81.09)	353.30 (44.23)	370.33 (62.99)	380.77 (52.69)
Sad	386.67 (67.23)	362.60 (54.24)	366.11 (34.71)	363.23 (55.68)
Go P3e Amplitude				
Happy	5.52 (2.75)	3.26 (3.42)	6.54 (3.62)	5.08 (3.26)
Sad	5.14 (3.15)	4.06 (2.86)	6.61 (3.94)	5.02 (2.59)

	Controls	*TBI*	*MDD*	*TBI-MDD*
Go P3e Latency				
Happy	294.44 (44.35)	294.70 (41.74)	301.89 (42.22)	298.46 (47.23)
Sad	294.44 (48.63)	294.40 (40.39)	307.22 (46.17)	302.62 (35.99)
Go SWN Amplitude				
Happy	-4.61 (4.12)	-7.25 (5.14)	-4.04 (3.35)	-5.66 (6.82)
Sad	-4.88 (3.91)	-7.13 (4.13)	-4.04 (4.33)	-6.19 (5.62)
Go SWN Latency				
Happy	459.11 (108.84)	480.20 (74.86)	506.00 (87.39)	520.31 (94.65)
Sad	431.22 (104.76)	470.80 (69.09)	513.67 (90.10)	544.62 (101.13)
Nogo N2a Area				
Happy	8.25 (359.74)	-13.95 (296.37)	46.27 (329.00)	-78.70 (393.22)
Sad	-63.28 (288.25)	-14.11 (303.38)	21.12 (265.40)	23.18 (365.29)
Nogo N2b Area				
Happy	-45.69 (373.73)	-108.46 (368.73)	194.32 (404.03)	67.20 (412.49)
Sad	-57.16 (301.14)	-65.41 (355.49)	147.93 (382.31)	217.59 (355.83)

4. Discussion

This study used an emotional Go/Nogo task to determine the effect of MDD, TBI, and TBI-MDD, on ERPs related to response inhibition and mood congruent emotional processing biases. The main finding was that individuals with both MDD and TBI-MDD groups displayed impairment in electrophysiological measures of response inhibition processing, with a different Nogo N2 pattern, in particular a reduction of the Nogo N2b.

The results also indicated that the negativity in the Nogo N2b component was related to response inhibition, and not conflict monitoring or sensory mismatch. We demonstrated the relationship between N2b and response inhibition by showing that

activity in the N2b window became more negative when response inhibition and conflict monitoring demands in the Nogo trials increased, but more positive in Go trials when conflict monitoring demands were equally increased, but no response inhibition demands were increased. This finding supports previous research which has suggested the Nogo N2 is related to response inhibition, as its amplitude increased when Go responses were more difficult to withhold (Falkenstein et al., 1999; Jodo and Kayama, 1992). Therefore, the current study has demonstrated that electrophysiological processing related to response inhibition is altered in individuals with MDD and TBI-MDD in comparison to healthy controls. The study has also indicated that individuals with TBI only do not show altered electrophysiological processing related to response inhibition when directly compared to healthy controls.

A Nogo N2 reduction in MDD has been found by previous research in both typical and late life MDD (Kaiser et al., 2003; Katz et al., 2010; Krompinger and Simons, 2009). However, other research has shown increases in N2. Ruchsow et al. (2008) showed N2 amplitude increases in MDD participants in remission, but the increases were in both Go and Nogo trials, so probably related to a cognitive function other than response inhibition. Zhang et al. (2007b) also found increased N2 amplitude in individuals with familial risk for MDD, but only when measuring the N2 at fronto-temporal electrodes (whereas this research measured N2 amplitude at Fz). None of the previous studies have focused specifically on the Nogo N2b, nor demonstrated the relationship between the ERP and response inhibition, so the inconsistency between this study and some previous studies (Ruchsow et al., 2008; Zhang et al., 2007b) may be because our N2b was generated

specifically by response inhibition processing, while other N2 ERPs may have been related to other cognitive processes.

In addition to Nogo N2b differences between groups, the Nogo N2b area for sad trials also correlated with MADRS measure of depression severity, perhaps suggesting the Nogo N2b does not simply differentiate the groups but also acts as a measure of the extent of negative mood. Research focusing on the Nogo N2 has indicated that in healthy controls it is generated in the ACC (Bokura et al., 2001; Katz et al., 2010; Malloy et al., 1993; Nieuwenhuis et al., 2003). Research with fMRI has also indicated that response inhibition is related to processing in the ACC (Malloy et al., 1993). However source localisation does not show that the N2 is generated by the ACC in MDD, possibly due to dysfunctional ACC processing (Katz et al., 2010). These Nogo N2 amplitude changes in MDD for response inhibition tasks may relate to MRI research indicating that ventral ACC volumes are smaller in MDD, and activity in this area has been shown to be altered in both MDD and TBI MDD (Chen et al., 2008; Harvey et al., 2005; Tang et al., 2007).

Interestingly, the results also indicated that MDD only participants showed increased P3e amplitude in Go trials. Bokura et al. (2001) indicated with source localization that this ERP was generated by the medial parietal lobe. The results of this study demonstrated that it was present in Go but not Nogo trials, and that it was larger for harder compared to easier Go trials. The P3e was also was found to occur in the same time period but in the opposite direction to the Nogo N2b deflection, which appears to be related to response inhibition, and the P3e correlated with reaction time. These factors suggest it is related to response production. No previous research has revealed differences between MDD and control groups in the P3e (indeed, very few Go/Nogo studies have reported a P3e deflection). This,

combined with the fact that the TBI-MDD group did not show a difference in P3e amplitude suggests caution in the interpretation of this result. This result may indicate that rather than a simple impairment in response inhibition related processing, a combination of this and over-active response production mechanisms may be apparent in MDD. The TBI-MDD group may not have shown the same as a result of their smaller group size, or it may be that the processes generating the P3e are impaired as a result of the TBI. Further research may be able to offer more insight into this issue.

In addition to the Nogo N2b alteration, the frontal slow wave negativity (SWN) in response to Go trials was delayed in both MDD and TBI MDD groups compared to the control and TBI only groups. This deflection was present only in Go trials, and has been thought to be related to motor activity (Kaiser et al., 2003; Salisbury et al., 2004). The latency of this deflection was weakly correlated with reaction time in this study, but the deflection peaked on average 100-150ms after average reaction time, and reaction time did not differ between groups. Since it is unclear which processes relate to the SWN, it is uncertain what differences between the groups signify. However, it is notable that the delay was specific to the mood impaired groups.

There was also no evidence of mood congruent bias for the MDD groups in any of the behavioural data or ERPs. This differs from Cavanagh and Geisler (2006) who found MDD participants had delayed and reduced P3b to happy stimuli compared to controls, and from other researchers (Ilardi et al., 2007; Krompinger and Simons, 2009; Rossignol et al., 2008) who reported that MDD showed larger P3b in response to negative compared to positive stimuli. These researchers proposed that P3b amplitudes are reduced to positive and increased to negative stimuli in MDD because of increased attention towards negative

stimuli, which influences increased P3b amplitude (Wickens et al., 1983). However, the opposite pattern has also been reported, with reduced amplitude P3b for negative stimuli, and increased for positive (Blackburn et al., 1990). Blackburn et al. (1990) argue that their result is due to the expectation of negative stimuli in MDD participants, so negative stimuli have a higher subjective probability, resulting in lower P3b amplitudes. The inconsistency between the results of ERP studies of mood congruent bias in MDD may be an indication that mood congruent bias has an unreliable impact on ERPs, which would explain the current results.

Alternatively, it is possible that the very simple depictions of happy and sad faces used as stimuli in this study did not elicit mood related processing and as a result did not distinguish the MDD from non-MDD groups with a differential response to happy and sad stimuli. However, sad trials showed a larger P3b than happy trials, similar to previous research (Rossignol et al., 2008), suggesting that the faces were differentially processed and that there was an effect on mood related processing.

Overall, our results indicated that there were differences in ERPs between MDD and the non-MDD groups, but the behavioural data did not. On the Cogstate assessment differences were only seen in the Grotton maze and only for the TBI-MDD group. Generally, this suggests that ERP data is more sensitive to between group differences in processing than only behavioural data, similar to previous research (Krompinger and Simons, 2009). Unexpectedly, the non-depressed TBI group did not differ from the healthy control group in any ERP. This lack of difference perhaps suggests that TBI alone does not alter the ERPs related to the processes challenged by this task (particularly response inhibition – reflected by the Nogo N2b). The lack of differences may be because relatively mild severity of injury in

our TBI group did not impact the physiological process enough to be revealed as ERP alterations. Alternatively the lack of differences may indicate that the electrophysiological processes that generate the Nogo N2b (related to response inhibition and potentially generated in the ACC) are unaffected by TBI. Because there were changes demonstrated in the MDD groups, the result are not likely to be methodological flaws, or insufficient power. As no previous research has used the Go/Nogo task to measure ERPs in mild to moderately injured TBI, no direct comparisons to previous literature are possible. Previous research has shown ERP changes in mTBI groups using the oddball task, but usually when studying participants who have a neuropsychological impairment, or ongoing symptoms (Ford and Khalil, 1996; Reinvang et al., 2000; Solbakk et al., 2000). Other studies have found no differences (Dupuis et al., 2000; Potter and Barrett, 1999; Potter et al., 2001; Sivak et al., 2008).

There are a number of limitations of the current study. Perhaps the most important is the lack of correction for multiple comparisons. These corrections were not performed as they can be overly conservative in exploratory studies with small sample sizes as per the current study (Cook and Farewell, 1996), which examined response inhibition in TBI-MDD for the first time. Additionally, the N2 comparisons were planned, the direction of change was expected, and a consistent change was found in both the MDD and TBI-MDD group. The likelihood of this consistent effect of MDD in two separate MDD groups being due to Type I error is extremely low. The majority of the MDD group were medicated, and almost half of the TBI-MDD group were medicated. Previous research has suggested that medication can affect EEG results (Johannes et al., 2001). However, no differences were found when comparing medicated to unmedicated MDD. Another potential limitation is that ERP

changes in MDD groups did not relate to behavioural performance, so although the results demonstrate that the N2b is related to response inhibition, the study cannot determine if the Nogo N2b reduction in the MDD and TBI-MDD groups results in altered behaviour. The lack of behavioural differences is most likely due to a ceiling effect in all groups' behavioural data – as average performance in all groups was over 90%. More difficult tasks with shorter stimulus presentation times and faster inter-trial intervals may resolve this in future research. Lastly, because this study is cross-sectional it does not offer any insight as to whether Nogo N2b reductions in MDD are related to depressed mood state, or MDD traits. The correlation between MADRS scores and Nogo N2b area suggests it may be related to mood state, but this appeared only in sad trials, and not for the BDI-II. Future researchers could examine longitudinal data to resolve the issue of causality.

4.1 Conclusions

This study indicates that one of the features of MDD is reduced Nogo N2b amplitude. The reduced Nogo N2b amplitude is found in both MDD and TBI-MDD, and was shown to be related to response inhibition. The finding supports arguments for impairment in response inhibition in MDD and TBI-MDD. The results suggest that ERP measurements may offer additional information not available with traditional behavioural measures. Additionally, the results may indicate that response inhibition related processes are not impaired following a mild to moderate TBI. Further research is required before this can be confirmed.

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Conflicts of Interest

PBF has received equipment for research from Medtronic ltd, Magventure A/S and Brainsway Ltd. ZJD has received equipment and operational expenses for research from Brainsway Ltd.

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Chapter Eight

Error Positivity is Reduced in Depression and Traumatic Brain Injury

Depression

The following chapter is comprised of a study that has been submitted for publication in Cerebral Cortex. Following from the chapter on successful response inhibition, this chapter presents a comparison of the differences between the four groups on electrophysiological measures of processing when response inhibition errors are made. Previous research indicates that these measures are altered in MDD groups, and that negative affect following a TBI was a specific modulator (Larson et al., 2009). As such, it was expected that the ERPs would be altered in TBI-MDD and MDD groups, and this would differentiate those groups from healthy controls and individuals who had not developed MDD following a TBI.

Error Positivity is Reduced in Depression and Traumatic Brain Injury Depression

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Running Title: ERROR POSITIVITY IN TBI-MDD

Abstract

Poorer outcome following a traumatic brain injury (TBI) is associated with impairments in error awareness. Major depressive disorder (MDD), a common sequalae of TBI, has also been associated with difficulties in error awareness. Research has not yet examined whether error awareness is altered in MDD following TBI (TBI-MDD). Error processing can be assessed with electroencephalography (EEG), through two response locked measures - Error related negativity (ERN) and Error Positivity (Pe). In this study, we investigated whether the ERN or Pe are altered in individuals with TBI-MDD. We compared four groups – healthy controls (n = 15), MDD only (n =16), TBI only (n = 15), and TBI-MDD (n = 12). Participants completed a Go/Nogo task while EEG was recorded, and the ERN and Pe were compared between groups. The ERN did not differ between groups. Pe amplitude was significantly reduced in the MDD group. We also found a trend towards reduced Pe amplitude in the TBI-MDD group compared to healthy controls. The TBI only group did not differ from the control group on either measure. These results suggest reduced awareness of errors in MDD and TBI-MDD.

Keywords: EEG; ERN; MDD; Pe; TBI

1. Introduction

Individuals who have suffered a traumatic brain injury (TBI) are significantly more likely to develop a major depressive disorder (MDD) than the general population (Jorge et al. 1993; Kaponen et al. 2002; Kreutzer et al. 2001; Pagulayan et al. 2008; Satz et al. 1998). While research has examined the psychosocial factors contributing to the development of TBI-MDD, very little research has examined changes in brain activity. Knowledge about how brain activity is altered in this group would be useful for both prediction of the development of TBI-MDD, and treatment methods for the disorder. Impairment in the conscious recognition of mistakes, or error awareness, is associated with poorer outcome following TBI, and may also be a feature of MDD (Pizzagalli et al. 2006; Sherer et al. 1998; Trudel et al. 1998; Wise et al. 2005). Therefore, impaired error awareness following TBI may be related to the development of MDD following TBI (TBI-MDD). Electroencephalographic (EEG) measures have the capacity to uncover neural activity that consistently follows an erroneous response.

Two EEG recorded event related potentials (ERPs) have been found to reliably index error processing, the error related negativity (ERN) (Falkenstein et al. 2000) and the error positivity (Pe) (Nieuwenhuis et al. 2001). The ERN is a frontal deflection occurring within 150ms of an error, and is thought to be related to error detection (Falkenstein et al. 2000) or response evaluation (Vidal et al. 2000). The ERN can also be compared to the similar but smaller amplitude deflection that occurs during the same time window following correct responses. This is termed the correct response negativity (CRN), and is thought to reflect a similar process to the ERN (Vidal et al. 2000). The ERN is generated even when participants are unaware of having made an error (Nieuwenhuis et al. 2001). As such, it is considered a

good indicator of whether reduced error awareness is related to impairments in early automatic processes.

Increased ERN amplitude has been reported in MDD groups (Chiu and Deldin 2007; Holmes and Pizzagalli 2010). However, ERN amplitude increases are not a consistent finding (Olvet et al. 2010; Schrijvers et al. 2008; Schrijvers et al. 2009). This variability has been suggested to be due to severity of MDD across studies, namely that in moderate MDD the ERN amplitude is enhanced (possibly as a result of hypervigilance to mistakes) and that in severe MDD it is reduced (as a result of apathy) (Olvet et al. 2010). Only two studies have examined the ERN in TBI, both focusing on severe TBI. One study showed no changes (Larson and Perlstein 2009), but the other showed smaller ERN amplitudes in individuals with negative affect following a severe TBI (Larson et al. 2009).

In contrast to the ERN, the Pe (a central-parietal deflection occurring 150-450ms after an error) is thought to represent processes related to *conscious awareness* of the error, as it is only generated when participants are aware they have made an error (Nieuwenhuis et al. 2001). Similar to the ERN literature, the Pe findings are not entirely consistent in MDD with studies showing both no change and reductions in amplitude (Chiu and Deldin 2007; Holmes and Pizzagalli 2008, 2010; Olvet et al. 2010; Schrijvers et al. 2008; Schrijvers et al. 2009). The inconsistency may again be an artifact of differences in severity between studies, as reductions in Pe have been found in groups with severe MDD (Olvet et al. 2010; Schrijvers et al. 2008; Schrijvers et al. 2009) and no differences reported in groups in the mild to moderate range (Chiu and Deldin 2007; Holmes and Pizzagalli 2008). Smaller mean Pe amplitude has also been related to reduced awareness of impairment in severe TBI

(Larson and Perlstein 2009), but not correlated with negative affect a severe TBI group (Larson et al. 2009).

Despite the fact that impairments in error awareness are seen following a TBI, and neurophysiological markers of error awareness are altered in MDD, research has not yet examined whether error awareness is altered in TBI-MDD. Comparison of error awareness measures between individuals with TBI and individuals with TBI-MDD is likely to inform us about whether or not this factor is involved in the development of MDD following a TBI.

As such, the aim of this study was to use electrophysiological measures to investigate whether error awareness is impaired in TBI-MDD, and whether any impairment is consistent with the presence of the TBI, MDD, or unique to the occurrence of TBI-MDD. We compared the ERN and Pe across control, TBI, MDD, and TBI-MDD groups. In order to avoid the heterogeneity in neural response that focal lesions introduce, we examined only mild to moderate TBI. We included moderate to severe MDD severity to allow examination of the effect of the spectrum of severity on error processing, in order to assess the effect of severity on inconsistencies seen in previous studies. We hypothesised that individuals with TBI-MDD would exhibit enlarged ERN amplitudes and reduced Pe amplitudes, reflecting reduced conscious awareness of errors. We also hypothesised that these changes would be similar to those found in the MDD group, while our mild to moderate TBI group would show no changes.

2. Materials and Methods

2.1 Participants

In total, 75 people were recruited for this study. Four groups were recruited: healthy controls (n = 19), MDD (n = 24), TBI (n = 20), and TBI-MDD (n = 15) from a combination of community advertising and the emergency department of the Alfred Hospital in Melbourne. All participants were aged between 17 and 65 years of age. Participants were assessed with the MINI International Neuropsychiatric Interview for the DSM-IV (Sheehan et al. 1998) and excluded if they displayed any comorbid axis 1 psychiatric disorder (with the exception of anxiety in the MDD groups). Participants in the MDD or TBI-MDD groups were excluded if they did not meet the MINI criteria for current depressive episode. Participants who reported either current benzodiazepine use or a history of neurological illness other than closed TBI were also excluded. All participants had normal or corrected to normal vision. MDD and TBI-MDD participants were included if their depression severity on the BDI or MADRS fell in the moderate to severe range. All TBI participants were tested more than 6 weeks post injury, and were only included if their injury fell into the mild-moderate range. This criteria for this was a Glascow Coma Scale (GCS) (Teasdale and Jennett 1974) score of 9 or above, and loss of consciousness (LOC) of less than 24 hours (Rao and Lyketsos 2000). Length of post-traumatic amnesia (PTA) was also assessed.

The data from one MDD and one TBI-MDD participant was excluded due to post testing disclosure of probable medication effects (benzodiazepine and oxycontin respectively). Two MDD participants did not reach MINI severity criteria, and two others did not complete the EEG session. One healthy control's data was lost due to equipment fault. This resulted in a total of 18 healthy controls, 19 MDD, 20 TBI and 14 TBI-MDD participants

with behavioural data to be analysed. Further exclusions for insufficient number of accepted error related epochs will be referred to in the Event-Related Potential section.

The study was approved by the ethics committees of the Alfred Hospital and Monash University. Written informed consent was obtained from each participant. Assessments and EEG testing took place over two sessions within two weeks of each other. One session was for the EEG, which took approximately two hours to complete. The other involved mood, demographic, and cognitive assessments. The mood assessment involved the Beck Depression Inventory-II self report scale (BDI) (Beck and Steer 1984), and the Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg 1979). Pre-injury or depression IQ was estimated using the Weschler Test of Adult Reading (WTAR) (Wechsler 2001), which has been validated in TBI populations (Green et al. 2008). Handedness was also assessed with the Edinburgh Handedness Inventory (Oldfield 1971). Means for the demographic data can be seen in Table 1. Twelve of the MDD and six of the TBI-MDD groups were medicated with anti-depressants (Table 1).

Table 1. Current medication for the MDD and TBI-MDD groups.

	MDD	TBI-MDD
No Medication	6	7
SNRI	4	3
SSRI	4	2
Tricyclic	1	0

2.2 Task and Stimuli

EEG data was recorded while participants completed a modified Go/Nogo task, with simplified representations of happy and sad faces as stimuli (see Figure 1). The task was presented on a computer screen 75-85cm from the participant's eyes. It involved brief sequential presentations of each emotion in a pseudorandom order, so that no more than three of one type occurred in sequence. Stimuli presentation lasted 250ms, with an inter-trial interval of 900ms (+ or – a 50ms jitter to avoid bandwidth entrainment). Participants were instructed to respond with a button press by both index fingers at the same time, as fast as possible to one emotion, but to withhold responses to the other emotion. Reaction time and accuracy data was recorded from the dominant hand's button press. Four blocks, each with 75 happy and 75 sad faces were presented. Participants were given a brief two to five minute break between each block. Emotion/response pairing was to one face for the first half of the study, and switched to the opposite emotion for the second half. This was counterbalanced between participants and groups, so that half the participants in each group responded to the happy face for the first and second blocks then the sad face for the third and fourth. Prior to the first block and the third block, participants were given a brief

practice version in which they responded to the same stimuli that they would respond to in the next block. The task was performed in a darkened, sound attenuated room.

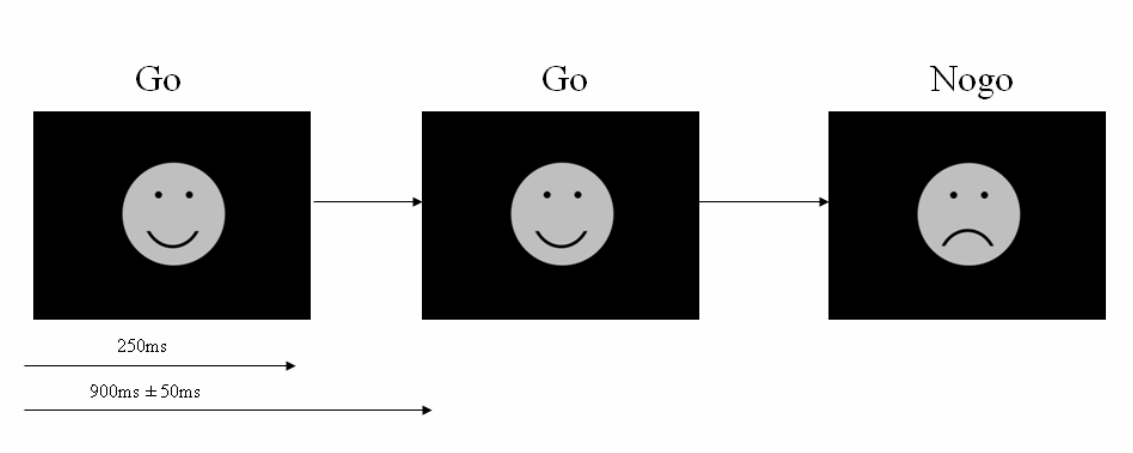

Figure 1. Go/Nogo stimuli and task design.

2.3 Electrophysiological Recording

A 64-channel Neuroscan EEG Ag/AgCl Quick Cap (following the 10-20 montage) was used to acquire data to Neuroscan software through a SynAmps2 amplifier (Compumedics, Melbourne Australia). All electrodes were referenced to an electrode between Cz and CPz online. Horizontal and vertical eye movements were recorded using four EOG electrodes. Impedances were maintained at less than 5kΩ. Recordings were sampled at 500Hz, and bandpass filtered from 0.1-100Hz (24dB/octave roll off). Offline, data was re-referenced to linked mastoids, and digitally band pass filtered from 0.1-30Hz (24dB/octave roll-off). Blink and eye movement artifacts were removed with an algorithm (Croft and Barry, 2000). Epochs were selected from -200 to 800ms around erroneous responses that occurred more than 100ms following stimulus presentation. These epochs were baseline corrected to the pre-response interval (Chiu and Deldin 2007). Trials exhibiting voltage shifts of more than

+/-75 μv across the epoch were rejected, as were trials judged to be contaminated with noise in a visual data inspection.

2.4 Event Related Potentials

Epochs were averaged around the time of erroneous responses following a Nogo trial. Errors following both happy and sad stimuli were averaged together to ensure a sufficient number of noise free error related epochs are included for analysis. Because the ERPs are response locked rather than stimulus locked the latency variability added by variable reaction times reduces the influence of stimulus valance on the average activity. Also, pooling happy and sad trials averages the differences between valances, leaving only the activity related to error production. A minimum of six error related epochs were required for inclusion in the analysis, as evidence suggests this number of trials is sufficient. Averages of six error trials show strong correlation with larger trial number samples occurs, do not significantly differ from grand averages, and internal reliability reaches moderate levels (Olvet and Hajcak 2009; Pontifex et al. 2010). The data from a number of participants were excluded with too few noise free error epochs. This included three healthy controls, five TBI only participants, three MDD only participants, and two participants with TBI-MDD. This left 15 healthy controls, 16 MDD, 15 TBI and 12 TBI-MDD participants. Demographic, mood, and injury severity information for these participants can be viewed in Table 2. Of these remaining participants, nine of the MDD and five of the TBI-MDD groups were medicated with anti-depressants (Table 1).

Automatic peak detection windows were selected based on visual inspection of individual participant and grand average epochs, and the previous literature (Chiu and Deldin 2007; Compton et al. 2008; Holmes and Pizzagalli 2010). The ERN and CRN

components were defined as the largest negative peak at Fz (where it was maximal) from -50 to 150ms around the response. The Pe component was defined as the largest positive peak at Cz (where it was maximal) from 150-450ms following the response. Amplitude was measured from baseline for all three of these ERPs, and latency was measured from the response.

2.5 Statistical Analysis

Mood and demographic data were compared using one-way ANOVAs in SPSS 17.0. The number of accepted epochs in each group was also compared using a one-way ANOVA, as were the proportion of correct responses and number of errors. Both Pe amplitude and Pe latency were compared between groups using a one-way ANOVA. Two way repeated measures ANOVAs were used to compare the CRN and ERN amplitude and latencies in order to determine whether any interactions were present between and correct or incorrect response negativity, as well as overall between group differences. Pearson correlations were calculated between BDI and MADRS measures of severity and ERN and Pe amplitude.

3. Results

3.1 Demographic and Mood Assessment

Including participants who completed the behavioural, demographic, and mood assessments, the groups did not significantly differ in age, years of education, or handedness ($p > 0.05$). However, the MDD group showed significantly lower WTAR estimated pre-morbid IQ ($p = 0.045$). The two TBI groups did not differ in GCS, LOC, or PTA ($p > 0.05$). When only participants who showed sufficient number of errors for ERP data

analysis were included, no significant differences remained on any of these measures ($p > 0.05$).

