Cognitive impairment and frontostriatal dysfunction in Major Depression and Alcohol Dependence.

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of the requirements for the Degree of Doctor
of Psychology.

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ADDENDUM

p 70: Add to the end of the final paragraph:

"The stimulations which will be described in these deepTMS studies were administered to the left prefrontal cortex (Harel et al 2011; Isserles et al 2011; Levkovitz et al., 2009; Levkovitz et al., 2011; Rosenberg et al 2010a; b; Rosenberg et al., 2011) and the bilateral prefrontal cortex (Levkovitz et al., 2009; Levkovitz et al., 2011)".

p106, para 2, line 10: after (i.e. negative stimuli), add "which could possibly".

p136, para 4, sentence 3: After age, gender or education. add "No significant correlations were observed between SART, ES and RNG cognitive variables".

ERRATA

p137, para 2, first sentence: delete "within" and replace with "with"

p137, para 2, sentence 8: delete "There was" and begin the sentence with "A"

p138, para 1, sentence 1: delete "this was no" and after significant differences add "were not"

p138, para 2, sentence 1: replace "as" with "at"

TABLE OF CONTENTS

LIST OF PUBLICATIONS

The following publications arose from the literature review and research conducted during the course of my candidature.

Published

Feil J, Sheppard D, Fitzgerald PB, Yücel M, Lubman DI, Bradshaw JL, (2010), Addiction, compulsive drug seeking, and the role of frontostriatal mechanisms in regulating inhibitory control, Neuroscience and Biobehavioral Reviews, Volume 35, Issue 2, Pages 248 - 275

Feil J and Zangen A, (2010), Brain stimulation in the study and treatment of addiction, Neuroscience and Biobehavioral Reviews, Volume 34 , Issue 4, Pages 559 - 574

Feil J and Zangen A, (IN PRESS), Research applications: Brain Stimulation and Addiction, Volume on Brain Stimulation, Handbook of Clinical Neurology.

Submitted for Peer-Review

Feil J, Bradshaw JL, Fitzgerald PB, Sheppard D, Rosenberg O, Dannon P, Isserles M, Zangen A, (submitted), Impaired cognitive inhibition, attentional control and emotional biases in patients with severe depression

Feil J, Bradshaw JL, Fitzgerald PB, Lubman DI, Sheppard D, (submitted), Frontally-mediated cognitive deficits, craving and cognitive recovery among alcohol dependent individuals following detoxification

Feil J, Sheppard D, Bradshaw JL, Rogasch NC, Daskalakis ZJ, Lubman DI, Fitzgerald PB, (submitted), Cortical Inhibition within Motor and Frontal Regions in Alcohol Dependence: A TMS-EEG study.

THESIS SUMMARY

A critical feature of human cognition is the ability to flexibly adapt one's thoughts and behaviours towards a current goal. The capability to select and process those mental representations which are contextually appropriate, while simultaneously suppressing responses to prepotent, yet inappropriate representations (i.e. cognitive inhibition), is fundamental to the control of basic behaviours and thoughts. Recent studies have suggested that deficits of cognitive inhibition may underlie key symptoms of a number of psychiatric disorders. This association is further supported by brain imaging studies; whereby, cognitive inhibitory processes involve the activation of frontostriatal circuitry, the same brain circuitry implicated across a number of psychiatric disorders. However, to date, the specific nature of these frontally-mediated cognitive inhibitory deficits within various psychiatric disorders is poorly understood.

This thesis explores the presence of these neurocognitive inhibitory deficits across two highly prevalent and devastating psychiatric disorders: Major Depressive Disorder (MDD) and Alcohol Dependence (AD). Despite significantly different clinical symptomatology, the cognitive inhibitory processes, and the involvement of frontostriatal circuitry, are nevertheless remarkably similar across both disorders. Therefore, the current thesis aimed to (i) examine the presence of cognitive inhibitory deficits across both psychiatric populations, (ii) utilize newly developed brain stimulation techniques to assess the involvement of the disrupted frontostriatal circuitry, and (iii) discuss the potential clinical ramifications of these frontally-mediated cognitive inhibitory deficits.

To examine regulatory deficits across the two disorders, three cognitive inhibitory tasks were administered: The Sustained Attention to Response Task, Emotional Stroop, and the Random Number Generation Task. Each of these tasks characterizes a distinct aspect of cognitive inhibitory function and provides a frontally-mediated measure of cognitive inhibition within

depressive and alcohol dependent patients. To assess the involvement of the frontostriatal circuitry, two newly-developed transcranial magnetic stimulation (TMS) techniques were delivered across both patient groups. Deep TMS was administered to the MDD patients to explore whether stimulation of the frontal cortex and deeper cortical structures could attenuate cognitive inhibitory impairment within a MDD sample. The combined TMS and electroencephalography (TMS-EEG) technique was administered to the AD group to provide the first direct measure of altered cortical excitability within the frontal cortex of an alcohol dependent sample.

The major research aims were achieved. In terms of MDD, significant cognitive inhibitory deficits were observed within the depressive population, and the frontostriatal circuitry was found to play a critical role in cognitive symptoms of depression. With regards to AD, enduring cognitive inhibitory deficits were revealed within the alcohol dependent post-detoxification population, and a direct index of altered cortical inhibition within the frontal cortex of alcohol dependent patients was demonstrated for the first time.

When combined, these studies provide empirical evidence of the presence of cognitive inhibitory deficits, and the involvement of the frontostriatal circuitry, across both depressive and alcohol dependent disorders. Further insight into these frontally-mediated cognitive inhibitory deficits may advance our understanding of the cognitive features of these disorders, and expand the current pathophysiological models of depression and alcohol dependence.

General Declaration

In accordance with Monash University Doctorate Regulation 17 Doctor of Philosophy and Research Master's 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 two original papers published in peer reviewed journals and three unpublished publications submitted for review. The core theme of the thesis is cognitive inhibitory deficits and frontostriatal dysfunction across psychiatric disorders. 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 B Fitzgerald, E/Professor John L Bradshaw and Dr Dianne Sheppard.

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 Chapter 2, 4, 7, 8, 9, 10 and Appendix I, my contribution to the work involved the following:

Thesis chapter	Publication title	Publication status*	Nature and extent of candidate's contribution
Chapter 2	Addiction, compulsive drug seeking, and the role of frontostriatal mechanisms in regulating inhibitory control	Published	Reviewed the literature and prepared the manuscript.
Chapter 4	Brain stimulation in the study and treatment of addiction	Published	Reviewed the literature and prepared the manuscript.
Chapter 7	Impaired cognitive inhibition, attentional control and emotional biases in patients with severe depression	Submitted for Peer Review	Conceptualisation of the study, development of the protocol, participant recruitment, conducting experimental sessions, data entry, analysis of the data and preparation of the manuscript.
Chapter 8	Effects of repetitive deep transcranial magnetic stimulation of the frontal regions on neurocognition in severely depressed patients.	Prepared for Journal Submission	Conceptualisation of the study, development of the protocol, participant recruitment, conducting experimental sessions, data entry, analysis of the data and preparation of the manuscript.

Chapter 9	Frontally-mediated cognitive deficits, craving and cognitive recovery among alcohol dependent individuals following detoxification	Submitted for Peer Review	Conceptualisation of the study, development of the protocol, participant recruitment, conducting experimental sessions, data entry, analysis of the data and preparation of the manuscript.
Chapter 10	Cortical Inhibition within Motor and Frontal Regions in Alcohol Dependence: A TMS-EEG study.	Submitted for Peer Review	Conceptualisation of the study, development of the protocol, participant recruitment, conducting experimental sessions, data entry, analysis of the data and preparation of the manuscript.
Appendix I	Chapter Manuscript Research applications: Addiction	Accepted for publication	Reviewed the literature and prepared the chapter manuscript.

Signed: 

Date: 31/1/2013

Declaration for Thesis Chapter 2

Declaration by candidate

In the case of Chapter 2, the article titled, *Addiction, compulsive drug seeking, and the role of frontostriatal mechanisms in regulating inhibitory control* the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Conceptualisation of the article, review of the literature and preparation of the manuscript.	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
Dianne Sheppard	Conceptualization of article and review of manuscript
Paul B. Fitzgerald	Conceptualization of article and review of manuscript
Murat Yucel	Review of manuscript
Dan I. Lubman	Review of manuscript
John L. Bradshaw	Conceptualization of article and review of manuscript

Candidate's Signature	[redacted]	**Date** **31/1/2013**

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:

Location(s)	Monash Alfred Psychiatry Research Centre, Alfred Hospital.

Dianne Sheppard: [redacted] **Dan I. Lubman:** [redacted]

Paul P. Fitzgerald: [redacted] **John L. Bradshaw:** [redacted]

Murat Yucel [redacted]

Declaration for Thesis Chapter 4

Declaration by candidate

In the case of Chapter 4, the article titled, *Brain stimulation in the study and treatment of addiction*, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Conceptualisation of the article, review of the literature and preparation of the manuscript.	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
Abraham Zangen	Review of manuscript

Candidate's Signature	[redacted]	**Date** **31/1/2013**

Declaration by co-authors

1. The undersigned hereby certify that:
2. 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.
3. 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;
4. they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
5. there are no other authors of the publication according to these criteria;
6. 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
7. the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)	Weizmann Institute of Science, Department of Neurobiology; Hadassah Hospital; Beer Yaakov Mental Health Hospital

Abraham Zangen: [redacted]

Declaration for Thesis Chapter 7

Declaration by candidate

In the case of Chapter 7, the article titled, *Impaired cognitive inhibition, attentional control and emotional biases in patients with severe depression*, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Conceptualisation of the study, development of the protocol, participant recruitment, conducting experimental sessions, data entry, analysis of the data and preparation of the manuscript.	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
John L. Bradshaw	Conceptualisation of the study, development of the protocol, analysis of data and review of manuscript
Paul B. Fitzgerald	Conceptualisation of the study, development of the protocol, analysis of data and review of manuscript
Dianne Sheppard	Conceptualisation of the study, development of the protocol, analysis of data and review of manuscript
Oded Rosenberg	Recruitment and testing
Pinhas Dannon	Recruitment and testing
Moshe Isserles	Recruitment and testing
Abraham Zangen	Conceptualisation of the study, development of the protocol, analysis of data and review of manuscript

Candidate's Signature	[redacted]	**Date** **31/1/2013**

Declaration by co-authors

1. The undersigned hereby certify that:
2. 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.
3. 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;
4. they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
5. there are no other authors of the publication according to these criteria;
6. 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
7. the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)	Weizmann Institute of Science, Department of Neurobiology; Hadassah Hospital; Beer Yaakov Mental Health Hospital

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Dianne Sheppard: [redacted]

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Oded Rosenberg: [redacted]

Abraham Zangen: [redacted]

Pinhas Dannon: [redacted]

Declaration for Thesis Chapter 8

Declaration by candidate

In the case of Chapter 8, the article titled, *Effects of repetitive deep transcranial magnetic stimulation of the frontal regions on neurocognition in severely depressed patients*, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Conceptualisation of the study, development of the protocol, participant recruitment, conducting experimental sessions, data entry, analysis of the data and preparation of the manuscript.	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
John L. Bradshaw	Conceptualisation of the study, development of the protocol, analysis of data and review of manuscript
Paul B. Fitzgerald	Conceptualisation of the study, development of the protocol, analysis of data and review of manuscript
Dianne Sheppard	Conceptualisation of the study, development of the protocol, analysis of data and review of manuscript
Oded Rosenberg	Recruitment of patients and technical support in the testing sessions
Pinhas Dannon	Recruitment of patients and technical support in the testing sessions
Moshe Isserles	Recruitment of patients and technical support in the testing sessions
Abraham Zangen	Conceptualisation of the study, development of the protocol, analysis of data and review of manuscript

Candidate's Signature	[redacted]	**Date** **31/1/2013**

Declaration by co-authors

1. The undersigned hereby certify that:
2. 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.
3. 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;
4. they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
5. there are no other authors of the publication according to these criteria;
6. 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
7. the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)	Weizmann Institute of Science, Department of Neurobiology; Hadassah Hospital; Beer Yaakov Mental Health Hospital

Paul P. Fitzgerald: [redacted]

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Dianne Sheppard: [redacted]

Moshe Isserles: [redacted]

Oded Rosenberg: [redacted]

Abraham Zangen: [redacted]

Pinhas Dannon: [redacted]

Declaration for Thesis Chapter 9

Declaration by candidate

In the case of Chapter 9, the article titled, *Frontally-mediated cognitive deficits, craving and cognitive recovery among alcohol dependent individuals following detoxification*, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Conceptualisation of the study, development of the protocol, participant recruitment, conducting experimental sessions, data entry, analysis of the data and preparation of the manuscript.	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
John L. Bradshaw	Conceptualisation of the study, development of the protocol, analysis of data and review of manuscript
Paul B. Fitzgerald	Conceptualisation of the study, development of the protocol, analysis of data and review of manuscript
Dianne Sheppard	Conceptualisation of the study, development of the protocol, analysis of data and review of manuscript
Dan I. Lubman	Recruitment and review of manuscript

Candidate's Signature	[redacted]	**Date** **31/1/2013**

Declaration by co-authors

1. The undersigned hereby certify that:
2. 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.
3. 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;
4. they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
5. there are no other authors of the publication according to these criteria;
6. 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
7. the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)	Monash Alfred Psychiatry Research Centre, Alfred Hospital.

Paul P. Fitzgerald: [redacted] **John L. Bradshaw:** [redacted]

Dianne Sheppard: [redacted] **Dan I. Lubman:** [redacted]

Declaration for Thesis Chapter 10

Declaration by candidate

In the case of Chapter 10, the article titled, *Cortical Inhibition within Motor and Frontal Regions in Alcohol Dependence: A TMS-EEG study,* the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Conceptualisation of the study, development of the protocol, participant recruitment, conducting experimental sessions, data entry, analysis of the data and preparation of the manuscript.	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
John L. Bradshaw	Conceptualisation of study, protocol development, analysis of data and preparation of manuscript.
Nigel C Rogasch	Technical assistance in TMS-EEG sessions, review of manuscript (**Monash Student**: Extent of contribution approximately 5%)
Zafiris J. Daskalakis	Technical advice regarding TMS-EEG, review of manuscript
Dianne Sheppard	Conceptualisation of study, protocol development, analysis of data and preparation of manuscript.
Dan I. Lubman	Recruitment for study, review of manuscript
Paul B. Fitzgerald	Conceptualisation of study, protocol development, analysis of data and preparation of manuscript.

Candidate's Signature	[redacted]	**Date** **31/1/2013**

Declaration by co-authors

1. The undersigned hereby certify that:
2. 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.
3. 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;
4. they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
5. there are no other authors of the publication according to these criteria;
6. 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
7. the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)	Monash Alfred Psychiatry Research Centre, Alfred Hospital.

Dianne Sheppard: [redacted]

Paul P. Fitzgerald:

Nigel C. Rogasch:

Dan I. Lubman: [redacted]

John L. Bradshaw:

Zafiris J. Daskalakis:

Declaration for Thesis Appendix

In the case of the Appendix, the Chapter Manuscript titled, *Research applications: Addiction*, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Conceptualisation of the article, review of the literature and preparation of the chapter manuscript.	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
Abraham Zangen	Review of manuscript

Candidate's Signature	[redacted]	**Date** **31/1/2013**

Declaration by co-authors

1. The undersigned hereby certify that:
2. 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.
3. 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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5. there are no other authors of the publication according to these criteria;
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7. the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)	Weizmann Institute of Science, Department of Neurobiology

Abraham Zangen: [redacted]

ACKNOWLEDGEMENTS

Ithaca

When you set sail for distant Ithaca,
wish for the road to be long,
full of adventures, full of knowledge,
Of the Laestrygonians and the Cyclopes,
of the angry god Poseidon - have no fear.
You shall not encounter such on your path,
if your thoughts remain lofty, and fine emotion
touches you in body and spirit
Not the Lestrygonians and not the Cyclopes,
nor the fierce Poseidon, shall you meet,
if you do not carry them within your spirit,
and if your spirit does not place them before you.

Wish for the road to be long.
Many the summer mornings to be when
with what pleasure, what joy
you will anchor into ports seen for the first time,
Stay at Phoenician markets,
and purchase the fine goods,
nacre and coral, amber and ebony,
and exquisite perfumes of all sorts,
the most delicate fragrances you can find.
Sojourn in many a city of the Nile,
to learn and learn from the cultivated.

Always keep Ithaca in your mind.
To arrive there is your final destination.
But do not hurry the voyage at all.
It is better if you travelled many years,
and when old to rest in the island,
rich with all you have gained on the way,
not expecting Ithaca to offer your wealth.

Ithaca has given you the beautiful journey.
Without her you would have never set out on the road.
Nothing more does she have to give you.

And though you should find her wanting,
Ithaca will not surprise you; for you will arrive,
wise as you have become, with so much experience,
you must already have understood what Ithacas mean.

Constantine P. Cavafy, 1911

The research and writing of this doctoral thesis has been a wonderful and challenging journey. Foremost, I would like to express sincere gratitude to my advisors Professor Paul B. Fitzgerald, Emeritus Professor John L. Bradshaw and Dr Dianne Sheppard for sharing this remarkable research journey with me. Each of my advisors contributed to the mentoring of the thesis in a unique and special way. Professor Paul Fitzgerald provided me with endless guidance, inspiration and the tools to explore my passion of frontal brain dysfunction in psychiatric disorders. E/Professor John Bradshaw helped me realise my academic potential, provided endless support and always encouraged me to think beyond the box. Dr Dianne Sheppard was extremely warm and encouraging throughout the PhD and always provided detailed insight into the writing up of the thesis. I would also like to further extend my appreciation to my advisors and to Dr Abraham Zangen for their belief in me and willingness to support my initiation of a collaborative study between the Weizmann Institute of Science and Monash Alfred Psychiatry Research Centre. The wonderful opportunity for this collaborative study was generously supported by the Australia-Israel Scientific Exchange Foundation. Further financial support was contributed by the philanthropic foundation of Graduate Women Victoria who aspire to empower women through education.

I would also like to thank all of my colleagues and friends at Monash Alfred Psychiatry Research Centre (MAPRC). A special thank you to Nigel Rogasch, Neil Bailey, Karyn Richardson, Jerome Maller, and Richard Thomson for their direct contribution to experimental set up and sessions involved in the brain stimulation study conducted at MAPRC.

A continual source of support and strength came from my family and friends. I would like to deeply thank my family, Herta Winter, Alan and Yvonne Feil, Danielle Latowicz and Erin Oyberman for their constant support, encouragement and patience for their 'perpetual student'. I would also like to thank my close friends for always being there for me,

appreciating my passion for research, and resisting the temptation to ask 'how much longer'. A special mention to Tibor Winter, Rosa and Henry Joseph Feil, who unfortunately are not here to celebrate this wonderful achievement, but who bestowed upon me a deep understanding of the importance and value of education. Finally, I would like to sincerely thank my husband, Erez Naim, who joined me on this wonderful doctoral journey and showed unwavering patience, love, and support throughout every stage of the PhD.

FREQUENT ABBREVIATIONS

AD	Alcohol Dependence
ANOVA	Analysis of Variance
ANCOVA	Analysis of Co-Variance
BDI	Beck Depression Inventory
CI	Cortical Inhibition
CS	Control Subjects
CSP	Cortical Silent Period
deepTMS	deep Transcranial Magnetic Stimulation
DLPFC	Dorsolateral Prefrontal Cortex
EEG	Electroencephalogram
EMG	Electromyography
ERP	Event Related Potential
ES	Emotional Stroop
GABA	γ-Aminobutyric acid
GLU	Glutamate
Hz	Hertz
ICF	Intracortical Faciliation
LICI	Long Interval Cortical Inhibition
MDD	Major Depressive Disorder Obsessive
OCDS	Compulsive Drinking Scale
PFC	Prefrontal Cortex
RNG	Random Number Generation Task
SART	Sustained Attention to Response Task
SICI	Short Interval Intracortical Inhibition
TMS	Transcranial Magnetic Stimulation
TMS-EEG	Combined Transcranial Magnetic Stimulation and Electroencephalogram
WTAR	Wechsler Test of Adult Reading

Chapter One

Introduction and Thesis Overview

The capability to flexibly adapt one's thoughts and behaviours towards a current goal is a dynamic feature of the human cognitive system (Blasi et al., 2006; Garavan et al., 2002). A fundamental aspect of cognitive control is the ability to inhibit responses to automatic yet irrelevant representations. In everyday life, many representations are simultaneously active; the ability to select and integrate those representations which are considered contextually relevant, while suppressing irrelevant representations, is critical to the control of basic behaviours and thoughts. Recent research has indicated that deficits in cognitive inhibition, the processes required to adequately inhibit prepotent and inappropriate representations, may be closely related to key characteristics of a number of psychiatric disorders (Baune et al., 2010; Clark et al., 2009; Davidson et al., 2002b; Fossati et al., 2002; Hammar and Årdal, 2009). This association is also reflected by neuroimaging studies, whereby cognitive inhibitory processes rely on the integrity of the frontostriatal circuitry (Blasi et al., 2006; Bradshaw, 2001; Casey, 2005; Chambers et al., 2006; Chambers et al., 2009; Fuster, 2001, 2006; Miller and Cohen, 2001) (described in further detail in Chapter 2 of thesis), the same brain circuitry disrupted across a number of psychiatric disorders (Austin et al., 2001; Eugène et al., 2010; Feil et al., 2010).

In the current thesis, the presence of these neurocognitive inhibitory deficits are explored across two highly prevalent and debilitating psychiatric disorders: Major Depressive Disorder (MDD) and Alcohol Dependence (AD). Previously, there has been extensive review of the general concept of cognitive inhibition (Casey et al., 2001; Garavan et al., 2006; Houghton and Tipper, 1996) and related frontal regions (Blasi et al., 2006; Bradshaw, 2001; Casey, 2005; Chambers et al., 2006; Chambers et al., 2009; Fuster, 2001, 2006; Kelly et al., 2004; Miller and Cohen, 2001). Therefore, the current thesis is designed to expand on those

concepts by exploring the processes and involvement of cognitive inhibitory dysfunction and related frontostriatal dysfunction within depressive and alcohol dependent populations. Although these two disorders are characterized by significantly different clinical symptomotology, the cognitive inhibitory processes and related neurobiological structures underlying the cognitive symptoms of these disorders are remarkably similar. The following section briefly describes how the concept of cognitive inhibitory dysfunction relates to cognitive symptoms of MDD and AD.