Table 2. Demographics, depression rating scores, and head injury severity measures for each group after exclusion based on number of accepted epochs

	Controls	TBI	MDD	TBI-MDD
N	15	15	16	12
Gender (F/M)	8/7	3/12	6/10	6/6
Age	46.60 (14.40)	33.86 (13.65)	38.88 (11.27)	43.08 (11.58)
Years of Formal Education	15.93 (2.99)	16.67 (3.52)	15.19 (3.92)	14.82 (4.07)
WTAR pre-morbid IQ	111.20 (3.43)	107.57 (5.52)	105.50 (8.18)	108.91 (6.09)
MADRS	1.13 (1.30)	2.33 (3.96)	26.06 (3.96)	27.58 (8.04)
BDI	1.60 (2.16)	3.07 (3.49)	23.13 (8.57)	32.82 (7.72)
EHI	88.27 (29.75)	70.39 (54.67)	86.06 (45.08)	57.55 (70.13)
GCS	N/A	13.00 (1.58)	N/A	13.50 (0.71)
LOC (hours)	N/A	0.48 (0.68)	N/A	2.35 (6.84)
PTA (hours)	N/A	38.64 (78.47)	N/A	34.50 (84.81)

WTAR IQ: Weschler Test of Adult Reading; MADRS: Montgomery-Asberg Depression Rating Scale; BDI-II: Beck Depression Inventory II; EHI: Edinburgh Handedness Inventory; GCS: Glasgow Coma Scale; LOC: Loss of Consciousness; PTA: Post-Traumatic Amnesia.

3.2 Behavioural Data

No significant differences between groups were displayed for the percent of correct Nogo trials ($F = 1.496$, $p = 0.224$) and number of errors on Nogo trials ($F = 1.304$, $p = 0.280$). Neither was there a group difference in reaction times for correct or incorrect trials ($F = 0.400$, $p = 0.754$), nor interaction between correct/incorrect trial reaction time and group ($F = 0.616$, $p = 0.607$). Consistent with previous literature, errors showed faster reaction times than correct trials ($F = 280.171$, $p = 0.000$). Means and standard deviations for behavioural data can be viewed in Table 3.

Table 3. Behavioural means with all participants included (SD in parentheses)

	Controls	TBI	MDD	TBI-MDD
Number of Errors	13.33 (8.93)	16.95 (13.09)	22.26 (17.69)	18.14 (14.29)
Percent Correct	95.99 (2.68)	94.92 (3.93)	93.09 (5.51)	94.40 (4.34)
Incorrect Response RT (ms)	301.22 (41.20)	306.82 (45.77)	312.12 (67.54)	304.78 (48.36)
Correct Response RT (ms)	375.21 (38.65)	381.94 (41.28)	393.82 (41.41)	395.48 (46.97)

3.3 ERN/CRN

No significant between group differences were detected for ERN or CRN amplitude at Fz ($F = 0.976$, $p = 0.411$). Consistent with previous research, the ERN was significantly larger in amplitude than the CRN across groups ($F = 20.955$, $p = 0.000$). A trend towards an

interaction between group and CRN/ERN amplitude was detected ($F = 2.695$, $p = 0.055$). This appeared to be a result of the MDD group exhibiting the same amplitude for both correct and incorrect deflections, while other groups showed a larger ERN than CRN. However, the omnibus ANOVA did not reach significance so the result was not analysed in further post hoc comparisons. No significant between group differences were found with regards to CRN or ERN latency ($F = 2.490$, $p = 0.070$), nor within subjects between the CRN and ERN latency ($F = 0.135$, $p = 0.715$). Neither were there any interactions between group and CRN/ERN latency ($F = 0.1579$, $p = 0.205$). Additionally, no correlations between ERN amplitude and MADRS or BDI score were found within the combined MDD and TBI-MDD groups ($p > 0.050$). Data on the CRN and ERN amplitudes and latencies can be viewed in Table 3. The ERN waveform for each group can be viewed in Figure 2, and the CRN waveform for each group can be viewed in Figure 3. Means and standard deviations for ERN and CRN amplitude and latency can be viewed in Table 4.

3.4 Pe

Figure 4 depicts the Pe waveform for each group, and Figure 5 depicts the mean Pe amplitude for each group. The omnibus ANOVA revealed significant group differences in Pe amplitude ($F = 3.437$, $p = 0.023$). Post hoc Tukey tests indicated that the differences present between the MDD group and the control group ($p = 0.050$), and trended towards differing between the TBI-MDD and control groups ($p = 0.096$). No significant differences were found between the groups in Pe peak latency ($F = 0.741$, $p = 0.532$). Means and standard deviations for Pe amplitude and latency can be viewed in Table 4. Similar to the ERN amplitude, no correlations were found between the Pe amplitude and the MADRS or BDI score within the MDD and TBI-MDD groups ($p > 0.050$).

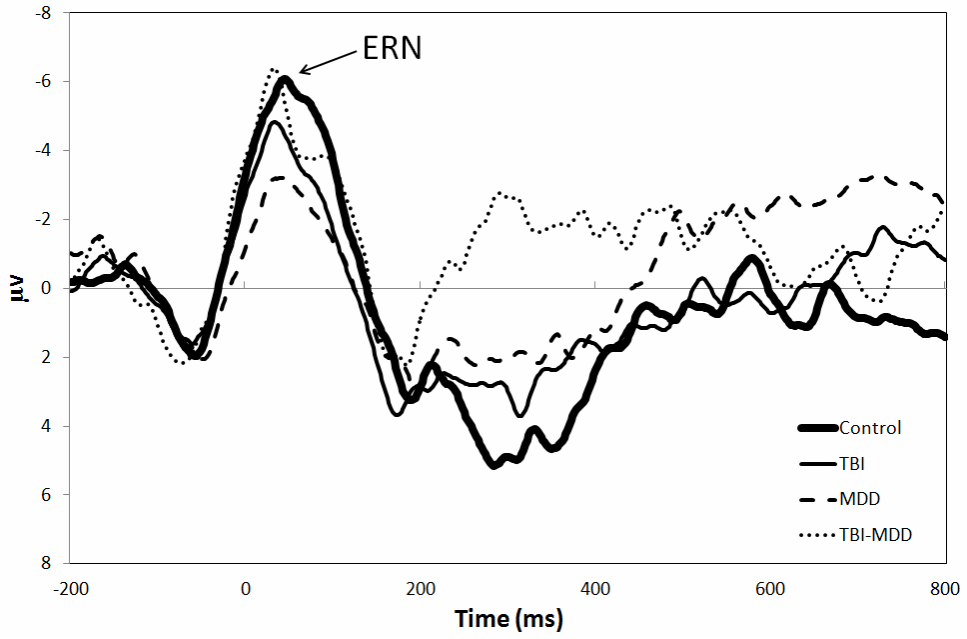

Figure 2. Grand average of the error response locked waveform for each group at Fz.

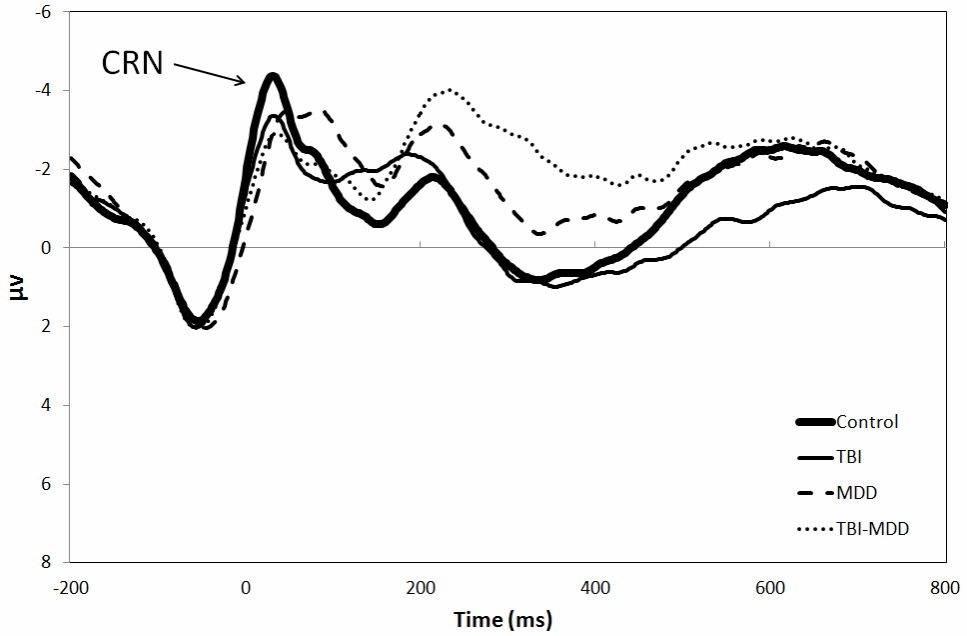

Figure 3. Grand average of the correct response locked waveform for each group at Fz.

Table 4. ERP peak amplitude and latencies for each group (ERN and CRN at Fz, and Pe at Cz, standard deviations in parentheses)

	Controls	TBI	MDD	TBI-MDD
Number of accepted error epochs	14.73 (7.08)	20.13 (13.33)	25.19 (4.28)	19.08 (14.86)
ERN amplitude	-7.49 (3.38)	-5.69 (3.01)	-5.01 (4.02)	-8.15 (5.77)
CRN amplitude	-5.04 (2.81)	-3.95 (1.79)	-4.88 (3.00)	-4.71 (4.53)
Pe amplitude	9.77 (5.17)	8.92 (3.60)	6.00 (2.96)	6.15 (3.80)
ERN latency	58.53 (36.00)	40.40 (30.97)	63.75 (34.63)	49.50 (31.93)
CRN latency	40.53 (25.36)	42.53 (32.00)	71.38 (33.06)	51.00 (35.34)
Pe latency	274.80 (73.95)	247.47 (82.76)	267.63 (69.39)	238.67 (72.54)

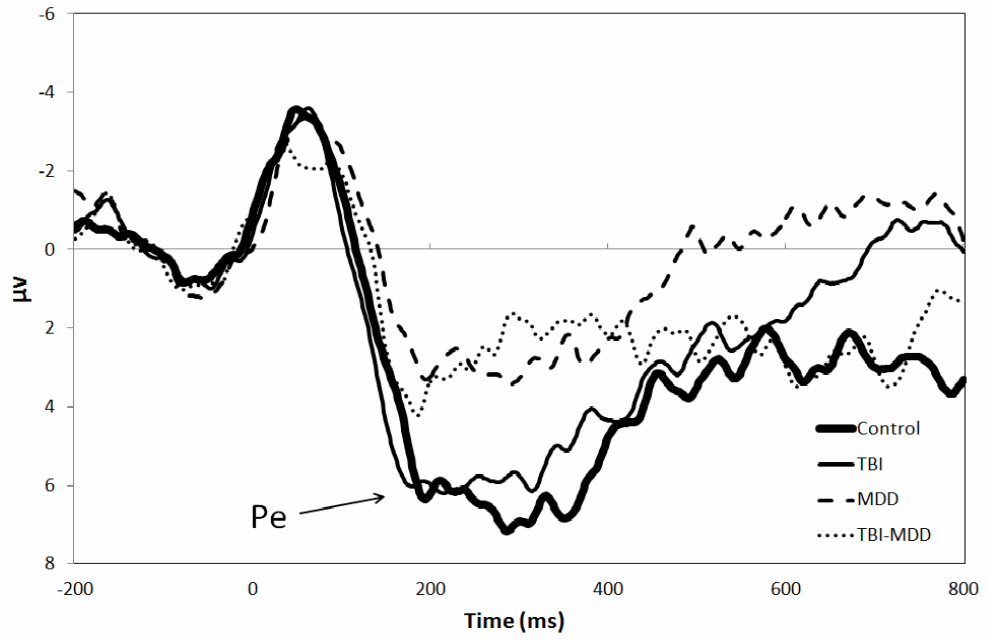

Figure 4. Grand average of the correct response locked waveform for each group at Cz

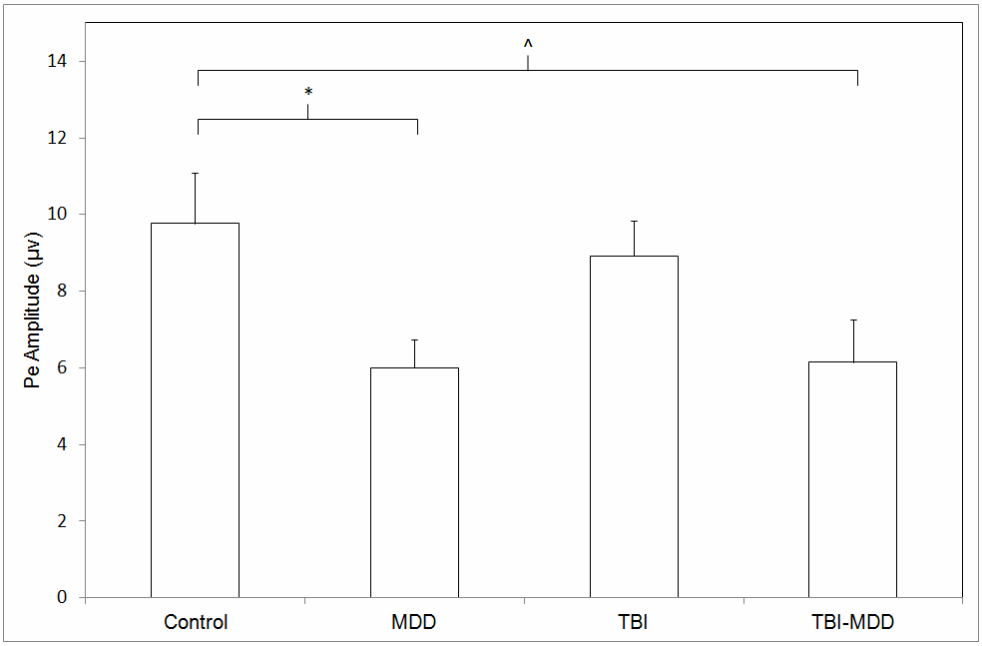

Figure 5. Mean Pe amplitude for each group. Error bars represent standard error. * represents significant differences $p \leq 0.05$, and ^ represents a trend towards significant differences $p \leq 0.10$.

4. Discussion

The goal of the current study was to use electrophysiological markers of error processing to determine if individuals with TBI-MDD suffer from impaired awareness of deficits. We found that the MDD group showed reduced Pe amplitude, and the TBI-MDD group showed a trend in the same direction. However, the Pe amplitude was not effected in the TBI alone group. This supports previous research indicating a reduction in Pe amplitude in MDD (Holmes and Pizzagalli 2010; Olvet et al. 2010; Schrijvers et al. 2008; Schrijvers et al. 2009). There were no differences in the second measure of error processing, ERN, across any of the groups.

Pe amplitude is thought to reflect conscious awareness of an error (Falkenstein et al. 2000; Nieuwenhuis et al. 2001), so the reduced Pe amplitude in the current study suggests that individuals with MDD, and to a lesser extent TBI-MDD, experience diminished error awareness. There are a number of potential explanations for the reduced Pe amplitude seen in the MDD and TBI-MDD groups in the current study. The first possibility is that the reduced Pe amplitude reflects a general impairment in the ability to synchronise neural activity in response to an event (Overbeek et al. 2005). The Pe amplitude reductions in the current study are similar to P3b amplitude reductions in oddball studies of MDD (Kemp et al. 2009; Roschke and Wagner 2003; Urretavizcaya et al. 2003), and some authors have suggested that the Pe is actually a P3b that follows a rare error response rather than a rare external stimulus (Arbel and Donchin 2009; Overbeek et al. 2005; Ridderinkhof et al. 2009). This bottom-up interpretation suggests that altered neural response causes a general reduction in conscious awareness, rather than a specific impairment in error awareness. In support of this explanation, the Pe has been hypothesized to be generated by activity in the anterior cingulated cortex (ACC) (van Boxtel et al. 2005; van Veen and Carter 2002), a region in which previous research suggests activity is altered in MDD (Anderer et al. 2002; Gotlib and Hamilton 2008; Holmes and Pizzagalli 2008). A second possibility is that the reduced Pe amplitude may be a result of apathy or blunted affect in the MDD group. Apathy may reduce attention to the task, conscious awareness of errors, and both apathy and blunted affect would reduce the amount of concern over mistakes, all of which would lead to a reduced Pe amplitude. Perhaps the most likely explanation is that these bottom up and top down explanations are in fact intertwined. Conscious awareness of errors may be reduced due to focus on internal ruminations, which is reflected at an electrophysiological level as reduced ability to synchronise neural activity to the external environment. Finally, reduced

Pe amplitude may reflect impulsivity. More impulsive participants exhibit smaller Pe amplitudes (Ruchsow et al. 2005), and although not typically considered to be a core aspect of MDD, impulsivity has been argued to be strongly linked to MDD (Ngo et al. 2011). It may be that the MDD groups are more impulsive, and this factor results in the reduced Pe. However, because the mechanism linking Pe reductions and impulsivity is unclear, this explanation cannot be evaluated further at this stage.

In addition to the reduced Pe amplitude found in the MDD group, a trend towards reduced Pe amplitude was found in the TBI-MDD group. This was not found in the TBI group, suggesting that the reduced awareness of deficits following TBI may be important in the subsequent development of MDD. It may be that the individuals who develop MDD following TBI are injured in a manner that disrupts the networks that subsume error processing, while those who do not develop MDD do not experience disruptions to these networks. This might reflect the fact that brain regions involved in error processing also display alterations in MDD, and as such the results of the current study may be indicators of disrupted mood processing in addition to disrupted error processing (Anderer et al. 2002; Gotlib and Hamilton 2008; Holmes and Pizzagalli 2008; van Boxtel et al. 2005; van Veen and Carter 2002). Alternatively, impaired error processing might result in psychosocial stressors related to an inability to modify behaviour in light of mistakes, resulting in MDD in some individuals following a TBI. However, it is also possible that the reduced Pe is simply a result of the development of MDD in the TBI-MDD group, and not related to injury factors. Regardless of which explanation is correct, the fact that reduced Pe amplitude is common in MDD and TBI-MDD, but not TBI without MDD suggests that considerations of error

awareness in the treatment of TBI may be vitally important for the subsequent development of MDD.

Unlike some previous research (Chiu and Deldin 2007; Holmes and Pizzagalli 2010; Larson et al. 2009), the current study did not find changes in the ERN amplitude in the MDD or TBI-MDD groups. This may be because, as Olvet et al. (2010) have suggested, there is a non-linear relationship between depression severity (measured by current mood assessments) and ERN amplitude, such that individuals with low depression severity show medium ERN amplitudes, individuals with mild to moderate severity show large ERN amplitudes, and individuals with higher severity show small amplitudes. However, if this were the case in the current sample, we would expect ERN amplitude to correlate with BDI or MADRS scores within the MDD groups, which contain only mild (large ERN amplitude) to severe depression (small ERN amplitudes). No such correlation was found. Another possibility is that the ERN is related to response uncertainty rather than depression severity (Schrijvers et al. 2010). Behavioural data from the current study showed no differences between groups, suggesting that the task was not sufficiently difficult to modulate response uncertainty between groups. A third alternative is that the ERN is actually unaffected by MDD, as a number of other studies have indicated (Olvet et al. 2010; Schrijvers et al. 2008; Schrijvers et al. 2009).

The other result of interest is that the TBI only group shows no difference to the healthy control group. This group had sustained an injury of mild to moderate severity. While not formally assessed, none of the TBI group reported any continuing deficits, and no the TBI and control groups did not differ in a computerised cognitive assessment (currently unpublished data). These results suggest that individuals who make a full 'apparent

recovery' (i.e. no development of TBI-MDD which is indicative of an incomplete recovery) do not show any long term neural alterations in error processing compared to healthy controls.

There are a number of limitations to the current research. Our results are limited by small sample size, particularly in the TBI-MDD group. In part, the small sample sizes are due to some participants performing too well, i.e. not committing enough errors for a valid ERP analysis. Future research could use shorter inter-trial intervals to enhance task difficulty. Another limitation to the interpretation of these results is our lack of certainty about the processes the Pe reflects. There is some debate about whether the Pe reflects conscious awareness of errors or affective appraisal of the error (Falkenstein et al. 2000). This might be addressed in future studies by manipulating the degree to which participants are aware of having made an error, or manipulating the subjective importance that a participant places upon making an error. This could inform as to whether Pe amplitude reductions in MDD are a result of reduced conscious awareness, or reduced affective processing of the error. A third limitation is the possibility of medication effects. As is common in studies of MDD and TBI, some of our participants were medicated. While the effect of medication on error related ERPs is unknown, this may have influenced our results independently of MDD or TBI. One more potential limitation is that error related processing following both happy and sad stimuli were combined. Although no research has examined the effect of emotionally valanced imperative stimuli on response locked processing, we assume the combination of happy and sad trials would not confound the group differences. Firstly, the impact of each valence on the average activity following erroneous responses would have been minimised by the latency variability that is introduced by variable reaction times. Secondly, the differences in activity generated by happy and sad stimuli would have averaged to the mean

of both, so that only the differences in error processing remain to compare between groups. One final limitation is that the TBI only group was mostly male, while other groups contained an approximately even mix of both genders. There is no evidence from previous research to suggest that gender modulates Pe amplitude, but we cannot rule out that this variable may have affected the results of comparisons involving this group.

4.1 Conclusions

Error positivity amplitude reductions are found in individuals with MDD, and to a lesser extent TBI-MDD. This is likely to reflect an impaired conscious awareness of errors. The impaired awareness of deficits may be an integral factor in the development of MDD following TBI. Error processing in individuals with TBI alone appears to be unaffected by the injury, perhaps indicating that error related activity is unaffected. The result suggests that treatment of the MDD component of TBI-MDD may be the most effective allocation of rehabilitation resources, and that error awareness training may be an important target for cognitive rehabilitation in this population.

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Conflicts of Interest

PBF has received equipment for research from Medtronic ltd, Magventure A/S and Brainsway Ltd. NWB, KEH, JJM, and DJU have no relevant conflicts to declare.

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Chapter Nine

Impaired Alpha Synchronization During Working Memory Retention in Depression and Depression Following Traumatic Brain Injury

The following chapter is comprised of a study that is currently being reviewed for publication in the Journal of Affective Disorders. In contrast to the previous two chapters, this chapter focuses on band power activity measures of brain activity rather than event related potentials. The study presented examines how alpha and theta bands in working memory are affected by TBI, MDD, and TBI-MDD. Both alpha and theta measures are important for working memory performance, which has been shown to be impaired in MDD and TBI groups, and even more impaired in groups with TBI-MDD. Alpha activity alterations have also been found in individuals with MDD, suggesting that this activity would be likely to differentiate individuals who develop MDD following a TBI from individuals who do not.

Impaired Alpha Synchronization During Working Memory Retention in Depression and Depression Following Traumatic Brain Injury

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Abstract:

Background: Rates of depression (MDD) following traumatic brain injury (TBI) are elevated compared to rates in the general population. Individuals with TBI, MDD and depression following traumatic brain injury (TBI-MDD) frequently exhibit working memory (WM) impairments. Successful WM performance relies on processes to focus attention on the information being retained, and processes which inhibit irrelevant distracting information from interfering with the retention of that information. Electrophysiological evidence indicates that focused attention is related to frontal-midline theta synchronisation, and inhibition is related to parietal-occipital alpha synchronisation.

Methods: The current research measured frontal-midline theta and parieto-occipital alpha activity during the retention period of a WM task, in order to determine which processes are disrupted in groups with TBI, MDD, and TBI-MDD compared to healthy controls.

Results: The results showed that parietal-occipital alpha was disrupted in the group with MDD, and trended towards showing a disruption in the TBI-MDD group, but was unaffected in a group with TBI only. Frontal-midline theta did not differ between groups.

Limitations: Small sample size may have limited the power of the study to detect differences between the control and TBI-MDD groups. Additionally, some participants were medicated with anti-depressants.

Conclusion: These findings suggest that inhibitory deficits may account for WM impairments in individuals with MDD and TBI-MDD, and that for individuals with TBI-MDD it may be the depression rather than the TBI that impairs WM.

Keywords: EEG, Alpha, Major Depression, Traumatic Brain Injury, Inhibition, Working Memory.

1. Introduction

Following a traumatic brain injury (TBI), rates of major depressive disorder (MDD) are higher than in the general population. Estimates suggest a rate of between 20% and 45% at any point measured between 3 months and 30 years after injury, as compared with annual prevalence of between 5% and 10% for the general population (Jorge et al., 1993; Kaponen et al., 2002; Kreutzer et al., 2001; Pagulayan et al., 2008; Satz et al., 1998; Seel et al., 2003; World Health Organisation, 2001). Unfortunately, this has a significant negative impact on recovery outcomes (Rapoport et al., 2006; Satz et al., 1998).

Working memory (WM) is one aspect of cognition that is commonly impaired in both TBI and MDD, and when both occur together (Burt et al., 1995; Chuah et al., 2004; Jorge et al., 2004). Brain activity that is assessable in two electroencephalography (EEG) bands is vital for effective WM performance: frontal midline theta, which is thought to represent attention, and increases when task demands require more attention (Jensen and Tesche, 2002; Sauseng et al., 2007), and parieto-occipital alpha - increases in which are thought to represent more inhibition of non-relevant brain regions (Jensen et al., 2002; Klimesch et al., 2007). Evidence suggests that activity in both of these bands is disrupted in individuals who have experienced a TBI and those with MDD.

Following a TBI, individuals have been found to demonstrate reduced alpha desynchronisation during motor inhibition (Dockree et al., 2004), reduced resting alpha peak frequency (Angelakis et al., 2004), and reduced coherence in a WM task (Kumar et al., 2009). However, no research has directly examined parieto-occipital alpha during WM retention in this population, and it has been suggested that alpha alterations post-TBI are related to anxiety and mood rather than the injury itself (Nuwer et al., 2005). As such, it is

unclear how a mild to moderate TBI affects WM retention alpha. Research into individuals with MDD, however, has examined alpha activity specifically during WM: Segrave et al. (2010) found increased upper alpha in MDD. These changes were apparent over the left parieto-occipital region during WM retention. This study, like many others that have examined WM, used the Sternberg task. This task is constructed so that encoding, retention, and recall periods are separated, enabling researchers to distinguish the processes involved in each.

Research using the Sternberg task has also examined the theta band. For example, poorer WM performance in individuals with mild cognitive impairment is related to reduced theta activity (Cummins et al., 2008). Reductions in theta coherence have also been found in individuals performing a WM task following a TBI (Kumar et al., 2009). However, no research has focused on WM theta in individuals with MDD. In addition to this, neither of the two bands that seem to support WM have been studied in individuals with TBI-MDD, so it is not clear which affliction is responsible for disruption to either process.

The aim of current study was to investigate the neural changes associated with MDD, TBI, and TBI-MDD. It was hypothesised that both individuals with TBI and individuals with MDD would show reductions in alpha and theta activity compared to healthy controls, and that the TBI-MDD group would show even larger reductions. It was also hypothesised that these differences would be more apparent with larger memory loads, as both theta and alpha are modulated by WM load (Gevins et al., 1997; Jensen et al., 2002; Jensen and Tesche, 2002).