MDD is a severe and debilitating disorder which is defined by a range of heterogeneous clinical features. Effective treatment remains a critical challenge for clinicians, with almost one-third of patients remaining symptomatic, even after adequate anti-depressant treatment. Although MDD is primarily a mood disorder, cognitive impairment is also emerging as a defining feature of the disorder (Austin et al., 2001; Elliott et al., 2002; Rogers et al., 2004). Cognitive models suggest that the difficulty *inhibiting* intrusive negative representations and thoughts is critically involved in the onset, persistence and recurrence of depressive symptoms (Beck et al., 1979; Clark et al., 2009; Gotlib and Joormann, 2010; Joormann, 2010; Joormann and Gotlib, 2010; Joormann et al., 2007; Paelecke-Habermann et al., 2005; Ravnkilde et al., 2002). However, the specific characteristics of these cognitive inhibitory impairments, and how they impact on depressive disorders, remain unclear. From a neurobiological perspective, neuroimaging studies have identified the involvement of hypoactivity within the prefrontal cortex (Drevets, 1999, 2000; Fitzgerald et al., 2006) and altered activity within the mesolimbic dopaminergic pathways (Drevets et al., 2008; Mayberg, 2003b, 2006; Mayberg et al., 1997; Nestler and Carlezon Jr, 2006) in the pathophysiology of depressive disorders; the same frontal circuitry recruited for various aspects of cognitive processing, such as cognitive inhibition (Blasi et al., 2006; Chambers et al., 2009; Garavan et al., 2002; Miller and Cohen, 2001). Notably, this frontal circuitry is also

implicated in the persistence of depressive disorders (Brody et al., 2001; Davidson et al., 2002b; Drevets, 1999; Drevets et al., 2008; Mayberg et al., 1999) and the degree of treatment response (Kumari et al., 2003; Langenecker et al., 2007; Mayberg, 1997; Pizzagalli et al., 2001; Pizzagalli, 2011). Therefore, these frontally-mediated cognitive impairments appear to be inextricably related to the persistence of depressive symptoms and the compromised ability to recover from depression. However, the exact nature of this association is not yet well-established and the role of cognitive impairments and frontostriatal dysfunction in depressive disorders requires further elucidation.

AD is also a debilitating disorder which is characterized by persistent cravings and chronic relapse. A constant challenge for the treatment of AD is the patient's diminished capacity to regulate alcohol consumption regardless of negative consequences (Hyman and Malenka, 2001; Noël et al., 2010). Both acute intoxication (Fillmore et al., 2005) and chronic alcohol consumption (Vogel-Sprott et al., 2001) have been associated with reduced executive function and impaired cognitive control. In addition, preliminary neuroimaging studies have identified alterations within the frontal circuitry (Moselhy et al., 2001; Oscar-Berman and Marinkovic, 2003; Oscar-Berman and Marinković, 2007; Sullivan and Pfefferbaum, 2005; Sullivan et al., 2010; Volkow et al., 2007) in the pathophysiology of AD; the same circuitry proposed to subserve cognitive control (Blasi et al., 2006; Chambers et al., 2009; Garavan et al., 2002; Miller and Cohen, 2001). These cognitive impairments have been found to directly relate to frontostriatal dysfunction in alcohol dependent patients (Noël et al., 2001; Noël et al., 2002) and are associated with the development of AD in heavy drinkers (Rubio et al., 2008) and poor treatment outcome (Bates et al., 2002; Bowden-Jones et al., 2005; Noël et al., 2002). Although these studies provide initial insight into the presence of frontally-mediated cognitive impairment, further studies are required to expand on these preliminary studies to

provide a better characterization of the cognitive impairments and the involvement of the related frontal circuitry in alcohol dependent populations.

Therefore, the broad research aim of the current thesis is to explore the presence of cognitive impairment and frontostriatal dysfunction across both depressive and alcohol dependent populations. Across both disorders, further insight into the deficits could contribute to the development of screening and treatment models which might more accurately target these cognitive deficits and frontostriatal dysfunction, possibly leading to improved intervention and treatment efficacy.

The following experimental studies were designed:

1. The first study examines the presence of regulatory deficits across the domains of cognitive inhibition, attentional control and emotion regulation in a sample of severely depressed patients. There follows an assessment of whether these cognitive impairment are interrelated, or rather, exert an independent effect on patients with MDD.
2. The second study investigates whether delivery of frontal deep Transcranial Magnetic Stimulation (deepTMS), which is capable of stimulating deeper cortical regions such as the mesolimbic dopamine pathways (i.e. fronto-limbic circuitry), can lead to improved cognition in patients with severe depression. This is the first study to examine the cognitive efficacy of deepTMS within a depressive population.
3. The third study explores the presence of neurocognitive impairments in patients diagnosed with alcohol dependence post-detoxification. There follows an examination of whether these cognitive impairments relate to craving, and whether they improve following abstinence.

4. The fourth study administers the novel combined Transcranial Magnetic Stimulation and Electroencephalography (TMS-EEG) technique to examine the presence of altered frontal and motor cortical excitability in patients diagnosed with AD post-detoxification. This is the first application of the combined TMS-EEG technique to index cortical excitability within the frontal cortices of patients with AD.

Therefore, the introductory chapters of the thesis appear in the following format:

Chapter 2: In the second chapter, the published review titled, *Addiction, compulsive drug seeking, and the role of frontostriatal mechanisms in regulating inhibitory control*, is presented. In this article the general background of cognitive inhibition and the involvement of the frontostriatal cortical network in the pathophysiology of cognitive inhibitory deficits is described. Next, the article suggests that dysregulation of the frontal circuitry is involved in the persistence of drug-seeking behaviours. There follows a comprehensive and critical review of recent neuropsychological, neuroimaging and brain stimulation studies which have assessed the relationship between dysregulation of inhibitory control and impaired frontal activity within the context of substance dependence. Finally, the article highlights the implications of these cognitive deficits within substance dependent populations, and suggests the implementation of treatment options to address these cognitive deficits in an attempt to reduce problematic behaviours associated with compulsive drug use.

Chapter 3: In the third chapter, a brief overview of MDD and the involvement of cognitive impairments and the frontal circuitry in the persistence of depressive-related behaviours will be presented. Following this, two key components of cognitive dysfunction will be explored: Cognitive biases in the processing of affective stimuli and cognitive deficits in the processing of neutral stimuli. Clinical implications of identifying these cognitive impairments, and whether they are interrelated, or independent processes, within a depressive population are discussed.

Chapter 4: In the fourth chapter, the published review titled, *Brain stimulation in the study and treatment of addiction,* is presented. This review describes the basic mechanisms underlying the electromagnetic brain stimulation technique called Transcranial Magnetic Stimulation (TMS), and how these TMS inhibitory techniques can be used to investigate the pathophysiology of psychiatric disorders. The article also discusses the neurobiology of addiction and the potential effect of brain stimulation on addictive behaviours. There follows a review of previous addiction studies which have administered TMS to assess addiction-related alterations in cortical excitability. The article then outlines the therapeutic potential of repetitive brain stimulation techniques in attenuating symptoms of craving and dependence. Finally, the research and therapeutic potential of TMS in substance dependent populations is discussed. Following the published review, the newly developed combined TMS-EEG procedure is introduced and its research utility within an alcohol dependent population is discussed.

Chapter 5: In the fifth chapter, the effects of these brain stimulation techniques in depressive populations are discussed. The brain stimulation techniques described in Chapter 4 will be expanded and the novel brain stimulation technique known as deep Transcranial Magnetic Stimulation (deepTMS) introduced. DeepTMS is capable of stimulating deeper cortical regions and is emerging as a promising technique for reducing clinical symptoms of depression. All of the previous studies which have previously administered deepTMS within major depressive populations are reviewed. Application of frontal deepTMS is thought to attenuate clinical symptoms of depression; however, it seems highly plausible that stimulation of the frontal cortex may also affect frontally-mediated cognitive function within depressive populations. Therefore, the chapter concludes with a discussion of the implications of delivery of frontal deepTMS in improving cognitive symptoms of depression.

Chapter 6: To conclude, a brief summary of the literature review is provided, followed by an outline of the specific aims of the thesis.

The current thesis is presented in a thesis-by-publication format. Therefore, within the introductory literature review two published reviews are included, followed by four experimental papers in the sequential chapters. Three of these experimental papers have been submitted for peer-review and are to be found in the current thesis according to the submitted manuscript format (including the formatting of tables and figures). The fourth paper is in its final preparation stages before journal submission. Appended to the thesis is a recently accepted book chapter which was written during the PhD candidature. The book chapter further expands on the research and therapeutic potential of brain stimulation techniques for reducing addictive behaviours in dependant populations.

Given the thesis-by-publication format there will be some unavoidable repetition of material between the literature review, general discussion, and across the four articles. Preceding each of the introductory chapters and experimental studies, explanatory notes are included to introduce specific aspects of each article and to make a theoretical link between the articles. Finally, to avoid excessive repetition, the study methods and behavioural tasks (Random Number Generation Task (RNG), Sustained Attention to Response Task (SART) and Emotional Stroop (ES)) are outlined in detail within each study, rather than as a separate chapter.

The four experimental study chapters:

Chapter 7: Impaired cognitive inhibition, attentional control and emotional biases in patients with severe depression.

Chapter 8: Effects of repetitive deep transcranial magnetic stimulation of the frontal regions on neurocognition in severely depressed patients.

Chapter 9: Frontally-mediated cognitive deficits, craving and cognitive recovery among alcohol dependent individuals following detoxification.

Chapter 10: Cortical Inhibition within Motor and Frontal Regions in Alcohol Dependence: A TMS-EEG study.

The appended book chapter:

Appendix I: Chapter Manuscript Research Applications: Addiction.

To conclude, a general discussion integrates the main findings from the series of studies presented in the current thesis and explores their significance within a broader context. Additionally, the merit of the studies conducted, methodological considerations and limitations, and future research possibilities, are explored.

CHAPTER TWO

Cognitive deficits and frontostriatal dysfunction: Alcohol Dependence

2.1. General overview

In the current chapter our published review, *Addiction, compulsive drug seeking, and the role of frontostriatal mechanisms in regulating inhibitory control*, is presented. The article describes the general background of the processes involved in cognitive inhibition and the implicated frontostriatal cortical networks. The presence of these cognitive deficits and dysregulation of the frontal circuitry are then explored within the context of persistent drug-seeking behaviours. Following this, a detailed review of preliminary psychological, neuroimaging and brain stimulation studies which have assessed the relationship between impaired inhibitory control and frontal dysfunction across various substance-dependent populations is presented. The article concludes by discussing the potential therapeutic benefits of addressing these cognitive deficits, and the associated frontostriatal dysfunction, within substance-dependent populations.

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Review

Addiction, compulsive drug seeking, and the role of frontostriatal mechanisms in regulating inhibitory control

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ABSTRACT

A principal feature of drug addiction is a reduced ability to regulate control over the desire to procure drugs regardless of the risks involved. Traditional models implicated the neural 'reward' system in providing a neurobiological model of addiction. Newer models however, have expanded on this circuitry to include two separate, but interconnecting systems, the limbic system in the incentive sensitization of drugs, and the prefrontal cortex (PFC) in regulating inhibitory control over drug use. Until the recent developments in neuroimaging and brain stimulation techniques, it has been extremely difficult to assess the involvement of the PFC in addiction. In the current review, we explore the involvement of the frontostriatal circuitry in regulating inhibitory control, and suggest how dysregulation of these circuits could be involved in an increased difficulty in ceasing drug use. Following this, we investigate the recent neuropsychological, neuroimaging and brain stimulation studies that explore the presence of these inhibitory deficits, and frontostriatal dysfunctions, across various different substance groups. Further insight into these deficits could contribute to the development of treatment strategies which target these cognitive impairments, and frontostriatal dysfunction, in reducing drug-seeking behaviors.

Contents

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1. Introduction

Drug dependence is characterized by repeated drug administration and recurrent relapse. Perhaps the most debilitating consequence of repetitive substance use is the development of psychological dependence (i.e. addiction). Addiction can be described as a persistent state in which there is diminished capacity to regulate compulsive drug seeking, regardless of whether it involves risk of serious negative consequences (Hyman and Malenka, 2001). There has been extensive review of the molecular and cellular neurobiological factors involved in drug administration, and their involvement in the development of drug addiction (Di Chiara and Bassareo, 2007; Kalivas and Volkow, 2005; Koob, 2006). Recently, researchers have expanded the traditional neural 'rewarding' circuits proposed to be involved in addiction (Koob and Le Moal, 2001) to include two separate, yet interconnected systems: the limbic system in the incentive-sensitization of drugs (Robinson and Berridge, 1993, 2001, 2003) and the prefrontal circuitry in regulating inhibitory control involved in drug seeking (Goldstein and Volkow, 2002; Jentsch and Taylor, 1999; Lubman et al., 2004).

Up until recently, it has been very difficult to investigate the role of the frontal cortical structures in the pathophysiology of addiction and craving. Advances in human neuroimaging and brain stimulation techniques however, have made it possible to conduct more informative research into the frontal circuitry of humans. These novel developments have led to the emergence of preliminary exploratory studies into the association between chronic drug consumption, inhibitory impairments, dysregulation of the prefrontal circuitry, and their involvement in prolonged drug seeking. Even though drug action varies across different substance classes, neuropsychological studies have found that chronically exposed individuals exhibit executive, inhibitory and decision-making impairments (Baicy and London, 2007; Li et al., 2006; Monterosso et al., 2005; Neuhaus et al., 2006; Noël et al., 2007b; Tapert et al., 2007; Tomasi et al., 2007a; Verdejo-García et al., 2007; Yücel et al., 2007). In addition, recent structural and functional neuroimaging studies have found that these deficits are accompanied by abnormalities in frontal brain regions such as the dorsolateral prefrontal cortex (DLPFC—goal identification and selection), orbitofrontal cortex (OFC—decision-making and regulation of impulsivity), and anterior cingulate cortex (ACC—assessment of consequences and error detection) across the various substance dependent populations (Blasi et al., 2006; Garavan et al., 2002; Verdejo-García et al., 2006a, 2007; Yücel and Lubman, 2007; Yücel et al., 2007). These findings were supported by preliminary brain stimulation studies which discovered that stimulation of these frontal regions is associated with transient reductions in drug consumption and levels of craving (Amiaz et al., 2009; Boggio et al., 2008; Camprodon et al., 2007; Eichhammer et al., 2003; Fregni et al., 2008; Johann et al., 2003; Politi et al., 2008). Thus converging evidence suggests that chronic substance abuse is associated with frontal and executive impairments, and a better understanding of this dysregulation may provide insight into the mechanisms underlying prolonged drug seeking. Development of therapeutic strategies which can adequately address these inhibitory deficits, and frontostriatal dysfunction, could lead to improved intervention and treatments which deal more effectively with an increased difficulty in regulating control over persistent drug-seeking behaviors.

In the current review, we explore the proposition that chronic drug use could be inextricably linked to frontal cortical-cognitive dysfunction, specifically an inability to inhibit prepotent behavioral responses to drug seeking (Goldstein and Volkow, 2002; Jentsch and Taylor, 1999; Lubman et al., 2004). In the first section of the review, we examine the role of the prefrontal cortex (PFC), specifically the three implicated PFC-striatothalamic circuits, in regulating inhibitory control, and we suggest how dysregulation of these circuits could be involved in the persistence of drug-seeking behaviors. Following this, we provide a comprehensive and critical review of the most recent neuropsychological, neuroimaging and brain stimulation studies which have uncovered difficulties regulating inhibitory control and reduced decision-making skills, reflected by dysregulation of frontostriatal circuitries, across the various substance dependent populations. Many of the studies which we review have not yet been reviewed within a model of frontostriatal dysfunction. Therefore, we reviewed these studies with a specific focus of highlighting the interaction between inhibitory dysfunction, frontostriatal dysfunction and difficulties regulating drug-seeking behaviors. In the final section, we discuss how further insight into these deficits could contribute to the development of treatment models which target cognitive impairments, and frontostriatal dysfunction, in reducing problematic behaviors associated with prolonged drug use.

2. The involvement of prefrontal inhibitory control in drug-seeking behavior

Neuropsychological studies have demonstrated that substance dependent individuals exhibit impaired performance with inhibitory control tasks (for a review, see Verdejo-García et al., 2008). Subjects with chronic exposure to cocaine (Li et al., 2006; Tomasi et al., 2007a,b), methamphetamine (Baicy and London, 2007; Monterosso et al., 2005), nicotine (Neuhaus et al., 2006), alcohol (Noël et al., 2007a,b), cannabis (Tapert et al., 2007) and opiates (Verdejo-García et al., 2007; Yücel et al., 2007) demonstrate diminished executive and inhibitory skills. These findings, supported by neuroimaging studies, indicate that these inhibitory deficits involve a number of different neural systems within the prefrontal cortex. Therefore, in the following sections, we focus on the role of the PFC in regulating cognitive inhibitory control, and suggest how

dysregulation of the frontostriatal circuits may impact upon the maintenance of, and relapse to, substance dependence.

2.1. Cognitive inhibition

Cognitive control refers to a capacity to flexibly adapt one's thoughts and behavior towards a current goal (Blasi et al., 2006). A fundamental component of cognitive control is the capacity to suppress responses to prepotent yet inappropriate representations. When many representations are simultaneously active, cognitive inhibition refers to the ability to select those representations which the brain will fully process, and those to be disregarded; those selected for further processing act to control action and thought (Houghton and Tipper, 1996).

The PFC serves a specific function in cognitive control (Miller and Cohen, 2001) and is highly interconnected with a vast array of other neural systems. Concepts of the functional role of these afferent and efferent connections between the PFC and the interconnected cerebral regions are largely derived from the functions of the contributing structures (Fuster, 2001).

It is proposed that, collectively, the afferent connections from the basal ganglia and thalamus convey to the PFC information regarding internal representation of goals and the means to achieve them (Bradshaw, 2001; Fuster, 2001; Miller and Cohen, 2001), in so doing, inhibiting competing representations. The PFC is responsible for the active maintenance of the patterns of activity that represent goals, which originate from other regions of the brain (Burruss et al., 2000; Miller and Cohen, 2001). Put simply, the PFC is responsible for selecting and maintaining task-relevant information, a function which requires a great deal of flexibility and demands a degree of robustness from interference and distraction. Therefore, the PFC comprises the highest level of the cortical hierarchy, responsible for both the representation and the implementation of actions (Bradshaw, 2001; Fuster, 2001). Recent studies have suggested that the basal ganglia are largely responsible for the inhibition of conflicting behaviors, while facilitating the release of appropriate cortically mediated behaviors. The following section of the review explores the role of the basal ganglia, thus providing insight into the brain regions underlying deficits in inhibitory control, and furthermore, how dysregulation of these circuits may be involved in compulsive drug seeking.

2.2. Role of the basal ganglia

Traditional models of the basal ganglia have proposed that frontal-subcortical circuits (Tekin and Cummings, 2002) are formed principally from five different parallel, yet largely segregated circuits, which have been classified as the basal ganglia-thalamocortical circuits (Alexander and Crutcher, 1990; Bradshaw, 2001; Liddle et al., 2001). Refer to Kopell and Greenberg (2008) for an in-depth and broader review of recent research regarding the anatomy and physiology of the basal ganglia. Each of the subcortical frontal loops are modulated by the basal ganglia via three different pathways (Alexander and Crutcher, 1990; Aron et al., 2007; Aron and Poldrack, 2006; Nambu et al., 2002; Tekin and Cummings, 2002); the direct (excitatory), the indirect (inhibitory) and the hyperdirect pathway (Fig. 1).

The direct pathway involves inhibitory projections from the striatum to the internal segment of the globus pallidus and substantia nigra pars reticulata. This inhibitory projection in turn acts to dampen the inhibitory projection to the thalamus, which subsequently results in the disinhibition of the thalamus. Thus it is presumed that the direct pathway is responsible for the release of appropriate cortically mediated behavior. On the other hand, the indirect pathway engages an inhibitory projection from the striatum to the external segment of the globus pallidus. This reduces the inhibitory projection to the subthalamic nuclei, causing an increase in the excitation of the internal segment of the globus pallidus and substantia nigra pars reticulata. These projections lead into the inhibition of the thalamus and therefore, the indirect pathway is considered to inhibit (normally unwanted) cortically mediated behavior. The most recent addition to this model is the hyperdirect pathway which is characterized by frontal (inferior frontal cortex) inputs received by subthalamic nuclei; these projections convey excitatory output from motor-related cortical areas to the globus pallidus, which results in the inhibition of large areas of the thalamus. Importantly, the hyperdirect pathway bypasses the striatum, resulting in a shorter conduction time, when compared to the direct and indirect pathways (which project their effects through the striatum). Activation of subthalamic nuclei, through either the indirect or hyperdirect pathways, could act to block the direct pathway (which is involved in cortically mediated activated behaviors). Given the shorter conduction time, the hyperdirect pathway has been implicated in Stop Signal Response, more specifically, the ability to inhibit/intercept an already initiated behavior (Aron et al., 2003, 2003; Aron and Poldrack, 2006; Nambu et al., 2002).

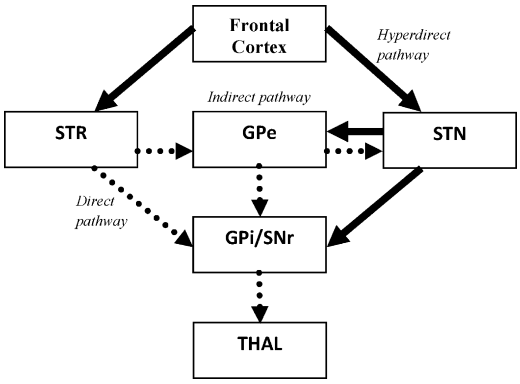

Fig. 1. A new model which proposes that the subcortical frontal loops are modulated by the basal ganglia via three pathways (direct, indirect, and hyperdirect). The *direct* pathway involves inhibitory projections from the striatum (STR) to the internal segment of the globus pallidus (GPi) and substantia nigra pars reticulata (SNr) and acts to disinhibit the thalamus (THAL). The *indirect* pathway describes the inhibitory projection from the STR to the external segment of the globus pallidus (GPe). The inhibitory projection to the subthalamic nuclei (STN) is reduced, thus increasing excitation of the GPi and SNr, which in turn leads to the inhibition of the thalamus (THAL). The *hyperdirect* pathway is characterized by direct frontal input received by the STN (bypassing the STR), which sends excitatory output to the GPe and GPi/SNr, resulting in the inhibition of the THAL. Filled arrows represent excitatory glutamatergic projections; dotted arrows represent inhibitory GABAergic projections. Figure adapted from Nambu et al. (2002) and Aron and Poldrack (2006).

Therefore, a balance between these three basal ganglia pathways is proposed to be involved in modulating corticostriatal and corticosubthamalic projections, which in turn, activate, and inhibit, the frontal circuitry responsible for movement, cognitive and limbic functions (Aron et al., 2007; Aron and Poldrack, 2006; Bradshaw, 2001; Nambu et al., 2002).

Another critical function of the PFC, with respect to cognitive control, is the ability to relay and integrate information about both internal and external inputs to the circuits (Miller and Cohen, 2001). It is presumed that, alongside the previously described closed frontal-subcortical loops, there are also open connections of the circuits; afferent and efferent connections integrate the information from these anatomically separated, but functionally related structures (Tekin and Cummings, 2002). Therefore, the circuits' ability to function in both a closed and open-loop mode allows the regulation of the processing of input and output from the various different structures (Bradshaw, 2001).

The basal ganglia-thalamocortical circuits, which include motor, oculomotor, prefrontal and limbic circuits (Kopell and Greenberg,

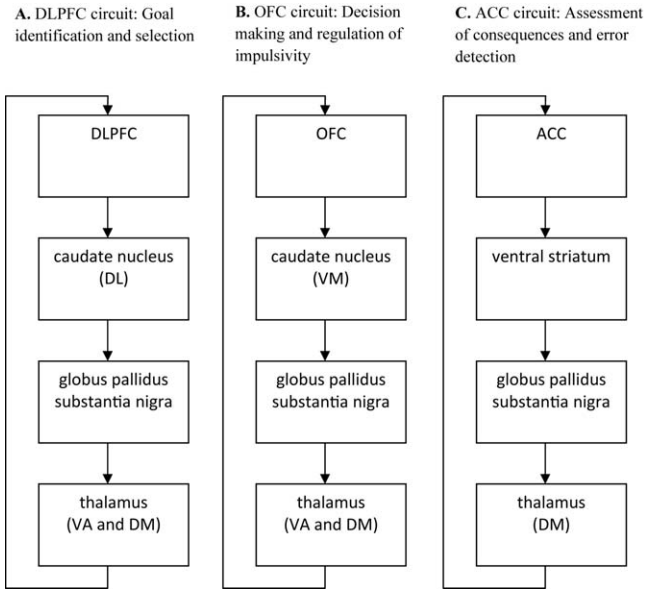

Fig. 2. The three frontostriatal cortical circuits proposed to be involved in executive functioning and inhibitory control. DL: dorsolateral; DM: dorsomedial; VA: ventroanterior; VM: ventromedial.

2008), constitute the main network responsible for both actions and behavior in humans. Even though each of these circuits involve the basal ganglia, thalamus and cortex, their projections differ significantly, and subsequently they are each unique in supporting different aspects of human behavior (Alexander and Crutcher, 1990; Kopell and Greenberg, 2008).

Within these basal ganglia-thalamocortical circuits, the sensorimotor system is comprised of the motor and oculomotor circuits, which involve voluntary skeletal, motor and eye movement control (Bradshaw, 2001; Tekin and Cummings, 2002). Dysfunction of the other three circuits relevant to executive function (i.e. the dorsolateral prefrontal, orbitofrontal and anterior cingulate circuits), is of primary interest to this review of inhibitory dysfunction and its proposed relationship with addiction and relapse.

2.3. Frontostriatal cortical network

Recent neuropsychological and neuroimaging studies have begun to uncover the cortical structures implicated in cognitive inhibitory control, and consistently reveal two cortical systems: one involving the dorsolateral prefrontal and orbital prefrontal circuitry, and the second, involving the anterior cingulate (Blasi et al., 2006; Chambers et al., 2009; Garavan et al., 2002; Ridderinkhof et al., 2004). These findings are consistent with recent brain imaging studies which indicate that substance dependence is also associated with impairments of these same three PFC-striatothalamic circuits (Verdejo-García et al., 2006b, 2008; Yücel and Lubman, 2007). When combined, these studies suggest that cognitive inhibitory dysfunction in the PFC of substance dependent individuals is inextricably linked to the compulsive desire to procure drugs despite the aversive risks involved (Fig. 2).

2.3.1. The dorsolateral prefrontal circuitry

The dorsolateral prefrontal circuitry originates from the dorsolateral prefrontal cortex (DLPFC) and neurons from this site project to the dorsolateral head of the caudate nucleus (Alvarez and Emory, 2006; Bradshaw, 2001), passing through the globus pallidus pars interna, substantia nigra pars reticulata (basal ganglia output) and thalamus. This circuitry is predominately involved in executive functioning, including planning, organization, set shifting and attention (Kopell and Greenberg, 2008; Tekin and Cummings, 2002). Findings from neuroimaging studies, administered during the performance of cognitive inhibitory tasks, suggest that the DLPFC, in playing an executive role, is involved in controlling response inhibition (Blasi et al., 2006; Garavan et al., 2002; Kelly et al., 2004). Furthermore, the DLPFC is pivotal in representing the context necessary to perform a task, and in updating and selecting information appropriate to the task (Bunge et al., 2001; Garavan et al., 2002). Anatomically, given the connections between the DLPFC and the OFC, amygdala and hippocampus, it is not surprising that the DLPFC is considered to be fundamental in its involvement in reward processing and guiding behaviors. Thus, the DLPFC may play a regulatory role in the integration and selection of both cognitive and goal-motivated behavior, which would include the ability to assimilate information regarding the potential outcomes, whether negative or positive, in selecting the most appropriate behavior. Dysfunction of this circuitry could logically be related to inappropriate behavioral choices, such as drug seeking regardless of the potential negative outcome.

2.3.2. The orbitofrontal circuitry

The orbitofrontal circuitry commences at the OFC and neurons from this site project to the ventromedial caudate nucleus (Alvarez and Emory, 2006; Bradshaw, 2001), also passing through the globus pallidus pars interna, substantia nigra pars reticulata (basal ganglia output), and thalamus. Dysfunction of the orbitofrontal circuitry is linked primarily to anomalous social behaviors, such as impulsivity and behavioral disinhibition (Kopell and Greenberg, 2008; Tekin and Cummings, 2002; Wallis, 2007). Horn et al. (2003) used functional magnetic resonance imaging (fMRI) to examine the neural correlates of response inhibition during a Go/No-Go task in assessing impulsivity. The most prominent neural activation occurred in the right lateral OFC. Their findings supported the role of the OFC in behavioral disinhibition and also its function in overriding prepotent responses (Horn et al., 2003). Szatkowska et al. (2007) examined the effects of focal lesions of the medial OFC on cognitive inhibition. They suggest that the OFC is involved in lower level processing in cognitive inhibition, such as response inhibition and switching of attention (Szatkowska et al., 2007). Studies looking at the relationship between the PFC and addictive behaviors emphasize the involvement of the OFC in the compulsive nature of addiction and relapse to substance use (London et al., 2000; Schoenbaum et al., 2006; Schoenbaum and Shaham, 2008; Volkow and Fowler, 2000). However, although OFC dysfunctions have been frequently found in substance dependent individuals, the exact role of the OFC is still under investigation (for a review, see Dom et al., 2005). Recent studies propose that the OFC is central to motivation, perceived outcomes in guiding decision-making and the subsequent implementation of behavior (Olausson et al., 2007; Tanabe et al., 2009). Therefore, the OFC is proposed to function in the more impulsive aspects of decision-making and behavioral inhibition (Everitt et al., 2007; Wallis, 2007). The OFC has connections with subcortical regions such as the basolateral amygdala and nucleus accumbens (NAc); integrating information from these regions allows the OFC to generate outcome expectancies. Dysfunction of this predictive mechanism could explain why individuals would seek continued drug use regardless of aversive outcomes, because they may not be able to adequately incorporate the previously learnt negative outcomes into their decision-making schema (Schoenbaum et al., 2006). Thus, the role of the OFC in decision-making has been strongly implicated in continued substance use, despite knowledge of harmful or risky consequences (Dom et al., 2005). In addition, the OFC has also been repeatedly implicated in the execution of compulsive repetitive behaviors (Volkow and Fowler, 2000). This could explain the continued consumption of substances after they are

no longer pleasurable, regardless of the possibility of a negative outcome.

2.3.3. The anterior cingulate circuitry

The anterior cingulate circuit begins in the ACC, and neurons from this site project to the ventral striatum (Tekin and Cummings, 2002), also passing through the globus pallidus pars interna, substantia nigra pars reticulata (basal ganglia output), and thalamus. Anterior cingulate functioning is associated with motivated behavior, response selection, error and conflict detection, and focusing attention (Kopell and Greenberg, 2008; Ridderinkhof et al., 2004; Tekin and Cummings, 2002). One particular study used event-related fMRI to measure hemodynamic response during a Go/No-Go cognitive task in healthy controls (Liddle et al., 2001). The ACC was activated during both the Go and No-Go trials, suggesting that it is involved in error, interference and conflict monitoring (Blasi et al., 2006), while the DLPFC and OFC are engaged in specific tasks related to response inhibition (No-Go) trials. This is supported by Chevrier et al. (2007) who conducted an fMRI study during the administration of the Stop Signal Task in examining the neural substrate of motor inhibition. They found that the dorsal ACC was activated during the process of error detection invoked by failed inhibition (Chevrier et al., 2007). The above findings have been supported by further fMRI studies into the Stroop Task by MacDonald et al. (2000) and Kerns et al. (2004). In addition, whereas the DLPFC has been described as being involved in the process of controlling response inhibition, the ACC has been proposed to play an additional role when more 'urgent' or unpredictable response inhibitions are required (Garavan et al., 2002). Neuropsychological and neuroimaging studies have indicated that the dorsal ACC is dysfunctional in substance dependent individuals (Forman et al., 2004; Yücel et al., 2007). These studies propose that the ACC is not only involved in error detection but also error-likelihood (Leland et al., 2008). Yücel and Lubman (2007) suggest that addictive behaviors may involve dysfunction in the dorsal ACC response. More specifically, such dysfunction may result in an impaired ability to appropriately assess negative consequence associated with continued drug use (Yücel and Lubman, 2007).

2.4. Integrated model of prefrontal cortex-striatothalamic dysfunction and substance dependence

On the basis of the evidence reviewed above, it appears that the association between prolonged drug-taking, neuroadaptions of the PFC, specifically the dysregulation of three PFC-striatothalamic circuits, may play a central role in compulsive drug seeking and relapse. The DLPFC functions in an executive manner, assimilating and integrating information regarding potential outcomes and translating this input into the selection of suitable cognitive and goal-motivated behavior. Dysfunction of this circuitry could modify an individuals' ability to appropriately assimilate information regarding the projected outcome and result in the selection of risky behavioral choices, such as consuming substances regardless of potential negative outcomes. Dysregulation of the OFC is associated with both faulty decision-making ability and the incapacity to inhibit compulsive, repetitive behaviors. Impaired decision-making skills would make abstinence from substance use remarkably difficult. A reduced ability to inhibit compulsive behaviors provides an explanation for continued 'repetitive' drug seeking, even after the drugs are no longer pleasurable. The ACC has been found to be associated with both error detection and error-likelihood. Dysfunctional ACC circuitry could disrupt the process of error evaluation and have a serious effect on the ability to detect the possibility of negative consequence. Therefore, individuals with substance dependence could have a lowered sensitivity to the risk and aversive consequences associated with sustained drug use.

The predictions of PFC-striatothalamic dysfunction in addiction are supported by recent studies which show that chronic drug use is associated with significant deficits in executive and cognitive inhibitory control functions. Both Verdejo-García et al. (2008) and Li and Sinha (2008) have provided extensive reviews describing the widely used cognitive tasks which assess these particular functions across different drug groups. Thus, neuropsychological studies have begun to explore the impact of chronic drug use on cognition, while recent neuroimaging and brain stimulation studies have provided support for a disrupted neural network of PFC function in substance dependent populations. Even though these studies have uncovered an association between dysfunction of the PFC and drug-seeking behaviors, it remains largely unknown whether these alterations are a direct consequence of exposure to drugs, or result from pre-existing vulnerabilities. The following section provides a review of a comprehensive selection of preliminary experimental neurocognitive, neuroimaging and brain stimulation studies which investigate the involvement of frontostriatal brain circuitries, and inhibitory deficits, in drug-seeking behavior. Descriptions of the neuroimaging methods and qualifications (Bandettini, 2009; Daglish et al., 2005; Lingford-Hughes, 2005), and brain stimulation techniques (Feil and Zangen, 2010), have been addressed in previous reviews.

In our review, the studies have been summarized according to four typical classes of substances: stimulants (e.g. cocaine), opiates (e.g. heroin), alcohol and nicotine. These drug groups were specifically chosen for review because the majority of the neuropsychological, neuroimaging and brain stimulation studies were conducted within these specific drug groups. Further review, although it was not within the scope of the current review, of additional drug groups, such as cannabis and methamphetamine, would be a welcomed addition to the addiction field. Many of the studies which we review have small sample sizes and are exploratory in nature; however, combined results across the various different substances provide substantial support for the role of dysregulated PFC-striatothalamic circuits, in better understanding core aspects of continued substance dependence.

3. Chronic substance use and the prefrontal cortex

3.1. Overview: chronic cocaine use and the prefrontal cortex

Cocaine, a short acting central nervous system psychostimulant, is one of the most highly reinforcing drugs available. Acute cocaine use induces both physiological and behavioral changes in both humans and animals. Repetitive cocaine use can generate profound addiction in humans and is characterized by compulsive drug seeking and high rates of relapse. Recent studies have highlighted that chronic cocaine abusers display impaired memory, attention and decision-making. In addition, individuals with a history of cocaine abuse exhibit dysfunctional inhibitory control of impulsive behaviors (Fillmore and Rush, 2002; Kaufman et al., 2003). These findings are consistent with recent data which have suggested that frontal brain regions are affected by both acute and chronic exposure to cocaine (Fillmore et al., 2002; Garavan and Hester, 2007; Garavan et al., 2008; Goldstein et al., 2004). These studies propose that deficits in decision-making amongst cocaine-dependent individuals could be due to dysfunction in the OFC (Bolla et al., 2003; Goldstein et al., 2001), while reduced inhibitory control due to faulty error-processing and diminished neural response to errors could be due to dysregulation of the DLPFC and the ACC (Childress et al., 1999; Goldstein et al., 2004; Hester and Garavan, 2004; Hester et al., 2007). Furthermore, these reduced inhibitory skills have been found to be associated with poorer treatment outcomes (Aharonovich et al., 2006; Brewer et al., 2008; Fox et al., 2007; Streeter et al., 2007).

3.1.1. Neuropsychological studies: cognitive inhibitory deficits and cocaine administration

3.1.1.1. Cognitive studies. To assess the presence of cognitive inhibitory deficits in cocaine-dependent individuals, Fillmore et al. (2002) conducted a randomized and double-blind study of the effects of acute administration of oral cocaine on inhibitory control of 8 cocaine users. Performance on the Stop Signal Task just prior to, and 1 h after, administration of 0 (placebo), 50, 100 and 150 mg of oral cocaine was measured. Acute cocaine administration was found to be associated with a reduced number of successfully inhibited responses, while there was no significant difference in execution response time. These findings provide an indication that acute cocaine administration can affect the ability to inhibit responses (Fillmore et al., 2002), but these findings must be interpreted cautiously, as there was a small sample size and absence of a comparison cocaine-naïve control group.

The same research group then explored neurocognitive functioning in cocaine dependence. They tested performance on the Stop Signal Task in 22 cocaine users and 22 matched controls (Fillmore and Rush, 2002). Compared to controls, the cocaine users presented with significantly decreased ability to inhibit their behavioral responses, while there was no significant difference in reaction time to execute the responses (Fillmore and Rush, 2002). Li et al. (2006) replicated this study in 18 abstinent cocaine-dependent patients and 41 matched controls (Li et al., 2006). Cocaine subjects presented with reduced ability on inhibitory tasks and diminished performance monitoring. Verdejo-García et al. (2007) further investigated the presence of cognitive deficits across cocaine and heroin polysubstance users. They tested 39 cocaine and 25 heroin polysubstance abusers (after a minimum abstinence of 15 days), and 30 healthy controls. Response inhibition was assessed by measuring performance on the Stroop, 5-Digit Test and Go/No-Go Tasks, while decision-making ability was tested with the Iowa Gambling Task. Although both cocaine and heroin polysubstance abusers had reduced performance on decision-making tasks compared to controls, cocaine, but not heroin abusers, performed worse on measures of response inhibition (Verdejo-García et al., 2007). Colzato et al. (2007) explored whether these findings extend to recreational cocaine users, without a diagnosis of abuse or dependence. They also investigated the relationship between cocaine consumption and the degree of detected inhibitory dysfunction. They administered the Stop Signal Task to 13 recreational cocaine users and 13 non-using controls. Consistent with the previous studies, recreational users presented with impaired inhibitory control, and with no significant difference in response execution reaction time. Furthermore, there was a positive correlation between inhibitory impairment and level of cocaine consumption (Colzato et al., 2007). These findings suggest relationship between cocaine consumption and the presence of compromised inhibitory ability. Furthermore, it is interesting to note that these deficits were exhibited across a range of different levels of cocaine administration, from individuals who are cocaine dependent, to individuals only recreationally exposed to cocaine. However, it is important to note that these exploratory cognitive studies consist of small samples; nevertheless, they highlight the need for further research into these deficits (Table 1).

3.1.2. Neuroimaging and brain stimulation studies: the relationship between frontostriatal dysfunction, craving and cocaine dependence

3.1.2.1. Structural MRI studies. Franklin et al. (2002) scanned 16 cocaine-dependent and 16 cocaine-naïve individuals using high resolution structural magnetic resonance imaging (MRI), and assessed gray and white matter tissue densities using voxel-based morphometry. When compared to cocaine-naïve participants, cocaine-dependent individuals displayed decreased gray matter concentration in the ventromedial orbitofrontal, ACC, anteroventral insular, and superior temporal cortices (Franklin et al., 2002). Matochik et al. (2003) also assessed the presence of structural abnormalities in cocaine users. They scanned a group of 14 cocaine users after 20 days of abstinence, compared to 11 healthy controls, using high resolution MRI, while assessing gray and white matter tissue densities using voxel-based morphometry. They found that cocaine users had significantly lower gray matter tissue density in the frontal cortex (bilateral ACC, medial OFC and lateral OFC) and middle/dorsal cingulate gyrus in the right hemisphere (Matochik et al., 2003). Matochik et al. (2003) suggested that the use of small volume correction, based on their priori regions of interest, facilitated a more robust detection of lower gray matter density within the OFC, ACC regions, which were not detected in the Franklin et al. (2002) study. In both studies, there were no group differences in white matter density. These preliminary studies suggest that there are structural differences in frontal cortical brain regions of cocaine users compared to controls.

Table 1
Cognitive studies: cocaine use and executive dysfunction.

Study	Participants	Measurements/Methodology	Significant findings
Fillmore et al. (2002)	8 Cocaine users	Stop Signal Task Performance on Stop Signal Task assessed before and after acute administration of 0, 50, 100 and 150 mg of oral cocaine.	Acute cocaine administration was associated with reduced inhibitory skill. There was no significant difference in execution response time.
Fillmore and Rush (2002)	22 Cocaine users 22 Matched controls	Stop Signal Task	Compared to controls, cocaine users presented with reduced inhibitory ability. No significant differences in execution response time.
Li et al. (2006)	18 Abstinent cocaine-dependent individuals 41 Matched controls	Stop Signal Task	Compared with controls, cocaine users presented with reduced inhibitory skills and diminished performance monitoring.
Verdejo-García et al. (2007)	39 Cocaine-dependent individuals 25 Heroin polysubstance users (both drug groups recruited after minimum abstinence of 15 days) 30 Healthy controls	Stroop 5-Digit Test Go/No-Go Task Iowa Gambling Task	Both drug groups showed reduced performance on decision-making tasks when compared to controls. In addition, cocaine, but not heroin users, performed worse on measures of response inhibition.
Colzato et al. (2007)	13 Recreational cocaine users 13 Non-using controls	Stop Signal Task	Recreational users presented with impaired inhibitory control and no significant difference in response execution reaction time.

Abbreviations—mg: milligrams.

3.1.2.2. Functional MRI studies. FMRI was used to investigate the brain circuitry underlying cocaine-induced euphoria and craving in cocaine-dependent subjects. Breiter et al. (1997) conducted a double-blind fMRI study in which participants were administered either cocaine (0.6 mg/kg) or saline infusions, and the entire brain was imaged for 5 min prior to, and 13 min after the infusion, with participants required to complete scales regarding levels of 'rush', 'high', 'low' and 'craving'. Overall, interpretable fMRI results from 10 cocaine-dependent participants suggested that cocaine brain regions which correlated with 'rush' ratings included the ventral tegmentum, pons, basal forebrain, caudate, cingulate, and most regions of lateral prefrontal cortex. Brain regions which correlated with 'craving' ratings included the NAc/subcallosal cortex, right parahippocampal gyrus, some regions of the lateral prefrontal cortex and amygdala (Breiter et al., 1997). Risinger et al. (2005) set up a more 'naturalistic' mode of cocaine self-administration. Eight cocaine-dependent individuals were allowed to choose when and how often intravenous cocaine administration occurred throughout the session. Instead of passive delivery, the researchers tried to simulate real-life situations. Unknown to the participants, throughout the testing session, cocaine administration was monitored and limited. The participants were scanned using blood-oxygen-level-dependent (BOLD)-fMRI and were required to give behavioral ratings of their 'high' and 'craving' levels throughout the study. The drug-induced 'high' correlated negatively with activity in limbic, paralimbic and mesocortical regions, including NAc, OFC and ACC. In contrast, 'craving' correlated positively with activity in these regions (Risinger et al., 2005). An important consideration, regarding these high vs. craving studies, is that the measurement is based on the premise that these constructs are independent. It is highly plausible that these states are actually entangled and it is difficult for the participant to report whether they are feeling a rush, high or craving state. However, findings from these studies highlight a difference in brain activation between the experience of rush, high and craving. Furthermore, these studies indicate an association between frontal regions and the behavioral experience of craving.