2. Methods

2.1 Participants

Initially 34 healthy controls, 20 MDD, 20 TBI, and 16 TBI-MDD participants were recruited. Of these, the data from three controls were excluded (one who showed mild depression in rating scales, and two whose data recording session experienced equipment faults). Data from three MDD participants was excluded (one who showed only mild depression on rating scales, and two with too few noise-free EEG epochs). Data from one TBI-MDD participant was excluded (this participant was medicated with oxycontin). This left 31 control, 17 MDD, 20 TBI, and 15 TBI-MDD participants. Participants were recruited through the Monash Alfred Psychiatry Research Centre database, the Alfred Hospital emergency department, and community advertising. The study was approved by the Ethics Committee of the Alfred Hospital and Monash University and all participants gave informed consent. All participants had normal or corrected to normal vision and were between 17 and 65 years of age. A number of participants were medicated (Table 1).

Participants in the MDD and TBI-MDD groups had previously been diagnosed with MDD, and current diagnosis was confirmed with the MINI International Neuropsychiatric Interview for DSM-IV (Sheehan et al., 1998b). Co-morbid psychiatric diagnoses were exclusion criteria for the MDD and TBI-MDD groups (with the exception of generalised anxiety disorder). Current benzodiazapine, mood stabiliser, antipsychotic, and multiple anti-depressant use was also an exclusion criterion. Depression prior to the TBI was an exclusion criterion for the TBI-MDD group, and injury and depression information was assessed by a psychiatrist (PBF) to ensure the MDD was causally related to the TBI. All TBI and TBI-MDD participants were tested more than 6 weeks after their injury. In the TBI and TBI-MDD

groups, only participants with mild to moderate closed head injuries were included. This was determined by patient reports and hospital records of an initial Glasgow Coma Scale [GCS] score of 9-14, and/or loss of consciousness [LOC] or length of post-traumatic amnesia [PTA] of more than 10 minutes, and LOC of less than 24 hours (Kay et al., 1993; Malec et al., 2006; Rao and Lyketsos, 2000). Controls and TBI individuals were excluded if they met criteria for current or prior DSM-IV psychiatric illness.

2.2 Procedure

Participants completed two sessions, each lasting approximately 2.5 hours. All sessions were conducted within two weeks of each other. One session consisted of the demographic, TBI history, and depression severity assessments. The other session involved the EEG recording. All rating scales were administered by a single trained researcher. All participants were assessed with the MINI neuropsychiatric interview for DSM-IV (Sheehan et al., 1998a). All participants had their current depression severity assessed with the Beck Depression Inventory-II (BDI-II) (Beck and Steer, 1984) and the Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979). Estimated pre-morbid IQ was assessed with the Weschler Test of Adult Reading (WTAR) (Wechsler, 2001), which has been shown to be a valid measure of pre-morbid IQ post TBI (Green et al., 2008). Handedness was recorded using the Edinburgh Handedness Inventory (EHI) (Oldfield, 1971).

2.3 Task and Stimuli

Participants performed a modified Sternberg task while EEG activity was recorded. Stimuli were presented via Neuroscan STIM2 software (Compumedics, Melbourne Australia). Memory sets contained either five or seven pseudo-randomly selected consonants (presented simultaneously). The letters were selected from a set of fifteen (B, C,

D, F, H, J, K, L, N, R, S T, Y, W, and Z). The five letter condition contained + symbols at the end of each string, so that it displayed an equal visual angle to the seven letter condition. The number of letters in each trial was determined by a pseudo-random sequence so that no more than three of each condition occurred consecutively. Trials began with a fixation cross (517ms) followed by a blank screen (500ms). The memory set was presented for 3017ms. After a retention period of 3017ms a probe letter was presented for 2017ms. Participants were instructed to respond with a yes or no button press (with their right hand) to indicate whether or not they had seen the probe in the preceding memory set. Responses occurring after this time were considered incorrect. Each trial ended with a brief visual mask (133ms), followed by a blank screen (1867ms) before the onset of the fixation cross for the following trial. The probe had a 50% probability of being present in the memory set. The position of the probe in the memory set was pseudo-randomly allocated so that it was not located in the same position twice consecutively. No digit was presented as the probe more than once consecutively and no more than three consecutive present or absent trials occurred in a row. The sequence of memory set size and probe present/absent was the same for each participant. Participants performed six blocks of twenty trials per block. Task design is illustrated by Figure 1. Accuracy and reaction times were recorded for each participant.

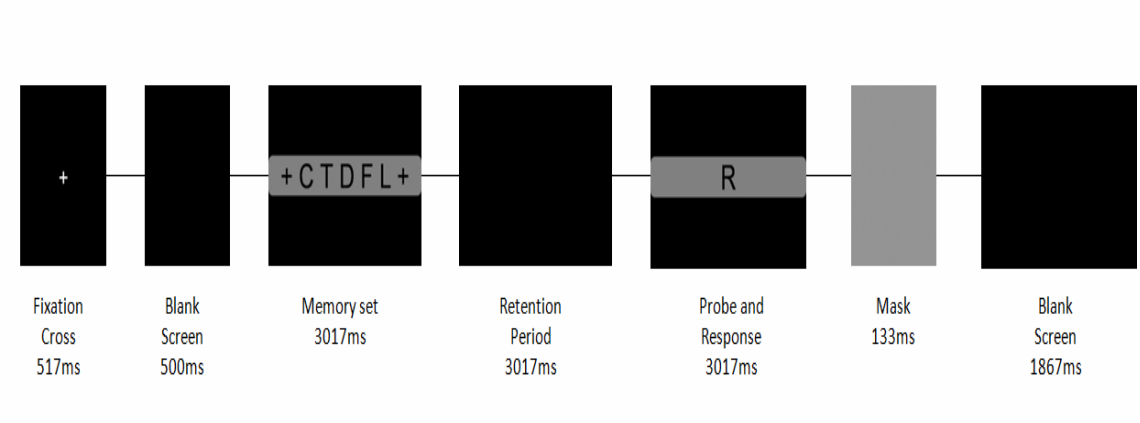

Figure 1. Task design and stimuli timing for the Sternberg task. All letters in the memory set were presented simultaneously, and the memory set varied by trial as to whether it contained either five or seven letters. Responses were only included if made during the probe presentation.

2.4 Electrophysiological Recording and Analysis

A Neuroscan 64 electrode EEG Quick cap with Ag/AgCl electrodes was used to record EEG activity via a Synamps 2 amplifier onto Neuroscan Acquire software (Compumedics, Melbourne Australia). Electrodes were referenced online to a point between Cz and Cpz. Eye movements were recorded with vertical and horizontal EOG electrodes located above and below the left eye and adjacent to the outer canthus of each eye. Electrode impedances were kept below 5kΩ. The EEG was digitised at 500Hz, with a bandpass of 0.1-100Hz (24dB/octave roll-off).

Scan 4.3 (Compumedics, Melbourne Australia) was used to analyse the EEG data offline. Eye movements were corrected for using the eye correction algorithm designed by Croft and Barry (2000). Epochs containing amplitudes which exceeded +/- 75µv were rejected. EEG recordings were re-referenced offline to a common average. Only trials with

correct responses were analysed. These were epoched from the beginning of the fixation cross to the end of the end of trial blank screen in order to calculate event related desynchronisation/synchronisation (ERD/ERS). ERD/ERS is the percentage change in a specific band power of a test interval compared to a reference interval. It is calculated as follows: ERD/ERS% = (R – A)/R*100, where A refers to the active test period, and R to the reference period. This calculation provides negative values when power increases in the test period compared to the reference period (neural synchronization at that frequency). This was calculated for spectral power in both the theta and alpha ranges (4-8Hz and 8-13Hz respectively). Power in the middle 300ms window of the blank pause between the fixation cross and memory was set as a reference period, and the retention period 750ms post memory set to 250ms pre-probe as the active test period. The test period was selected to avoid response preparation effects at the end of the retention interval, and because healthy controls show maximal alpha enhancement later in the retention interval (Jensen et al., 2002).

2.5 Statistical Analysis

2.5.1 Demographic and Behavioural Analyses

One way analysis of variance (ANOVA) compared depression severity measurements between the groups assessed by the BDI and MADRS, as well as demographic data. Independent samples t-tests compared GCS, LOC, PTA, and time since injury between the two TBI groups.

Groups were not matched for years of education, so Pearson's correlations were conducted between this variable and behavioural and ERD/ERS data in order to assess

whether years of education was a confounding variable. A three way repeated measures ANOVA compared percentage correct within groups for number of letters (five or seven) and whether the probe was present or absent, and between groups (control, TBI, MDD, TBI-MDD). A three way repeated measures ANOVA was performed for participant reaction times. Although probe present reaction times correlated with years of education, comparisons were not conducted with ANCOVA, as this test is not valid when variation in a covariate is found between groups (Miller and Chapman, 2001).

2.5.2 EEG Analyses

Analyses were pooled across both probe present and probe absent trial types, as the retention period precedes the probe presentation, so it is not influenced by probe presentation. To normalise the distribution of the alpha and theta activity, logarithmic transforms were computed. To enable log transform (which cannot be performed on negative values) polarity of each value was reversed, and 50 was added to the alpha ERD/ERS values, and 100 to the theta ERD/ERS values. This preserves the essential relationships between each data point. Theta comparisons focused on frontal midline electrodes, as retention theta is maximal in frontal midline areas (Sauseng et al., 2007). A three way repeated measures ANOVA compared theta ERD/ERS within subjects for electrode (Fz, FCz, and Cz) and memory set size (five or seven letters), and between groups (control, TBI, MDD, TBI-MDD). Alpha comparisons focused on P07 and P08 electrodes, as magneto-encephalography (MEG) localisation suggests retention period alpha is generated in the parieto-occipital sulcus (Tuladhar et al., 2007), and that alpha is maximal at these electrodes (Segrave et al., 2010). A three way repeated measures ANOVA compared alpha retention ERD/ERS within subjects for electrode (PO8, PO7), memory set size (five or seven

letters) and between groups (control, TBI, MDD, TBI-MDD). Pearson's correlations were run between theta and alpha ERD/ERS, and depression rating scores within the combined MDD and TBI-MDD groups.

Post-hoc Tukey tests were performed when omnibus ANOVAs were significant. All sphericity violations were corrected for using the Greenhouse-Geisser correction.

3. Results

3.1 Demographics, Depression, and TBI Severity

Table 2 displays the means and standard deviations for the demographic and severity measures. All groups were matched for gender, age, handedness, and estimated pre-morbid IQ (all $F < 2.05$, all $p > 0.10$). Significant differences were found for years of education ($F(3,78) = 2.96$, $p < 0.05$), with the TBI-MDD group showing fewer years than the healthy control group ($F(3,78) = 2.94$, $p < 0.05$). Both TBI groups were matched for brain injury severity as measured by length of PTA, GCS, and duration of LOC (all $t < 1.50$, all $p > 0.10$). The TBI-MDD group had significantly longer time since injury than the TBI group ($t(30) = 2.78$, $p < 0.05$). Groups significantly differed in BDI ($F(3,78) = 223.29$, $p < 0.01$) and MADRS scores ($F(3,78) = 86.95$, $p < 0.01$). As expected, for both measures the MDD and TBI-MDD scored significantly higher than the control and TBI only groups (both $p < 0.01$). The TBI and control groups did not differ in depression severity, nor did the MDD and TBI-MDD groups (all $p > 0.05$).

Table 1. Demographics, depression rating scores, and head injury severity measures, and medications for each group (means with SD in parentheses)

	Controls	*TBI*	*MDD*	*TBI-MDD*
N	31	20	17	15
Gender (F/M)	18/13	4/15	8/9	7/6
Age	38.48 (13.67)	33.15 (13.83)	38.47 (12.18)	43.73 (10.44)
Years of Formal Education	17.87 (3.26)	16.98 (3.41)	15.71 (3.58)	14.87 (3.67)
WTAR pre-morbid IQ	111.59 (3.28)	107.47 (5.66)	107.31 (7.78)	109.69 (5.94)
MADRS	1.73 (1.70)	2.45 (2.42)	26.47 (4.47)	16.47 (7.75)
BDI	2.45 (2.97)	3.30 (3.53)	24.41 (10.01)	29.36 (9.75)
EHI	80.97 (44.52)	75.54 (48.32)	86.29 (43.66)	66.64 (64.11)
GCS		13.00 (1.41)		13.67 (0.58)
LOC (hours)		0.42 (0.42)		1.09 (3.49)
PTA (hours)		30.83 (70.26)		34.73 (77.59)
Time since injury (months)		22.89 (59.66)		176.77 (197.68)
Medications:				
None			7	7
SNRI			4	3
SSRI			5	3
Tricyclic			1	2

The TBI-MDD group showed significantly fewer years of education than the healthy control group, and significantly longer since injury than the TBI group. Both the TBI-MDD and MDD groups showed higher BDI and MADRS scores than the control and TBI groups.

3.2 Sternberg Behavioural Data

Behavioural data is summarized in Table 2. No relationship was found between accuracy in any condition and years of education (all $p > 0.05$). There was a significant difference in accuracy across the memory load conditions, with higher accuracy associated with lower memory load ($F(1,79) = 49.84$, $p < 0.01$). There was also a significant difference between groups ($F(3,79) = 3.914$, $p < 0.05$). Post-hoc Tukey tests showed the control and TBI group were more accurate than the MDD group ($p < 0.05$). No other between group differences were detected, including between the TBI-MDD and control group (all $p > 0.05$). No differences were found between probe present and absent conditions ($F(1,79) = 1.73$, $p < 0.05$), and no interactions between memory load, probe present or absent, and group were detected (all $p > 0.10$).

A moderate negative relationship was found between probe present condition reaction times and years of education ($r = -0.31$, $p < 0.01$ for the 7 letter memory load, and $r = -0.35$, $p < 0.01$ for the 5 letter memory load). No relationship was found between the probe absent condition reaction times and years of education ($r = -0.21$, $p > 0.05$ for the 7 letter memory load, and $r = -0.19$, $p > 0.05$). Reaction time comparisons revealed a significant difference for memory load, with faster reaction times in the five letter condition ($F(1,79) = 125.68$, $p < 0.01$). Faster reaction times were also shown for the probe present compared to the probe absent condition ($F(1,79) = 26.87$, $p < 0.01$). Significant differences were also detected between the groups ($F(3,79) = 5.18$, $p = 0.01$). Post hoc between group comparisons showed that the MDD group had significantly slower reaction times than the control group ($p < 0.01$) and TBI group ($p < 0.05$), and the TBI-MDD group had significantly slower reaction times than the control group ($p < 0.05$). No other between group

differences were significant (all $p > 0.05$), and no interactions between group, probe present or absent, or memory load were present (all $p > 0.05$).

Table 2. Mean Percent Accuracy and Reaction Times for Sternberg Task Performance (SD in parentheses)

Percent Correct – Mean (SD)				
	Controls	*TBI*	*MDD*	*TBI-MDD*
Seven Letters – Probe Present	83.9 (13.7)	86.8 (9.6)	78.8 (13.0)	79.0 (14.8)
Seven Letters – Probe Absent	88.5 (10.6)	89.0 (9.7)	80.7 (17.6)	83.6 (8.8)
Five Letters – Probe Present	90.8 (9.8)	92.3 (4.7)	87.1 (9.3)	87.0 (8.4)
Five Letters – Probe Absent	92.5 (7.5)	91.6 (6.9)	84.5 (16.0)	89.7 (6.1)
Reaction Time (ms) – Mean (SD)				
	Controls	*TBI*	*MDD*	*TBI-MDD*
Seven Letters – Probe Present	976 (162)	973 (167)	1096 (130)	1119 (169)
Seven Letters – Probe Absent	1061 (204)	1069 (220)	1219 (183)	1192 (154)
Five Letters – Probe Present	879 (139)	923 (179)	1029 (164)	997 (123)
Five Letters – Probe Absent	964 (177)	982 (182)	1128 (203)	1066 (139)

Overall there was significantly more accuracy and faster reaction times in the five letter conditions, and faster reaction times in the probe present conditions. The MDD group showed significantly less accuracy than the control and TBI groups, and slower reaction times than the control group.

3.3 EEG Activity

Alpha ERD/ERS

Figure 2 illustrates the grand average ERD/ERS across the seven letter trials for each group at PO8 and PO7. Figure 3 illustrates mean ERD/ERS during the retention period for each group at PO8 and PO7. All groups showed an increase in ERS during the retention period. A weak negative relationship was found between PO7 alpha in the 5 letter memory load and years of education ($r = 0.23$, $p < 0.05$). No relationship was found between alpha in other conditions and years of education (all $p > 0.05$). Alpha comparisons showed a significant effect of laterality, with the PO8 electrode showing more synchronisation than PO7 ($F(1,79) = 62.50$, $p < 0.01$). A significant effect of group was also shown ($F(3,79) = 3.97$, $p < 0.05$), with post-hoc Tukey between group comparisons indicating that the TBI-MDD group showed less alpha activity than the control group ($p < 0.05$), and the MDD group showed a trend towards less alpha activity than the control group ($p = 0.079$). No significant effect of memory set size was detected ($F(1,79) = 1.74$, $p > 0.10$), and no interactions between group, electrode, or memory load were found (all $p > 0.05$). Table 3 shows log transformed retention period alpha ERD/ERS values.

Within the combined MDD and TBI-MDD groups, moderate positive correlations were detected between alpha activity and MADRS scores at PO8 for both the five ($r = 0.362$, $p < 0.05$) and seven letter memory sets ($r = 0.355$, $p < 0.05$), but were not significant at PO7 (all $p > 0.10$). BDI scores also correlated with five letter memory set retention period alpha at PO8 ($r = 0.375$, $p < 0.05$) and PO7 ($r = 0.389$, $p < 0.05$), but were not significant for the seven letter memory sets (all $p > 0.10$). Note that with ERD/ERS calculations, negative values

reflect synchronisation, so positive correlations indicate greater depression severity is related to less alpha synchronisation.

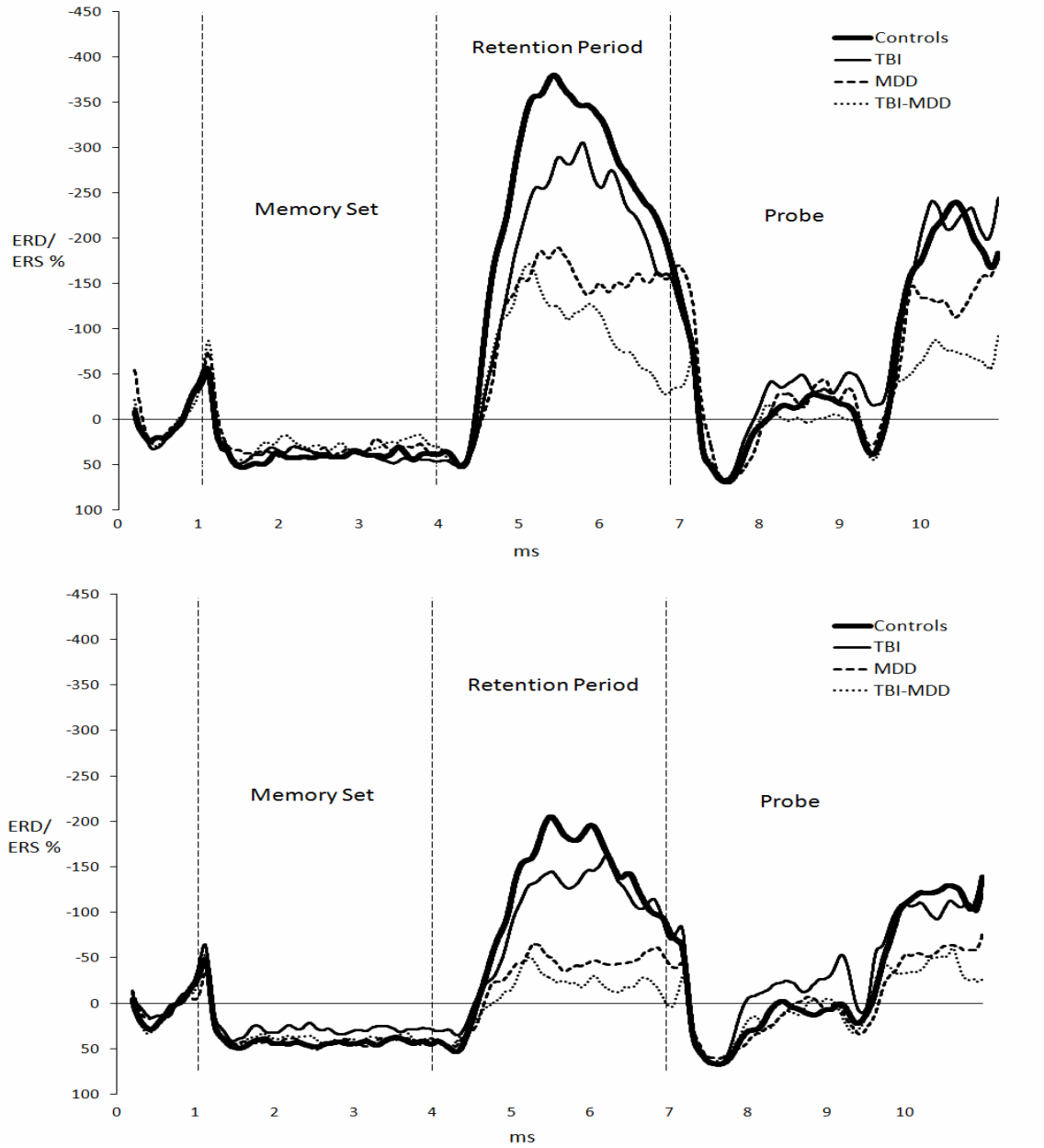

Figure 2. Alpha ERD/ERS % for PO8 (top) and PO7 (bottom), in comparison to the reference period (between the fixation cross and the memory set presentation). Significant differences were detected between the control group and the TBI-MDD group, and a trend towards significance was detected between the control group and the MDD group.

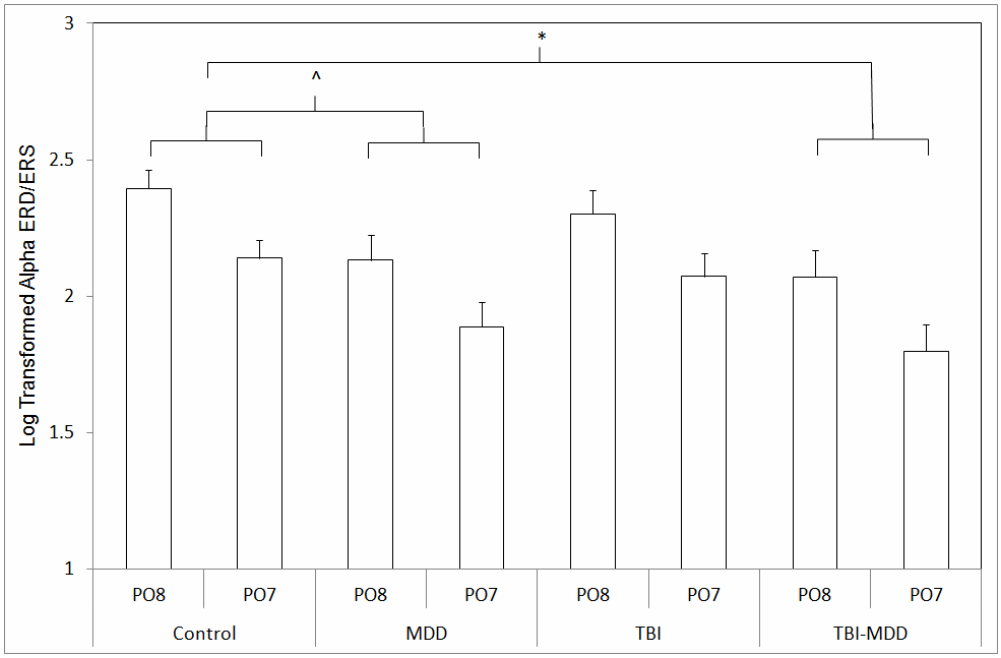

Figure 3. Mean log transformed alpha ERD/ERS at PO8 and PO7 for each group. Error bars represent standard error. * represents significant differences at $p < 0.05$, ^ represents a trend towards significant difference $p < 0.10$.

Theta ERD/ERS

Theta comparisons indicated a significant effect of number of letters ($F(1,79) = 4.504$, $p < 0.05$), with the five letter condition showing more theta, and a significant effect of location ($F(1,78) = 4.224$, $p < 0.05$). Fz showed more theta than FCz ($p < 0.01$) and Cz ($p < 0.05$). No significant effect of group was detected $F(3,79) = 1.717$, $p > 0.10$), and no interaction was detected (all $p > 0.05$). Table 3 shows mean theta ERD/ERS values.

No significant correlations were detected between theta and BDI and MADRS measures of depression severity within the combined MDD and TBI-MDD groups (all $p > 0.05$).

Table 3. Mean and Standard Deviation Retention Period Alpha ERD for Control, MDD, TBI and TBI-MDD Participants.

	Controls	*TBI*	*MDD*	*TBI-MDD*	*Total*
			Alpha		
Seven Letters					
P08	2.41 (0.41)	2.29 (0.42)	2.13 (0.44)	2.03 (0.41)	2.25 (0.44)
P07	2.12 (0.45)	2.06 (0.41)	1.85 (0.38)	1.78 (0.30)	1.99 (0.42)
Five Letters					
P08	2.38 (0.43)	2.32 (0.36)	2.14 (0.36)	2.11 (0.24)	2.26 (0.38)
P07	2.15 (0.41)	2.08 (0.34)	1.92 (0.43)	1.82 (0.30)	2.03 (0.40)
			Theta		
Seven Letters					
Fz	2.01 (0.15)	2.06 (0.10)	2.02 (0.18)	1.92 (0.10)	2.00 (0.14)
FCz	1.98 (0.11)	2.01 (0.08)	1.98 (0.17)	1.92 (0.11)	1.98 (0.12)
Cz	1.97 (0.11)	1.97 (0.12)	1.93 (0.11)	1.96 (0.14)	1.96 (0.12)
Five Letters					
Fz	1.98 (0.16)	2.07 (0.10)	2.03 (0.16)	1.98 (0.07)	2.01 (0.14)
FCz	1.97 (0.13)	2.03 (0.10)	2.00 (0.15)	1.99 (0.12)	1.99 (0.13)
Cz	1.98 (0.14)	2.06 (0.10)	1.98 (0.11)	2.00 (0.15)	2.00 (0.13)

Data was log transformed. This involved reflecting the polarity and adding 50 to each value so that all values were positive. Post-hoc Tukey tests indicated significant overall differences between the TBI-MDD and control groups in alpha, and a trend towards significant differences between the MDD and control groups in alpha. No between group differences were detected for the theta band.

4. Discussion

The aim of this study was to determine the impact of TBI and MDD on inhibitory (alpha) and attentive (theta) processes during WM retention. We found that individuals with MDD, whether in the presence of TBI or not, show changes in WM performance. No WM impairments were detected in the TBI group. We also found that the depressed participants (especially the TBI-MDD group) showed less elevated posterior alpha activity while information is being retained in WM. Lastly, the groups did not differ in measures of theta activity.

These results support previous research which indicates less alpha activity is related to reduced WM performance (Haegens et al., 2010; Klimesch et al., 1993; Missonnier et al., 2011). The findings also align with previous studies which have reported WM impairments in MDD and TBI-MDD (Burt et al., 1995; Jorge et al., 2004). The current research also extends the field, suggesting that it is the reduced alpha activity that results in WM impairments in MDD and TBI-MDD individuals. Alpha activity is thought to reflect inhibition, so the current results suggest that individuals with MDD and TBI-MDD show impaired inhibitory processes (Jensen and Tesche, 2002; Klimesch et al., 2007). The alpha changes found in the MDD and TBI-MDD groups may suggest a mechanism for the cognitive changes experienced in these disorders. Reductions in alpha activity reflect fewer neuronal populations generating synchronised post-synaptic potentials (Pfurtscheller and da Silva, 1999). Although the mechanism responsible for generating the alpha rhythm is not well understood, animal research suggests that it may be related to gamma-aminobutyric acid (GABA) inhibitory feedback (Lorincz et al., 2009). Jensen and Mazaheri (2010) propose the alpha rhythm results in a pulsing inhibition that disrupts ongoing gamma synchronization,

preventing gamma from binding information between areas. Accordingly, reduced alpha in MDD and TBI-MDD may be due to impairments in GABAergic inhibitory pathways, which may lead to impaired ability to inhibit non-relevant signals from interfering with memory traces. Perhaps this offers an explanation for the difficulty individuals with MDD have in restraining negative ruminations, which impacts on WM performance (Gohier et al., 2009; Lau et al., 2007). In support of this idea, it seems that these changes in alpha are related to severity measures within the MDD groups, so that those with more severe depression (who presumably suffer more severe negative rumination) show reduced alpha.

However, further research is required to confirm these assertions, as the results of the current study are in contrast to those reported by Segrave et al. (2010). This study found increased upper alpha in the left hemisphere during WM retention in a group with MDD compared to a control group. There are a number of differences between the two studies that may explain the apparent contradiction. Segrave et al. (2010) only tested female participants, while the current study tested both genders. They also used an eight letter memory set, while the current study compared five and seven letter memory sets. It may be that alpha activity in MDD individuals is modulated by gender, or that the effect of MDD on alpha activity is reversed when WM demands are increased. Segrave et al. (2010) also analysed an individualised upper sub-band of alpha, whereas the current study analysed the same 8-13Hz alpha band for each participant. Further research could endeavour to resolve these issues, contrasting a wider range of WM loads, gender, and upper and lower alpha activity. This research should also more directly test that alpha changes in MDD are due to disrupted inhibition, by varying distractions presented during the retention period.

Although the research indicates alpha processes are disrupted in TBI-MDD and MDD groups, it suggests theta activity is intact. Higher frequency rhythms are more readily disrupted than lower frequency rhythms, as activity has to be more temporally precise to maintain synchrony (Buzsaki, 2006, pg. 76). As such, it may be that the higher frequency alpha rhythm is more susceptible to impairment following neural changes in MDD, while theta activity is unaffected. Theta activity is thought to reflect attention (Jensen and Tesche, 2002; Sauseng et al., 2007). This suggests impaired attentional processes may not contribute to WM impairments in MDD or TBI-MDD individuals. However, an alternative explanation may be offered; midline theta was not modulated specifically by the retention period in comparison to other periods in the Sternberg task, and previous research indicates that prominent retention period theta is only generated by a minority of individuals (Jensen et al., 2002). It may be that the current study did not challenge the underlying mechanisms generating the theta rhythm sufficiently to differentiate the groups. Theta modulations are more commonly found during n-back tasks which require constant WM updating (Gevins et al., 1997), so future research using the n-back or a similar task might show altered theta in MDD groups.

This research also suggests that MDD is the factor that causes WM impairment in TBI-MDD, rather than the TBI. In addition to the TBI group showing no differences to controls on any measure, another factor suggests the TBI is not responsible for alterations in the TBI-MDD group - this group had a longer time since injury to recover than the TBI group. If the TBI was responsible for WM impairments and disrupted alpha and theta activity in the TBI-MDD group, we would expect the TBI group to show more disruptions since they had less time to recover. This research is in disagreement with some previous research on TBI,

which has found alpha alterations, WM impairments, and alpha coherence reductions in a WM task (Angelakis et al., 2004; Chuah et al., 2004; Kumar et al., 2009). However, meta-analysis of the neuropsychological effects of a mild TBI has indicated that memory is unaffected, and only 6% of those injured show lingering impairments (Binder et al., 1997). It may be that individuals with mild to moderate TBI fully recover in the absence of a mood disorder, and that, as Nuwer et al. (2005) has suggested, alpha activity changes found in individuals following a mild to moderate TBI are the result of mood and anxiety changes, rather than the injury. Additionally, studies demonstrating alpha changes post TBI may have studied a more severely affected sample then we did. For example Dockree et al. (2004) found alpha alterations in a sample of moderate to severely injured participants.

There are a number of limitations in interpreting the results of the current study. The sample size in each group is relatively small, which may explain the weaker evidence for differences between the TBI-MDD group and healthy control group in WM performance, and between the MDD and control group for alpha activity. Despite this, both MDD and TBI-MDD group appear to show WM and alpha alterations in the same direction, suggesting a consistent effect of MDD. Secondly, many of the MDD participants were medicated with anti-depressants. Although Segrave (2010) found no differences in alpha activity between medication free MDD participants and those taking anti-depressants, it is possible the theta results may have been influenced by this factor. Additionally, the TBI-MDD group had fewer years of education compared to healthy controls. It is possible this confounds the current results, however, the current study showed only a weak relationship with only one alpha measure, suggesting the difference in years of education does not explain the results. A final limitation relates to the method by which alpha was measured in each individual. Using the

average ERD/ERS to determine alpha activity does not allow the results to indicate whether MDD individuals show reduced retention alpha in all WM trials, or whether they generate similar alpha levels to controls on some trials but on others none at all. The first alternative would indicate impaired alpha generation in individuals with MDD, while the second might only indicate wandering focus in some trials, resulting in no alpha activity being generated. Individual trial analysis of alpha may resolve this issue in future research.

This study indicates that individuals with TBI-MDD have impaired alpha activity in the parieto-occipital area during WM retention, and suggests the same is true for individuals with MDD. It is likely that this results in impaired inhibition of non-relevant information, which interferes with the information being held in WM, resulting in poorer performance. This provides a physiological basis for the impaired WM in individuals with MDD. In contrast, frontal theta measures were unaffected in TBI, MDD or TBI-MDD groups. Neither rhythm is affected by mild to moderate TBI alone, suggesting that in the absence of a mood disorder, perhaps full recovery from the TBI could be expected. This may also suggest that the WM impairments found in the TBI-MDD group are due to depression rather than to the brain injury.

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Conflicts of Interest

PBF has received equipment for research from Medtronic ltd, Magventure A/S and Brainsway Ltd and funding for research from Cervel Neurotech. NWB, RAS, KEH, JJM have no conflicts to declare.

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Chapter Ten

Functional connectivity alterations during working memory in depression following traumatic brain injury

The following chapter has been submitted for publication in the Journal of Psychiatry and Neuroscience. Similar to the previous chapter, this study examined alpha and theta during working memory. However, rather than using measurements only from single electrodes, measures of coherence between two electrodes were compared, both during working memory and at rest in groups with TBI, MDD, and TBI-MDD. Measures of coherence represent functional connectivity between different brain areas, thought to be mediated by white matter conduits. As such, these measures have the potential to inform us about the functional result of DAI. Because MDD is conceptualised as a disorder of disrupted brain networks, it may be that these impairments in functional connectivity as a result of TBI are the cause of MDD in some individuals.

Because the initial testing sessions with the Sternberg task were conducted as pilot sessions (in order to confirm the methodologies were valid, and verify the tasks functioned as expected), mastoid electrodes were not applied to a number of participants. As a result, while these participants could be included in the previous chapter's ERD/ERS analyses of the Sternberg task (which used an average reference montage), they could not be included in a coherence analyses of the same data (which could not use an average reference montage, as this has been found to be invalid for coherence measures [Essl and Rappelsberger, 1998]). This means that data from fewer participants was available for analysis in this chapter.

Functional connectivity alterations during working memory in depression following traumatic brain injury

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Running page heading: INCREASED THETA COHERENCE IN TBI-MDD

Abstract

Major Depressive Disorder (MDD) is a significant issue following a traumatic brain injury (TBI). This may be due to alterations in functional connectivity following a TBI, occurring as a result of diffuse axonal injury (DAI). We attempted to determine if individuals with MDD following a TBI (TBI-MDD) showed reduced functional connectivity by using EEG coherence in the alpha and theta bands, both while participants were at rest and while they performed a working memory (WM) task. Coherence was measured from a group of controls (N = 15), MDD participants (N = 16), TBI participants (N = 19) and TBI-MDD participants (N = 14). Contrary to our predictions, we found the TBI-MDD group showed higher interhemispheric theta coherence in the WM task. This may reflect inefficient functional connectivity in the TBI-MDD group, resulting from maladaptive neuroplastic reorganisation.

Key words: Alpha; Theta; EEG Coherence; Major Depression; Traumatic Brain Injury

1. Introduction

After a traumatic brain injury (TBI) rates of major depressive disorder (MDD) are significantly higher than in the general population. In addition, these rates are also higher than those seen following a spinal injury of equivalent severity, indicating that the elevated rates of MDD following TBI (TBI-MDD) are not solely related to psychosocial or psychological factors (Varney, Martzke et al., 1987). Changes in neural function may also contribute. At this stage however, very little research has focused on characterising changes in neural function in those with TBI-MDD. Current perspectives on non-injury related MDD conceptualise the disorder as the result of an impaired functional network between the limbic system and cortical regions (Mayberg, 1998). Disruptions in structural connectivity between areas following a TBI are also seen, due to diffuse axonal injuries (DAI) which disrupt white matter axonal connections (Baker, Phan et al., 2002; Povlishock and Christman, 1995). The outcome of DAI related connectivity disruptions could be expressed in some individuals as post TBI-MDD. Indeed, research using diffusion tensor imaging (DTI) has demonstrated weakened white matter pathways in TBI-MDD (Maller, Thomson et al., In Press). Therefore, measures of connectivity between brain areas may offer a window into the neural changes that underpin TBI-MDD.

Changes in *functional* connectivity (defined as the temporal correlation between activity in separate brain regions; (Friston, Frith et al., 1993) as a result of DAI are not easily detected with imaging techniques. However, research in animal models has indicated that even when morphological changes are almost undetectable by direct examination of individual axons, electrophysiological measures reveal altered nerve function (Tomei, Spagnoli et al., 1990). Scalp recorded electroencephalography (EEG) allows for the

calculation of coherence, which is a measure of how neural oscillations in one region are coupled to oscillations at another region. This reflects functional connectivity through white matter conduits (Thatcher, Biver et al., 2007). Therefore, coherence measurements can give an indication of functional connectivity. This sensitive measure is therefore a potential neurophysiological marker of DAI.

EEG measures of functional connectivity have been used to compare resting activity between individuals with MDD and healthy controls. Three studies have investigated connectivity at rest in MDD, with the two most recent showing widespread increases in theta and alpha structural synchrony and coherence in MDD (Fingelkurts, Fingelkurts et al., 2007; Knott, Mahoney et al., 2001; Leuchter, Cook et al., 2012). Given that MDD is thought to be caused by impairments in network connectivity, this result might seem counterintuitive. The authors offer a number of potential explanations. First, increased coherence may result from altered neurotransmitter function in MDD, and as such the increased theta activity may not reflect better functional connections, but rather a maladaptive functional connection (Fingelkurts, Fingelkurts et al., 2007; Leuchter, Cook et al., 2012). Secondly, the broad increase in coherence could reflect reduced selectivity of functional connectivity in MDD (Leuchter, Cook et al., 2012). This might be the result of increased associations between negative affective nodes (Fingelkurts, Fingelkurts et al., 2007). This is supported by research indicating that rumination in healthy individuals is associated with alpha and theta coherence increases (Andersen, Moore et al., 2009). Third, the increased coherence could be a compensatory mechanism for the decreased brain function found in MDD, to order to achieve a similar performance of semantic context processing to non-depressed individuals (Fingelkurts, Fingelkurts et al., 2007). A final

possibility is that the results could arise from a factor other than MDD, as Knott et al (2001) examined coherence in MDD in males only and showed alpha and theta coherence reductions rather than increases. Similar to coherence increases in MDD, studies have demonstrated increased resting alpha and theta coherence in TBI groups that have experience a mild injury, particularly in frontal and frontal/temporal regions (Cao and Slobounov, 2010; Thatcher, Walker et al., 1989). Research using magnetoencephalography to measure coherence following TBI also found increased theta coherence, which returned to similar levels to those shown by healthy controls following rehabilitation and cognitive recovery (Castellanos, Paul et al., 2010). In addition to measuring the effect of a TBI on functional connectivity, coherence measures were also found to be the best predictor of outcome following a TBI (Thatcher, Cantor et al., 1991), and to relate to MRI indicators of white matter integrity (Thatcher, Biver et al., 1998). The coherence alterations following a TBI are thought to reflect a malfunction of the connecting circuits (Castellanos, Paul et al., 2010). However, the pattern of increased resting coherence after a TBI is not universal, with one study finding no difference compared to controls (Kumar, Rao et al., 2009).

While resting coherence comparisons are useful for suggesting the state of default network connectivity, this does not necessarily relate to functional processes. Measuring coherence during active cognition is likely to offer information above and beyond that found by resting recordings. One aspect of cognition that is frequently affected by both TBI and MDD, and is affected to an even greater extent in TBI-MDD, is working memory (WM) (Burt, Zembar et al., 1995; Chuah, Maybery et al., 2004; Jorge, Robinson et al., 2004). WM refers to the brief storage of information in order to enable manipulation of that information by other executive functions (Baddeley, 2003). WM can be separated into three periods – the

encoding period, during which an internal representation of the information is created, the retention period, during which the encoded information is maintained, and the retrieval period, when the internal representations are recalled to guide behaviour. WM relies on effective connectivity between frontal-central and frontal-posterior brain regions (Postle, 2006; Silberstein, Song et al., 2004). Frontal impairments in functional connectivity have been demonstrated in both TBI and MDD individuals, and are thought to be related to WM impairments (Cudmore, Segalowitz et al., 2000; Kumar, Rao et al., 2009; Leuchter, Cook et al., 2012; Mattson and Levin, 1990; Okamoto, Hashimoto et al., 2007; Scheid, Preul et al., 2003). Two bands of EEG activity have been shown to be crucial for effective WM function – alpha (8-13Hz) and theta (4-8Hz). In WM, alpha is believed to represent inhibitory processes that potentially buffer WM related activity from interference by bottom-up sensory input (Jensen, Gelfand et al., 2002; Klimesch, Sauseng et al., 2007). Increases in alpha activity are found in particular during the retention periods in particular of WM tasks (during which encoded information is maintained), which is thought to reflect inhibition of non-relevant areas (Klimesch, Sauseng et al., 2007; Segrave, Thomson et al., 2010). Research has also shown that as memory load increases, alpha coherence during retention increases (Payne and Kounios, 2009). Therefore, the ability to modulate alpha coherence for task specific demands is likely to be important for WM performance. Theta on the other hand is thought to represent focused attention to activated neural representations of the information that is being retained, through frontal-posterior connectivity increases (Sarnthein, Petsche et al., 1998). The function of the processes reflected by these two bands in combination increase the signal to noise ratio of the retained information (Payne and Kounios, 2009).

Only one study has focused on changes in alpha and theta coherence during a WM task following a TBI. Reductions in alpha and theta coherence were found when individuals with a TBI were compared to healthy individuals during a visual Sternberg WM task, but no changes were found while at rest (Kumar, Rao et al., 2009). The authors suggest that because successful WM relies on alpha and theta connectivity between different regions, their result reflects a reduced ability in individuals with a TBI to modulate functional connectivity to meet cognitive demands. They also suggest that this impairment may be the result of DAI. No research has examined WM coherence in MDD at this stage, nor in TBI-MDD.

The aim of this study was to explore whether TBI-MDD is associated with a disruption in functional connectivity. We investigated functional connectivity by recording EEG concurrent with the Sternberg WM task (Sternberg, 1966) in participants with MDD, TBI-MDD, TBI, and healthy controls. We also measured functional connectivity via EEG while participants were at rest. Based on the aforementioned findings, it was hypothesised that both TBI and MDD groups would show more alpha and theta coherence during resting recordings relative to controls, and the TBI-MDD group would show even larger increases. With regards to WM related coherence, it was expected that both the TBI and MDD groups would show decreases in alpha and theta coherence compared to the control group in the WM task, and the TBI-MDD group would show even further reductions. Lastly, we hypothesised that the control group would show a larger increase in coherence from the encoding to the retention period than the other groups, reflecting impairment in the ability of individuals with TBI, MDD, and TBI-MDD to modulate coherence for task specific demands.

2. Methods

2.1 Participants

Seventeen healthy controls, 18 MDD participants, 19 TBI participants, and 15 TBI-MDD participants were recruited to the study. Data from a number of these participants was excluded after testing due to excessive recording artifact (two MDD participants), equipment fault (two controls), and possible medication effects (one TBI-MDD participant medicated with oxycontin). This left a total of 15 control, 16 MDD, 19 TBI, and 14 TBI-MDD participants. All participants were recruited through a participant database, the Alfred Hospital emergency department, or community advertising. Ethics approval for the study was obtained from the Alfred Hospital and Monash University's ethics committees, and all participants gave written informed consent. Participants had normal or corrected to normal vision and were aged 17-65 years. Some participants in the MDD and TBI-MDD groups were medicated – these can be viewed in Table 1.

Inclusion criteria for the MDD and TBI-MDD groups involved a previous diagnosis of MDD. This was confirmed by the MINI International Neuropsychiatric Interview for DSM-IV (Sheehan, Lecrubier et al., 1998). Current depression severity was moderate-severe for all MDD and TBI-MDD participants, defined as a score above 19 on either the Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979), or the Beck Depression Inventory-II (BDI-II) (Beck and Steer, 1984). With the exception of anxiety disorder for the MDD and TBI-MDD groups, co-morbid psychiatric diagnoses detected with the MINI were excluded, and all psychiatric diagnoses were excluded in the TBI and control groups. TBI-MDD participants were only included if the MDD was deemed to be causally related to the TBI by a psychiatrist (PBF). As such, depression prior to the TBI was an

exclusion criterion. For the TBI and TBI-MDD groups hospital records of the injury were obtained where possible. To avoid the significant heterogeneity in neural activity that focal lesions would introduce, TBI and TBI-MDD participants were excluded if their injury was open or if focal lesions were detected in post-injury hospital MRI or CT scans. Only individuals with mild-moderate TBI were included. This was determined by patient reports and hospital records of a loss of consciousness (LOC) of less than 24 hours, and an initial GCS of more than 9 (Rao and Lyketsos, 2000). To ensure injuries were at least mild, a LOC or post-traumatic amnesia (PTA) of at least 10 minutes or an initial GCS of < 15 was required (Headway, 2001; Kay, Harrington et al., 1993). All TBI and TBI-MDD participants were tested at least 6 weeks post injury.

2.2 Procedure

All participants were assessed over two sessions conducted within two weeks of each other. One session involved a demographic, TBI history, and depression severity assessment. These measures were all taken by a single trained researcher (NWB). Current depression severity was assessed with the BDI-II (Beck and Steer, 1984) and the MADRS (Montgomery and Asberg, 1979). Pre-morbid IQ was estimated using the Weschler Test of Adult Reading (WTAR), which is demonstrated to be valid following TBI (Green, Melo et al., 2008). The Edinburgh Handedness Inventory (EHI) was taken to assess hand preference (Oldfield, 1971). The second session involved the EEG recording during resting and a Sternberg WM task (described below).

Table 1. Current medication for the MDD and TBI-MDD groups

	MDD	*TBI-MDD*
No Medication	7	7
SNRI	3	3
SSRI	5	2
Tricyclic	1	2

2.3 Task and Stimuli

EEG activity was recorded during a three minute eyes open resting period and a Sternberg WM task. The Sternberg task was presented with Neuroscan STIM2 software (Compumedics, Melbourne Australia). This task simultaneously presented a set of five or seven letters to remember, followed by a probe letter. Participants were instructed to respond with a yes or no button press with their right hand to indicate whether they had seen the letter in the preceding memory set. A set of 15 consonants were used as stimuli (B, C, D, F, H, J, K, L, N, R, S, T, Y, W, and Z). Either five or seven letters were used in each memory set, which were presented simultaneously. Letters were drawn pseudo-randomly so that no letter appeared in the same location twice in a row. Trial sequence was also pseudo-randomly determined so that no more than three of each WM load (i.e. five vs seven stimuli) appeared consecutively. Crosses were placed at the ends of the five letter sets so they subtended the same visual angle as the seven letter memory sets. Participants were instructed to attend to the letters and ignore the crosses. Probe letters were present in the memory set at a 50% probability. The order of this was also pseudo-randomly determined so that no more than three 'probe present' or 'probe absent' trials occurred consecutively. In addition to this, no letter was presented twice in succession. Trials began

with a fixation cross (517msec) followed by a blank screen (500msec). The memory set (encoding period) was then presented (3017msec), followed by another blank screen for the retention period (3017msec). The probe letter was then presented (2017msec) followed by a brief visual mask (133msec) and a blank screen pause before the next trial's fixation cross (1867msec). Participant responses were only recorded during the presentation of the probe – responses outside of this time were considered incorrect. All participants performed a brief practice version prior to the recording, and all were presented with the same sequence, consisting of six blocks of twenty trials per block. In addition to EEG activity, accuracy and reaction times were recorded for each participant. Task design is illustrated by Figure 1.

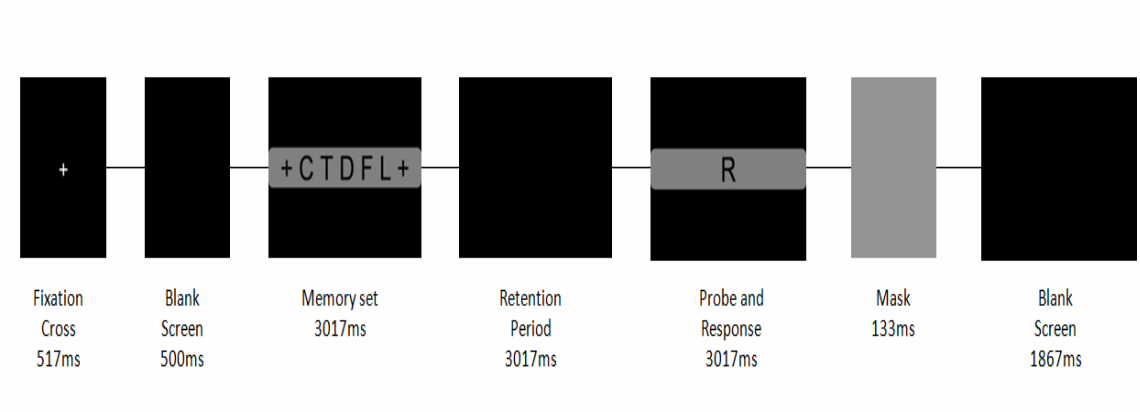

Figure 1. Task design and stimuli timing for the Sternberg task. All letters in the memory set were presented simultaneously. Memory sets contained either five or seven letters.

2.4 Electrophysiological Recording and Analysis

Recordings were performed in a darkened and sound attenuated room. A Neuroscan 64 channel quick cap with Ag/AgCl electrodes recorded EEG activity to Neuroscan Acquire

software using a Synamps 2 amplifier (Compumedics, Melbourne Australia). Online, electrodes were referenced to an electrode between Cz and CPz. Verticle and horizontal eye movements were recorded from electrodes above and below the left eye, and outside the outer rim of each eye. Electrode impedances were kept below 5kΩ. Digital conversion took place at 500Hz, with a bandpass filter of .1-100Hz (24dB/octave roll-off).

The data was analysed offline using Scan 4.3. Eye movements were corrected for using an automated algorithm (Croft and Barry, 2000). Recordings were re-referenced offline to linked mastoids, which provides the least common signal to electrode pairs, and thus the least confounding for coherence measures (Essl and Rappelsberger, 1998). Data was visually inspected, and periods containing muscle artefact or excessive noise were excluded. Epochs of event related EEG activity were extracted from the encoding period (550msec to 2950msec time locked to the onset of the memory set) and retention period (550msec to 2950msec time locked to the onset of the blank screen). Trials with incorrect responses were excluded from analysis. Eyes open resting data was segmented into consecutive non-overlapping 1022msec epochs for analysis. Epochs containing amplitude variations exceeding 75μv were also excluded. Each participant provided over 30 accepted epochs for each condition, and no significant differences were detected between groups in number of accepted epochs ($p < .05$). Bandpass filters selected activity within the alpha (8-13Hz) and theta (4-8Hz) bands in each epoch with a 24dB/octave roll off. To avoid artefact created by filtering near the edge of an epoch, the first and final 200msec of each epoch was excluded from analyses.

2.5 Coherence Computation

Inter- and intra-hemispheric coherence in the alpha (8-13Hz) and theta (4-8Hz) bands was calculated in the resting, encoding, and retention conditions. Coherence represents the proportion of variance in the phase changes at each electrode that can be explained by a linear relationship between the two. This gives values between 0 (a random relationship) and 1 (complete consistency). Coherence is calculated as $|C_{xy}(f)|^2$ where:

$$C_{xy}(f) = \frac{\Sigma_i (x_i(f) - \bar{x}(f))(y_i(f) - \bar{y}(f))^*}{\sqrt{\Sigma_i |x_i(f) - \bar{x}(f)|^2 \Sigma_i |y_i(f) - \bar{y}(f)|^2}}$$

$x_i(f)x_i(f)$ and $y_i(f)y_i(f)$ represent the Fourier transformed frequency spectrum sampled at electrodes x and y, at time i.

Coherence calculations combine information from autospectrum values, which contain information about in phase activity (reflecting volume conductance and local activity), and the cross spectrum values, which contain information about out of phase activity (reflecting network connectivity). The normalisation of the cross spectrum as a ratio of the autospectrum and cross spectrum controls for volume conduction, so that network connectivity is the measure extracted (Nunez, 1981, 1997; Thatcher, Biver et al., 2004). In addition to this, because the presence of a focal lesion was an exclusion criterion, we can assume that volume conductance is similar between groups. As a result, between group differences in coherence can be assumed to be the result of differences in network connectivity.

2.6 Statistical Analysis

2.6.1 Demographic, Severity, and Behavioural Analyses

One way analysis of variance (ANOVA) compared BDI and MADRS depression severity measurements between groups, as well as years of education, WTAR, age, and EHI scores. Independent samples t-tests compared GCS, LOC, PTA, and time since injury between the TBI and TBI-MDD groups.