The following two studies used fMRI scans to measure BOLD responses to acute cocaine administration in the brain of cocaine users. Kufahl et al. (2005) conducted a study which required each participant to undergo two fMRI scans; during one, a single dose of cocaine (20 mg/70 kg) was intravenously administered, during the other scan, saline was administered. Results from 10 participants' scans found that acute cocaine administration activated mesolimbic dopaminergic regions, including the ventral tegmental area, NAc, subcallosal cortex, basal forebrain/ventral pallidum and amygdala. In addition, they found that cocaine also activated orbitofrontal and anterior prefrontal cortices (Kufahl et al., 2005). Garavan et al. (2008) also investigated the effects of acute cocaine administration in cocaine-dependent individuals; however, they expanded the previous study by also exploring the effects of acute cocaine on cognitive inhibitory control. Thirteen active cocaine users were injected with cocaine or a saline solution, and fMRI scanning was conducted while participants performed a Go/No-Go Task. The study did not include a drug naïve control group. Interestingly though, acute cocaine administration improved task performance in cocaine users, and this was coupled with increased activation of the right DLPFC and the inferior frontal cortex. The authors postulated that the brain regions implicated in inhibitory control, which have been previously reported to be hypoactive in cocaine users, were 'normalized' with acute administration of cocaine (Garavan et al., 2008).

When combined, the above studies provide initial evidence for mesolimbic and mesocortical activation upon acute exposure to cocaine in cocaine-dependent individuals, and furthermore, an improvement in inhibitory ability. However, these findings are contrary to Fillmore et al. (2002) who found that acute cocaine administration is associated with reduced inhibitory ability. These mixed findings could be attributed to different study designs and small exploratory samples. Further elucidation of the acute effects of cocaine on inhibitory control is required.

FMRI has also been used to investigate the relationship between inhibitory deficits, and altered frontal brain activity, in active cocaine users. Kaufman et al. (2003) conducted an fMRI study during the administration of the Go–No-Go task in a sample of 13 active cocaine users vs. 14 healthy controls. They found that cortical areas, such as the ACC, were less responsive in active cocaine users; at the same time, cocaine users displayed significant cingulate, presupplementary motor and insula hypoactivity throughout the cognitive task (Kaufman et al., 2003). In support of these findings, Hester and Garavan (2004) used fMRI to assess brain activation of 15 active cocaine users compared to 15 controls in a modified Go/No-Go Task with increased working memory demands. They found that cocaine users demonstrated poorer performance in inhibitory skills, and furthermore, these deficits were associated with reduced ACC and right PFC function (Hester and Garavan, 2004). Overall, these studies highlight that cocaine users have increased difficulty inhibiting prepotent urges, and provide support for the involvement of frontal brain regions, such as the PFC and ACC, in understanding these cognitive difficulties.

Combined, these preliminary fMRI studies provide intriguing insight into altered PFC activity related to craving, acute cocaine administration and cocaine dependence. These studies encourage further research into these deficits and related altered neural activity. A concern with BOLD-fMRI studies in cocaine-dependent individuals however, is the potentially confounding cerebrovascular and psychoactive effects induced by cocaine administration on these BOLD signals (Kufahl et al., 2005).

3.1.2.3. PET studies. Bolla et al. (2003) conducted a preliminary positron emission tomography (PET) with $H_2\ ^{15}O$ study to assess cerebral blood flow in the OFC in cocaine abusers during a decision-making task. Thirteen cocaine abusers (after 25 days of abstinence) and 13 controls were administered PET while performing the Iowa Gambling Task (decision-making) and a control task (no decision-making). Cocaine abusers demonstrated increased activation of the right OFC and reduced activation in the right DLPFC and left medial PFC compared to controls. Improved decision-making ability was associated with increased activation of the right OFC in both groups. Additionally, cocaine consumed prior to abstinence was negatively correlated with activity of the left OFC (Bolla et al., 2003). In a second study, Bolla et al. (2004) used $H_2\ ^{15}O$ PET during performance of a modified Stroop Task to assess activity of the ACC and lateral PFC in 13 abstinent cocaine abusers compared to 13 controls. Cocaine abusers showed less activity in the left ACC and right lateral PFC, and greater activation in the right ACC. Cocaine consumption was negatively correlated with activity in the rostral ACC and right lateral PFC (Bolla et al., 2004). When combined, these two studies suggest the presence of prefrontal cortical abnormalities in abstinent cocaine abusers; the OFC during decision-making tasks (Bolla et al., 2003), and the ACC and lateral PFC in tasks of attention and cognitive control (Bolla et al., 2004). Furthermore, the amount of cocaine consumed prior to abstinence was associated with changes in activity levels in these frontal regions.

3.1.2.4. TMS studies. Recent advances in technology have allowed researchers to utilize new brain stimulation techniques in assessing the role of the PFC in cocaine addiction. These studies are highly novel and quite exploratory in nature. Camprodon et al. (2007) investigated whether a single session of high frequency repetitive Transcranial Magnetic Stimulation (TMS) to the DLPFC could

Table 2
Cocaine, cognitive inhibition and frontostriatal dysfunction: neuroimaging and brain stimulation studies.

Study	Participants	Measurements/methodology	Significant findings and frontal brain activations
Structural MRI studies			
Franklin et al. (2002)	16 Cocaine-dependent individuals	High resolution structural MRI	Cocaine-dependent individuals displayed decreased grey matter concentration in the ventromedial orbitofrontal, ACC, anteroventral insular, and superior temporal cortices.
	16 Cocaine-naïve controls	Assessed grey and white tissue densities using VBM	
Matochik et al. (2003)	14 Cocaine users after 20 days of abstinence	High resolution structural MRI	Cocaine users had significantly lower grey matter tissue density in the frontal cortex (bilateral ACC, medial OFC and lateral OFC) and middle/dorsal cingulated gyrus in the right hemisphere.
	11 Healthy controls	Assessed grey and white tissue densities using VBM	
Functional MRI studies			
Breiter et al. (1997)	17 Cocaine-dependent individuals (10 cocaine-dependent interpretable results used)	BOLD-fMRI	Rush correlated with activation of ventral tegmentum, pons, basal forebrain, caudate, cingulate, and most regions of lateral PFC.
		Scales regarding 'rush', 'high', 'low' and 'craving' levels.	Craving was associated with activation of nucleus accumbens/subcallosal cortex, right parahippocampal gyrus, regions of the lateral prefrontal cortex and amydala.
		Participants were administered either cocaine (0.6 mg/kg) or saline infusions	
Kaufman et al. (2003)	13 Active cocaine users	BOLD-fMRI	Compared to controls. Active cocaine users presented with reduced activity in cortical areas, such as the ACC, and increased activity in cingulate, presupplementary motor and insula during the cognitive task.
	14 Healthy controls	Go/No-Go Task	
Hester and Garavan (2004)	15 Active cocaine users	BOLD-fMRI	Cocaine users performed more poorly on the inhibitory skills tasks and these deficits were associated with reduced ACC and right PFC activity.
	15 Healthy controls	Modified Go/No-Go Task (increased working memory demands)	
Risinger et al. (2005)	8 Cocaine-dependent individuals (after 8–48 h of abstinence from cocaine).	BOLD-fMRI	High correlated negatively with activity in the limbic, paralimbic and mesocortical regions, including NAc, OFC and ACC.
		Scales regarding 'high' and 'craving' levels.	Craving correlated positively with activity within these regions.
		Participants self-administered cocaine infusions (20 mg/70 kg)	
Kufahl et al. (2005)	15 Cocaine-dependent individuals (10 cocaine-dependent interpretable results used)	BOLD-fMRI	Acute cocaine administration activated orbitofrontal and anterior prefrontal cortices, and also, mesolimbic dopaminergic regions, including the VTA, NAc, subcallosal cortex, basal forebrain/ventral pallidum and amygdala.
		Participants were administered two fMRI scans. One during cocaine infusion (20 mg/70 kg) and one during a saline infusion.	
Garavan et al. (2008)	13 Cocaine-dependent individuals	BOLD-fMRI Go/No-Go Task	Acute cocaine administration improved task performance and this was associated with an increase in activation of the right DLPFC and the inferior frontal cortex.
PET studies			
Bolla et al. (2003)	13 Cocaine abusers (after 25 days of abstinence)	$H_2\ ^{15}O$ PET	Compared with controls, cocaine abusers had increased activation of the right OFC and reduced activation in the right DLPFC and left medial PFC. In both groups improved decision-making ability was associated with increased activation of the OFC. A history of increased cocaine consumption was negatively correlated with activity in the left OFC.
	13 Controls	Iowa Gambling Task Control Task	

Table 2 (*Continued*)

Study	Participants	Measurements/methodology	Significant findings and frontal brain activations
Bolla et al. (2004)	13 Cocaine abusers (after 23 days of abstinence) 13 Controls	H_2 ^{15}O PET Modified Stroop Task	Compared to controls, cocaine abusers had reduced activity in the left ACC and the right lateral PFC, and greater activation in the right ACC. A history of greater cocaine use was negatively associated with activity in the rostral ACC and right lateral PFC.
Brain stimulation studies			
Camprodon et al. (2007)	6 Cocaine-dependent males	Two sessions of High frequency rTMS (10 Hz), once over the right and once over the left DLPFC VAS Craving Scale	rTMS to the right DLPFC significantly reduced cocaine craving.
Politi et al. (2008)	36 Cocaine-dependent individuals	Ten sessions of High frequency rTMS (15 Hz) to the left DLPFC Craving Scale	Throughout the rTMS sessions there were gradual reductions in levels of cocaine craving.

Abbreviations—MRI: magnetic resonance imaging; VBM: voxel-based morphometry; ACC: anterior cingulate cortex; OFC: orbitofrontal cortex; BOLD: blood-oxygen-level-dependent; fMRI: functional magnetic resonance imaging; NAc: nucleus accumbens; VTA: ventral tegmental area; mg: milligram; kg: kilogram; DLPFC: dorsolateral prefrontal cortex; PFC: prefrontal cortex; H_2 ^{15}O: radioactive water; PET: positron emission tomography; rTMS: repetitive transcranial magnetic stimulation; VAS: Visual Analogue Scale; Hz: hertz.

reduce craving in a sample of 6 cocaine-dependent males. They administered high frequency (10 Hz) repetitive TMS to both the right and the left DLPFC. They found that repetitive stimulation to the right DLPFC significantly reduced cocaine craving (Camprodon et al., 2007). These findings were supported by a recent study by Politi et al. (2008) who administered daily sessions (ten sessions in total) of high frequency (15 Hz) repetitive TMS to the left DLPFC in 36 cocaine-dependent individuals post-detoxification. They noted gradual, yet significant reductions in cocaine craving over the course of sessions (Politi et al., 2008). The frequency, intensity and inter-train intervals between these studies varied slightly (see Feil and Zangen (2010) for a more detailed description of the TMS parameters), which could account for the different outcomes regarding laterality of effective repetitive TMS (Bestmann et al., 2008; Vanderhasselt et al., 2007; Ziemann, 2010). Regardless, both studies suggest that transient increase in DLPFC excitability plays a significant role in reducing cocaine craving (Table 2).

3.1.3. *Summary: chronic cocaine use and the PFC*

In summary, neuropsychological studies found an association between acute, recreational and long-term cocaine use, and impaired behavioral response inhibition, performance monitoring and decision-making abilities. Results regarding the effects of acute cocaine administration on inhibitory ability in cocaine-dependent individuals are mixed. In one study, acute cocaine reduced inhibitory ability, while in another study, acute cocaine was associated with increased inhibitory control, and these improvements were reflected by increased activity in the frontal regions. Though there are discrepancies in these findings, it is important to note that these studies consist of small sample sizes and varied experimental designs. Therefore, the acute effect of cocaine administration on cognitive inhibition requires further examination. FMRI studies found that acute cocaine administration and subjective ratings of 'craving' were associated with increased activity in mesocorticolimbic regions. While, structural and functional neuroimaging studies provide initial evidence for a relationship between cognitive inhibitory impairments and the presence of frontostriatal dysfunction in cocaine-dependent individuals. Neurocognitive studies found a correlation between levels of cocaine consumption and inhibitory impairment, while neuroimaging studies revealed a relationship between severity of lifetime cocaine consumption and altered activity in frontal regions. Finally, TMS studies found that stimulation of the DLPFC of cocaine-dependent individuals transiently reduced cocaine craving. Overall, these studies provide initial support for the relationship between the presence of frontostriatal dysfunction and impaired inhibitory skills in cocaine dependence.

3.2. *Overview: chronic opiate use and the prefrontal cortex*

Heroin is the most abused opiate amongst adult populations and is associated with substantial morbidity and mortality. However, to date, there is only limited empirical literature examining the neurocognitive effects of 'pure' chronic opioid use (Gruber et al., 2007). As many studies have included poly-drug abusers, it remains difficult to isolate the specific neurocognitive effects of opiates from those of other drugs (Fishbein et al., 2007; Gruber et al., 2007). Bearing this limitation in mind, a growing literature suggests that chronic opiate administration is associated with executive dyscontrol (Ersche and Sahakian, 2007) including the ability to inhibit inappropriate behavioral responses (Gruber et al., 2007) and risky decision-making (Brand et al., 2008) directed by frontal regions (Ersche and Sahakian, 2007; Ersche et al., 2005, 2006; Fishbein et al., 2007; Lee et al., 2005; Ornstein et al., 2000; Pau et al., 2002; Verdejo-García et al., 2007), even after abstinence from opiate use (Ersche and Sahakian, 2007; Pau et al., 2002; Rapeli et al., 2006). A

recent study conducted by Passetti et al. (2008) found that performance on tests of decision-making was able to predict abstinence from opiate use at 3 months (Passetti et al., 2008). Although there are only a limited number of neuroimaging studies investigating chronic opiate use, the emerging studies have suggested irregular brain activity in both frontal (Botelho et al., 2006; Lyoo et al., 2006; Xiao et al., 2006) and temporal (Lyoo et al., 2006) brain regions in opiate-dependent populations.

3.2.1. Neuropsychological studies: cognitive inhibitory deficits and opiate dependence

3.2.1.1. Cognitive studies. There is limited research investigating the neurocognitive consequences of heroin, with most studies including poly-drug users (Verdejo-García et al., 2007). Recent studies however, have begun to uncover a relationship between the presence of impaired executive abilities, deficits in decision-making skills, and opiate dependence. Ornstein et al. (2000) used a battery of neurocognitive tasks to characterize patterns of cognitive impairments across 22 heroin and 23 amphetamine dependent individuals and 22 controls as a comparison group for each of the tasks. Tasks included: Verbal Fluency Task, Pattern and Spatial Recognition Task, Attentional Set-shifting Task, Spatial Working Memory Task, One Touch Tower of London Task and the Visuospatial Strategy Task. Chronic heroin and amphetamine use was associated with distinct patterns of cognitive impairments (Ornstein et al., 2000). Ersche et al. (2006) compared cognitive performance of 42 current opiate users, 25 current amphetamine users and a group of 26 former users of either or both of these drugs, as well as 27 controls. To assess cognitive function across these different groups, participants completed the Tower of London planning task and the 3D-IDED Attentional Set-shifting Task to assess executive function, and the Paired Associates Learning and Delayed Pattern Recognition Memory tasks to test visual memory function. As expected, all drug groups demonstrated significant impairment in executive function and visual memory tasks. The amphetamine dependent groups had greater impairment on cognitive tasks than the opiate-dependent group. Interestingly, there was no significant difference in performance between current drug dependent groups and former users, suggesting that these impairments may not reflect effects of current drug use and can persist beyond abstinence (Ersche et al., 2006). A limitation to this study however, is that since 50% of the former drug users reported previous dependence on both opiates and amphetamines, it is possible that this poly-drug use could have an additive effect, exacerbating the impairments; therefore this study does not necessarily reflect the association between opiate use (in isolation) and cognitive impairments.

Fishbein et al. (2007) administered a battery of neurocognitive tests designed to measure frontal cortically modulated cognitive function to 100 heroin-dependent individuals, 102 alcohol-dependent patients, 60 heroin and alcohol abusers and 160 controls. The CANTAB cognitive tests included: Cambridge Decision-Making Task, Stroop colour/word interference and the Stop Change Tasks. All drug groups presented with cognitive deficits compared to controls. A primary finding of the study however, was performance on the Cambridge Decision-Making Task. Heroin-dependent individuals selected significantly more risky options and demonstrated reduced decision-making skills, while exhibiting the lengthiest deliberation time. Additionally, both the heroin and alcohol-dependent groups showed reduced cognitive flexibility and conflict monitoring on the Stroop Interference Task compared to controls (Fishbein et al., 2007). Brand et al. (2008) further investigated executive ability and risk-taking behavior in patients with opiate dependence. They examined 18 opiate-dependent individuals and 18 healthy controls on the Game of Dice Task, which is both a gambling and a decision-making task. Study participants were administered a comprehensive neurocognitive psychological test battery. Supporting the findings of Fishbein et al. (2007), opiate-dependent individuals chose significantly more risky alternatives in the decision-making task than controls. Additionally, deficits in decision-making ability under risky conditions were associated with performance on tests of executive function and feedback processing (Brand et al., 2008). Taken together, these preliminary neurocognitive studies suggest that opiate-dependent individuals present with deficits in executive cognitive skills and impaired decision-making abilities (Table 3).

3.2.2. Neuroimaging studies: the relationship between frontostriatal dysfunction, craving and opiate dependence

3.2.2.1. Structural MRI studies. Structural MRI and voxel-based morphometry analyses have been used to explore the presence of structural brain changes in opiate-dependent subjects. Lyoo et al. (2006) compared the gray matter density of 63 opiate-dependent subjects and 46 matched controls. Compared to controls, opiate-dependent individuals demonstrated reduced gray matter density in the bilateral PFC, bilateral insula, bilateral superior temporal cortex, left fusiform cortex and right uncus. The authors proposed that these structural deficits may be associated with neuropsychological deficits in opiate-dependent subjects (Lyoo et al., 2006). However, many of the opiate-dependent subjects were polysubstance users. To address this limitation, the authors conducted posthoc analyses of the participants without polysubstance use and the results followed a similar trend. Comorbidity of heroin use with other drugs is an issue which affects many of the studies into opiate dependence. It is extremely difficult to measure a 'pure' opiate-dependent group. Liu et al. (2009) also used MRI and voxel-based morphometry to explore gray matter volume difference in 15 heroin-dependent individuals compared with 15 controls. Heroin-dependent individuals showed reductions of gray matter volume in the right PFC, left supplementary motor cortex, and bilateral cingulate cortex. It is possible that further and more extensive anatomical reductions may exist in opiate-dependent population. A limitation to this study is that all of the heroin-dependent subjects were healthy and volunteered to participate in heroin abstinence. Furthermore, heroin dependents displaying withdrawal symptoms were excluded from the study. It would be worthwhile to conduct this study in a larger sample and a population more representative of the full heroin-dependent population. Regardless, taken together, these structural brain imaging studies provide initial evidence of reduced gray matter density (Lyoo et al., 2006) and gray matter volume (Liu et al., 2009) in the frontal regions of opiate-dependent individuals. These studies highlight the importance of future studies assessing the associations between gray matter structural changes and neuropsychological functioning.

3.2.2.2. Functional MRI studies. Forman et al. (2004) used rapid event-related fMRI to compare performance on a Go/No-Go task in 13 opiate-dependent individuals involved in a methadone maintenance treatment and 26 matched healthy controls, and found that opiate-dependent individuals exhibited poorer signal detection. Additionally, these participants also showed attenuated rostral ACC activity associated with these tasks. A potential limitation to this study is the exclusion of nicotine smokers from the control, but not the opiate-dependent group, which may have had an effect on inhibitory performance. Nevertheless, results from this study suggest the presence of impaired control, associated with attenuated ACC activity, in opiate-dependent individuals (Forman et al., 2004). Lee et al. (2005) recently investigated further cognitive regulation and impulsivity in heroin users prior to detoxification. During an fMRI scan, 11 heroin-dependent patients (who were not concurrently abusing other drugs) and 10 healthy con-

Table 3
Cognitive studies: opiate use and executive dysfunction.

Study	Participants	Measurements/methodology	Significant findings
Ornstein et al. (2000)	22 Heroin-dependent individuals	Verbal Fluency Task	Chronic heroin and amphetamine use was associated with distinct patterns of cognitive impairment. Heroin abusers performed more poorly in learning the intra-dimensional shift component of the set-shifting task and showed difficulties in strategic performance. Amphetamine abusers were impaired in their performance on the extra-dimensional shift task. Both groups were impaired in tasks of Spatial Working Memory and in Pattern Recognition Tasks.
	23 Amphetamine dependent individuals 22 Controls (per task)	Pattern and Spatial Recognition Task Attentional Set-shifting Task Spatial Working Memory Task One Touch Tower of London Task Visuospatial Strategy Task	
Ersche et al. (2006)	42 Current opiate users	Tower of London Planning Task	All drug groups were impaired in executive function and visual memory tasks. Amphetamine displayed greater impairment than the Opiate group. No significant difference between current drug dependent groups and previous users was found.
	25 Current amphetamine users 26 Former users of either opiate or amphetamine 27 Controls	Paired Associates Learning Delayed Pattern Recognition Memory Task	
Fishbein et al. (2007)	100 Heroin-dependent individuals	Cambridge decision-making task	All drugs groups presented with cognitive deficits. On the Cambridge decision-making Task, heroin-dependent individuals selected more risky options, demonstrated reduced decision-making skills, and extended deliberation time. Compared to controls, both the heroin and alcohol groups showed reduced cognitive flexibility and conflict monitoring.
	102 Alcohol-dependent individuals 60 Heroin and alcohol abusers 160 Controls	Stroop colour/word interference Stop change tasks	
Brand et al. (2008)	18 Opiate-dependent individuals 18 Healthy controls	Game of Dice (decision-making task) Neuropsychological test battery	Opiate-dependent individuals chose significantly more risky alternatives than controls. These deficits in decision-making skills were associated with executive functioning and feedback processing.

trols were administered the Arrow Task, an experimental measure specifically designed to assess cognitive regulation and impulsivity. At the behavioral level, the heroin dependents were found to be significantly more impulsive and committed more task errors. These differences between groups were reflected at the neural level, whereby compared to controls, heroin-dependent individuals exhibited significant neural activation of the left DLPFC, the bilateral inferior parietal and the left middle temporal regions, while activity of the ACC was attenuated (Lee et al., 2005).

In response to these studies, Yücel et al. (2007) explored the biochemical and physiological properties of the dorsal ACC in opiate dependence. They assessed 24 opiate-dependent individuals (stabilized on methadone/buprenorphine) and 24 healthy controls in a combined spectroscopic and fMRI study. Participants were required to complete the Multi-Source Interference Task: a cognitive task to assess behavioral and inhibitory regulation and which has been previously associated with ACC functioning. Opiate-dependent individuals exhibited reduced concentrations of N-acetylaspartylglutamate and glutamate/glutamine (one of the primary neurotransmitters in the PFC) within the dorsal ACC, and demonstrated increased activation of fronto-parietal and cerebellar regions with a similar level of behavioral regulation as controls. Additionally, opiate-dependent individuals did not show the same association between dorsal ACC activity and performance on the behavioral tasks as controls (Yücel et al., 2007). These studies suggest that opiate-dependent individuals have compromised activity of the dorsal ACC, and may need to engage other brains regions to compensate for dorsal ACC dysfunction.

Fu et al. (2008) further investigated the role of impulsivity and response inhibition in heroin addiction; this study however, was conducted within a group of abstinent heroin-dependent individuals. Thirty abstinent heroin-dependent individuals and 18 healthy controls were administered Go/No-Go association tasks during an fMRI scan. In healthy controls, activation induced by response inhibition occurred in the bilateral medial prefrontal gyrus and ACC, left middle frontal gyrus, insula, bilateral inferior frontal gyrus and limbic system. In the heroin-dependent individuals however, significant neural response to the response inhibitions was only found in the bilateral superior frontal gyrus and the left middle frontal gyrus (Fu et al., 2008). It is possible that this lack of recorded activity in the medial PFC and ACC in the heroin-dependent individuals supports the previous reports of attenuated activity of the ACC in heroin-dependent individuals (Forman et al., 2004; Lee et al., 2005; Liu et al., 2009; Yücel et al., 2007).

3.2.2.3. PET studies. Ersche et al. (2005) investigated risky decision-making using the Cambridge Risk Task during H_2 ^{15}O PET scans across four population groups: 15 current opiate and 15 amphetamine dependent individuals, 15 former drug dependent individuals and 15 controls (Ersche et al., 2005). However, unlike the findings of Fishbein et al. (2007) and Brand et al. (2008) they found no difference in performance on the Cambridge Risk Task (a decision-making task) between the groups. A possibly limiting factor was the small sample size. Interestingly though, there were significant differences in regional cerebral blood flow of the OFC and right DLPFC between drug dependent groups and controls, brain regions which have been implicated in impulsive behavior and executive functioning. Participants with current or former drug dependence activated the left OFC during the risky decision-making task, while controls presented decreased activation in this area during the task. Additionally, controls exhibited increased activation of the right DLPFC compared to the drug dependent groups. It is possible that increased OFC activity reflects increased response suppression, which allows opiate-dependent individuals to perform at the same level as the controls on the risky decision-making task. Additionally, similar to the Bolla et al. (2003) study in cocaine-dependent individuals, the presence of functional frontal abnormalities persisted in former drug dependent individuals after many years of abstinence.

Botelho et al. (2006) used single-photon-emission tomography (SPET) with 740 MBq of ^{99m}Tc-hexametazine (HMPAO) and computational brain mapping methods to assess patterns of vascular brain alterations in 17 heroin-dependent individuals before and after 10 weeks of detoxification. When compared with controls (from the software database), subjects with heroin dependence displayed decreased brain perfusion in the frontal cortex, mainly the OFC, as well as the occipital, temporal regions, basal ganglia and cerebellum. Patients did not show improvements in the scan 10 weeks later (Botelho et al., 2006). Similar to Forman et al. (2004), many of the patients in this sample were also diagnosed with nicotine dependence. This could have exacerbated the reduction in brain perfusion in the frontal cortex, and the results may not reflect the association between 'pure' heroin dependence and decreased global perfusions in the frontal cortex. Overall though, these studies provide initial evidence that reduction in regional perfusion of the PFC may reflect ongoing neurocognitive deficits, such as inhibitory control and decision-making, in heroin-dependent individuals (Table 4).

3.2.3. Summary: chronic opiate use and the PFC

Neurocognitive studies revealed an association between the presence of impaired decision-making skills, executive functioning, and opiate dependence. A core finding of the studies was that opiate-dependent individuals chose significantly more risky options and showed reduced decision-making skills. Structural and functional neuroimaging studies found that poorer decision-making ability, error response, signal detection, and behavioral control, may be explained by attenuated ACC activity and altered activity in the OFC and DLPFC. Additionally, these studies proposed that opiate-dependent individuals may enlist compensatory involvement of other brains regions due to ACC dysfunction. Finally, these decision-making and frontal region deficits were found to persist after years of abstinence in opiate-dependent individuals. Overall, findings of these preliminary studies promote the need for further research into decision-making skills, and the role of the ACC and frontal regions, in better understanding core features underlying opiate dependence.

3.3. Overview: chronic alcohol use and the PFC

Ethanol, a psychoactive drug with both relaxant and euphoric effects, is a major component of all alcoholic beverages. During the last decade, research has increasingly focused on better understanding the neurobiological basis of alcohol craving and the brain regions implicated in this process. Acute intoxication (Fillmore et al., 2005) and chronic alcohol consumption (Fadardi and Cox, 2006) have been associated with impairments of executive functions, such as behavioral control, disinhibition and cognitive ability (Vogel-Sprott et al., 2001; Weafer and Fillmore, 2008). Recent MRI, PET, SPECT and brain stimulation studies have found alterations in activity within the PFC (Sullivan et al., 2003), OFC (Volkow et al., 2007) and ACC (Ridderinkhof et al., 2004), suggesting that the frontal lobes may be vulnerable to alcohol-induced neuroadaptations (Goldstein et al., 2004; Moselhy et al., 2001; Oscar-Berman and Marinković, 2007; Sullivan and Pfefferbaum, 2005). These studies provide evidence for dysregulated frontostriatal activity and compromised cognitive abilities in alcohol-dependent individuals, and furthermore, have suggested that these impairments are associated with the development of alcohol dependence in heavy drinkers (Rubio et al., 2008), treatment outcomes (Bates et al., 2002; Noel et al., 2002) and relapse (Bowden-Jones et al., 2005).

Table 4
Opiates, cognitive inhibition and frontostriatal dysfunction: neuroimaging and brain stimulation studies.

Study	Participants	Measurements/methodology	Significant findings and frontal brain activations
Structural MRI studies			
Lyoo et al. (2006)	63 Opiate-dependent individuals	High resolution structural MRI	Compared to controls, opiate-dependent individuals presented with reduced grey matter density in the bilateral PFC, bilateral insula, bilateral superior temporal cortex, left fusiform cortex and right uncus.
	46 Matched controls	Assessed grey and white tissue densities using VBM	
Liu et al. (2009)	15 Heroin-dependent individuals	High resolution structural MRI	Heroin-dependent individuals presented with reduced grey matter volume in the right PFC, left supplementary motor cortex, and bilateral cingulate cortex.
	15 Controls	Assessed grey and white tissue densities using VBM	
Functional MRI studies			
Forman et al. (2004)	13 Opiate-dependent individuals in a methadone maintenance treatment	BOLD-fMRI	Opiate-dependent individuals demonstrated both reduced signal detection and attenuated rostral ACC activity associated with these tasks.
	26 Healthy controls	Go/No-Go Task	
Lee et al. (2005)	11 Heroin-dependent individuals	BOLD-fMRI	Compared to controls, heroin-dependent individuals were more impulsive and committed more task errors. Heroin-dependent individuals also presented with increased activity in the left DLPFC, the bilateral inferior parietal and the left middle temporal regions, while there was reduced activity in the ACC.
	10 Healthy controls	Arrow Task	
Yücel et al. (2007)	24 Opiate-dependent individuals (stabilized on methadone/buprenorphine)	MRI -Spectroscopy	Compared to controls, when performing the behavioral tasks at a comparable level, opiate-dependent individuals had reduced concentrations of N-acetylaspartylglutamate and glutamate/glutamine with the dorsal ACC, and increased activation of fronto-parietal and cerebellar regions.
	24 Healthy controls	Multi-Source interference Task	
Fu et al. (2008)	30 Abstinent heroin-dependent individuals prior to detoxification	BOLD-fMRI	In healthy controls, neural activation associated with the response inhibition task, included bilateral medial prefrontal gyrus and ACC, left middle frontal gyrus, insula, bilateral superior frontal gyrus, and limbic system. In the opiate dependents, neural activations were found only in the bilateral superior frontal gyrus and the left middle frontal gyrus.
	18 Healthy controls	Go/No-Go Task	
PET studies			
Ersche et al. (2005)	15 Opiate-dependent individuals	$H_2\ ^{15}O$ PET with water injections	Although between the groups there were no differences in performance on the behavioral task, there were differences in rCBF of the OFC and right DLPFC between the drug dependent groups (former and currently using) and controls. Drug dependent groups activated the OFC during the task, while the control group presented with reduced activations in this region. Also, the control group exhibited increased activation of the right DLPFC compared to drug dependent groups.
	15 Amphetamine dependent individuals 15 former drug (opiate/amphetamine) dependent individuals 15 Controls	Cambridge Risk Task Barrett Impulsiveness Scale II Beck Depression Inventory II	
Botelho et al. (2006)	17 Heroin-dependent individuals (before and after 10 weeks of detoxification).	SPET ^{99m}Tc-HMPAO	Compared to controls, heroin-dependent individuals presented with decreased brain perfusion in the frontal cortex, mainly the OFC, and the occipital, temporal regions, basal ganglia and cerebellum. Heroin-dependent individuals did not show improvement in these regions after 10 weeks of detoxification.
	Controls (data normalized from software database)	Computational brain mapping	

Abbreviations—MRI: magnetic resonance imaging; VBM: voxel-based morphometry; PFC: prefrontal Cortex; BOLD: blood-oxygen-level-dependent; fMRI: functional magnetic resonance imaging; ACC: anterior cingulate cortex; DLPFC: dorsolateral prefrontal cortex; $H_2\ ^{15}O$: radioactive water; PET: positron emission tomography; rCBF: regional cerebral blood flow: OFC: orbitofrontal cortex; ^{99m}Tc-HMPAO: ^{99m}Tc-hexametazine or hexamethylpropyleneamine oxime; SPET: single-photon-emission tomography.

3.3.1. Neuropsychological studies: cognitive inhibitory deficits and alcohol consumption

3.3.1.1.1. Cognitive studies. Neuropsychological studies have begun to establish a relationship between executive function deficits and alcohol consumption. Kamarajan et al. (2004) administered the Go/No-Go Task to 58 alcohol abusers (after 5 days of abstinence) compared to 29 matched controls. During the task, they used EEG to measure differences in oscillatory neural responses between the groups. They found that the oscillatory responses associated with the No-Go (response inhibition) condition were compromised. They proposed that these attenuated oscillatory responses were associated with deficits in frontal inhibitory control; specifically, three major network systems of the PFC, the DLPFC, OFC and ACC (Kamarajan et al., 2004). Thus findings support the role of disrupted frontal inhibitory control in alcohol abusers. Noël et al. (2007b) tested whether impairments in cognitive inhibition are increased when alcohol-dependent individuals are required to inhibit stimuli associated with alcohol. They administered the Alcohol Shifting Task, a modified version of the Go/No-Go Task which includes alcohol-related words, to 40 recently detoxified alcohol-dependent individuals and 40 controls. Alcohol-dependent individuals made significantly more errors in response inhibition and attentional control. Furthermore, these deficits were exacerbated by exposure to alcohol cues (Noël et al., 2007b).

Rubio et al. (2008) conducted a longitudinal, 4-year follow-up study, investigating the association between behavioral impulsivity and the development of alcohol dependence in heavy drinkers. At baseline, 471 heavy drinkers and 149 controls were administered the Continuous Performance Test to test sustained attention, and the Stop Signal Task to assess behavioral inhibitory control. The Differential Reinforcement for Low-rate Responding Task was used to measure responses to delayed reward. At baseline, heavy drinkers exhibited poorer performance than the control group on all of the behavioral tasks. At the follow-up session, 380 of the previously heavy drinkers were re-assessed on all behavioral tasks. A structured clinical interview was conducted to determine alcohol dependence. The authors found that poor performance in the Stop Signal Task, which measures behavioral inhibition, was associated with increased risk of the development of alcohol dependence at follow-up (Rubio et al., 2008) (Table 5).

3.3.2. Neuroimaging and brain stimulation studies: the relationship between frontostriatal dysfunction, craving and alcohol dependence

3.3.2.1. Structural MRI studies. Chanraud et al. (2007) investigated the relationship between brain morphometry, executive cognitive performance and drinking history. They measured volumetric differences in gray and white matter using MRI and voxel-based morphometry. Participants completed the Trail Making Test Part B, The Wisconsin Card Sorting Test, The Letter Fluency Test, The Stroop Colour Word Test and the Letter-Number Sequencing Test, tests which are all sensitive to frontal dysfunction. MRI scans from 26 alcohol-dependent individuals (recruited upon admission to detoxification program) were compared with 24 matched controls. The most significant relative decrease in gray matter was detected bilaterally in alcohol-dependent individuals in the DLPFC; reduced gray matter was also detected in the temporal cortex, insula, thalamus and cerebellum, while decreases in white matter volume were widespread. They also found that impairments in neuropsychological performance were correlated with reductions in gray matter volume in fronto-parietal regions, as well as white matter decreases in the brain stem. In addition, Chanraud et al. (2007) presents evidence of a relationship between reduced brain matter volumes and neuropsychological impairment in alcohol-dependent individuals (Chanraud et al., 2007). It is important to note however, that most of the patients (not controls) were also active nicotine smokers and this may have exacerbated the decreases of brain morphometry in the alcohol-dependent group.

Makris et al. (2008) used segmentation-based MRI morphometry to assess the presence of volumetric changes of the brain reward system in 21 abstinent long-term chronic alcoholic men compared to 21 controls. They found that volumetric reductions were most pronounced in the DLPFC, right anterior insula, right NAc, and left amygdala. They found that length of abstinence correlated positively with increase in volumes of NAc and anterior insula, thus it is possible that length of abstinence is associated with more 'normalized' brain volume in the reward circuitry. In addition, they did not find significant association between length of abstinence and improvements to volumetric reductions in the DLPFC and amygdala, which may suggest the persistence of reductions within these neural circuits beyond abstinence (Makris et al., 2008). Therefore, both of these preliminary structural studies provide support for frontal volume reductions in alcohol-dependent individuals. Further studies into structural changes in alcohol-dependent groups are warranted.

3.3.2.2. Functional MRI studies. Many studies into alcohol dependence have reported findings from predominantly male populations. In response to this limitation, the presence of alterations in frontal regions in female alcohol-dependent individuals was explored by Tapert et al. (2004) and Clark et al. (2007). In a pilot study, Tapert et al. (2004) measured fMRI BOLD responses to alcohol-related words in 8 female alcohol-dependent individuals and 8 female controls (light social drinkers). Compared to controls, alcohol-dependent women showed a significant BOLD response during alcohol cues in subcallosal, ACC, left prefrontal and bilateral insular regions. Additionally, heightened craving after exposure to alcohol cues was correlated with increased response in the subcallosal cortex (Tapert et al., 2004). Clark et al. (2007) used fMRI to assess differences in cerebral perfusion between 8 young alcohol-dependent females and 8 young female controls. They found that alcohol-dependent females exhibited decreased perfusion in prefrontal and left parietal regions (Clark et al., 2007). Therefore, these studies provide initial evidence of alterations in the frontal regions in female alcohol dependents.

Akine et al. (2007) assessed brain activation in 9 young abstinent alcohol-dependent patients compared with 9 controls. Throughout the fMRI scans, the participants completed a modified False Recognition Task, a memory task which activates the frontal lobe. Participants did not show a significant difference in cognitive ability or task performance compared to controls. However, the alcohol-dependent patients showed reduced activation in the right DLPFC, ACC, left pulvinar in the thalamus, and in the right ventral striatum during the task (Akine et al., 2007). Li et al. (2009) sought to identify the neural circuitry underlying impaired impulse control in 24 abstinent alcohol-dependent patients compared to 24 controls. fMRI was conducted while all participants completed the Stop Signal Task; the alcohol-dependent group was also required to complete the Alcohol Urge Questionnaire. They found that alcohol-dependent patients exhibited altered activity in various cortical structures while performing response inhibition, error-processing and post-error behavioral adjustment. Overall, altered impulse control was associated with a decrease in cortical activation of the DLPFC, while risk-taking decisions were related to decreased activation of the medial OFC, bilateral parietal cortices and rostral ACC (Li et al., 2009). Taken together, these exploratory studies provide initial evidence of reduced activation in the frontal brain regions of alcohol-dependent individuals. However, there are some important limitations to consider: firstly, these studies consisted of small sample groups, larger samples being required to increase statistical power of the studies, and secondly, alcohol-dependent subjects had

Table 5
Cognitive studies: alcohol use and executive dysfunction.

Study	Participants	Measurements/methodology	Significant findings
Kamarajan et al. (2004)	58 Alcohol abusers (after 5 days of abstinence)	Go/No-Go Task	In alcohol abusers, there were attenuated oscillatory responses associated with the No-Go condition (response inhibition). The deficits were specifically found in the network systems of the PFC, the DLPFC, OFC and ACC.
	29 Matched controls	EEG	
Noël et al. (2007a,b)	40 Detoxified alcohol-dependent individuals	Alcohol Shifting Task (modified version of the Go/No-Go Task)	Compared to controls, alcohol-dependent individuals presented with reduced response inhibition skills and attentional control. These deficits were further exacerbated by exposure to alcohol cues.
	40 Controls		
Rubio et al. (2008)	471 Heavy drinkers	Longitudinal design measured at baseline and after 4 years.	At baseline, heavy drinkers performed worse on all behavioral tasks compared to controls. Reduced performance on Stop Signal Task at baseline was associated with increased risk of alcohol dependence at follow-up.
	149 Controls	Continuous Performance Test (sustained attention) Stop Signal Task The Differential Reinforcement for Low-rate Responding Task.	

Abbreviations—EEG: electroencephalography; PFC: prefrontal cortex; DLPFC: dorsolateral prefrontal cortex; OFC: orbitofrontal cortex; ACC: anterior cingulate circuitry.

extensive histories of previous drug and nicotine use, while controls had no history of substance use, thus potentially confounding the results. Despite the limitations, these studies provide promising results and highlight the need for further research into the presence of altered brain activity and impulse control, in alcohol dependence.

3.3.2.3. PET studies. A small number of PET studies found that alcohol dependence correlates with frontal hypometabolism, and suggest that altered metabolism, may be associated with the presence of deficits in cognitive inhibitory ability. Dao-Castellana et al. (1998) used [^{18}F] fluorodeoxyglucose PET and MRI to study frontal dysfunction in 17 alcohol-dependent individuals and 9 controls. Frontal executive functions were assessed using Verbal Fluency Task and the Stroop Task. They located metabolic abnormalities in the mediofrontal and the left DLPFC but not in the OFC. Alcohol-dependent individuals also showed poorer performance on the neuropsychological tasks, with the left DLPFC hypometabolism being associated with number of errors on the Stroop Task (Dao-Castellana et al., 1998). Noel et al. (2001) further explored the possible correlation between altered regional blood flow in frontal areas and executive dysfunction in alcohol-dependent patients. Twenty alcohol-dependent males and 20 controls completed neuropsychological assessments of inhibition, the Hayling Test, and working memory, the Alpha-Span Task. Regional cerebral blood flow was measured using a ^{99m}Tc-Bicisate single-photon-emission computed tomography (SPECT) procedure. Alcohol-dependent individuals performed worse on the neuropsychological assessments than controls. There was a significant negative correlation between the working memory task performance and regional cerebral blood flow in bilateral middle frontal gyrus area. While inhibition assessment was significantly correlated with both the inferior and middle frontal gyri (Noel et al., 2001). Demir (2002) used ^{99m}Tc-HMPAO SPECT to measure regional cerebral blood flow after detoxification in 10 late onset, 10 early onset male alcohol-dependent individuals and 6 controls. Neuropsychological performance was measured by the Wisconsin Card Sorting Test, the Word Fluency Test and the Wechsler Memory Scale-Revised. Compared with controls, both alcohol-dependent groups presented with deficits in frontal lobe function and verbal memory on neurocognitive tasks. The early onset group showed reduced perfusion in the left superior frontal regions, while decreased perfusion was found in right and left superior frontal regions in the late onset group (Demir, 2002). Although consisting of small samples, these studies provide support for the relationship between altered regional cerebral blood flow measured in frontal regions and executive deficits in alcohol dependents.

The effect of craving and cue exposure on frontal regions in alcohol-dependent individuals has been recently assessed using functional neuroimaging techniques. In a preliminary study, Olbrich et al. (2006) used PET to map regional cerebral blood flow in 21 detoxified alcohol-dependent patients during exposure to alcoholic and non-alcoholic beverages. When presented with the alcoholic cue, there was a significant increase in cerebral blood flow in the ventral putamen. There was also an increase in cerebral blood flow in the DLPFC, insula and cerebellum. Activation of these regions were correlated with self-reports of craving (Olbrich et al., 2006). These findings are consistent with the reported activation of the DLPFC in craving across the various drug groups. These results need to be interpreted somewhat cautiously though, as no control group was studied. This study however, highlights the need for further research into the activation of brain areas associated with craving in alcohol-dependent populations (both currently using and abstinent).