Three way repeated measures ANOVAs compared both percent correct and reaction times, with WM load (five or seven letters) and probe (present or absent) as within subject factors, and group (control, TBI, MDD, and TBI-MDD) as the between subject factor. Post hoc Tukey tests were conducted to control for multiple comparisons where omnibus ANOVAs indicated significant between group differences.

2.6.2 Coherence Analyses

All coherence values were subjected to a Fisher z-transformation to ensure normal distribution. Electrode pairs of interest were similar to those chosen by Kumar et al. (2009), but to reduce the number of comparisons fewer electrode pairs were selected. Frontal-central (F3-C5, F4-C6), fronto-parietal (F3-P3, F4-P4), and central-parietal (C5-P3, C6-P4) coherence was calculated intra-hemispherically, while frontal (F3-F4), central (C5-C6), and parietal (P3-P4) coherence was calculated inter-hemispherically. Coherence pairs for comparison are illustrated in Figure 2. Coherence analyses for the Sternberg task were conducted using repeated measures ANOVA for the alpha and theta band separately, and for inter- and intra-hemispheric factors separately. Intra-hemispheric comparisons were conducted for each band with a five way repeated measures ANOVA, with WM period

(encoding and retention), WM load (five or seven letters), hemisphere (left and right), electrode pair (frontal-central, frontal-parietal, and central-parietal) as within subject factors, and group (control, TBI, MDD, and TBI-MDD) as a between subject factor. Inter-hemispheric comparisons were conducted for each band with a four way repeated measures ANOVA, with WM period (encoding and retention), WM load (five or seven letters), electrode pair (frontal-frontal, central-central, and parietal-parietal) as within subject factors and group (control, TBI, MDD, and TBI-MDD) as a between subject factor. Resting period analyses were also conducted with repeated measures ANOVA for the alpha and theta band and intra- and inter-hemispheric comparisons separately. Intra-hemispheric comparisons were conducted for each band with a with a three way repeated measures ANOVA, with hemisphere (left and right) and electrode pair (frontal-central, frontal-parietal, and central-parietal) as within subject factors, and group (control, TBI, MDD, and TBI-MDD) as a between subject factor. Lastly, inter-hemispheric comparisons were conducted for each band with a two way repeated measures ANOVA, with electrode pair (frontal-frontal, central to central, and parietal-parietal) as a within subjects factor, and group (control, TBI, MDD, and TBI-MDD) as a between subject factor. All sphericity violations were corrected for using the Greenhouse-Geisser correction. For the sake of brevity, only main effects and interactions involving group differences are reported. To elucidate the origin of significant interactions, follow up ANOVAs were conducted comparing within group effects on WM period and electrode pairs, and between group effects in these variables. Post hoc Tukey tests were conducted to control for multiple comparisons where omnibus ANOVAs indicated significant between group differences. In order to assess the impact of between group differences in coherence on performance, correlations were conducted between the more difficult seven letter WM load reaction times and percent correct, and coherence during the

seven letter conditions at select electrode pairs that differed between groups. These correlations were analysed both within each group and overall. To avoid type I error inflation, a more stringent alpha of 0.01 was set for the correlations. This method of conservative significance adjustment is consistent with past EEG studies that have made similar number of comparisons (Segrave, Thomson et al., 2010).

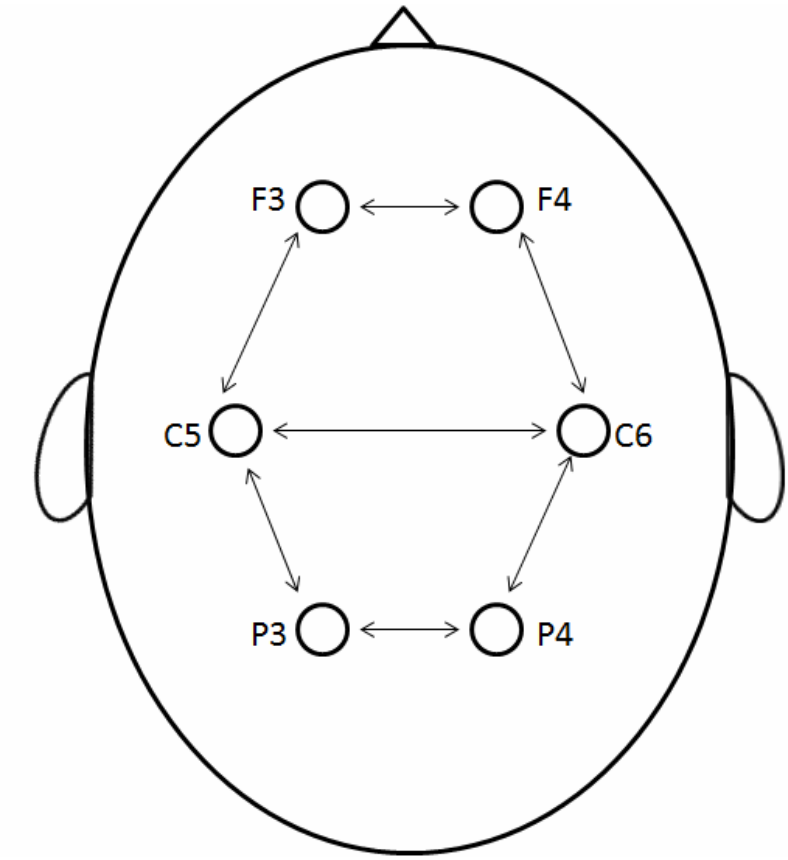

Figure 2. Electrodes of interest for coherence measures. Arrows represent pairs of electrodes that coherence was calculated between.

3. Results

3.1 Demographic and Severity Analyses

Means and standard deviations for the demographic and depression severity scores can be viewed in Table 2. No significant group differences were present in years of education, age, handedness, or WTAR estimated pre-morbid IQ (all p's > .05). As expected, the TBI-MDD and MDD group showed significantly higher MADRS and BDI scores than the control and TBI groups (all p's < .01). The TBI-MDD group showed significantly higher BDI scores than the MDD group ($p < .05$). The control and TBI group did not differ from each other on either measure, nor did the TBI-MDD and MDD groups on MADRS score (all p's > .05). The TBI and TBI-MDD groups did not differ on any measure of injury severity (GCS, LOC, or PTA, all p's > .05). The TBI-MDD group showed significantly longer time since injury ($t(28) = -2.81$, $p < .05$) than the TBI group.

3.2 Sternberg Behavioural Data

Behavioural data is summarised in Table 3. Omnibus group comparisons indicated there was a significant difference in accuracy ($F(3,60) = 6.510$, $p < .01$). Post hoc tests indicated this was due to the MDD group displaying lower accuracy than the TBI and control group (both $p < .05$), and the TBI-MDD group displaying lower accuracy than the control group ($p < .05$), but no other between group differences. Reaction time also differed between groups ($F(3,60) = 3.01$, $p < .05$). Post hoc tests indicated this was due to the MDD group showing a trend towards slower reaction times than the TBI group ($p = .06$), but no other between group differences. Overall there was significantly more accuracy and faster reaction times in the five letter conditions, and faster reaction times in the probe present

conditions. The MDD and TBI-MDD groups showed significantly less accuracy than the control group, and the MDD group showed a trend towards slower reaction times than the TBI group.

Table 2. Demographics, depression rating scores, and head injury measures

	Controls	*TBI*	*MDD*	*TBI-MDD*
N	15	19	16	14
Gender (F/M)	7/8	5/14	8/8	8/6
Age	42.00 (14.73)	33.32 (14.19)	39.44 (11.88)	43.29 (10.68)
Years of Formal Education	16.47 (3.04)	16.81 (3.43)	15.81 (3.67)	14.71 (3.63)
WTAR pre-morbid IQ	111.73 (3.43)	107.47 (5.66)	107.31 (7.78)	109.69 (5.94)
MADRS	1.20 (1.26)	2.48 (2.43)	25.81 (3.67)	16.47 (7.75)
BDI	1.53 (2.17)	3.47 (3.53)	23.00 (8.41)	26.50 (8.05)
EHI	94.07 (8.16)	75.26 (49.29)	86.06 (45.08)	64.08 (65.97)
GCS		12.91 (1.45)		13.67 (0.58)
LOC (hours)		0.45 (0.64)		1.16 (2.12)
PTA (hours)		32.35 (72.12)		33.63 (80.93)
Time since injury (months)		23.77 (59.66)		188.67 (197.68)

The TBI-MDD group showed significantly fewer years of education than the healthy control group, and significantly longer since injury than the TBI group. Both the TBI-MDD and MDD groups showed higher BDI and MADRS scores than the control and TBI groups.

Table 3. Percent Accuracy and Reaction Times for Sternberg Task Performance

Percent Correct – Mean (SD)				
	Controls	*TBI*	*MDD**	*TBI-MDD**
Seven Letters – Probe Present	87.00 (9.12)	86.33 (9.59)	79.20 (13.33)	77.98 (14.82)
Seven Letters – Probe Absent	89.96 (10.52)	88.78 (9.91)	79.53 (17.49)	84.14 (8.89)
Five Letters – Probe Present	94.15 (4.57)	92.12 (4.77)	86.51 (9.28)	86.07 (7.91)
Five Letters – Probe Absent	95.30 (4.68)	91.54 (7.05)	83.79 (16.16)	89.23 (5.99)
Reaction Time (ms) – Mean (SD)				
	Controls	*TBI*	*MDD^*	*TBI-MDD*
Seven Letters – Probe Present	1031 (117)	978 (170)	1090 (132)	1126 (173)
Seven Letters – Probe Absent	1124 (173)	1079 (222)	1223 (188)	1196 (159)
Five Letters – Probe Present	930 (92)	930 (181)	1024 (168)	1005 (124)
Five Letters – Probe Absent	1008 (113)	992 (181)	1132 (209)	1070 (143)

*Percent correct: MDD < Controls and TBI, $p < 0.05$; TBI-MDD < Controls, $p < 0.05$.

^ Reaction time: MDD < TBI, $p = 0.06$.

3.3 Alpha Coherence

3.3.1 Sternberg:

Interhemispheric comparisons indicated a significant WM period by group interaction ($F(3,60) = 3.87$, $p < .05$). This was due to a trend towards increased coherence from the encoding to the retention period in the control group ($F(1,14) = 3.61$, $p = .08$), and a trend in the opposite direction for the TBI group ($F(1,14) = 3.70$, $p = .07$), but no significant differences between retention and encoding for the MDD or TBI-MDD groups (all $p > .10$). This interaction is illustrated by Figure 3. The control group also showed a trend towards

more retention period coherence than the TBI group ($p = .068$). A significant electrode pair by group interaction was also found ($F(3,60) = 3.04$, $p < .01$). The electrode pair by group interaction was due to the TBI-MDD group showing more coherence between parietal electrodes than the TBI group ($p < .05$). This interaction can be viewed in Figure 4. No other interactions involving group or group main effects (all $p > .05$). Overall, higher P3-P4 coherence during the encoding period correlated with lower accuracy in the seven letter probe absent condition ($r = -.33$, $p < .01$). No other correlations or within group correlations were significant for these measures (all $p > .01$).

The intrahemispheric comparisons indicated a significant electrode pair by group interaction ($F(3,60) = 4.24$, $p < .01$). The TBI group showed lower frontal-central coherence than central-parietal coherence ($F(1,18) = 9.97$, $p < .01$), while the control group showed the reverse pattern (non-significant). Additionally, the control group showed higher frontal-central coherence than the TBI group ($p < .05$). This interaction can be viewed in Figure 5. No other significant interactions or main effects involving group were present. No overall correlations were found between frontal-central coherence and seven letter performance measures, but within the TBI group probe absent accuracy negatively correlated with frontal-parietal alpha in both the left ($r = -.63$, $p < .01$) and right hemispheres ($r = -.69$, $p < .01$).

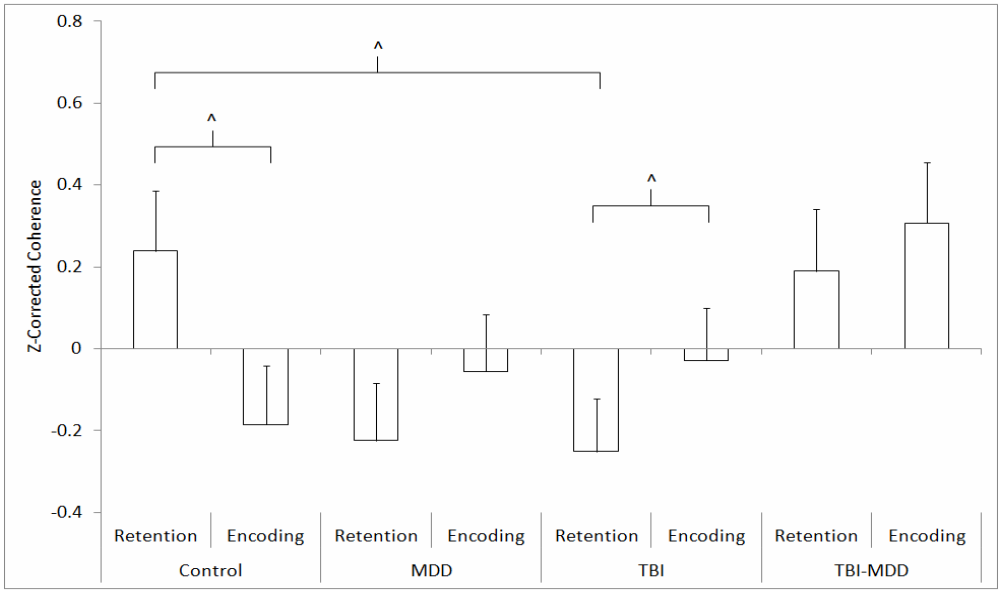

Figure 3. Mean z-corrected inter-hemispheric alpha coherence pooled across electrodes and WM load during encoding and retrieval periods for each group. Error bars represent Standard Error. ^ indicates a trend towards difference.

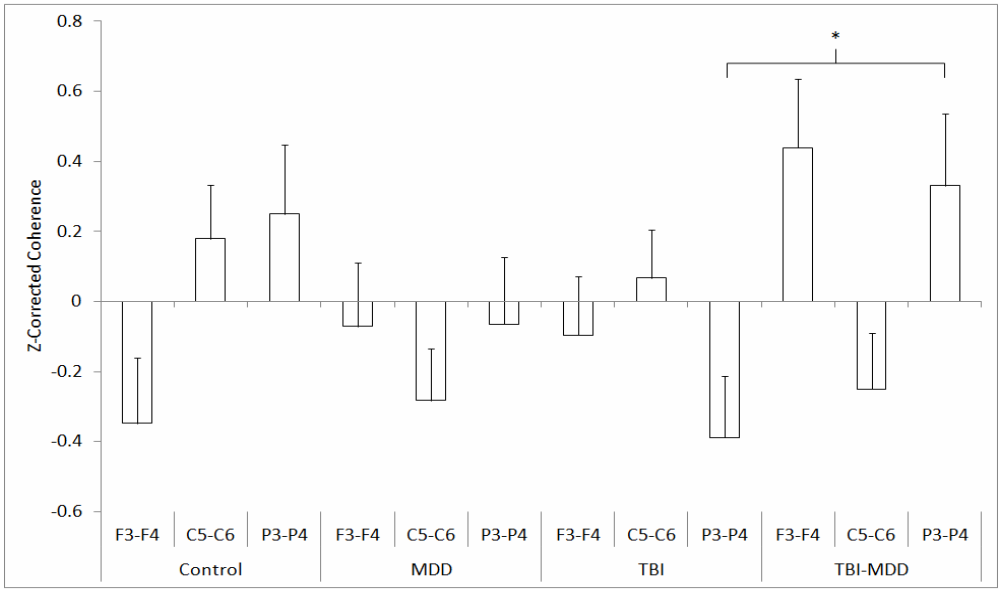

Figure 4. Mean z-corrected inter-hemispheric alpha coherence combined across WM period and WM load at each electrode for each group. Error bars represent Standard Error. * indicates a significant difference at $p < .05$.

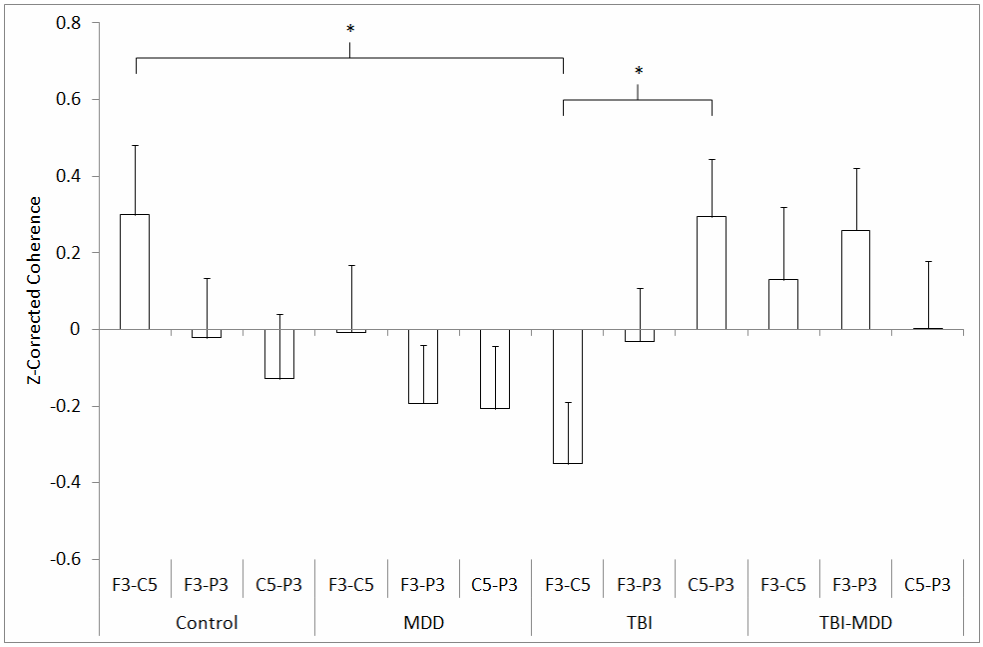

Figure 5. Mean z-corrected intra-hemispheric alpha coherence pooled across WM load and WM period at each electrode for each group. Error bars represent Standard Error. * indicates a significant difference at $p < .05$.

3.3.2 Resting:

With regards to the interhemispheric alpha coherence, a significant group by electrode pair interaction was found ($F(3,60) = 2.65$, $p < .05$). This was due to the TBI group showing less parietal-parietal coherence than central-central or frontal-frontal (both $p < .05$), while no other groups showed this pattern. No main effect involving group was found for the interhemispheric coherence measures ($F(3,60) = .767$, $p > .05$). No between group differences or interactions involving group were significant for the resting intrahemispheric alpha coherence (all $p > .05$).

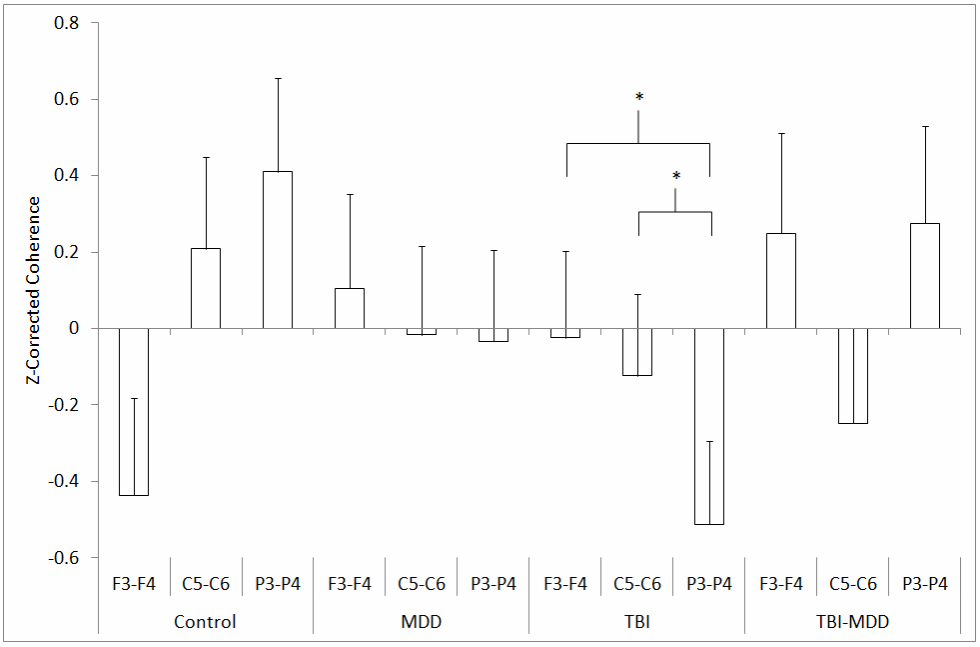

Figure 6. Mean z-corrected inter-hemispheric resting alpha coherence at each electrode for each group. Error bars represent Standard Error. * indicates a significant difference at $p < .05$.

3.4 Theta Coherence

3.4.1 Sternberg:

Interhemispheric comparisons indicated a main effect of group ($F(3,60) = 4.12$, $p < .01$). Post-hoc comparisons revealed this was due to significantly more coherence in the TBI-MDD group than the TBI group ($p < .01$), and a trend towards more than the control group ($p = .079$). This finding can be viewed in Figure 7. No interactions involving group were significant (all $p > .05$). Over all groups, higher encoding period P3-P4 coherence correlated with slower reaction times in the seven letter probe present condition ($r = .42$, $p < .01$), and more retention period C5-C6 coherence correlated with lower accuracy in the probe absent condition ($r = -.339$, $p < .01$). Within group correlations were significant for the control

group, showing more retention period P3-P4 coherence related to longer seven letter probe absent reaction time ($r = .72$, $p < .01$), and more encoding period P3-P4 coherence correlated with longer seven letter probe present reaction time ($r = .74$, $p < .01$). No other correlations were significant.

Intrahemispheric comparisons indicated a significant electrode pair by group interaction ($F(3, 60) = 4.51$, $p < .01$). This was due to the TBI group showing lower coherence in frontal-central than central-parietal electrodes ($F(1,18) = 10.73$, $p < .01$) while other groups show the reverse pattern (non-significant). In addition to this, post hoc tests indicated the TBI-MDD showed higher coherence than the TBI group between frontal-central electrodes ($p < .05$). These results can be viewed in Figure 7.

Overall, higher F3-C5 coherence during the encoding period correlated with slower reaction times in the seven letter probe present condition ($r = .34$, $p < .01$) but not with other performance measures (all $p > .01$). There was also a significant correlation in the TBI-MDD group, with more F3-C5 coherence in the seven letter condition's retention period relating to lower percent correct ($r = -.67$, $p < .01$). No other theta coherence measures correlated with any performance measure.

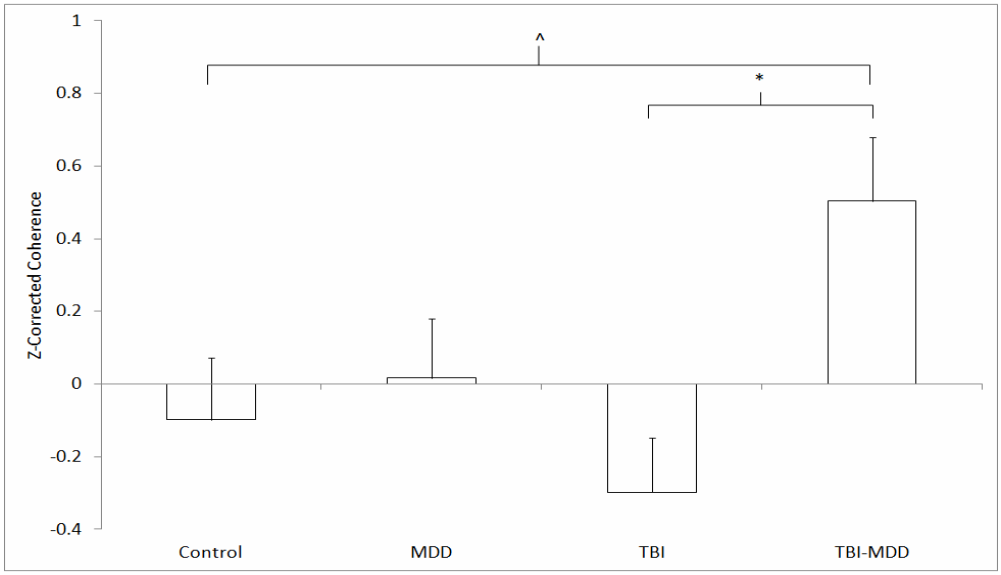

Figure 7. Mean z-corrected inter-hemispheric theta coherence between each group combined across WM period, WM load, and electrode. Error bars represent Standard Error. * indicates a significant difference $p < .05$, ^ indicates a trend towards significant difference $p < .10$.

3.4.2 Resting:

No main effects of group or interactions involving group were significant for measures of interhemispheric theta coherence (all $p > .05$). A significant three way intrahemispheric electrode pair by hemisphere by group interaction was present ($F(3,60) = 2.31$, $p < .05$). This was due to an interaction in the MDD group between hemisphere and electrode pair, with the left hemisphere showing higher frontal-central coherence than central-parietal ($p < .05$), but the right hemisphere showing no difference ($p < .10$), and no significant differences in other groups. There was also a significant intrahemispheric electrode pair by group interaction ($F(3,60) = 2.66$, $p < .05$), where the MDD group showed higher frontal-central than central-parietal coherence ($p < .05$), while the TBI showed the reverse ($p < .05$). These interactions can be viewed in Figure 9.