To further assess dysregulation of the frontostriatal circuits in alcohol-dependent individuals, Volkow et al. (2007) used [^{18}F] fluorodeoxyglucose and PET to examine activity of the PFC and the release of dopamine induced by Methylphenidate (stimulant drug) in 20 detoxified alcoholics compared to 20 healthy controls. Similar to previous studies, the alcoholic groups consisted of nicotine smokers, which may have confounded the results. However, the authors suggest that the prevalence of alcohol and nicotine use is representative of the general population. Methylphenidate increased striatal dopamine in all participants. However, the rewarding effects of the drug were reduced in the alcoholic group. Furthermore, within the control group, but not the alcoholic group, metabolism in the OFC had a negative association with the dopamine increase (Volkow et al., 2007). Based on these findings, Volkow et al. (2007) suggested the possibility that the OFC plays a role in the valuing of rewards through the regulation of dopamine increases in the ventral striatum. Dysregulation of this system may be significant in understanding the decreased sensitivity to the value of rewards in alcohol-dependent individuals and subsequent faulty decision-making.

3.3.2.4. Brain stimulation studies. In a novel brain stimulation study, Boggio et al. (2008) used transcranial direct current stimula-

tion (tDCS) to investigate whether modulation of the DLPFC could cause a reduction in craving for alcohol in 13 recently abstinent patients with a history of alcohol dependence. The participants were exposed to videos exhibiting alcohol cues to increase craving levels. Following this, the authors conducted a randomized sham-controlled study in which participants received both sham and active bilateral tDCS (constant current of 2 mA for 20 min) to the DLPFC. Participants were also required to complete an Alcohol Urge Questionnaire and Visual Analogue Scale for mood domains. Results suggested that both the anodal left/cathodal right and anodal right/cathodal left DLPFC stimulation caused a significant decrease in alcohol craving when compared to the sham condition. In addition, after active tDCS treatment to the DLPFC, alcohol craving was not enhanced by alcohol cues (Boggio et al., 2008). The authors suggest that when alcohol-dependent individuals are abstinent from alcohol, DLPFC activity is reduced, and exposure to alcohol cues can induce a response in the mesolimbic pathways, thus stimulating an increase in DLPFC activity. This process could help to explain the relationship between drug stimuli and the generation of drug-seeking behavior. Stimulating activity in the DLPFC was found to transiently improve levels of craving in alcohol-dependent individuals. The authors propose that tDCS could interfere with activity in DLPFC, thus having a modulatory effect on the relationship between alcoholic cues and activity in the DLPFC, which could then result in reductions in the strong craving for alcohol consumption (Table 6).

3.3.3. Summary: chronic alcohol use and the PFC

In summary, preliminary neuropsychological studies revealed an association between impaired cognitive inhibitory control and alcohol dependence. Additionally, in heavy drinkers, behavioral inhibitory deficits were related to an increased risk of developing alcohol dependence. Neuroimaging studies provide further support for inhibitory deficits and frontal abnormalities in alcohol-dependent individuals. Structural neuroimaging studies found reduced DLPFC brain volume matter in alcohol-dependent individuals, and these findings were supported, and further expanded, by functional neuroimaging studies, which revealed that altered impulse control was reflected by a decreased in DLPFC activity, while risk-taking decisions were associated with reduced activity of the OFC and ACC. Finally, a novel brain stimulation tDCS study presented promising results, whereby stimulation to the DLPFC of alcohol-dependent individuals was able to transiently reduce alcohol craving. Therefore, these studies, although preliminary and explorative, provide support for further research into frontostriatal dysfunction and cognitive deficits in alcohol addiction, and the potential of novel targeted treatments to address these deficits.

3.4. Overview: chronic nicotine use and the prefrontal cortex

Tobacco smoke consists of thousands of compounds, many having toxic effects on the brain, cardiovascular and pulmonary systems (Swan and Lessov-Schlaggar, 2007). Nicotine, the major psychotropic agent in tobacco, is a highly addictive psychostimulant (Dani et al., 2001). Tobacco addiction is one of the most common chronic and relapsing medical conditions of nicotine use (Mitrouska et al., 2007). Many cigarette smokers actively attempt to quit smoking; however, only a very small percentage will successfully achieve abstinence after 6 months or more of treatment (Brody, 2006; Ray et al., 2008). Dependent smokers can experience craving for cigarettes within minutes of the last cigarette, the levels of craving then intensifies over the next 3–6 h (Jarvik et al., 2000). Short-term administration of nicotine may enhance several cognitive domains, including executive functioning, attention and working memory (Brody, 2006; Swan and Lessov-Schlaggar, 2007). There are mixed findings regarding chronic effects of nicotine use on brain activity and neurocognitive functioning (Friend et al., 2005). Emerging studies have used neuroimaging techniques to explore the effect of chronic nicotine exposure on brain activity (Azizian et al., 2009; Brody, 2006). Preliminary structural and functional neuroimaging studies have found that nicotine-dependent individuals show a relationship between abnormal neural responses in the PFC, OFC and ACC, nicotine exposure and craving levels (Domino et al., 2000a,b). Additionally, preliminary brain stimulation techniques have found that stimulation of the PFC in nicotine-dependent individuals is capable of transiently reducing craving levels and cigarette consumption. Therefore, these studies provide support for further research into the role of the PFC in nicotine craving and addictive behaviors.

3.4.1. Neuropsychological studies: executive function, response inhibition and nicotine exposure

3.4.1.1. Cognitive studies. To date, there is relatively sparse literature regarding chronic nicotine smoking and cognition. Razani et al. (2004) assessed the effect of smoking history on cognitive functioning in a sample of 127 older healthy smoking adults (between ages of 47–83). Cognitive executive ability was evaluated through a number of neurocognitive tasks. Self-reported smoking histories were also collected. The authors found that smoking history had an effect on the Wisconsin Card Sorting Task, a paradigm which measures executive/problem solving skills, with heavy smokers performing significantly worse than both moderate and light smokers (Razani et al., 2004). However, in interpreting these results, it is important to note that the elderly heavy smokers consisted of only a very small subgroup of the overall study. It is also possible that the 'healthy' elderly smokers, even though classified as heavy smokers, may not be representative of generalized heavy smoking in elderly people with extensive smoking histories. On the other hand, the sensitivity of these tasks to indicate poorer performance in heavy smokers who are relatively healthy, and of above-average intelligence, highlights even further the importance of future research into these deficits in populations more reflective of the general population.

Dawkins et al. (2007) conducted a study into executive functioning and response inhibition in 145 chronic smokers. Participants completed a battery of neurocognitive tests: the Oculomotor Task of Response Inhibition, Continuous Performance Task, Spatial Working Memory Test and the Verbal fluency test. These tests were administered in a counterbalanced order: once after overnight abstinence, and then again, 1 week later after overnight abstinence. In this double-blind study, participants received either a 4-mg NiQuitin lozenge or a placebo lozenge. Acute smoking abstinence was associated with impaired response inhibition; there was no evidence of other significant deficits in global executive functioning in nicotine users during abstinence. Overall, the study found that chronic nicotine users present with impaired inhibitory control which could be reversed with nicotine administration. The authors proposed that impairments of this nature could be related to disrupted ACC circuitry in chronic smokers (Dawkins et al., 2007). These findings are supported by Stein et al. (1998) fMRI study, which found that administration of acute nicotine to 16 current smokers had an impact on several behavioral parameters, such as reported feelings of "rush" and "high" and "drug liking". The fMRI scans found that acute nicotine exposure resulted in increased neuronal activity in the frontal lobes, cingulate, NACC and amygdala (Stein et al., 1998). Therefore, the authors suggest that the reinforcing effects and behavioral improvements associated with acute nicotine administration could be associated with the perpetuation of nicotine dependence. Thus, these above studies suggest that the increase in the frontal neural activity could reflect a 'normalising' effect of nicotine on attention chronic nicotine users.

Dawkins et al. (2009) extended this study and conducted a longitudinal study into patterns of change in withdrawal symp-

Table 6
Alcohol, cognitive inhibition and frontostriatal dysfunction: neuroimaging and brain stimulation studies.

Study	Participants	Measurements/methodology	Significant findings and frontal brain activations
Structural MRI studies			
Chanraud et al. (2007)	26 Alcohol-dependent individuals	High resolution structural MRI	Alcohol-dependent individuals presented with significant bilateral decreases in grey matter in the DLPFC, and also reductions in grey matter in the temporal cortex, insula, thalamus and cerebellum. Decreases in white matter volume were widespread. Impairments in neuropsychological performance were associated with decreased grey matter volume in fronto-parietal regions and white matter decreases in the brain stem.
	24 Matched controls	Assessed grey and white tissue densities using VBM Trail Making Test Part B The Wisconsin Card Sorting Test The Letter Fluency Test The Stroop Colour Word Test Letter-Number Sequencing Test	
Makris et al. (2008)	21 Abstinent long-term chronic alcoholic men	Segmentation-based MRI morphometry to assess volumetric reductions in the brain	Chronic alcoholic men presented with volumetric reductions in the DLPFC, right anterior insula, right NAc, and left amygdala. Length of abstinence was associated with an increase in volumes in NAc and anterior insula. However, there was no association found between length of abstinence and volumetric reductions in the DLPFC and amygdala.
	21 Controls		
Functional MRI studies			
Tapert et al. (2004)	8 Alcohol-dependent females	BOLD-fMRI	In response to the alcohol cues, alcohol-dependent females showed a significant BOLD response in the subcallosal, ACC, left prefrontal and bilateral insular regions. Heightened craving after presentation of alcohol cues was associated with an increased response in the subcallosal cortex.
	8 Controls (light social drinkers)	Measured responses to alcohol –related cues.	
Clark et al. (2007)	8 Young female alcohol dependent	Perfusion-fMRI	Compared to controls, alcohol-dependent females showed decreased perfusion in the prefrontal and left parietal regions.
	8 Young female controls		
Akine et al. (2007)	9 Young abstinent alcohol-dependent individuals	BOLD-fMRI	During the task, compared to controls, alcohol-dependent individuals presented with reduced activation in the right DLPFC, ACC, left pulvinar in the thalamus, and the right ventral striatum. However, no significant difference in task performance was found.
	9 Controls	Modified False Recognition Task	
Li et al. (2009)	24 Abstinent alcohol-dependent individuals	BOLD-fMRI	Alcohol-dependent individuals showed a difference in impulsivity compared to controls. Altered impulse control was related with a decrease in cortical activation of the DLPFC, while risky decision-making skills were associated with reduced activation of the medial OFC, bilateral parietal cortices and rostral ACC.
	24 controls	Stop Signal Task Alcohol Urge Questionnaire	
PET studies			
Dao-Castellana et al. (1998)	17 Alcohol-dependent individuals 9 Controls	^{18}F-FDG PET and MRI Stroop Task Verbal Fluency Task	Alcohol-dependent individuals performed more poorly on the neuropsychological tasks. There were metabolic differences in the mediofrontal and in the left DLPFC, but not the OFC. Hypometabolism of both of these brain regions were associated with the reduced performance on the neuropsychological tasks.

Table 6 (*Continued*)

Study	Participants	Measurements/methodology	Significant findings and frontal brain activations
Noel et al. (2001)	20 Alcohol-dependent males	^{99m}Tc-Bicisate SPECT	Alcohol-dependent individuals performed more poorly on neuropsychological tests compared to controls. There was a negative correlation between working memory task performance and regional cerebral blood flow in the bilateral middle frontal gyrus area. Performance on tasks of inhibition significantly correlated with both the inferior and middle frontal gyri.
	20 Controls	The Hayling Test The Alpha-Span Task	
Demir (2002)	10 Late onset alcohol-dependent individuals	^{99m}Tc-HMPAO SPECT	Compared to controls, both alcohol-dependent groups, presented with deficits in frontal lobe functioning and verbal memory on the neurocognitive tasks. The early onset alcohol dependents had reduced perfusion in the left superior frontal regions. Later onset alcohol dependents had decreased perfusion in right and left superior frontal regions.
	10 Early onset alcohol-dependent individuals 6 controls	Wisconsin Card Sorting Task Word Fluency Test Wechsler Memory Scale (revised)	
Olbrich et al. (2006)	21 Recently abstinent (7–35days) alcohol-dependent males	H_2 ^{15}O PET	Presentation of an alcoholic cue was associated with a significant increase in CBF in the ventral putamen. Increases in CBF were also found in the DLPFC, insula and cerebellum. Activation of these regions had a positive correlation with self-reports of craving.
		Presentation of alcoholic and non-alcoholic cues.	
Volkow et al. (2007)	20 Detoxified alcohol-dependent individuals	^{18}F-FDG PET	Methylphenidate increased striatal dopamine in all participants. The rewarding effect of the stimulant drug was reduced in the alcohol-dependent group. In the control group there was a negative association between metabolism in the OFC and dopamine decrease.
	20 Healthy controls	Methylphenidate (stimulant drug)	
Brain stimulation studies			
Boggio et al. (2008)	13 Recently abstinent alcohol-dependent individuals	Single session of anodal 2 mA tDCS stimulation of either left DLPFC, right DLPFC, or sham, for 20 min Alcohol Urge Questionnaire VAS (mood levels)	tDCS of DLPFC temporarily reduced alcohol craving and blocked the effects of alcohol cues on craving levels. No mood changes

Abbreviations—MRI: magnetic resonance imaging; VBM: voxel-based morphometry; DLPFC: dorsolateral prefrontal cortex; NAc: nucleus accumbens; BOLD: blood-oxygen-level-dependent; ACC: anterior cingulate cortex; fMRI: functional magnetic resonance imaging; OFC: orbitofrontal cortex; ^{18}F-FDG: fluorine 18-fluorodeoxyglucose; PET: positron emission tomography; SPECT: single-photon-emission computed tomography; ^{99m}Tc-HMPAO: ^{99m}Tc-hexametazine or hexamethylpropyleneamine oxime; H_2 ^{15}O: radioactive water; CBF: cerebral blood flow; tDCS: transcranial direct current stimulation; mA: milliampere.

toms, craving, reward motivation and response inhibition across 3 months of smoking abstinence in the same sample of 145 chronic smokers. After the second session (described in the previous study), participants were divided randomly into 2 groups: those who attempted to quit and those who continued to smoke. The executive function and response inhibition tests were repeated at 7 days, 1 month and 3 months. Overall, the authors found that abstainers had a significantly reduced desire to smoke when compared to ongoing smokers. Both abstainers and ongoing smokers showed improvement of appetitive processes and affective states over 3 months of abstinence, while impairment in response inhibition did not change (Dawkins et al., 2009). Although these preliminary findings support the association between nicotine consumption and response inhibition, further studies, which replicate these findings, are required to clarify the consistency of these results (Table 7).

3.4.2. Neuroimaging and brain stimulation studies: the relationship between frontostriatal dysfunction, craving and nicotine dependence

3.4.2.1. Structural MRI studies. Two structural MRI studies measured regional gray matter volume and density in current smokers when compared to non-smoking individuals. Brody et al. (2004) examined regional gray matter volume and density differences between 19 nicotine-dependent individuals and 17 non-smoking healthy controls. Smokers demonstrated significantly smaller cortical gray matter volumes and densities in the DLPFC and ventrolateral PFC, as well as reduced left dorsal ACC gray matter volume and right cerebellar gray matter densities (Brody et al., 2004). These findings were supported by Gallinat et al. (2006) who investigated the presence of structural deficits in 22 smokers compared to 23 non-smokers. Smokers presented significantly reduced gray matter volume and low gray matter density was found in frontal regions, such as the ACC, PFC and OFC, the occipital lobe and the temporal lobe, including the parahippocampal gyrus. Altered gray matter volume or gray matter density was also found in the thalamus, cerebellum and substantia nigra. Additionally, in both of these studies, a correlation was observed between lifetime severity of smoking (pack-year) and reduced prefrontal cortical gray matter density (Brody et al., 2004) and decreased volume of frontal, temporal lobes and cerebellum (Gallinat et al., 2006). The authors postulated that these density and volumetric decreases in the frontal regions could be involved in neurocognitive dysfunction in smokers.

3.4.2.2. Functional MRI studies. The following studies used fMRI investigated changes in regional brain activation associated with cigarette-cue-induced craving. Franklin et al. (2007) used arterial spin-labelled perfusion-fMRI to characterize regional brain activation during cigarette-cue-induced craving in 21 chronic smokers. Participants completed two fMRI sessions; one scan while exposed to a smoking-cue video and holding a cigarette, and the other scan, during exposure to a non-smoking (neutral) stimuli and holding a pencil. Increased blood flow (perfusion) was found in the amygdala, ventral striatum, thalamus, hippocampus, left insula and OFC when exposed to the smoking stimuli. Additionally, there was a positive correlation between perfusion in the DLPFC and posterior cingulate and the subjective reports of craving (Franklin et al., 2007). Wang et al. (2007) used arterial spin-labelled perfusion-fMRI to examine the neural effects of abstinence-induced cigarette cravings. Fifteen chronic smokers were scanned twice (1–3 weeks apart) in a counterbalanced order: the first scan was conducted under normal smoking conditions, and the second scan, after overnight abstinence. Smoking abstinence was associated with increased cerebral blood flow in the ACC, medial and left OFC. However, abstinence-induced cravings were predicted by increases in cerebral blood flow in the right OFC, right DLPFC, occipital cortex, ACC, ventral striatum/NAc, thalamus, amygdala, bilateral hippocampus, left caudate and right insula (Wang et al., 2007). Therefore, these authors have highlighted, in particular, a correlation between, cue-induced craving, and abstinence-induced craving, and regional changes in frontal brain activity.

Wilson et al. (2005) used fMRI to investigate the effects of *smoking expectancy* on cue-induced neural response in 22 male smokers deprived for 8 h. Immediately before scanning, participants were randomly given instructions regarding whether they would be able to, or not able to, smoke during the experiment (2 h). During scanning, participants were exposed to either neutral or smoking cues. Both prior to, and after, cue exposure, self-report levels of craving were recorded. Significant increases in brain activation occurred

Table 7
Cognitive studies: nicotine use and executive dysfunction.

Study	Participants	Measurements/methodology	Significant findings
Razani et al. (2004)	127 Older healthy smoking adults (47–83 years) divided into non-light, moderate and heavy smokers.	Neurocognitive tasks Self-reported smoking histories	Heavy smoking history was associated with reduced executive/problem solving skills. Heavy smokers performed worse than both groups on tests assessing executive function and problem solving skills.
Dawkins et al. (2007)	145 Chronic smokers	Tests administered in once after overnight abstinence, and then again, 1 week after overnight abstinence. The Oculomotor Task of Response Inhibition Continuous Performance Task Spatial Working Memory Test Verbal fluency Test Throughout the test, participants received either 4-mg NiQuitin lozenge or placebo lozenge.	Acute smoking abstinence is associated with impaired response inhibition. Chronic nicotine smokers presented with impaired inhibitory control, and these impairments were reversed with nicotine administration.
Dawkins et al. (2009)	145 Chronic smokers were divided into those who attempted to quit and those who continued to smoke.	The cognitive tests from Dawkins et al. (2007) were repeated at 7 days, 1 month and 3 months.	Abstainers significantly reduced desire to smoke compared to continuing smokers. Both abstainers and ongoing smokers showed improvement in appetitive processes and affects states after abstinence. Impairment in response inhibition did not improve over time.

Abbreviations—mg: milligrams.

in the ACC during cigarette-cue exposure when compared to the neutral cue. Furthermore, activation of the subregions of the PFC (i.e. ventromedial, ventrolateral and DLPFC) was found when cue-induced smoking was modulated by smoking expectancy (Wilson et al., 2005). These findings are supported by McBride et al. (2006) who also assessed the effects of smoking expectancy and smoking cues in 20 chronic smokers. Participants were scanned twice in a randomized and counterbalanced order, once in an abstinent state, and once without any smoking limitations. During the scans, participants were exposed to either smoking or neutral cues; following this, they completed a self-report of craving. The neural response to smoking cues was largely associated with expectation, and substantially less so, to abstinence. Participants responded to the smoking cues, with increased levels of craving and neural activation of the ACC, posterior cingulate cortex, dorsomedial PFC, DLPFC, medial OFC, anterior insula, superior temporal gyrus, visuospatial areas, ventral pallidum and dorsomedial thalamus (McBride et al., 2006). Similar to Wilson et al. (2005), the DLPFC showed cue-induced activations which were associated with smoking expectancy. Overall, these studies demonstrate altered frontal neural responses to expectancy and cue-induced craving in chronic smokers.

3.4.2.3. PET studies. The effects of cigarette-cue-induced craving on frontal regions were also explored by Brody et al. (2002) who used 2 fluorine 18-fluorodeoxyglucose PET scans to examine brain metabolic changes during cigarette craving in 20 heavy smokers and 20 non-smokers. Participants were scanned 10 days apart and in a randomized order, one scan while watching a cigarette-cue video and holding a cigarette, and one scan while watching a neutral video and holding a pen. Exposure to the cigarette-cue correlated with increased bilateral ACC metabolism, as well as increased left anterior temporal lobe and PFC metabolism in heavy smokers. Additionally, participants' subjective levels of craving correlated with metabolism in the OFC, DLPFC, the anterior insula and the superior right sensorimotor cortex (Brody et al., 2002). Rose et al. (2007) used $H_2\ ^{15}O$ PET and MRI scans to assess regional cerebral glucose metabolism after overnight abstinence, in 15 chronic smokers, at 3 different time-points: (1) at baseline; (2) after 2 weeks of exposure to denicotinised cigarettes and nicotine patches; and (3) 2 weeks after resumption of normal smoking habits. Subjective ratings of craving were also recorded. Interestingly, they found that craving levels decreased at the second session, and during this session, regional brain metabolic activity was observed to be reduced in the right ACC. Furthermore, changes in craving across the different sessions negatively correlated with change in cerebral metabolism of the ventral striatum, OFC and pons (Rose et al., 2007). Overall, these fMRI and PET studies demonstrate altered frontal neural responses to expectancy and cue-induced craving in chronic smokers.