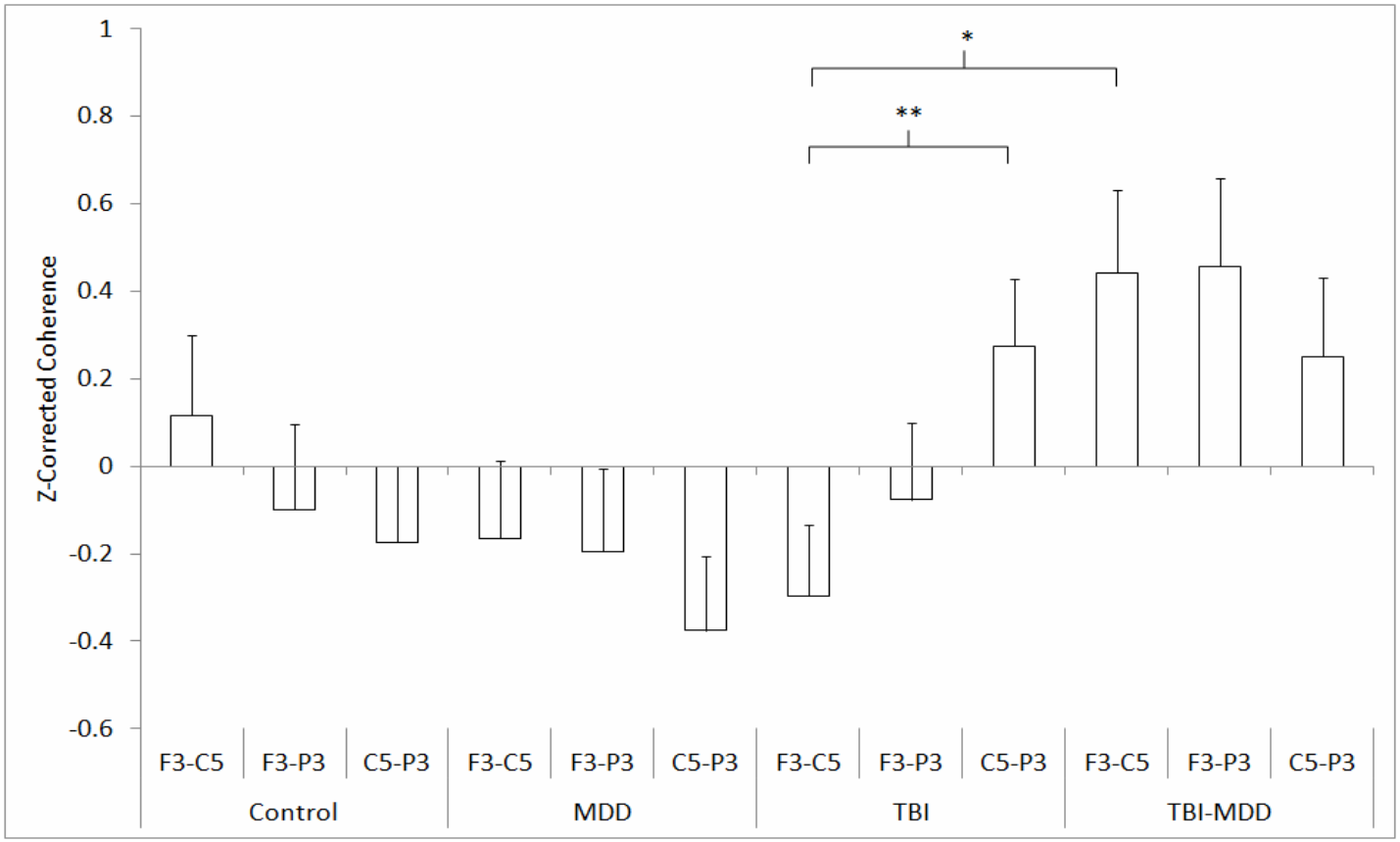

Figure 8. Mean z-corrected intra-hemispheric theta coherence for retention and encoding periods combined between frontal-central electrodes and central-parietal electrodes for each group. Error bars represent Standard Error. ** indicates a significant difference $p < .01$, * $p < .05$.

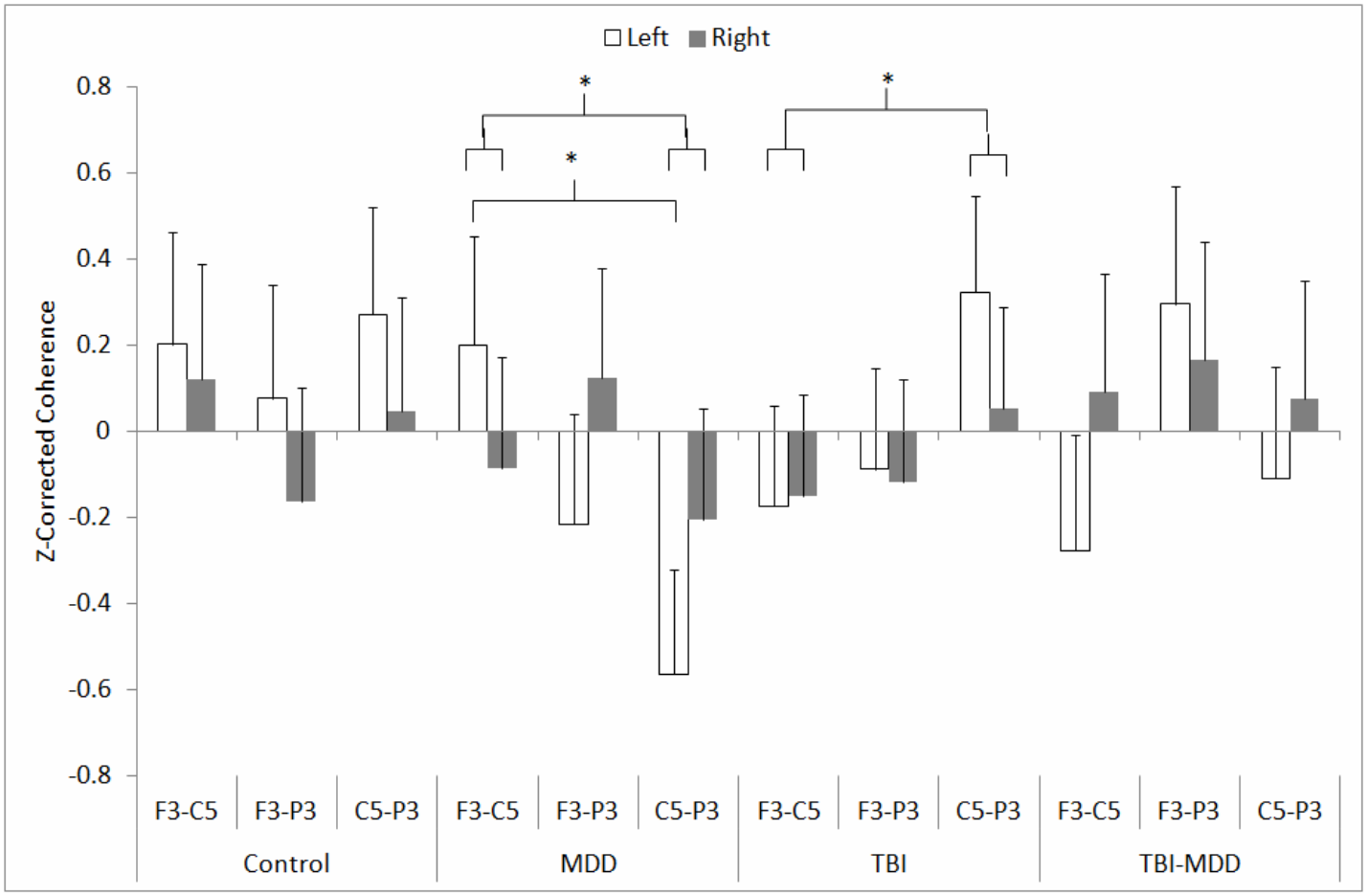

Figure 9. Mean z-corrected intra-hemispheric resting theta coherence at each hemisphere and electrode location for each group. Error bars represent Standard Error. * indicates a significant difference at $p < .05$.

4. Discussion

This study examined functional connectivity in the alpha and theta bands at rest and during WM processing in individuals with TBI-MDD as compared with MDD, TBI and healthy controls. It is unique as it is the first study to examine functional connectivity in TBI-MDD and MDD during a WM task.

We found that the TBI-MDD and MDD groups exhibited poorer WM performance compared with controls, while WM performance was unaffected in the TBI group. Measures of EEG coherence suggested a complicated pattern of differences between groups. The first general pattern of interest is that during WM processes, the TBI-MDD group showed higher parietal interhemispheric alpha coherence compared to the TBI group, and higher interhemispheric theta over all regions compared to both the TBI and control group, but not the MDD group. Significant correlations suggested the higher coherence between these areas and bands was detrimental to WM performance. The second pattern differentiating the groups indicated that interhemispheric alpha coherence increased in WM from the encoding to the retention period in the control group, but did not differ in the MDD and TBI-MDD groups, and the opposite pattern was observed in the TBI group. Additionally, during WM the TBI group showed lower intrahemispheric frontal-central alpha and theta coherence. The last result of note is that, while at rest, the MDD group showed more frontal-central theta coherence than central-parietal (a pattern not shared by other groups), which was particularly the case in the left hemisphere.

The higher inter-hemispheric WM coherence in the TBI-MDD group has a number of potential explanations. One frequently presented explanation for increases in brain activity

in groups with psychiatric illnesses is that the increased activity reflects compensation. Examples of an increase in functional connectivity specifically to compensate for a decrease in another function are not found in previous literature, but fMRI research has indicated that increased activity in one brain area may compensate for inefficiency in order to maintain memory performance in healthy aging (Cabeza, Anderson et al., 2002). With regards to the current results, this explanation would suggest that coherence is increased between the hemispheres in the TBI-MDD group in order to compensate for impairment in another region/function, so that adequate WM performance is still possible. Supporting this idea, previous research has shown increased coherence in the theta band when the task in question becomes more difficult to perform, i.e. as WM load increases (Payne and Kounios, 2009). However, there are a number of issues with this explanation for the current results. Firstly, the explanation assumes that more coherence is better for performance. This interpretation of coherence is untested. Conversely, several lines of evidence suggest that higher coherence is not necessarily better for performance. First, higher coherence (particularly in the theta band) is detected in a number of different pathological groups that exhibit impaired cogntive performance (Cao and Slobounov, 2010; Fingelkurts, Fingelkurts et al., 2007; Leuchter, Cook et al., 2012; Locatelli, Cursi et al., 1998; Murias, Webb et al., 2007; Thatcher, Walker et al., 1989). Secondly, high coherence following a TBI appears to decrease as cognitive recovery progresses (Castellanos, Paul et al., 2010). Thirdly, higher coherence relates to lower IQ (Thatcher, North et al., 2005). The current results also indicated that higher coherence values were only negatively correlated with performance. If the higher coherence values were indicators of a compensatory process, we might expect those who are better able to compensate to show better performance rather than worse. The second issue with a compensation explanation for the current results is that the explanation

assumes that the existence of an impairment in another process without evidence for that impairment.

An alternative explanation is that higher coherence reflects the maladaptive neuroplastic reorganisation that might take place following a DAI (Povlishock and Christman, 1995). While the gross scalp coherence measures of common frequency variations might indicate more inter-hemispheric connectivity, actual signal fidelity from neuron to neuron may be reduced. In other words, in terms of information processing in the brain, the increased coherence we detected in the TBI-MDD group may reflect more noise/less signal. The finding that higher coherence values were found to correlate only with poorer WM performance supports this contention, as does previous research indicating higher alpha and theta coherence while at rest is associated with lower IQ and lower performance in second language acquisition (Reiterer, Hemmelmann et al., 2005; Thatcher, North et al., 2005). Thatcher et al. (2005) suggest the association between higher performance and lower coherence is indicative of more regional specificity, resulting in more complexity in the higher performing brain. The increased coherence in the TBI-MDD group may be explained in a similar manner.

It should also be noted that the two explanations (compensation and maladaptive connectivity) are not mutually exclusive. It may be that coherence in the theta band represents a maladaptive process in these groups (as coherence increases in this band are more commonly associated with pathology), that the alpha coherence increase attempts to compensate. Support for this combined explanation comes from the pattern of WM performance in the healthy control group. The control group showed an increase in inter-hemispheric alpha coherence from the encoding to the retention period. This might suggest

that in a healthy brain, increased coherence in the alpha band helps to retain information. Previous research in healthy controls shows support for this, with increasing memory loads resulting in increased alpha coherence (Payne and Kounios, 2009). The lack of differentiation between the encoding and retention period in other groups may reflect an impaired functional connectivity, possibly due to DAI in the TBI groups or neurotransmitter alterations in the MDD groups. This may suggest that the lower intrahemispheric alpha coherence in the TBI only group indicates impairment in this process, potentially as a result of DAI, which are thought to affect frontal areas in particular (Mattson and Levin, 1990; Okamoto, Hashimoto et al., 2007; Scheid, Preul et al., 2003). However, if the alpha coherence reductions are due to DAI, we might expect the TBI-MDD to show them as well. A potential explanation is that for the TBI-MDD group more time had passed since injury, so this group may have undergone a neuroplastic recovery of this process. In addition to potentially explaining the frontal alpha coherence, the differences in time since injury offer an interesting perspective on WM impairment differences between the groups. The TBI-MDD group showed impaired performance, while the TBI group did not – if the performance reductions are due to the injury, we would expect them to be worse for the individuals who have had less time to recover. As such, it seems likely that the MDD is the cause of memory impairments in the TBI-MDD group, rather than the TBI.

The last finding of interest is the increased resting theta coherence in the left hemisphere of the MDD group. Both previous research and the current study seem to suggest that higher theta coherence represents maladaptive function. As such, the increased left hemisphere coherence in MDD might reflect dysfunction in this area. This provides support to previous research, which has also found short range theta coherence increases in

the left hemisphere (Fingelkurts et al., 2007), and which has indicated left hemisphere hypoactivity while MDD participants are resting (Debener, Beauducel et al., 2000; Henriques and Davidson, 1991). However, if the process is related to MDD, it is unclear why the TBI-MDD group did not show the same pattern.

There are a number of limitations to the current study. As with all research that use coherence as a measure of functional connectivity, potential reference electrode effects or volume conduction effects may contribute to the signal (Nunez, 1997). This may have inflated our estimates of inter-region connectivity. However, these issues are unlikely to confound the between group comparisons, as optimum reference montages (averaged mastoids) were used for all participants (Nunez, 1997). Focal injuries were also an exclusion criterion, so volume conduction effects could be expected to be similar between groups. Therefore, the differences between groups are more likely to be due to alterations to the function of white matter conduits. In addition, coherence is only an indirect measure of connectivity, reflecting changes in regional connectivity properties that are as yet not well characterised. As such, interpretation of the meaning of differences in coherence is restricted by our current understanding of each process. A final limitation is that the TBI and TBI-MDD groups differed in time since injury, so although the most salient difference between these groups is the presence of MDD, the TBI-MDD group had longer for neuro-plastic recovery, so the differences in coherence may be related to recovery time rather than MDD.

4.1 Conclusions

Previous literature has indicated that in both individuals with TBI and MDD, increases in functional connectivity between brain regions can be found while at rest. The current

study extends this, indicating that more inter-hemispheric alpha and theta coherence is found in individuals with MDD following a TBI. These increases appear to be related to poorer performance, suggesting they might be the result of a maladaptive neuro-plastic reorganisation following DAI. This study provides the first evidence that MDD following a TBI may be related to changes in functional connectivity between brain regions.

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Conflicts of Interest

PBF has received equipment for research from Medtronic ltd, Magventure A/S and Brainsway Ltd and funding for research from Cervel Neurotech. NWB, RAS, KEH, JJM, NCR have no conflicts to declare.

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Chapter Eleven

General Discussion

Summary of Findings

MDD is a common sequalae of TBI, occurring in patients post TBI at rates much higher than the general population. MDD following TBI results in considerable individual suffering and poorer recovery outcomes when compared to TBI not complicated by depression. While a considerable amount of research has examined the psychosocial factors that contribute to the development of MDD following TBI, very little research has examined the neural factors that are likely to contribute to the disorder. This thesis aimed to provide an understanding of those neural factors, with a particular focus on functional activity. Four specific questions regarding neural activity changes in TBI-MDD were posed in order to achieve this goal.

1) Are electrophysiological processes related to response inhibition altered in TBI-MDD?

2) Are response error related electrophysiological processes altered in individuals with TBI-MDD?

3) Is brain activity related to working memory inhibition and attention altered in TBI-MDD?

4) Is functional connectivity between brain regions during working memory altered in TBI-MDD?

To address the goal of this thesis, and to answer these questions, four different electrophysiological measures of cognition related brain activity were examined in TBI-MDD, MDD, TBI, and a healthy control group. In general, the findings for each of these measures, when compared across the control groups of MDD alone, TBI alone, and healthy controls, indicated that cortical activity in the TBI-MDD group was altered in a similar fashion to that seen in MDD alone. The only exception to this was in measures of coherence, which indicated a potentially maladaptive increase in functional connectivity in the TBI-MDD group that was not seen in the MDD group. The other finding of note was that the electrophysiological measures of brain activity were largely unchanged in the TBI only group. Again, the only exception to this was in the coherence data, which showed a reduction in some measures of coherence. The following provides an overview of the results of each study, a discussion of how the findings are integrated and the overall conclusions of this thesis.

Study One: An exploratory analysis of the Go/Nogo N2 in major depression and depression following traumatic brain injury

The first study compared the four groups of participants across a number of ERPs which followed successful responding and successful response inhibition to simple happy and sad faces. The N2 in particular was reduced in the MDD and TBI-MDD groups following response inhibition trials, but unchanged in the TBI group when compared to the healthy control group. Comparisons of the activity in the N2 window between response and response inhibition trials confirmed that the N2 was related to response inhibition rather than conflict monitoring. This indicated that the MDD and TBI-MDD groups showed altered electrophysiological response inhibition processing compared to controls, suggesting

impairment in this process. In addition, the lack of a change in the TBI group suggests that following a mild to moderate TBI in which MDD does not develop, response inhibition is unaffected. Lastly, we found no differentiation between the TBI-MDD and MDD groups and the TBI and healthy controls in response to the simple emotional faces. This lack of a difference may indicate that mood congruent biases in TBI-MDD and MDD groups are not reflected in electrophysiological measures. However, previous research has suggested that ERPs to happy and sad stimuli are altered in MDD (Cavanagh and Geisler, 2006; Deldin et al., 2003; Ilardi et al., 2007), so these results may indicate that the simple stimuli used in the study did not adequately provoke emotional responses to show differences in mood congruent biases between the groups.

Study Two: Error Positivity is reduced in MDD and TBI-MDD

The second study compared the four groups on measures of electrophysiological processing that followed a response inhibition error. It examined the ERN, which is thought to reflect automatic response evaluation, and the Pe, thought to reflect conscious awareness of errors. The results indicated that while the ERN did not differ between any of the four groups, the Pe was smaller in amplitude in the MDD group, and in the TBI-MDD group (at a trend level of significance) compared to the control group. Again, the TBI group showed no change in either ERP compared to the control group. While unfortunately small sample sizes limited the power of this comparison, the results suggest that in individuals with both MDD and TBI-MDD, conscious awareness of errors is reduced. The results also suggest that the TBI group shows unaltered error processing. The find of altered error processing in these two groups strongly suggests that this finding is related to the presence of lowered mood / depression rather than other factors.

Study Three: Impaired Alpha Synchronization during Working Memory Retention in Depression and Depression Following Traumatic Brain Injury

The third study examined alpha and theta band activity in the retention period of a working memory task. Previous research indicated that alpha and theta band activity increases during the retention period, in order to allow successful working memory performance, and that alpha activity is related to the inhibition of non-relevant brain regions, while theta activity represents attentional processes. The results of this study indicated that individuals with MDD and TBI-MDD show reductions in working memory alpha activity in parieto-occipital regions compared to healthy controls, while fronto-midline theta activity is unaffected. The results also indicated that individuals with TBI show unaffected theta and alpha band activity in a working memory task. In a similar finding to the other studies, this pattern of results suggests that in the abnormalities in working memory related oscillations arise from depression rather than TBI itself.

Study Four: Functional connectivity alterations during working memory in depression following traumatic brain injury

My final study examined functional connectivity by measuring coherence between frontal, central, and parietal electrodes (inter- and intra-hemispherically) during the encoding and retention periods of working memory, and while participants were at rest. A number of differences were apparent between the groups in these measures. The most important difference with respect to the aims of this thesis was the finding of increased interhemispheric theta in the TBI-MDD group during both periods of the working memory task. This theta coherence increase was suggested to indicate maladaptive recovery from

DAI in this group, as previous research has concluded that theta coherence increases reflect pathophysiology (Locatelli et al., 1998; Murias et al., 2007), and the current research showed higher theta coherence to be related to lower working memory performance. The other finding of note was that while the control group showed increased interhemispheric alpha from the encoding to the retention period, none of the other groups did. Increased alpha coherence seems to be important for working memory retention (Payne and Kounios, 2009), so the increase in alpha coherence in the healthy control group is likely to represent task relevant modulation of functional connectivity. Likewise, the lack of differentiation between the encoding and retention periods in the TBI, MDD, and TBI-MDD groups may reflect impairment in task specific modulation of functional connectivity. This impairment may be a result of DAI in the TBI and TBI-MDD groups, and network connectivity impairments in the MDD and TBI-MDD groups. Unlike the findings of the first three studies, coherence related measures appeared to be sensitive to brain changes associated with both TBI and MDD.

General Conclusions and Implications

The first major conclusion of this study is that the majority of electrophysiological changes in brain activity seen in the TBI-MDD group appear to be related to 'the MDD', rather than 'the TBI'. This conclusion is made in light of the findings that the brain changes in TBI-MDD were consistent with those seen in the MDD only group and were not present in the TBI alone group. However, because this study was not a prospective study of TBI-MDD, this does not imply causation. The brain changes could be either the result of the MDD, or a result of the injury which lead to MDD. Despite this, combining the conclusions from the current thesis with previous research into injury mechanisms and hypotheses about the development of TBI-MDD allows for some speculation as to the possible causes of TBI-MDD.

There are a number of conclusions that can be made when viewing the results of this thesis as a whole. The first three studies measured processes generated by a common mechanism – synchronised regional neural activity – and each of these studies showed a common result – reductions in amplitude for the MDD and TBI-MDD groups. As a result, we can conclude with a reasonable level of confidence that both these groups show the same impaired ability to synchronise regional neural activity during specific cognitive tasks. This might reflect a reduction in the ability of the brain to allocate resources to processing, so that these individuals find tasks more difficult (Kok, 1997). It is likely that this finding would generalise to areas of cognition other than those assessed specifically in this thesis. It is also possible that impairments in the ability to synchronise neural resources to task stimuli may be a reflection of the focus on negative ruminations at the cognitive/emotional level. Indeed, MDD has been characterised as having an excessively fixed neural pattern, which implies an inability to flexibly respond to external stimuli (Holtzheimer and Mayber, 2011). In addition to these regional measures of activity, the fourth study indicated that the TBI-MDD group also shows inter-hemispheric connectivity increases (hypothesised to reflect a maladaptive process), which is not found in the MDD group. This finding is of particular interest, as it is the only electrophysiological marker that is distinct to the TBI-MDD group. As such, it may reflect the unique contribution of DAI to the MDD that develops following a TBI.

The pattern of the current findings, in addition to previous research identifying factors that may affect the brain in TBI and MDD, allow for some initial conclusions to be made regarding the genesis of brain activity alterations in TBI-MDD, and thus the potential neural causes of TBI-MDD:

1) The major initial mechanism of disruption to brain activity in the sample group studied in this thesis is likely to be DAI (as groups were restricted to mild-moderate injuries, and focal lesions were excluded). It is thought that DAI disrupts functional connectivity in some individuals more than others, thus somewhat selectively leading to the impaired brain network function found in MDD (Drevets, 2000; Gotlib and Hamilton, 2008; Mayberg, 1998). This explanation is supported by the fourth study, which indicated that only the TBI-MDD group showed altered inter-hemispheric theta coherence. It might be the case that DAI results in the depressive symptoms as well as the altered point measures of neural activity found (similar ERP and ERD/ERS changes to the MDD group) through injury specific alterations to brain network function, rather than the interactive stress, monoamine, and maladaptive coping that may lead to MDD in non-injured individuals. This explanation suggests that TBI-MDD and MDD arise from different processes, despite common symptoms and regional alterations in brain activity.

   In support of this explanation, MRI measurement of fractional anisotropy (which reflects white matter structural integrity) using a similar sample as the current research suggests that the TBI-MDD group showed greater altered white matter connections compared to the TBI group (Maller et al., In Press, see appendix). However, both the TBI and TBI-MDD groups had similar measures of injury severity – GCS, LOC, and PTA, which are assumed to reflect the extent of DAI (Gennarelli, 1996). Therefore, it may be that DAI differs between individuals in some quantitative manner that is not reflected by the extent of functional disruptions as measured by GCS, LOC or PTA, but appears to be reflected in EEG and DTI measures.

2) Alternatively, it may be that in the acute recovery phase following a TBI, brain activity is altered in a similar way to MDD, and that for some reason recovery of normal function does not occur in some individuals. A possible TBI mechanism that may result in this altered brain activity is the glutamatergic excitotoxicity, which may be related to altered neural plasticity in individuals with TBI (De Beaumont et al., 2012). Similarly, alterations to glutamatergic activity in individuals with MDD may also be related to altered neural plasticity (Maletic et al., 2007). In support of this idea, previous research has shown P3 latencies to be delayed during the acute phase following a TBI, (Onofrj et al., 1991; Papanicolaou et al., 1984). This finding is arguably similar to what is seen in the presence of typically developing MDD (refer to chapter 5 for a discussion of whether MDD delays P3 latencies). Acutely following a TBI, P3 amplitudes are reduced (Onofrj et al., 1991), which also appears to be similar to MDD. Additionally, increased theta band functional connectivity has been found in the first few months following a severe TBI (Castellanos et al., 2010), again similar to results in MDD (Leuchter et al., 2012). The results of this thesis indicate that individuals with TBI alone displayed similar activity to healthy controls, which supports the idea that following a TBI neural activity recovers in some individuals, but not in others, who later develop MDD. One factor which may prevent recovery of normal brain activity in some individuals and not others may be stress. Excessive stress is a mechanism known to lead to atrophy in healthy brains (Sapolsky, 2000; Uno et al., 1989; Watanabe et al., 1992), and similarly is likely to hinder neural recovery following injury (Sapolsky, 1996). In support of the idea that stress hinders recovery in some individuals, which may be causal in the development of TBI-MDD, research has shown that criticism and over-involvement from family members

(considered a significant stressor) is related to increased depressive symptoms in TBI patients (Alway et al., 2012).

3) The most likely explanation, however, is a combination of these factors. Both the initial effects of and subsequent recovery from a TBI vary widely between individuals. The first explanation - DAI differentially affecting functional connectivity - might explain the whole picture in some individuals. However, the development of TBI-MDD might be the result of initial brain changes not recovering due to stress in other individuals. And this stress might be the result of poor coping in some of these individuals as suggested by previous research (Anson and Ponsford, 2006), or simply high environmental stressors in others (Alway et al., 2012). Alternatively, the injury itself may reduce an individual's ability to devote neural resources to solving problems in general – leading to poor coping strategy use, or reduced flexibility in neural responses. This might result in higher stress levels, negative affect, and MDD. I suspect that while a single, simple explanation would be infinitely more useful for predictive and treatment purposes, the reality will be slightly different for each individual. Additionally, it is likely that even within individuals a combination of factors causes TBI-MDD. For some individuals, a DAI may result in dysfunctional network connectivity, setting up a tendency towards negative affect, which may be maintained by environmental stressors, which prevent recovery mechanisms, eventually leading to a diagnosis of MDD.

Having greater knowledge regarding the potential neural causes of TBI-MDD, allows for potential prevention as well as evidence based investigation of treatments which will be described in the future research section of the general discussion.