3.4.2.4. Brain stimulation studies. Recently, researchers employed non-invasive brain stimulation techniques, repetitive TMS and tDCS, to investigate whether stimulation of the DLPFC reduces levels of craving and cigarette consumption in heavy nicotine users. Johann et al. (2003) conducted a pilot study to investigate the effect of high frequency repetitive TMS to the DLPFC of 11 tobacco dependent individuals. They found that stimulation of the DLPFC significantly reduced cigarette consumption and craving levels (Johann et al., 2003). The same group performed another study into the effect of high frequency (20 Hz) repetitive TMS to the DLPFC on cigarette consumption and levels of craving (Eichhammer et al., 2003). Fourteen treatment-seeking smokers participated in the double-blind crossover trial. Participants were administered 2 trials of either active or sham stimulation to the left DLPFC, randomized over four days. The authors found that active high frequency repetitive TMS to the left DLPFC significantly reduced number of cigarettes smoked when compared to the sham group (Eichhammer et al., 2003). Despite the decrease in cigarette smoking, a reduction in craving levels was not found; perhaps the evaluation of craving was not sensitive enough, or the sample size was too small to detect significant differences. Amiaz et al. (2009) expanded on the previous two studies and explored whether exposure to smoking cues would modulate the effect of repetitive TMS. Participants were randomly divided into four groups: active TMS with smoking cues, active TMS with neutral cues, sham TMS with smoking cues and sham TMS with neutral cues. Over ten daily sessions, 48 nicotine-dependent individuals were exposed to either smoking or neutral visual cues, followed by high frequency (10 Hz) repetitive TMS to the DLPFC. High frequency repetitive TMS over the DLPFC transiently reduced cigarette consumption and nicotine dependence. In addition, repetitive TMS over the PFC disrupted craving-related circuitries by blocking craving induced by smoking cues (Amiaz et al., 2009).

Fregni et al. (2008) assessed whether the excitability enhancing anodal tDCS of the DLPFC would reduce cue-induced smoking craving. Craving was induced through cigarette manipulation and exposure to a smoking video. A sham-controlled crossover study was conducted, a sample of 24 smokers receiving both sham and active tDCS (2 mA for 20 min anodal tDCS to the left and right DLPFC) in a randomized order. Stimulation of the left and right DLPFC reduced both cue-induced and generalized smoking craving compared to the sham condition.

Overall, all of these preliminary brain stimulation studies suggest that excitatory stimulation of the DLPFC can have two transient effects: reduction in cigarette craving (Amiaz et al., 2009; Fregni et al., 2008; Johann et al., 2003) and a decrease in number of cigarettes smoked (Eichhammer et al., 2003; Johann et al., 2003). It is important to note though, that although these novel brain stimulations studies present intriguing results (across the different drug groups), these techniques are highly experimental and the effects and parameters of the stimulation need to be further explored. For example, stimulation of the DLPFC may be simultaneously inhibiting or stimulating interconnected cortical regions, which may in fact result in the suppression of craving (Table 8).

3.4.3. Summary: chronic nicotine use and the PFC

There is very limited data regarding chronic nicotine use and cognitive deficits. Rather, many of the studies focused on the involvement of the frontal regions in cue-induced craving and smoking expectancy. One study found a connection between severity of smoking and cognitive performance in elderly healthy chronic nicotine smokers; further studies are required to explore this association. A recent study though, revealed the presence of deficits in response inhibition in both current users and abstainers, which did not improve over 3 months of abstinence. Additionally, acute smoking abstinence was associated with impaired response inhibition in chronic smokers. Interestingly, these deficits could be reversed with acute nicotine administration, and these findings were supported by a neuroimaging study which found that acute nicotine increases activity in the frontal regions. It is possible that neural deficits in the frontal regions of chronic smokers, possibly resulting from chronic exposure, or perhaps, a pre-existing condition leading to chronic smoking, could lead to self-medication (acute nicotine) to temporarily rectify matters.

Structural neuroimaging studies found that chronic smokers showed reduced gray matter volumes and densities in the frontal regions, and furthermore, they also observed a correlation between lifetime severity of smoking and decreased PFC gray matter density and volume. Functional neuroimaging (fMRI and PET studies) revealed that exposure to smoking cues correlated with an increase in activity in the OFC, PFC and the ACC, while

Table 8
Nicotine, cognitive inhibition and frontostriatal dysfunction: neuroimaging and brain stimulation studies.

Study	Participants	Measurements/methodology	Significant findings and frontal brain activations
Structural MRI studies			
Brody et al. (2004)	19 Nicotine-dependent individuals	High resolution structural MRI	Nicotine-dependent individuals had significantly smaller cortical grey matter volumes and densities in the DLPFC and ventrolateral PFC, and reduced left dACC grey matter volume and right cerebellar grey matter densities. A correlation was found between lifetime severity of smoking (pack-year) and reduced prefrontal cortical grey matter density.
	17 Non-smoking healthy controls	Assessed grey and white tissue densities using VBM	
Gallinat et al. (2006)	22 Smokers	High resolution structural MRI	Smokers had reduced grey matter volume and density in frontal regions, such as the ACC, PFC and OFC, the occipital lobe and the temporal lobe, including the parahippocampal gyrus. Altered grey matter volume or grey matter density was also found in the thalamus, cerebellum and substantia nigra. A correlation was found between lifetime severity of smoking (pack-year) and decreased volume of frontal, temporal lobes and cerebellum.
	23 Non-smokers	Assessed grey and white tissue densities using VBM	
Functional MRI studies			
Stein et al. (1998)	16 Active cigarette smokers	BOLD-fMRI	In active smokes, acute nicotine administration induced dose-dependent increases in behavioral parameters such as feelings of "rush" and "high" and drug liking. Also, acute nicotine administration increased neuronal activity in the frontal lobes, cingulate, NAc and amygdala.
		Behavioral rating questionnaire	
Wilson et al. (2005)	22 Male smokers deprived of nicotine for 8 h	BOLD-fMRI	Significant activation of the ACC was found during cigarette-cue exposure when compared to the neutral cue exposure. In addition, subregions of the PFC, such as the ventromedial, ventrolateral and DLPFC were activated when cue-induced smoking was modulated by smoking expectancy.
		Craving urge scales Smoking and non-smoking cues Smoking expectancy cues	
McBride et al. (2006)	20 Regular heavy smokers	BOLD-fMRI (once during abstinent state and once when satiated)	Neural activation in response to smoking cues was largely associated with expectancy, and less so, with abstinence. Smoking cues was related to increased levels of craving and neural activation of the ACC, posterior cingulate cortex, dorsomedial PFC, DLPFC, medial OFC, anterior insula, superior temporal gyrus, visuospatial areas, ventral pallidum and dorsomedial thalamus.
		Smoking and neutral videotapes Craving scales Smoking expectancy cues	
Franklin et al. (2007)	21 Chronic smokers	Arterial spin-labelled perfusion-fMRI	Smokers responded to smoking cues with increased blood flow (perfusion) in the amygdala, ventral striatum, thalamus, hippocampus, left insula and OFC. A positive correlation was found between perfusion in both the DLPFC and posterior cingulate, and the self-reports of craving.
		Craving self-reports Smoking and non-smoking cues.	
Wang et al. (2007)	15 Chronic smokers	Arterial spin-labelled perfusion-fMRI	Smoking abstinence was associated with increased CBF in the ACC, medial and left OFC. Abstinence-induced cravings were predicted by CBF increases in the right DLPFC, occipital cortex, ACC, ventral striatum/nucleus accumbens, thalamus, amygdala, bilateral hippocampus, left caudate and right insula.
		The first scan measured perfusion during smoking satiety, and the second, after overnight abstinence. Craving scales.	

Table 8 (*Continued*)

Study	Participants	Measurements/methodology	Significant findings and frontal brain activations
PET studies			
Brody et al. (2002)	20 Heavy smokers	^{18}F-FDG PET scans	Smoking cue exposure in heavy smokers resulted in increased bilateral ACC metabolism, as well as increased left anterior temporal lobe and PFC metabolism. In addition, levels of craving correlated with metabolism in the OFC, DLPFC, the anterior insula and the superior right sensimotor cortex.
	20 Non-smokers	Smoking and neutral cues Craving scales	
Rose et al. (2007)	15 Chronic smokers	^{18}F-FDG and H_2 ^{15}O PET and MRI	Cravings levels were reduced in the 2nd session, while regional brain metabolic activity was reduced in the right ACC. Over all sessions, changes in craving negatively correlated with cerebral metabolism in the ventral striatum, PFC and pons.
		PET scan at: 1. Baseline 2. 2 weeks after exposure to only denicotinised cigarettes 3. 2 weeks after resumption of normal smoking habits. Fagerstrom test of Nicotine Dependence Self-report questionnaires (craving and smoking habits) Continuous Performance Task	
Brain stimulation studies			
Johann et al. (2003)	11 Tobacco dependent individuals	Single session of high frequency rTMS to the DLPFC VAS (craving levels)	rTMS reduced reported levels of tobacco craving.
Eichhammer et al. (2003)	14 Treatment-seeking heavy smokers	Single session of high frequency rTMS (20 Hz) to the DLPFC VAS (craving levels) Cigarette consumption	High frequency rTMS DLPFC reduced cigarette consumption. Craving levels did not change.
Fregni et al. (2008)	24 Chronic smokers	Single session of anodal 2 mA tDCS stimulation of either left DLPFC, right DLPFC, or sham, for 20 min VAS (craving levels) VAS (mood levels)	tDCS of DLPFC temporarily reduced general and cue-induced nicotine craving. No mood changes
Amiaz et al. (2009)	48 Nicotine-dependent individuals	Ten daily sessions of high frequency rTMS (10 Hz) to the DLPFC. VAS (craving levels) Cigarette consumption Smoking and non-smoking cues	High frequency rTMS DLPFC reduced cigarette consumption Cue-induced craving was reduced

Abbreviations—MRI: magnetic resonance imaging; VBM: voxel-based morphometry; DLPFC: dorsolateral prefrontal cortex; PFC: prefrontal cortex; dACC: dorsal anterior cingulate cortex; ACC: anterior cingulate cortex; OFC: orbitofrontal cortex; BOLD: blood-oxygen-level-dependent; fMRI: functional magnetic resonance imaging; NAc: nucleus accumbens; CBF: cerebral blood flow; ^{18}F-FDG: fluorine 18-fluorodeoxyglucose; PET: positron emission tomography; H_2 ^{15}O: radioactive water; rTMS: repetitive transcranial magnetic stimulation; VAS: Visual Analogue Scale; Hz: hertz.

subregions of the PFC were activated when cue-induced smoking was affected by smoking expectancy. Craving levels were related to altered metabolism of the OFC and DLPFC, and reduced ACC metabolic activity was associated with abstinence. Preliminary brain stimulation studies, both TMS and tDCS, found that stimulation of the DLPFC, in chronic nicotine smokers, could transiently reduce cigarette craving and cigarette consumption. Brain stimulation studies provide further evidence for frontostriatal dysfunction in chronic smokers, suggesting that future treatments should target the frontal regions (alongside the reward circuitry) in reducing craving in nicotine dependence. Therefore, even though the findings regarding chronic nicotine use and cognitive impairments are mixed, these preliminary studies provide support for further studies into the frontostriatal circuitry, and potential response inhibition impairments, in chronic nicotine use.

3.5. General summary

In summary, these preliminary studies provide consistent evidence of a relationship between prolonged drug administration, neuroadaptations of the PFC (specifically the three PFC-striatothalamic circuits, the DLPFC, OFC and ACC), and the persistence of drug-seeking behaviors. Chronic cocaine use was associated with impaired behavioral response inhibition, performance monitoring and decision-making abilities. Neuroimaging studies found that these deficits were associated with structural abnormalities in the OFC and ACC, and hypoactivity of frontal cortical regions, specifically the ACC and PFC. In cocaine-dependent individuals, these cognitive impairments, and alterations in frontal activity, may be related to increased difficulty inhibiting the prepotent urge to consume cocaine, reduced decision-making skills, and a diminished ability to monitor the potential negative outcome of continued cocaine use.

Opiate-dependent individuals showed diminished ability on decision-making tasks in risky situations and deficits in executive functioning. Preliminary neuroimaging studies reported abnormal neural responses in the PFC; they consistently revealed attenuated activity in the ACC, which is associated with error detection and signalling, while altered responses within the DLPFC and OFC were also found. Overall, dysfunction of these frontal regions was found to be associated with deficits in executive function and decision-making ability in opiate-dependent individuals. These deficits in decision-making could be associated with risky life-style choices leading to relapse, for example, returning to drug use despite long-term negative consequences.

Alcohol dependence was associated with reduced levels of cognitive inhibitory control, impulsive behaviors and risk-taking decision-making skills. Deficits in inhibitory control were correlated with an increased risk of developing alcohol dependence in a heavy drinking population. Structural neuroimaging studies of alcohol-dependent individuals revealed reduced DLPFC brain volume matter, which was supported by functional neuroimaging studies, which found that altered impulse control was reflected by hypoactivity of the DLPFC. In addition, functional neuroimaging studies found that poorer performance on risk-taking decisions was also associated with reduced activity of the OFC and ACC in alcohol-dependent individuals. These findings could reflect an increased difficulty in inhibiting the impulsive urge to consume alcohol, which is enhanced by poor risk-taking decisions. Therefore, it is possible that alcohol-dependent individuals present with compromised brain circuitry involved in the ability to inhibit the compulsive urge to drink, and to prevent a risky situation. This could decrease the likelihood of remaining abstinent and may help explain the high rates of relapse amongst alcohol-dependent individuals.

Unfortunately, there is scarce data regarding chronic nicotine use and cognitive deficits. One recent study however, revealed the presence of deficits in response inhibition in chronic nicotine smokers. Neuroimaging studies discovered structural abnormalities, such as reduced cortical gray matter volumes and density in the DLPFC, PFC and ACC. Furthermore, these reductions correlated with lifetime severity of smoking. Functional neuroimaging studies focused on the role of the frontal regions in cue-induced cravings and smoking expectancy. Smoking cues were associated with increases in activity of the PFC and ACC, while subregions of the PFC were activated when cue-induced smoking was influenced by smoking expectancy. In chronic smokers, acute smoking abstinence was associated with impaired response inhibition. While, acute nicotine administration increased activity in the frontal regions, and was able to reverse deficits in response inhibition. Therefore, it is possible that acute nicotine administration could initially act as a form of self-medication in individuals with inhibitory deficits. This could explain the high levels of comorbidity between nicotine consumption and other addictive drugs, and the potential use of nicotine to improve inhibitory dysfunction across various substance dependent populations. Over time however, continued nicotine administration may exacerbate reduced activity in the frontal regions, which may be associated with difficulties in ceasing nicotine consumption, regardless of the long-term negative consequences.

Across the drug groups, it was found that severity of drug use was correlated with frontostriatal dysfunction, inhibitory impairment and decision-making skills. It remains unclear whether these frontal abnormalities predate chronic drug consumption; however, these findings suggest that continued drug use exacerbates dysregulation of the frontal regions and the presence of cognitive deficits. In addition, these deficits, and frontostriatal dysfunction, were found to persist across cocaine, opiate and nicotine-dependent groups even after abstinence. Alcohol-dependent groups have presented mixed findings regarding improvement in the frontal regions during abstinence. These findings are preliminary, and further research is required to elucidate the persistence of frontal deficits across the various drug groups.

Finally, novel brain stimulation techniques, such as TMS and tDCS, have begun to target the frontal regions in an attempt to reduce behaviors associated with regulating control over drug seeking. Preliminary studies into the effects of brain stimulation of the DLPFC across cocaine, alcohol and nicotine-dependent groups, have found that stimulation of the frontal regions transiently reduces levels of drug consumption and craving. The clinical implications of these findings will be further discussed in the following section.

Overall, the reviewed studies offer further insight into the brain regions underlying deficits in inhibitory control, and furthermore, provide a suggestion of how dysregulation of prefrontal circuits may be involved in compulsive drug seeking, and finally, novel brain stimulation techniques highlighted the potential of stimulation to these frontal regions in reducing levels of drug craving and consumption.

4. Limitations

Although these studies illustrate abnormalities in the prefrontal cortex, the findings must be assessed somewhat cautiously. To begin with, many of the studies which we describe and review are preliminary empirical studies. As such, they often include only very small sample sizes. Therefore, although the findings support the model of frontostriatal dysfunction in addictive behaviors, we still need to be cautious in interpreting the results. That being said, the results of these exploratory findings

provide a strong basis for future larger, multi-site, and clinical studies.

Another complicating factor, it is difficult disentangle whether these deficits are a direct result of chronic drug administration, or rather, result from a pre-existing vulnerability, or perhaps even the combination of both (Jentsch, 2008). For example, in nicotine dependence, it is possible that dysregulation of the ACC circuitry could be impaired due to a pre-existing condition, which could then lead to impaired function. Therefore, acute nicotine (i.e. smoking) may be a form of self-medication to rectify pre-existing cognitive problems. Another possibility is that individuals with frontal deficits are more likely to engage in drug use, and that the administration of drugs could increase the severity of the impairments, which in turn could lead to repetitive drug administration. In the following paragraphs we will explore both of these possibilities.

The notion that pre-existing impulsivity may cause individuals to be more sensitive to developing substance-related problems has been investigated through both animal and human studies. A number of recent animal studies found that rats screened as exhibiting enhanced levels of impulsivity (prior to drug exposure) predicted a vulnerability to subsequent, and increased, rates of self-administered intravenous cocaine (Anker et al., 2009; Dalley et al., 2007; Perry et al., 2005, 2008), and furthermore, this effect was found to be associated with changes in dopamine function within the ventral striatum (Dalley et al., 2007). Poulos et al. (1995) and Mitchell et al. (2006) uncovered a similar relationship between impulsivity (prior to ethanol exposure) and heightened self-administration of ethanol/alcohol in rats (Poulos et al., 1995) and mice (Mitchell et al., 2006). This concept is further supported by Diergaarde et al. (2008) who found that poor impulse control (identified prior to drug exposure) is associated with increased self-administration of nicotine in rats, and furthermore, these effects are associated with reduced dopamine release in the accumbens core and medial prefrontal cortex (Diergaarde et al., 2008). These findings suggest that impulsivity could be a risk factor in increasing an individual's vulnerability to the development of drug addiction.

Human studies have also explored the relationship between pre-existing impulsivity, difficulties in behavioral regulation, and a predisposition to drug use. These studies investigated the association between behavioral/attentional problems in childhood and the development of addictive behaviors. Recent longitudinal and cross-sectional studies evaluated children, who were considered at low and high risk of substance use (on the basis of parental substance use history), for levels of neurobehavior disinhibition (deficits in behavioral regulation); they found that the presence of these regulatory deficits correlated with future substance-related problems (Kirisci et al., 2004, 2005, 2006; Tarter et al., 2004). Further studies in children also uncovered a relationship between behavioral problems (such as conduct disorder) and an increased vulnerability drug addiction (Button et al., 2006; Disney et al., 1999; Ernst et al., 2003; Teresa et al., 2009). Therefore, there appears to be a link between childhood difficulties in behavioral regulation and an increased susceptibility to engage in substance-related behaviors. In both child and adult studies, there has also been growing interest in the association between personality characteristics (such as an impulsive personality), temperament and substance use. For example, recent studies have found that personality dimensions, such as risk-taking and sensation seeking, are associated with an increased propensity for substance-related problems (Dawe et al., 2004; Dawe and Loxton, 2004). Taking the findings of both animal and human studies into consideration, there is considerable support for the proposal that the presence of cognitive inhibitory impairments (impulsive behaviors) and frontostriatal dysfunction (highlighted throughout the current review) may have existed prior to drug exposure.

At the same time, a number of studies have explored the effect that drug exposure can have on cognitive ability, frontal circuitry and the development of addiction-related problems. Animal studies have found that exposure to drugs can result in increased impulsive behaviors, neural alterations in the PFC and reduced OFC functioning. Jentsch et al. (2002) examined whether administration of cocaine to monkeys had a negative effect on performance of behavioral tasks which are sensitive to orbitofrontal cortical function. Long-term cocaine administration was associated with poorer performance on the behavioral tasks which assessed inhibitory skills; the authors proposed that these impairments may result from drug-induced disruption of the orbitofrontal circuitry (Jentsch et al., 2002). Olausson et al. (2007) also found that short-term cocaine exposure in monkeys produced impairments in cognitive skills sensitive to OFC functioning, and it is interesting to note, they also found that monkeys showed enhancements in the motivational processes involving the limbic-striatal regions (Olausson et al., 2007). Therefore, cocaine-induced neuroadaptations to the frontal regions can result in a loss of impulse control and increased motivation to procure the drug. These findings are consistent across various species. Schoenbaum et al. (2004) investigated whether cocaine would cause long-lasting neural changes in the prefrontal cortex of rats. They administered cocaine injections into the rats, followed by a 2-week withdrawal period; after the withdrawal period, rats were trained on an odor discrimination task which is sensitive to OFC dysfunction. Cocaine-treated rats presented with behavioral impairments usually associated with OFC lesions (Schoenbaum et al., 2004). Simon et al. (2007) examined the long-term effects of cocaine exposure on tasks of impulsivity in rats. Three months after the initial exposure to cocaine, cocaine-exposed rats continued to display increased impulsive choice behavior. Thus it is possible that cocaine administration can induce enduring increases in impulsive behaviors (Simon et al., 2007). Briand et al. (2008) also conducted a study to assess whether self-administration of cocaine produced long-lasting change in cognitive abilities of rats. Rats were allowed short (1 h) and long (6 h) access to self-administered cocaine, and following this, rats were administered a cognitive task of sustained attention sensitive to dysfunction of the medial prefrontal cortex. Rats with long access to cocaine self-administration presented with a disruption in cognitive flexibility both immediately, and up to 30 days after, discontinuation of drug exposure. These impairments were reflected by alterations in the PFC (Briand et al., 2008). When combined, the above studies suggest that cocaine exposure in monkeys and rats can increase impulsive behaviors and that these changes could be due to drug-induced dysfunction of the OFC. In addition, it is possible that these drug-induced behavioral and PFC neural changes could be long lasting. Supporting these animal studies, human studies (which were previously reviewed in this article) have found that acute cocaine administration is associated with reduced inhibitory skills (Fillmore et al., 2002) and activating the frontal regions (Breiter et al., 1997; Risinger et al., 2005). Unfortunately though, to date, due to methodological and ethical difficulties, there are limited studies assessing the effects of drug-induced neuroadaptations in humans. Future longitudinal and prospective studies may be able to address these complications.

Unfortunately, there appears to be no straightforward answer to the complex question of whether the cognitive deficits are present prior to drug use or are a consequence of drug use. The current research provides support for both possibilities. It is perhaps logical that both of these processes may occur and the extent to which each influences behavior may vary according to each individual case. Therefore, these studies highlight the somewhat circular conundrum; increased impulsivity and frontal cortex dysfunction is a serious risk factor in the development of drug addiction, and at

the same time, chronic drug exposure causes increased impulsivity and frontal cortex dysfunction.