Limitations and Future Research

An obvious avenue for future research is to attempt to directly assess the issue of causality – whether the changes in neural activity that occurred in the TBI caused the MDD, or whether the changes in neural activity seen in TBI-MDD are simply a reflection of the MDD. Because the current thesis was not a prospective study, we cannot determine with certainty whether the MDD is caused by neural changes, or is the cause of neural changes. However, practicality meant performing a prospective study of TBI-MDD was outside of the scope of the current thesis. After two years of recruitment through a wide variety of avenues, a total of 16 participants with depression following a traumatic brain injury and 20 participants with TBI had been tested. Estimates of the rates of development of depression following traumatic brain injury vary from 15-40% for the following year. These rates may be slightly lower for those with mild to moderate injuries, who were recruited to avoid the heterogeneity they would introduce to measurements of brain activity, and the impact of focal lesions on the development of depression. As such, in order to perform a prospective study examining neural changes following an injury and comparing them between groups that later developed depression and those who did not, a minimum of 100 TBI participants would have to be recruited (to ensure even a small group of TBI-MDD would be available for comparison). A future prospective study of individuals following a TBI could determine whether the differences in brain activity detected in the current studies might be present soon after the injury, and as such might be able to predict the development of TBI-MDD. The current studies suggests that response inhibition N2, error processing Pe, working memory alpha activity, and working memory theta coherence EEG measures might be relevant

indicators for assessment. Alterations in these markers may indicate which individuals are prone to developing TBI-MDD. Early interventions could be designed to assist these people.

The domains of cognition that are found to be altered in the current research could be used to guide treatment strategies for TBI-MDD. For example, it seems that alterations in processes are related more to the MDD than the TBI. This suggests that following a mild to moderate TBI, depressive symptomology may be a more important treatment target than cognitive alterations, and indicates that rehabilitation specialists pay particular attention to assessing mood alterations post injury. The measures used in the current research could also be assessed as indicators of recovery from MDD following a TBI, or be used to guide research into cognitive treatment targets following a TBI.

Future research examining neural changes in TBI-MDD would also benefit from larger sample sizes. After data processing, the 16 TBI-MDD participants tested in the current thesis were reduced in number even further, so analyses for the four studies may have lacked sufficient power to elucidate potentially significant differences between groups. The small sample size also limited the ability of the studies to explore potential mediating factors such as medication, anxiety, and gender. This was an unfortunately unavoidable result of performing a study in a difficult to recruit population of limited prevalence, which controlled for pre-injury psychiatric history, focal lesions, and severe injuries, but also consisted of a significant time demand for participants.

Another potential limitation of the current thesis was that the TBI-MDD group had a significantly longer time since injury compared to the TBI only group. However, it is probably safe to expect that a longer time since injury allows for more neuroplastic recovery, in which case we would expect more changes in brain activity to be found in the TBI group than the

TBI-MDD group. In general the reverse was true, suggesting that time since injury was not a factor in the altered brain activity detected. As a result, this limitation has the unexpected effect of strengthening our conclusion that the differences in brain activity detected in the TBI-MDD group are specific to the development of MDD following a TBI, rather than to factors found in all injuries.

Another avenue that would be valuable to examine with more research is how changes in electrophysiological measures relate to measures of DAI and functional connectivity taken with MRI. The comparisons with MRI measures of DAI (such as fractional anisotropy - FA) might be particularly informative for EEG coherence measures – this comparison could confirm whether the increased theta coherence in TBI-MDD individuals is a result of altered white matter connections due to DAI. The potential value of the combination of these two measures is suggested by research using the same sample groups as the current study, which did indicate reduced FA in the TBI-MDD and MDD groups (Maller et al., In Press, see appendix). Additionally, fMRI measures of blood flow could provide another modality for measuring alterations to functional connectivity. This could provide confirmation that the EEG measures of coherence do reflect functional connectivity alterations.

Concluding Statement

TBI-MDD occurs at a much higher rate than MDD in the general population, and is associated with significant personal distress and poorer recovery outcomes. The potential brain changes that lead to this disorder are currently poorly studied. This thesis examined the electrophysiological markers of brain activity changes in TBI-MDD, comparing them to groups with MDD, TBI, and a healthy control group. The goal of these comparisons was to

determine how brain activity might be altered in TBI-MDD, in order to allow speculation as to the cause of TBI-MDD. The results of the first three studies indicated that individuals with TBI-MDD show impairments in the ability to synchronise neural resources underlying specific scalp regions during response inhibition, error monitoring, and working memory processes. These impairments were similar to those found in the MDD group, but not found in the TBI group. This suggests that the alterations in brain activity are due more to the MDD than the TBI. Lastly, the fourth study indicated individuals with TBI-MDD suffer from maladaptive interhemispheric functional connectivity during working memory, which may be the result of DAI. This was not seen in the MDD or TBI alone groups. This thesis provides a vital addition to the scientific understanding about the neural origins of MDD following a TBI. While currently removed from clinical practice, these first steps in understanding are optimistically anticipated (following further research) to possibly result in methods to better prevent and treat TBI-MDD, hopefully improving the lives of those who are afflicted by this disorder.

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Appendices

Appendix A

Bailey, N.W., Hoy, K.E., Maller, J.J., Segrave, R.A., Thomson, R., Fitzgerald, P.B. (2011). Response inhibition changes in depression and depression post traumatic brain injury measured with EEG. Australasian Society for Psychiatric Research.

The following poster was presented at an international conference held in Dunedin, New Zealand.

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Monash Alfred Psychiatry Research Centre

Response Inhibition Changes in Depression and Depression Post Traumatic Brain Injury Measured with EEG

Neil W. Bailey, Kate Hoy, Jerome Maller, Rebecca Segrave, Richard Thomson, Nick Williams, Paul B. Fitzgerald

We mend minds

Background

• Rates of major depression (MDD) are high following a traumatic brain injury (TBI) - estimated to be between 25-45% (1,2)

• Very little research has focused on the neural pathophysiology of TBI-MDD, even though many neuroimaging studies focus on TBI or MDD independently.

• Executive function is found to be impaired in both TBI and MDD. EEG measures can reveal changes in neural processes related to executive function (in particular response inhibition).

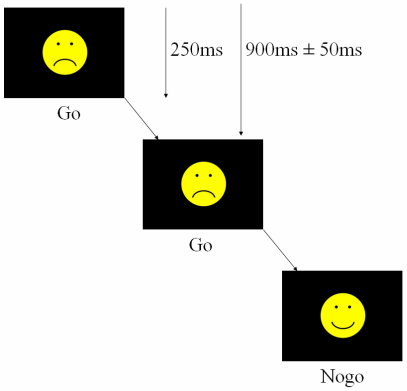
• Our aim was to measure response inhibition event related potentials (ERPs) to determine whether MDD and TBI-MDD exhibit similar changes in electrophysiology. We also attempted to assess mood congruent biases in MDD by using emotional stimuli.

Method

• Fourteen participants with TBI-MDD, 19 subjects with MDD only, 20 TBI only, and 18 healthy controls underwent clinical mood assessments and completed an emotional Go/Nogo task while EEG was recorded. Groups were matched for age and gender.

• The Go/Nogo task rapidly presented simple depictions of happy and sad faces (Figure 1). Participants were instructed to respond to one emotion, but withhold responses to the other.

Figure 1. Example of trial order and timing



ERP Measurements:

• Analysis focused on trials that followed two of the opposite trial type, so that ERPs were generated from trials which challenged inhibitory processes.

• ERPs were measured from Fz and Pz electrodes.

• Peak amplitude and latencies were calculated for each participant at Fz and Pz:

- ➢Frontal Nogo N2 (negative deflection between 170-360ms post stimulus)
- ➢Frontal Nogo P3 (positive deflection between 280-600ms post stimulus)
- ➢Frontal Go P3e (early P3 – positive deflection 220-420ms post stimulus)
- ➢Frontal Go slow wave negativity (SWN - negative deflection 300-650ms post stimulus)
- ➢Parietal Go and Nogo P3b (positive deflection between 280-600ms post stimulus).

• The N2 area was divided into an early N2a and late N2b, and measured with area under the curve analyses.

Results

• The MDD and TBI-MDD groups had significantly reduced N2 amplitude compared to controls and an *earlier* N2 peak compared to the TBI and control groups. This appeared to be due to increased amplitude for controls and TBI only groups in the late section of the N2.

• Comparisons of N2a and N2b area between groups revealed the MDD groups showed reduced negativity in the N2b window (but not the N2a).

• Area under the curve results for the N2b window showed that hard Nogo trials had more negative N2b area than easy trials. The same comparison for Go trials indicated the N2b area was more positive for the hard trials than the easy trials.

• Both the MDD and TBI-MDD groups showed significantly delayed SWN in Go trials.

• No other group differences were detected, and no interactions between emotional valence and group were detected.

Figure 2. Grand Averages for each trial type at Fz

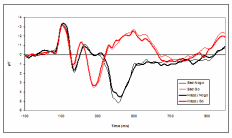


Figure 3. Grand Averages for each group for Nogo trials at Fz

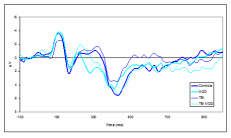


Figure 4. N2b window for easy and hard Go and Nogo trials

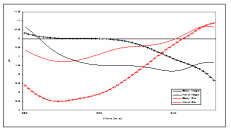
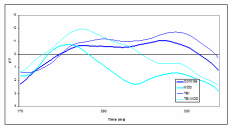


Figure 5. Grand Average N2 window for each group at Fz



Discussion

• N2b area is reduced in groups with MDD and post TBI MDD. This suggests similar processes to those in typical MDD may be responsible for MDD post TBI.

• The N2b area is related to response inhibition. It was more negative in hard Nogo trials, which follow two or more Go trials (setting up more of a pre-potent response habit) than easier trials. However, it was more positive in harder Go trials (which show the same sensory mismatch and response conflict demands, but no response inhibition).

•The N2 and response inhibition have both been shown to be generated by processing in the anterior cingulate cortex (ACC), so these results may indicate dysfunction in this area in MDD groups (3)

• At this stage it is unclear why the SWN latency differs between groups. Previous researchers have suggested it may be related to motor activity (4)

• No mood congruent biases were found in the ERP data. The simple emotional stimuli may not elicit emotional processing enough to differentiate the groups.

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Appendix B

Maller, J.J., Thomson, R.H.S., Pannek, K., Rose, S.E., **Bailey, N**., Lewis, P.M., Fitzgerald, P.B. (In Press). The (eigen) value of diffusion tensor imaging to investigate depression after traumatic brain injury. Human Brain Mapping.

The following paper presents the results of a collabouration between researchers that compared measures of functional anisotropy using diffusion tensor imaging with MRI in mostly the same participants as my thesis.

Complete Title: The (eigen)value of diffusion tensor imaging to investigate depression after traumatic brain injury.

Running Head: *Diffusion tensor imaging, TBI, and depression.*

Key words: brain injury, major depression, diffusivity, neuroimaging

Journal: *Human Brain Mapping*

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Number of words in Abstract: 234 (250 limit)

Number of Figures: 4

Number of Tables: 2

Supplemental information: zero

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COMPETING INTERESTS STATEMENT

The authors declare that they have no competing financial interests.

ABSTRACT: Background: Many people with a traumatic brain injury (TBI), even mild to moderate, will develop major depression (MD). Recent studies of patients with MD suggest reduced fractional anisotropy (FA) in dorsolateral prefrontal cortex (DLPFC), temporal lobe tracts, midline and capsule regions. Some of these pathways have also been found to have reduced FA in patients with TBI. It is unknown whether the pathways implicated in MD after TBI are similar to those with MD without TBI. The current study sought to investigate whether there were specific pathways unique to TBI patients who develop MD. Methods: A sample of TBI-MD subjects (N=14), TBI-no-MD subjects (N=12), MD-no-TBI (N=26) and control subjects (no TBI or MD, N=23), using a strict measurement protocol underwent psychiatric assessments and diffusion tensor brain MRI. Results: The findings of this study indicate that 1) TBI patients who develop MD have reduced axial diffusivity in DLPFC, corpus callosum, and nucleus accumbens white matter tracts compared to TBI patients who do not develop MD, and 2) MD patients without a history of TBI have reduced FA **along the corpus callosum**. We also found that more severe MD relates to altered radial diffusivity. Conclusions: These findings suggest that compromise to specific white matter pathways, including both axonal and myelination aspects, after a mild TBI underlie the susceptibility of these patients developing major depression.

Keywords: depression, magnetic resonance imaging, diffusion, dorsolateral prefrontal cortex, longitudinal fasciculus, white matter

INTRODUCTION

Previous volumetric investigations of patients with major depression (MD) have revealed smaller volumes compared to controls in areas such as the hippocampus, frontal lobe, and corpus callosum (CC; Geuze, et al. 2005; Lacerda, et al. 2005; Maller, et al. 2007). Similar regions have also been found to be reduced in volume in patients who have sustained a mild to moderate traumatic brain injury (TBI), as a result of the impact of the brain against the inside of the skull which leads to stretching and thinning of the white matter, often referred to as diffuse axonal injury (DAI; Beauchamp, et al. 2009; Tasker, et al. 2005). Mild TBI (mTBI) cases constitute approximately 85% of reported TBI cases (Bazarian, et al. 2005). Whilst this finding is not always consistent, it may be the result of studies potentially being confounded by age, sex, and other demographic factors as well as heterogeneous protocols developed for estimating volumetric values (von Gunten, et al. 2000). This could also result from not taking into account behavioural conditions such as MD which has been reported in up to 77% of patients post-TBI (Alderfer, et al. 2005; Gordon, et al. 2006; Jorge 2005; Silver, et al. 2009). The few volumetric studies that have considered post-TBI MD have found reduced volume in prefrontal and temporal structures such as the dorsolateral prefrontal cortex (DLPFC) and orbitofrontal cortex, cingulate gyrus and hippocampus (e.g. Chen, et al. 2008; Hudak, et al. 2011; Jorge, et al. 2004), when compared to TBI-no-MD or controls.

Diffusion tensor imaging (DTI; Basser, et al. 1994) is a technique that is more sensitive to axonal damage than conventional structural MR imaging (Kennedy, et al. 2009; Provenzale 2011). White matter integrity can be assessed using the fractional anisotropy (FA) index, a value between 0 and 1 with higher value indicating greater anisotropy and hence white matter integrity. We recently reviewed the literature of published articles reporting FA values in samples of patients with TBI or MD (Maller, et al. 2011) and found no studies that used DTI to investigate depression post-TBI, although there were some common brain regions identified between the TBI/DTI and MD/DTI studies, including fronto-temporal connections, CC, right parietal lobe and structures contained within the basal ganglia. The internal capsule was commonly reported to have significantly reduced FA.

During processing of diffusion tensor MRI data we estimate a tensor, D, that inherently contains intravoxel structural and dynamic information (Basser, et al. 1994). The eigenvalues of D are the diffusion coefficients in these orthotropic directions. Of the three eigenvalues (λ) measured by the DTI technique, the principal eigenvalue λ1 (also referred to as axial or parallel diffusivity) is thought to relate more to axonal morphology and degradation rather than myelin injury which relates more to radial diffusivity (average of the second and third eigenvalues; (Li, et al. 2011; Song, et al. 2002). As MD outcomes of TBI are currently thought of as system-diseases, rather than limited to a single region of interest, it is sensible to investigate white matter integrity in this population on a whole-brain basis. Therefore, we sought to employ a consistent imaging protocol and FA and eigenvalues estimation procedure in a sample of subjects with mTBI who developed MD, subjects with mTBI who did not develop MD, subjects with MD with no history of TBI, and controls with no history of

MD or TBI, to examine whether regions of different FA and diffusivity values are consistent with our review.

Our specific aims and hypotheses were

1. To investigate whether there is a specific relationship between changes in structural and functional integrity and the presence of post-TBI depression (Hypothesis 1: Patients with post-TBI depression will display significantly reduced anisotropy in prefrontal cortical - sub cortical white matter tracts compared to patients post-TBI who have no depression),

2. To investigate whether changes in structural and functional integrity are specific to post-TBI depression (Hypothesis 2: Patients with post-TBI depression will display significantly reduced anisotropy in prefrontal cortical - sub cortical white matter tracts compared to patients with depression not related to TBI),

3. To explore the structural and functional integrity specific to depression without TBI (Hypothesis 3: Patients with depression not related to TBI will display significantly reduced anisotropy in prefrontal cortical - sub cortical white matter tracts compared to healthy controls with no history of TBI or depression), and

4. To explore the functional implications of changes in integrity (Hypothesis 4: There will be a correlation between anisotropy in prefrontal cortical - sub cortical white matter tracts and depressive symptoms in patients with post-TBI depression).

MATERIALS AND METHODS

Subjects

A total of 78 subjects were recruited. 26 patients with MD without a history of TBI (MD-no-TBI), 15 patients with a history of mTBI who developed MD (TBI-MD), 12 patients with a history of mTBI who did not develop MD (TBI-no-MD), and 25 controls were included in this study. All participants underwent psychiatric and MRI assessments (Table 1). Patients were recruited through public notices and through the clinical services of the Alfred Hospital, Melbourne, Victoria, and were required to have no history of pre-TBI depression and TBI-MD patients were required to have developed MD between 6 weeks and 12 months post-TBI. All subjects with TBI were required to have a Glasgow Coma Sale score of 13 or 14 on ambulance arrival at the accident scene. Loss of consciousness among mTBI subjects ranged from 15 minutes to 2 hours, and post-traumatic amnesia ranged from 10 minutes to 48 hours, according to formal hospital records. One TBI patient had a very large head whose whole brain could not fit into the MRI Field Of View, hence their data were excluded from analyses (reducing the number of TBI-MD subjects to 14). Another TBI participant had a low volume subarachnoid haemorrhage over the left parietal lobe. Their data were included as their white matter skeleton registered well during the TBSS pre-processing steps with no

misalignments in the region of the haemorrhage. No participants had destructive white matter lesions on FLAIR images. All patients underwent CT scanning in the acute phase with all but one patient having a negative finding (as described above).

Twenty-five controls were recruited from notices and word of mouth. Two control scans were discarded due to incidental abnormalities, hence total control sample size was 23 (9 males). All MD patients (the MD only and TBI-MDD groups) were required to have a diagnosis of major depressive disorders made by a treating psychiatrist and confirmed with the Mini-International Neuropsychiatric Interview (MINI; (Sheehan, et al. 1998) and a score of at least 16 on the Montgomery-Åsberg Depression Rating Scale (MADRS; Montgomery and Asberg 1979). Exclusion criteria for controls included a current or previous DSM-IV (SCID; First, et al. 2001) axis I diagnoses, current active medical problem, and subjects were required to have no known neurological disease or a contraindication to MRI scanning. In addition, control subjects were required to have no history of psychiatric illness. All subjects provided written informed consent on a form approved by the Alfred Human Subjects Research and Ethics Committee.

Table 1 about here.

Image Acquisition

A 1.5T GE Signa Imaging System (General Electric Medical Systems, Milwaukee, WI) was used to acquire contiguous AC-PC aligned sagittal SPGR T1-weighted sequence (TR = 100, TE = 450, matrix size = 224 x 224, NEX = 1, slice thickness = 1.4mm), following a T2-FLAIR. A diffusion-based sequence was then acquired (slice thickness = 3mm, in-plane resolution = 0.90mm^2, TR/TE = 17s/86.6ms, b value = 1000mm^2/s along 12 non-collinear directions and 2 images at b = 0, NEX = 1). All scan files were de-identified so that FA and eigenvalue analyses occurred blind to subject group.

Image Processing and Analysis

Diffusion-weighted images were corrected for eddy current distortions using tools provided with FMRIB's Diffusion Toolbox (FDT, part of FMRIB Software Library FSL; (Smith, et al. 2004); http://www.fmrib.ox.ac.uk/fsl; version 4.1). The diffusion tensor, its three eigenvalues and FA images were then calculated using FSL. Voxel-wise analysis was carried out using TBSS (Smith, et al. 2006).

All participants' FA images were registered non-linearly to FMRIB's FA template (supplied with FSL). The results of this registration step were visually checked for accuracy for each

participant. Using the average of all participants' registered FA images, an FA "skeleton" was generated which best represents the centres of all white matter tracts common to all participants' brains (Smith, et al. 2006). An FA threshold of 0.2 was applied to the resulting skeleton. Each participant's aligned FA and eigenvalue images were then projected onto this common FA skeleton. The resulting images were analysed using the permutation-based nonparametric statistical technique "randomise" (Nichols and Holmes 2002). 5000 random permutation were applied for each analysis. Differences between groups were assessed using a two-tailed test. p-values are reported at the 0.05 significance level, corrected for multiple comparisons using threshold-free cluster enhancement (Nichols and Holmes 2002). Analysis of radial eigenvalues (λ2/3) will identify anatomical locations within white matter tracts where there is increased diffusion of water perpendicular to the principal axonal direction (λ1); such a measure may better highlight axonal injury within white matter pathways.

In TBI patients who developed MD, the white matter pathways that significantly correlated with a clinical measure of the MD severity (MADRS score) were identified. This offers an alternative approach for identifying the affected white matter pathways that relate to the development of MD after TBI. Hence, a regression analysis was performed, correlating diffusivity measures with the severity of depression using age as a confounding regressor. To assist with localisation of white matter tracts for all TBSS analyses, the MRI Atlas of Human White Matter (Mori, et al. 2005) was consulted.

Statistical Analysis of Demographic Data

All demographic data were statistically analysed using SPSS for Windows version 19.0 (SPSS Inc, Chicago, Illinois). Analyses were two-tailed and evaluated for significance at the 0.05 alpha level. Simple t-tests and analysis of variance (ANOVA) were employed to compare demographics between groups.

RESULTS

Demographics

There were more males in the MD-no-TBI and TBI-no-MD groups ($p = 0.04$). The ANOVA revealed a significant difference between the mean age of subjects in the TBI-MD and TBI-no-MD groups ($p = 0.035$), therefore age was covaried for in the TBSS analysis between these two groups. Time since injury varied from 6 weeks to 10 years. The number of medications that each MD subject was taking was between three and eight, and length of depression ranged from 1 year to 50 years. Preliminary TBSS analyses of medications

(number) and length of depression (years) demonstrated that these two variables were not related to FA or its constituents.

TBSS Differences In Fractional Anisotropy and Eigenvalues

All TBI vs Controls

An exploration of the differences in diffusivity between all TBI subjects (N = 26) and controls (N = 23) was first carried out in order to determine whether this patient population was consistent with previous DTI mTBI research. Whilst reduced FA in the TBI sample was not statistically significant ($p = 0.10$, corrected), radial diffusivity was greater in the TBI sample at the $p = 0.05$ level (corrected) across widespread areas including the CC, bilateral PFC, superior longitudinal fasciculi, and right internal capsule (Figure 1).

Figure 1 about here.

TBI-MD vs TBI-no-MD

We identified a decrease in axial diffusivity ($p < 0.007$) in the bilateral DLPFCs, anterior CC, right nucleus accumbens, right internal capsule, right inferior and superior longitudinal fasciculi, and brainstem for TBI-MD patients compared to TBI-no-MD patients (Figure 2 and Table 2). This indicates that there is widespread white matter damage unique to the development of MD after a TBI. FA and radial diffusivity did not differ significantly between groups.

Figure 2 about here.

TBI-MD vs MD-no-TBI

We found no significant differences between TBI-MD and MD-no-TBI. There were reductions in FA in the MD-TBI group compared to the MD-no-TBI group, although these differences between groups did not reach significance at the 0.05 level for the corrected analyses. No trends were found for non-FA values.

MD-no-TBI vs Controls

To statistically match MD-no-TBI and control groups by age and sex, 26 MD-no-TBI and 22 control subjects were compared. MD-no-TBI subjects had significant ($p < 0.05$) reduction in FA values along the anterior and midbody of the CC (Figure 3) in this corrected TBSS analysis. There was a significant increase ($p < 0.05$) in $\lambda 2$ located only along the CC and right SLF, and a trend towards increased radial diffusivity in these two regions at $p = 0.09$. No trends were found for the other diffusion metrics under investigation.

Figure 3 about here.

Depression Severity and DTI

In an exploration of the functional implications of changes in integrity among the 14 patients those who developed MD post-TBI, TBSS showed that radial diffusivity was significantly correlated with MADRS scores ($p < 0.05$) along the CC, bilateral nucleus accumbens, bilateral internal capsule, bilateral cingulated gyri, superior longitudinal fasciculi, and brainstem. At a significance level of $p = 0.028$ (corrected) the $\lambda 3$ TBSS analysis showed voxels along these same white matter pathways (Figure 4). Although the corrected analyses for axial diffusivity, $\lambda 2$, and mean diffusivity did not reach significance, they all suggested a trend of voxels of reduced values being located along only the CC.

Figure 4 about here.

DISCUSSIONS

This study is the first to investigate the development of major depression (MD) after mild traumatic brain injury (mTBI) using diffusion tensor imaging (DTI). It reports the finding of reduced FA and axial diffusivity values in the CC (specifically the anterior aspect) and right superior longitudinal fasciculus in MD patients without a history of TBI and further reduced FA in this region and bilateral PFCs in those who developed MD after a TBI. Furthermore, significantly increased $\lambda 3$ was seen along white matter pathways directly related to regions implicated in fronto-temporal models of MD and consistent with those elucidated from our recent review (Maller, et al. 2011).

Consistent with previous mTBI research, there were a number of regions with reduced white matter integrity in subjects with mTBI when compared with those without a history of TBI (or MD), including the prefrontal cortices and midline tracts. To investigate Aim 1 (whether there is a specific relationship between changes in structural and functional integrity and the presence of post-TBI depression), post-TBI MD and TBI participants with no depressive syndrome were initially studied. Significant microstructural changes in the frontal-parietal and fronto-temporal white matter tracts were investigated by the voxelwise comparison of FA and non-FA measures between the two groups. In an exploration of Aims 2 and 3 (to investigate whether changes in structural and functional integrity are specific to post-TBI depression, and to investigate the structural and functional integrity specific to depression without TBI), we found that those with MD-no-TBI had widespread reduction in FA (and axial diffusivity), mostly along the same tracts identified in the TBSS analysis between TBI-MD and TBI-no-MD.

Depression is common after a TBI (Silver, et al. 2009). Hudak et al. (2011) recently reported depressive symptoms in post-TBI patients to significantly correlate with volumetrics of three brain regions (left rostral anterior cingulate and bilateral orbitofrontal cortex); regions reported by previous studies of volumetric assessment in patients with depression post-TBI (Chen, et al. 2008; Jorge 2005; Jorge, et al. 2004) include the PFC, DLPFC, hippocampus, and anterior cingulate. As these areas have also been implicated by a number of studies linking depression not related to TBI (reviewed by Koolschijn et al (2009), they support a common link between spontaneous and non-spontaneous (e.g. post-TBI) MD models; that is, involvement of fronto-limbic pathways. However, structure size does not necessarily reflect underlying function or integrity (e.g. Foster, et al. 1999). Hence, the current study is the first to investigate post-TBI MD in the context of function by using measures of diffusion as biomarkers. We found reduced FA and axial diffusivity among similar regions to those reported from volumetric studies, but we also found reduced anisotropy in the CC, an area commonly reported as reduced in MD patients and TBI patients. The right inferior and superior longitudinal fasciculi were also implicated in the TBSS results, which is consistent with other studies which have found similar regions, and only on the right, to have reduced FA and/or axial diffusivity in MD or post-TBI in human and animal models (e.g. Kinnunen, et al. 2011; Li, et al. 2011). More importantly, we found FA in post-TBI MD when compared with post-TBI without MD, was most reduced (as supported by the axial diffusivity reduction and MD difference) in two of the most widely-reported regions reported as relevant to the development of MD, which are the CC and DLPFCs. The CC has been reported in many publications as reduced in size among post-TBI patients (Bigler and Maxwell 2011) and MD patients without a history of TBI (Maller, et al. 2011). Furthermore, we found the internal capsule and nucleus accumbens to have significantly reduced axial diffusivity in TBI-MD when compared against TBI-no-MD. This is supported by a main analysis which also found MD severity to significantly relate to radial diffusivity of the internal capsule and nucleus accumbens. These are important findings as they are consistent with DTI studies in deep brain stimulation (DBS) MD patients in which the nucleus accumbens (via the internal capsule) is often the target of the electrodes. (Gutman, et al. 2009) showed with DTI that the targets for DBS when used to treat depression have distinct and widespread projections to frontal and temporal poles as well as the cingulate, thalamus, hypothalamus, nucleus accumbens, and brainstem which was also implicated in our TBSS results; these are regions

implicated in antidepressant response mechanisms (Airan, et al. 2007; Schlaepfer, et al. 2008; Tanis, et al. 2007). Very similar tracts were identified as having reduced FA in a separate study of MD subjects (Zou, et al. 2008) which reported reduced FA restricted to the internal capsule (and parietal region). This is relevant because DBS is used for MD only in patients whose MD is highly treatment-resistant (i.e., non-responsive to medication, electroconvulsive therapy, and often other forms of neurostimulation as well). That we found this region to be of reduced integrity in those who develop MD after TBI, and related to the severity of their MD, is consistent with the anecdotal findings of these patients' MD often being treatment-resistant.

The final set of analyses found that diffusivity values were related to MD severity in regions reported by the literature in other groups of MD patients, as recently reviewed (Maller, et al. 2011). Specifically, the CC, medial frontal gyri, nucleus accumbens, cingulate bundles, internal capsules, brainstem and longitudinal fasciculi (Table 2). These are among the majority of regions identified in fronto-temporal models of MD. Importantly, the radial diffusivity values were implicated. This finding could suggest an issue relating to myelination rather than axonal integrity, which could in turn suggest that a degenerative process in addition to DAI is the precursor for the development of MD after mTBI. Although it is difficult to speculate about whether increased radial diffusivity relates to DAI or a myelination problem, DAI probably leads to Wallerian degeneration of multiple neural circuits, which will involve cortical degeneration (atrophy) at some stage.

Table 2 about here.

The decrease in FA and axial diffusivity along the right superior longitudinal fasciculus in subjects with MD post-TBI relative to TBI patients who did not develop MD, as well as in those with MD (no TBI) compared with matched controls (with no history of MD or TBI) is consistent with the literature. For example, the low FA regions reported in a DTI study of post-TBI patients (Salmond, et al. 2006) are very similar to those found in a study of patients with first-episode treatment-naïve MD (Ma, et al. 2007) and from a group of patients with first-episode remitted depression (Yuan, et al. 2007), which include the right parietal lobe and right frontal gyri. Furthermore, (Alexopoulos, et al. 2008) found similar regions to have reduced FA in a group of MD patients who did not achieve remission.

That axial and radial diffusivity analyses showed higher significance leve**ls** suggest that compared to FA, they are more sensitive markers of DAI. It is also consistent with rat studies (e.g. Li, et al. 2011; Song, et al. 2002) which tracked the changes in FA and its eigenvalue constituents from the acute phase to months afterwards validated by histological investigation such as optical immunochemical staining. The group differences in TBI-MD vs TBI-no-MD were in axial diffusivity, whereas MD severity was significantly related to radial diffusivity. Collectively, these results suggest that MD is related to both types of reduced white matter integrity i.e. from both radial and axial perspectives.

Although the underpinnings of the difference(s) between lambda 2 and lambda3 are currently unexplored, the results of our study and others (e.g. Thomalla et al., 2004) which report such examples of where only one of the two constituents of radial diffusivity is significant whilst the other is not, suggest that lambda 2 and 3 have different meanings i.e. they do not represent identical aspects of radial diffusivity. We also carried out separate lambda 2 and lambda 3 analyses to investigate whether radial diffusivity per se was related to TBI and/or depression, hence to accomplish this aim comprehensively we analysed not only the radial diffusivity conglomerate but its constituents as well. That is, we wanted to investigate whether either of its constituents was significant even if the conglomerate was not. Our results suggest that lambda 2 and 3 are not simple reflections of one another, but rather, tell different parts of the radial diffusivity story, which may be found in future research to represent quite distinct aspects of fractional anisotropy which may represent discrete white matter damage and/or are the basis for targeted treatment and therapy.

TBSS is a widely-used program specifically designed to compare groups on a voxel-by-voxel basis for differences in FA and its constituents. The programs authors suggest that it not be used on scans of brains that have sustained major damage as the white matter skeletons of those patients may not align accurately with that of the template. The current study was consistent this advice as only one of our patients had a positive CT finding which was very minor, superficial and distal to white matter, hence unlikely to influence the white matter skeleton registrations (this was confirmed by visual checks for accurate registration of each subject's white matter skeleton before group analyses proceeded).

Chronic primary or secondary dysfunction in dopaminergic, noradrenergic, and serotonergic systems, appear to be relatively common consequences of TBI (Arciniegas and Silver 2006; McAllister, et al. 2006). It is well-established that these systems are also compromised in MD patients (Bennett 2010; Drevets, et al. 2000; Muller, et al. 2011; Wagner, et al. 2010). In humans, MD is a common sequelae of TBI (Bombardier, et al. 2010), even when mild (Ryan and Warden 2003). The symptom overlap between MD and the common "post concussion syndrome" is substantial (Bryant 2008; Hoge, et al. 2008). Furthermore, there is evidence that late-life MD can be precipitated by accumulated small silent cerebral infarctions that appear as white matter hyperintensities on MRI scans (Alexopoulos, et al. 1997; Sheline, et al. 2010; Thomas, et al. 2002). The overlap between brain regions implicated in traumatic and non-traumatic MD is discussed in a recent comprehensive review by (Wager-Smith and Markou 2011). The authors propose stress-induced "microdamage" to the brain as a putative trigger for subsequent cellular repair and neuroinflammation leading to symptoms of depression. In susceptible individuals, impaired cellular repair mechanisms may lead to a chronic cycle of neuroinflammation, presenting as persistent depression. As examples, they offer some preliminary studies in experimental animals which have noted that depressive-like behaviours follow traumatic or ischemic brain injury, although the studies are not well controlled for confounds (Kato, et al. 2000; Milman, et al. 2005; Pandey, et al. 2009; Shapira, et al. 2007). Moreover, they describe previous findings of reduced hippocampal volume in depression, for which there is evidence the degree of volume loss is related to the number

of depressive episodes experienced. This again supports the theory that volume loss, secondary to stress-induced cellular damage, precipitates depressive symptoms. This general hypothesis fits well with our findings, wherein we describe reduced fractional anisotropy (indicating neuronal damage) in CC, DLPFC and basal ganglia in both the TBI-MD and MD-no-TBI groups alike.

It is notable that there was some predominance of right-sided changes in the depression analyses. The implication of right-sided involvement in depression post-TBI is consistent with much of the existing MRI and EEG depression literature. For EEG, depression is associated with a shift toward greater right than left activity, consistent with findings for unpleasant emotion (Herrington, et al. 2010). It was recently reported that in subjects at high-risk for developing depression, alpha power correlated inversely with cortical thickness particularly over the right posterior region (Bruder, et al. 2012) and another group (Shankman, et al. 2011) recently found relatively lower right posterior alpha activity in patients with melancholic depression. In general, alpha power is found to be reduced and fMRI activation more right-lateralised in patients with depression (Gordon, et al. 2010; Saletu, et al. 2010) depression. That is, there is often left hemisphere underactivation at rest and right hemisphere overactivation during tasks. In an fMRI study, for example, Garrett and colleagues (Garrett, et al. 2011) colleagues found patients with major depression to show hyperactivation in the right temporoparietal region associated with orienting to unexpected stimuli. Heller's (1993) model of emotion processing predicts that depression would be related to greater right than left frontal neural activity, combined with low levels of right temporo-parietal activity. In the context of structural MRI, a reduction of right hippocampal-entorhinal cortex volume with voxel-based morphometry in patients with depression is often reported (e.g. (Ahdidan, et al. 2011; Bell-McGinty, et al. 2002) and relative to the left hemisphere, depressed individuals have smaller right-parietal viable brain volumes than nondepressed individuals (Schonberger, et al.). I**n** general, there appears to be something specific about right sided changes and the development of depression post-TBI, and although less likely, it is possible that developing depression leads to greater right sided dysfunction. Only a study examining subjects before and after a TBI can suitably address this question.

A limitation of this study is that the time since injury was very broad; previous research indicates FA is most reduced during the acute post-TBI phase, hence it is possible that patients whose TBI was more recent had the most reduced white matter integrity along the tracts revealed to have reduced white matter integrity when compared to subjects without MD. Longitudinal research is required to understand how these pathways are affected over time and whether deficits accumulate or ameliorate over time. As TBI subjects were recruited and not prospectively retained, there must be unevenness in data collection with regards to day-of-injury clinical information. It is possible that 48 hours of truly documented post-traumatic amnesia would not be a mild TBI, but move it into the moderate range. Likewise, loss of consciousness of greater than one hour, for some would move the injury into the moderate category. Depending on how many these clinical features apply to, there may need to be a modification in using the mild TBI moniker in follow-up studies of these

patients. It is likely, however, that the use of more homogeneous groups in terms of the mechanism of injury would produce clearer or more consistent results. Finally, without longitudinal data, it is difficult to make a cause and effect judgement as to the relationship between white matter changes and symptoms. Injury related loss of white matter integrity may cause depression. However, it is also possible that the development of a depressive illness, through other mechanisms, may result in reduced intercortical connectivity which over time reduces white matter integrity**.** The current study enrolled a greater portion of women in the TBI-MD than the TBI-no-MD, and although there is a higher incidence of depression in women, the gender difference was not addressed as this was beyond the scope of the study's aims. This is an area which we aim to address in future investigations.

Although the current study focussed on major depression, other psychiatric disturbances have also been related to TBI. For example, (Hart, et al. 2011) reported minor depression and major depression to each be present in approximately a quarter of their TBI patients (N=1570), and (Koponen, et al. 2011) recently reported both axis I and II psychiatric disorders to be common among patients with TBI. Our future investigations will consider this.

CONCLUSION

Previous DTI studies of TBI patients (whether TBSS or other techniques were applied) have not considered the degree of depression among their samples, hence, this is the first study to attempt an investigation of the development of MD after TBI in the context of anisotropy. Consistent with a recent review, we have shown in mild TBI patients that the development of MD is related to compromised fractional anisotropy and axial and radial diffusivity in the prefrontal, corpus callosum, cingulated, internal capsule and parietal regions, supporting models of major depression without TBI. Reduced integrity in these regions may therefore be a biomarker for the development of MD post-TBI. Future studies should address this important issue.

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Tables

Table 1. Demographics of the four groups included in the DTI analyses.

MADRS = Montgomery-Åsberg Depression Rating Scale; MD = major depression; N/A = not applicable; TBI = traumatic brain injury.

Table 2. Regions of different FA and non-FA values as identified by TBSS.

Figures

Figure 1. Voxels **in red-yellow represent those which have siginificantly reduced radial diffusivity** at p = 0.05 (corrected) in TBI compared with controls. **The six slices are coronal with their positions** represented by Y co-ordinates (MNI space) **and white lines in the midsagittal slice (right side of figure).**

Figure 2. Reduced axial diffusivity voxels (red-yellow) at p = 0.007 (corrected) in those with post-TBI MD compared with TBI-no-MD. Numbers represent Y co-ordinates.

Figure 3. TBSS results of MD (N = 26) compared against Controls (N = 22) at p = 0.05 (corrected). A: Fractional anisotropy B. λ2. Numbers represent Y co-ordinates.

Figure 4. TBSS corrected analyses of correlations between MADRS scores in patients with post-TBI MD and radial diffusivity (p = 0.05, corrected). **The top row of coronal slices from posterior (left of screen) to anterior (right of screen), and midsagittal slice, illustrates the locations of voxels (red-yellow) which were significant in this analysis. The** 3-dimensional rendering of this set of significant voxels from an anterior-dorsal **perspective is presented on the left of the Figure**, and on the right is **a representation of those voxels** from a right-side dorso-lateral perspective. Numbers represent Y co-ordinates. A = anterior; P = posterior; I = inferior; S = superior.

Table 1.

Variable	**Group**			
	TBI-MD	*TBI-no-MD*	*MD-no-TBI*	*Control*
Number (M:F)	14 (6:8)	12 (10:2)	26 (17:9)	23 (9:14)
Age mean (SD)	48.00 (9.92)	33.08 (12.69)	44.08 (12.99)	38.35 (13.00)
MADRS mean (SD)	28.77 (7.68) Range: 16-43	2.25 (2.38) Range: 0-6	32.27 (4.11) Range: 25-39	N/A

Table 2.

Region	TBI-MD vs TBI (no-MD)		MD (no-TBI) vs TBI-MD	MD (no-TBI) vs Controls			MADRS (TBI-MD)		Analysis Frequency	Frequency order
	FA[£]	**Axial**[†]	**Axial**[¥]	**FA**[†]	**λ2**[†]	**Radial**[§]	**λ3**[†]	**Radial**[†]		
PFC (R)		*****	*****						**2**	**3**
PFC (L)		*							1	4
Cing (R)			*				*	*	2	3
Cing (L)							*	*	1	4
CC		*		*	*	*	*	*	3	2
IC (R)		*	*				*	*	3	2
Nucl Acc (R)		*					*	*	2	3
Nucl Acc (L)		*							1	4
SLF (R)	*	*	*		*	*	*	*	4	1
SLF (L)							*	*	1	4
ILF (R)		*							1	4
Brainstem		*					*	*	2	3

Note: CC = corpus callosum; FA = fractional anisotropy; IC = internal capsule; ILF = inferior longitudinal fasciculus; L = left; λ = eigenvalue; MD = major depression; Mean Diff = mean diffusivity; Nucl Acc = nucleus accumbens; PFC = prefrontal cortex; R = right; SLF = superior longitudinal fasciculus; TBI = traumatic brain injury; † $p < 0.05$ (corrected); § $p = 0.09$ (corrected); £ $p = 0.14$ (corrected); £ $p = 0.17$ (corrected); Axial = axial diffusivity; Radial = radial diffusivity.

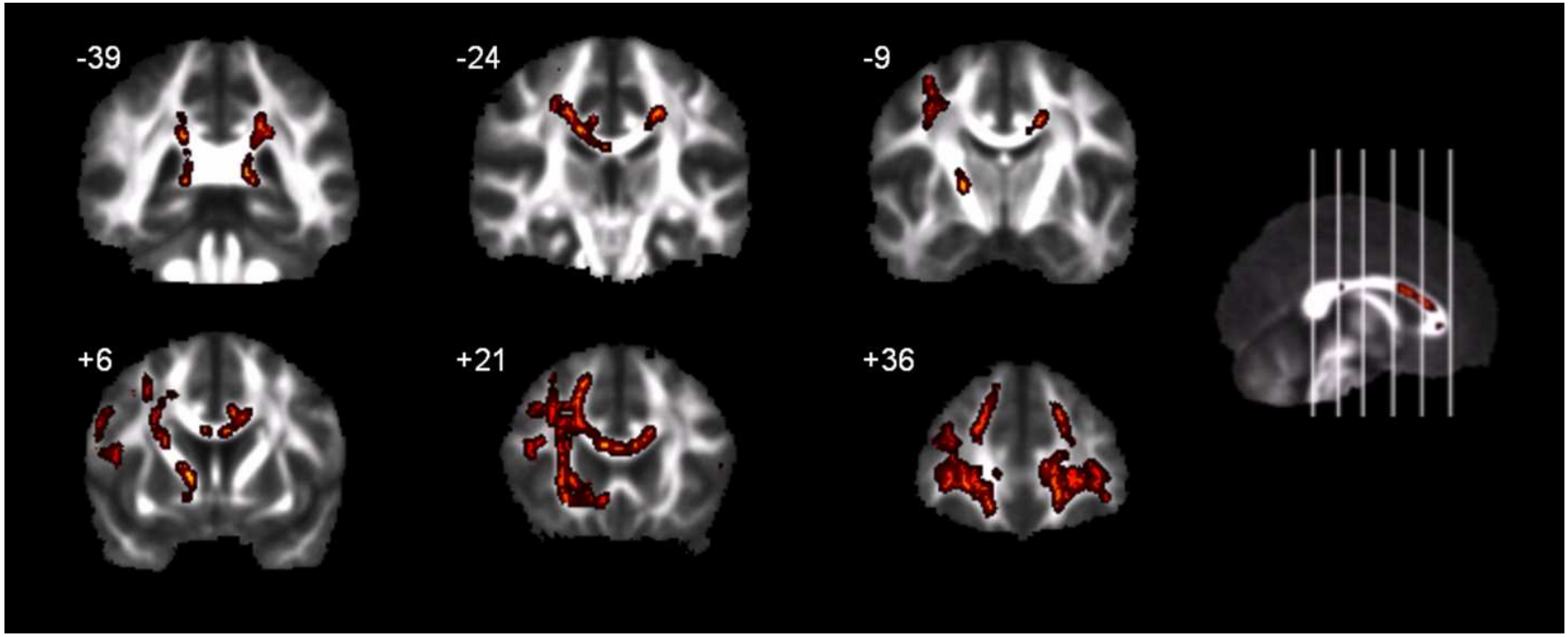

Figure 1.

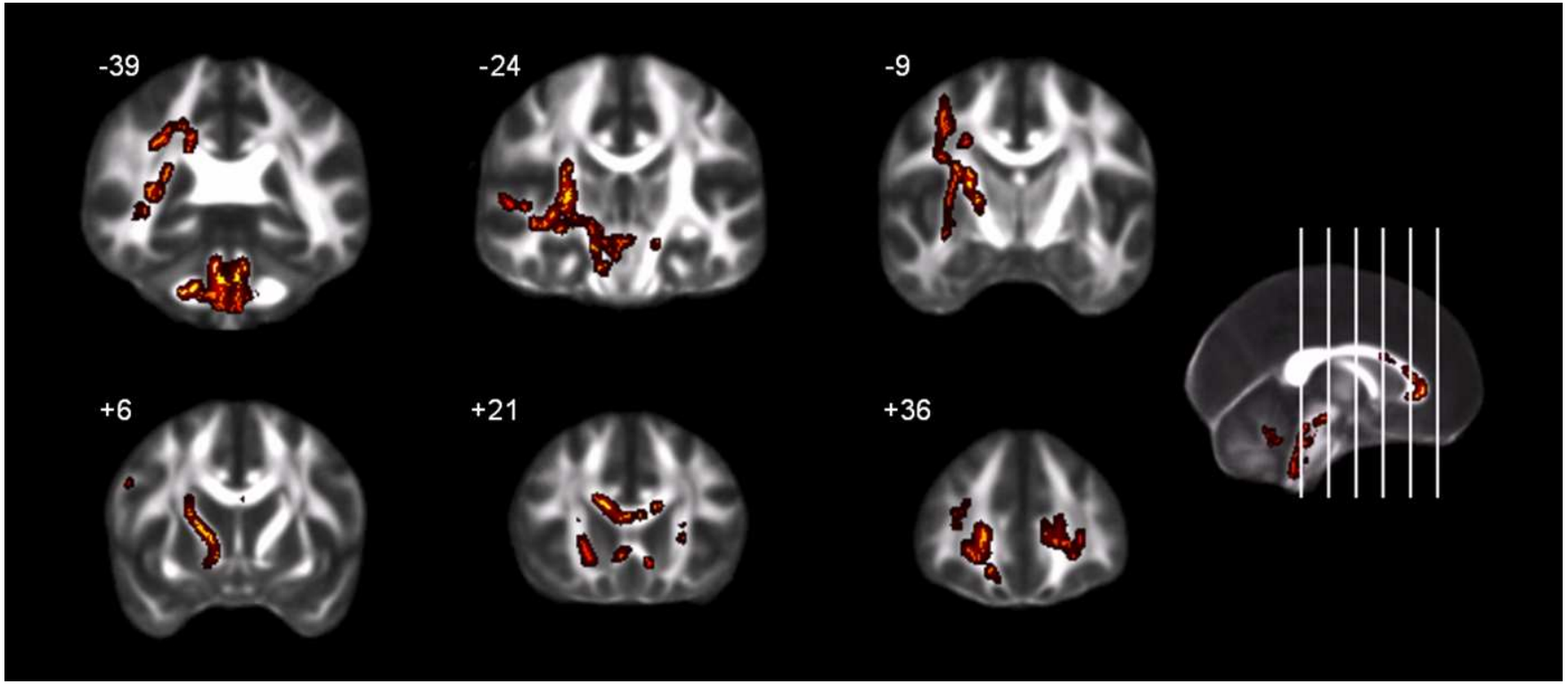

Figure 2.

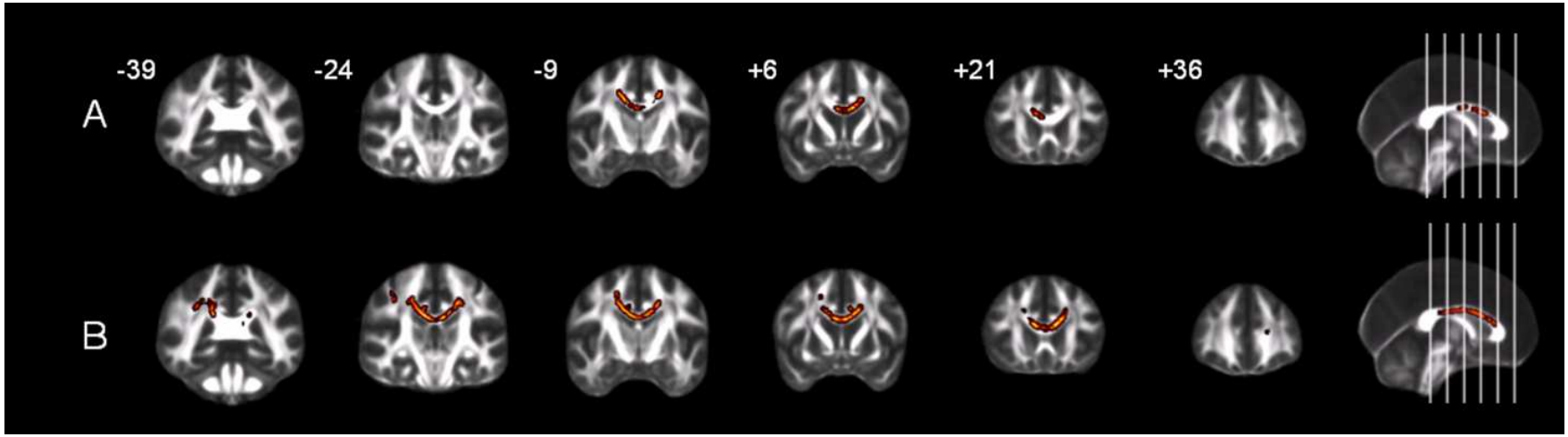

Figure 3.

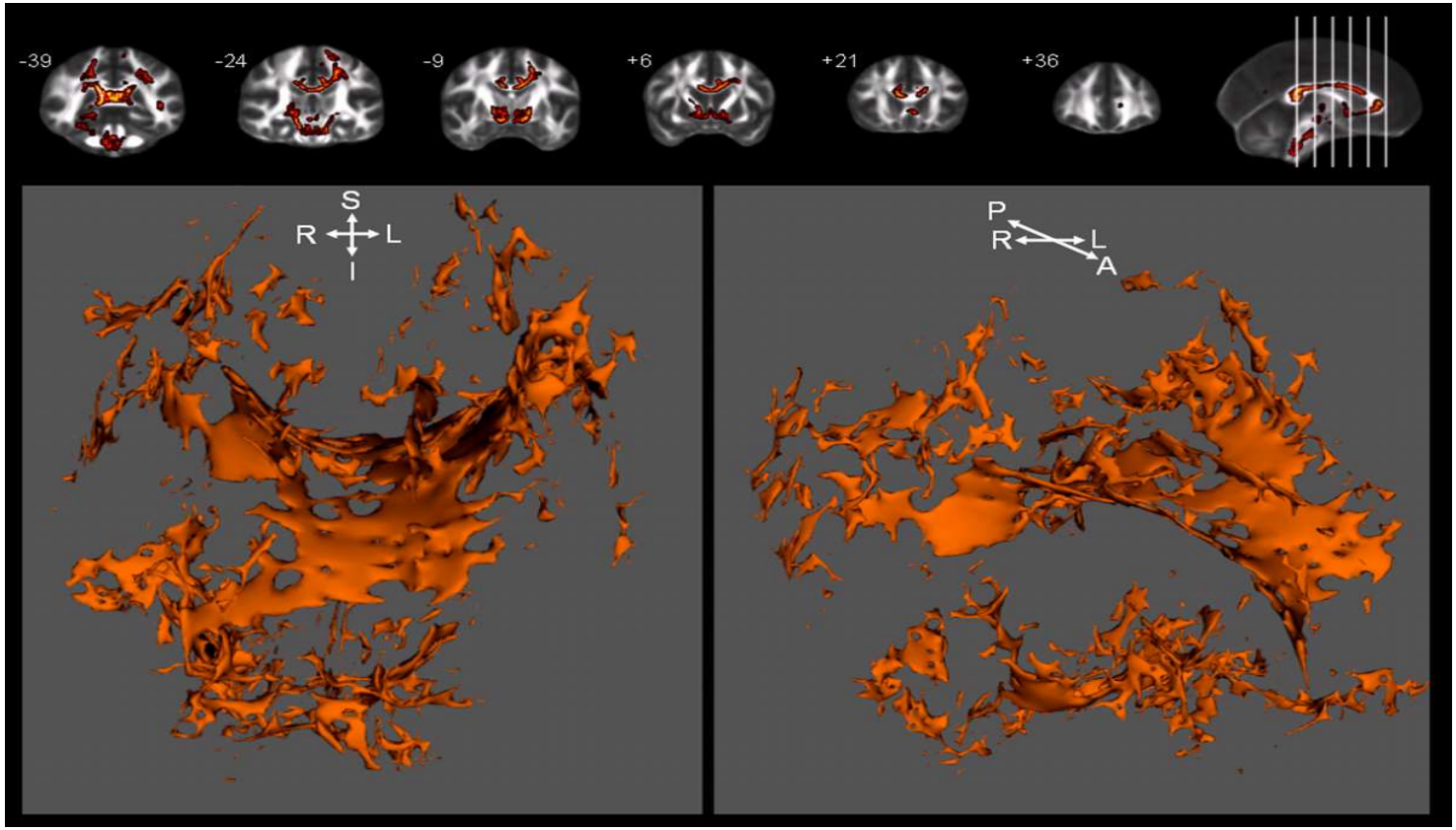

Figure 4.