Further complicating matters, these cognitive deficits could be exacerbated by a number of additional features such as: poly-drug use, a comorbid psychiatric condition, head and brain injury and adolescent drug use. For example, chronic nicotine use and alcohol abuse frequently co-occur. The consumption of any two or more drugs has the potential to produce additive, synergistic or even multiplicative effects on neurocognitive and brain functioning (Durazzo et al., 2007).

Finally, the impact of individual variability in patterns of substance use is worthy of consideration. Individual drug users vary considerably in terms of: the duration, frequency, dosage, and type of drug(s) consumed. All of these factors make it difficult to isolate the exact pathogenesis of frontal and consequent (or even pre-existing) neurocognitive dysfunction in the development of addiction. We should also not overlook the potential effect of a changed context/environment (for example, heroin injected in the street compared to within a laboratory setting) in which the drug is administered in exerting a confounding effect on the neural responses of craving measured in these studies. It is important for future studies to seriously consider these limitations.

5. Future directions and clinical applications

Even after withdrawal and detoxification, relapse frequently reoccurs, despite the strong desire to cease drug use. To date, available treatment options for addiction remain limited and long-term success rates remain poor (for a review see O'Brien, 2008). We have highlighted the involvement of the frontal regions in inhibiting uncontrollable urges to consume drugs regardless of risk, including their general involvement in impulsive behaviors, decision-making skills and performance monitoring. In substance dependent individuals, dysfunction of these regions has been found to be associated with an increased vulnerability to prolonged drug use and relapse. In response to these findings, *additional* neurobiological targets (as well as targeting the traditional 'reward' pathways) of treatment have emerged.

It is important that clinicians consider a variety of treatment methods to promote cessation of drug consumption, maintenance of abstinence, prevention of relapse and recovery of impaired cognitive functioning. Psychological treatments may provide initial relief; however, individuals with drug dependence often find it difficult to adhere to such programs. An increasing number of studies have indicated that substance dependent individuals *with* cognitive deficits are more likely to drop out of cognitive treatment programs early and, subsequently, these individuals are more vulnerable to relapse (Aharonovich et al., 2006; Ersche and Sahakian, 2007). These observations emphasize the importance of developing treatment programs that more adequately address such cognitive deficits, especially the cognitive impairments discussed throughout our review, highlighting the need to monitor and/or screen for cognitive deficits in establishing which individuals are more at risk of relapse (Ersche and Sahakian, 2007).

Traditional pharmacological interventions of addictive disorders have attempted to reduce the aversive effects of drug cessation (withdrawal) and lower the rewarding effects of drug administration (targeting the mesolimbic 'reward' circuitry) (O'Brien, 2008). Relevant to our review are the recent pharmacological approaches which have begun to address the need to reduce uncontrolled drug seeking (Kalivas and O'Brien, 2007) and the development of anti-craving agents which enhance prefrontal cortical metabolism (O'Brien, 2005, 2008). For example, Acamprosate is a medication which appears to reduce long-lasting neuronal effects of chronic alcohol use, resulting in a decreased desire for alcohol. Naltrexone, an opiate receptor antagonist, has also been reported to suppress alcohol craving (for a review of anti-craving agents refer to O'Brien, 2005). However, despite clinical trials showing the benefits of anti-craving agents such as these, these medications are still not very well known and not widely prescribed by clinicians (O'Brien, 2005).

Another potential pharmacological strategy is the application of cognitive enhancer drugs to counter the deficits associated with prolonged drug use; these medications have also been used for treatment of attention deficit/hyperactivity disorders. For example, Modafinil, a catecholaminergic agonist, increases extracellular dopamine in the prefrontal cortex, and has been investigated for its applicability in treating cocaine dependence (Anderson et al., 2009; Dackis et al., 2004). Previous studies have found that Modafinil improved cognitive functioning on the Stroop Task and Stop Signal Task, and is capable of modulating ACC activity during a working memory task (Ersche and Sahakian, 2007). Anderson et al. (2009) found that Modafinil, in combination with behavioral therapy, both reduced cocaine craving, and increased number of abstinent days, of cocaine-dependent individuals seeking treatment. Clinical trials into the potential use of cognitive enhancing drugs which act to increase activity in key neurotransmitter systems of the frontal regions of chronic drug users, await further investigation, and remain a promising area of research.

Non-invasive brain stimulation techniques (TMS and tDCS), which can modulate cortical excitability in the PFC, are also being evaluated for their efficacy in reducing drug craving and associated addictive behaviors. We reviewed the brain stimulation studies (TMS or tDCS) which increased activity within the DLPFC and measured the ability of these techniques to decrease levels of drug consumption and craving levels. These brain stimulation techniques were able to transiently reduce drug consumption and levels of craving. It is possible that stimulation to the PFC may alter dysfunctional neural processes in substance dependent individuals, which could lead to improved inhibitory control, breaking the cycle of craving and reduce levels of drug-seeking. Further studies into the appropriate target of brain stimulation, intensity, frequency and length of treatment are required to optimize the use of stimulation techniques for addiction treatments.

Overall, growing evidence suggests that addressing frontostriatal dysfunction, and cognitive deficits, within an addiction treatment setting, could vastly improve intervention and treatment efficacy. A multi-modal approach, utilising a combination of these behavioral, pharmacological and brain stimulation techniques, may have a synergistic effect and provide more robust and lasting treatments for addiction.

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2.3. General summary

One of the key features of Alcohol Dependence (AD) is the reduced ability to inhibit the compulsive desire to consume alcohol regardless of risk. In the above review, the involvement of the frontostriatal circuitry in regulating inhibitory control was examined, followed by an assessment of how dysregulation of this circuitry within an alcohol dependent population may relate to difficulty inhibiting compulsive drug use. A small group of preliminary neuropsychological studies suggest that both acute and chronic alcohol consumption are related to cognitive impairment. These findings are supported by recent neuroimaging studies which located alterations within the corresponding frontal circuitry. Furthermore, these neurocognitive impairments were related to the development of AD and poor treatment outcome. Therefore, when combined, these studies offer initial insight into the presence of frontally-mediated cognitive impairments within alcohol dependent populations. However, despite these promising findings, the scope of the literature remains somewhat limited: (i) only a small number of studies have examined cognitive inhibitory deficits within an AD population, (ii) cognitive inhibitory deficits are proposed to relate to compulsive urges to consume alcohol and levels of craving; however, there is only minimal research into this relationship, and (iii) to date, only very few preliminary neuroimaging studies have examined the involvement of the frontal circuitry in an alcohol dependent population.

Therefore, the current thesis aims to expand on the current findings of inhibitory dysregulation in patients with AD by investigating whether these cognitive deficits relate to clinical measures of craving, and further, whether recovery of these cognitive impairments are associated with duration of abstinence (Chapter 9). There follows a TMS-EEG investigation (described in further detail in Chapter 5) of whether individuals with AD post-detoxification exhibit altered cortical activity within the frontal circuitry (Chapter 10).

CHAPTER THREE

Cognitive deficits and frontostriatal dysfunction: Major Depressive Disorder

3.1. General overview

In the present chapter, the presence of general cognitive deficits and the implicated frontostriatal dysfunction are explored within the context of Major Depressive Disorder (MDD). In the beginning of the chapter, the basic background of MDD is presented. The general concept of cognitive inhibitory dysfunction and the implicated brain regions was previously described in the article presented in Chapter 2, and therefore, to avoid excessive repetition it is not presented again in this chapter. Thus, after the general description of MDD, the next section applies the general cognitive models of frontostriatal dysfunction to cognitive symptoms of MDD. A defining feature of cognitive control is the ability to suppress prepotent responses to inappropriate representations. Therefore, difficulties disengaging from negative stimuli appear to reflect the deficits in inhibitory control that are associated with depression. However, the exact cognitive processes underlying these cognitive inhibitory impairments remain largely unknown. Recently, separate lines of research have identified two key components of cognitive dysfunction in depressive disorders: 1. Cognitive biases which refer to emotion-related cognitive impairments (i.e. biased response to affective stimuli), and 2. Cognitive deficits which represent generalised cognitive impairments (i.e. deficient response to neutral stimuli). A detailed overview of these two separate cognitive components is provided, and their potential role in inhibitory control that is specific to depressive symptoms is examined. There follows a discussion of whether these cognitive components are interrelated, or rather, independently contribute to core depressive symptoms.

3.2. Background of Major Depressive Disorder

MDD is a debilitating and chronic psychiatric disorder characterized by a constellation of heterogeneous clinical features. Depression is a widely prevalent disorder (Kessler et al.,

2003), and is considered the fourth leading cause of disability worldwide (Moussavi et al., 2007). MDD is characterized by a significant loss of quality of life (Papakostas et al., 2004), reduced social functioning (Kennedy et al., 2007) and is considered a major risk factor for suicide (Rihmer, 2001). Neuroimaging studies implicate hypoactivity of the prefrontal cortex (Drevets, 1999, 2000; Fitzgerald et al., 2006) and alterations within the inter-connected mesolimbic dopaminergic pathways (Drevets et al., 2008; Mayberg, 2003b, 2006; Mayberg et al., 1997; Nestler and Carlezon Jr, 2006) in the pathophysiology of MDD. However, despite extensive research into the psychological and neurobiological underpinnings of MDD, much remains unknown. As such, treatment of MDD continues to pose a critical challenge for clinicians, with almost one-third of patients with MDD remaining symptomatic even after adequate anti-depressant therapy (Fava, 2003; Malhi et al., 2005). Therefore, depression research has begun to focus on better understanding of the neuropsychological processes involved in MDD, and the factors which may identify those individuals who are more vulnerable to MDD.

Although depression primarily involves mood disturbances, cognitive impairment is becoming increasingly recognised as a prevalent feature of the disorder (Austin et al., 2001; Elliott et al., 2002; Porter et al., 2007; Rogers et al., 2004). Cognitive theorists place emphasis on the difficulty disengaging from negative stimuli in the aetiology and persistence of depressive disorders (Gotlib and Joormann, 2010). Cognitive control is defined as the ability to suppress prepotent responses to inappropriate representations. Thus, the inability to disengage from negative stimuli and representations may reflect the deficits in inhibitory control in depressive disorders. These postulations are consistent with neurobiological models of MDD, such that these cognitive impairments recruit key structures within the frontal circuitry and the mesolimbic dopaminergic pathways (Blasi et al., 2006; Chambers et al., 2009; Garavan et al., 2002; Miller and Cohen, 2001); the same circuitry implicated in the

pathophysiology of depressive disorders (Drevets, 1999, 2000; Drevets et al., 2008; Fitzgerald et al., 2006; Mayberg, 2003b, 2006; Mayberg et al., 1997; Nestler and Carlezon Jr, 2006). However, the exact processes underlying these frontally-mediated cognitive inhibitory impairments in depression remain largely unknown.

Researchers have identified the presence of generalised frontally-mediated cognitive impairments in depressive populations across a number of domains: such as, emotion-regulation (Eugène et al., 2010; Gotlib and Joormann, 2010; Joormann et al., 2007; Koster et al., 2011; Koster et al., 2005; Watkins, 2008), cognitive inhibition (De Lissnyder et al., 2012; Kaiser et al., 2003; Langenecker et al., 2007), attention (Baune et al., 2010; Li et al., 2010; Ravnkilde et al., 2002; Vasic et al., 2008), executive function (Gohier et al., 2009; Hammar et al., 2011; Harvey et al., 2004; Paelecke-Habermann et al., 2005; Vanderhasselt and De Raedt, 2009) and memory (Hertel, 2004; Hertel, 2000). Additionally, a number of these cognitive impairments have been found to remain beyond remission (Airaksinen et al., 2006) and influence the ability of individuals with depression to functionally recover (Baune et al., 2010; Jaeger et al., 2006). However, despite these significant findings, cognitive impairments were not always consistently observed and the nature of the identified cognitive impairment varied considerably across the different studies (Grant et al., 2001; Ravnkilde et al., 2002).

Therefore, although cognitive impairments (Austin et al., 2001) and associated frontostriatal dysfunction (Drevets, 2000, 2001; Rogers et al., 2004) appear to play a central role in the persistence and recurrence of depressive symptoms (Beck et al., 1979; Clark et al., 2009; Gotlib and Joormann, 2010; Joormann, 2010; Joormann and Gotlib, 2010; Joormann et al., 2007; Paelecke-Habermann et al., 2005; Ravnkilde et al., 2002); the precise character of these cognitive inhibitory deficits and the involvement of frontostriatal dysregulation remains largely unknown. Therefore, the current thesis is designed to examine the nature of inhibitory processes underlying the difficulties disengaging from negative stimuli. It is anticipated that a

better understanding of these inhibitory processes and the related disrupted frontal circuitry will provide further insight into the pathophysiology of depressive disorders and contribute towards the development of improved therapeutic strategies.

3.3. Cognitive features of Major Depressive Disorder

Two major components of cognitive inhibitory dysfunction in depressive disorders have been identified (Joormann et al., 2007; Murrough et al., 2011); 1. *Cognitive biases* represented by cognitive impairments which are *specific* to emotion-regulation (Goeleven et al., 2006; Gotlib et al., 2004; Joormann, 2010), and 2. *Cognitive deficits* as reflected by *generalised* executive deficits in cognitive and attentional control (Chamberlain and Sakakian, 2006; Clark et al., 2009; Desseilles et al., 2009; West et al., 2010). Traditionally, researchers focused predominantly on cognitive biases and the difficulty suppressing emotion-related material (i.e. cognitive biases); recently however, researchers have begun to examine the cognitive mechanisms involved in the processing of neutral stimuli within depressive disorders (i.e. cognitive deficits). Surprisingly though, very few studies have attempted to integrate these separate lines of research (De Lissnyder et al., 2012; Joormann, 2010; Murrough et al., 2011). Therefore, the next section provides a detailed description of these two components of cognitive inhibitory dysfunction and applies these concepts within the context of MDD. Finally, there will be a discussion of whether these two cognitive components of depression exert interrelated, or rather, independent effects on dysregulated inhibitory control in depressive disorders.

3.3.1. Cognitive biases

Affective bias and emotion-regulatory dysfunction plays a critical role in depressive disorders (Goeleven et al., 2006; Gotlib et al., 2005; Joormann, 2004). Clinically, these impairments are reflected by the reduced ability to inhibit negative thoughts and disengage from negative stimuli (Beck et al., 1979; Eugène et al., 2010; Gotlib and Joormann, 2010; Joormann et al.,

2007; Koster et al., 2011; Koster et al., 2005; Watkins, 2008). These emotion-regulatory impairments have been found to contribute to the maintenance and exacerbation of depressive symptoms (Berman et al., 2011) and the compromised ability to functionally recover from MDD (Baune et al., 2010; Jaeger et al., 2006). Previous studies have found that exposure to negatively-valanced emotional material caused greater interference effects in depressive patients than in healthy controls (Goeleven et al., 2006; Gotlib and McCann, 1984; Lim and Kim, 2005; McNeil et al., 1999) which was related to dysfunction of the frontal-parietal regions (Dai and Feng, 2011; George et al., 1997; McNeely et al., 2008; Mitterschiffthaler et al., 2008). Consistent with these findings, further neuroimaging studies have identified the involvement of the limbic-frontal circuitry in emotion-regulation (Phillips, 2003; Phillips et al., 2003a, b), the same circuitry implicated in the pathophysiology of mood disorders (Drevets et al., 2008; Mayberg et al., 1997). For example, the anterior cingulate cortex (ACC) a key structure for the integration of emotional information and the ability to self-regulate (Davidson et al., 2002a; Davidson et al., 2002b; Mayberg, 1997; Pizzagalli et al., 2001; Pizzagalli, 2011) is also associated with processing of negative thoughts (Eugène et al., 2010) and clinical response to treatment (Mayberg et al., 1997; Mayberg et al., 1999; Pizzagalli, 2011) in depressive disorders. Therefore, these cognitive biases appear to play a critical role in the dysregulation of inhibitory control for negative material in depressive disorders and are likely to relate to the persistence of depressive symptoms. However, it seems likely that these cognitive biases do not act in isolation; the presence of general cognitive inhibitory deficits may also play a critical role in the difficulty inhibiting negative representations in patients with MDD.

3.3.2. Cognitive deficits

In addition to studies evaluating emotion-related cognitive aspects of depression, a number of recent studies have identified general inhibitory deficits in cognitive function which are

unrelated to emotional information (Clark et al., 2009; Hammar and Årdal, 2009). These findings are consistent with the clinical diagnosis of MDD, which includes "an impaired ability to think or concentrate" (DSM-IV-TR, American Psychiatric Association., 2000). As such, a growing literature suggests that depression-related inhibitory impairments are also involved in the processing of non-emotional information (Joormann et al., 2007). In the current thesis, we explore non-emotion related cognitive inhibitory deficits with a focus on dysfunction of cognitive and attentional control.

The concept of generalized cognitive control has already been described in detail in the above review (Feil et al., 2010). Therefore, in this section, I will relate the concept of cognitive inhibitory deficits to patients with MDD. Despite a number of behavioural studies exploring generalized executive dysfunction in patients with MDD (Austin et al., 2001; Elliott et al., 2002; Ochsner and Gross, 2005), very few studies have directly evaluated cognitive inhibitory deficits within depressive populations (De Lissnyder et al., 2012; Langenecker et al., 2007). These preliminary studies demonstrate that depressive patients present with cognitive inhibitory impairments (De Lissnyder et al., 2012; Kaiser et al., 2003; Langenecker et al., 2007) and associated alterations within the frontal and limbic circuitry (Kaiser et al., 2003; Langenecker et al., 2007). Moreover, these cognitive deficits are associated with increased rumination (De Lissnyder et al., 2012) and predictive of treatment response (Langenecker et al., 2007) in depressive disorders. Interestingly, studies regarding memory impairments within depressive populations (Burt et al., 1995) also suggest that depressed individuals perform more poorly in unconstrained memory tasks, more specifically, tasks that require cognitive flexibility, goal-orientated action and intact cognitive inhibition of irrelevant information (Hertel, 2004; Hertel, 2000). Therefore, when combined, these initial studies provide support for the proposition that depressed individuals are characterized by

reduced frontally-mediated cognitive control which occurs in the absence of negative stimuli, and thus, may not be specific to negative mood or affective processing.

In terms of attentional control, it is surprising that despite decreased concentration being a cognitive criterion for the clinical diagnosis of depression (DSM-IV-TR, American Psychiatric Association., 2000), very few studies have investigated generalised attentional processes in depression (Levin et al., 2007; Ravnkilde et al., 2002). Rather, research into attentional aspects of depression focused mainly on mood-congruent attentional bias (Baert et al., 2010). With regards to generalized attentional deficits, studies thus far have identified impaired sustained (Cornblatt et al., 1989; Mialet et al., 1996; Ravnkilde et al., 2002), divided (Majer et al., 2004; Thomas et al., 1998; Vasic et al., 2008), visual (Li et al., 2010) and general (Baune et al., 2010) attention across patients with depression. Recent neuroimaging studies employed voxel-based morphometry to measure the structural changes associated with attentional deficits in depressive disorders (Li et al., 2010; Taki et al., 2005; Vasic et al., 2008). Structural decreases were observed across the fronto-limbic circuitry and related to poorer performance attentional control in patients with MDD (Vasic et al., 2008), in non-remitters relative to remitters (Li et al., 2010), and in elderly men with subthreshold depression (Taki et al., 2005). Moreover, the presence of impaired attentional control is associated with increased depressive symptoms (Li et al., 2010; Paelecke-Habermann et al., 2005) which persist beyond remission (Baune et al., 2010; Weiland-Fiedler et al., 2004) and relates to the increased risk of relapse (Majer et al., 2004).

Thus, when combined, these studies provide preliminary empirical support for pervasive deficits in general cognitive inhibitory functioning. Additionally, these cognitive deficits appear to relate to dysfunction of the fronto-limbic circuitry, the same brain circuitry implicated in the presence (Brody et al., 2001; Davidson et al., 2002b; Mayberg et al., 1999), persistence (Drevets et al., 2008) and treatment response (Kumari et al., 2003; Langenecker

et al., 2007; Mayberg, 1997; Pizzagalli et al., 2001; Pizzagalli, 2011) in depressive disorders. Therefore, converging evidence is suggestive of a potential relationship between generalized cognitive inhibitory deficits and frontostriatal dysfunction in depressive disorders. However, to date, the scope of the literature is somewhat limited, as the majority of research has been directed towards biased processing of emotional information, and only a small number of studies have examined deficits in general cognitive inhibitory functioning within a depressive population.

3.3.3. Relationship between cognitive biases and cognitive deficits

Surprisingly, very few studies have attempted to integrate these two components of inhibitory dysfunction in depressive disorders (De Lissnyder et al., 2012; Joormann, 2010; Murrough et al., 2011). It is possible that these cognitive components are interrelated: the presence of cognitive deficits may enhance the processes involved in cognitive biases, and vice versa. Or rather, these cognitive components may exert independent, yet additive, effects on inhibitory control in depressive populations. Regardless of whether these cognitive components are interrelated or independent, it appears that the framework of cognitive inhibitory impairments in MDD may be more complex than initially perceived. Therefore, it is worthwhile investigating the presence of both cognitive deficits and cognitive biases in depressive disorders, and the extent of any possible interactions. A better understanding of these impairments will contribute to the neuropsychological profile of MDD, and it is anticipated that treatment models could be designed to target these specific cognitive inhibitory impairments.

3.4. General summary

A core feature of depressive disorders is the difficulty disengaging from negative stimuli. Traditionally, cognitive research focused on emotion-related inhibitory biases in depressive disorders; emerging studies however, have expanded on the inhibitory cognitive components

described in MDD to also include non-emotion related (i.e. neutral) cognitive inhibitory deficits. Therefore, the character of cognitive inhibitory impairment within depressive disorders may be more complex than previously conceptualized. However, to date, there has been minimal research into the presence of cognitive inhibitory deficits within depressive populations. Furthermore, the framework of how these emotion-related (cognitive biases) and non-emotion related (cognitive deficits) interact, and are involved in the impaired ability to disengage from negative representations, remains unknown.

In the current thesis, there will be an examination of whether both components of cognitive inhibitory impairment (cognitive biases and cognitive deficits) are indeed present within a severely depressed population. There follows an evaluation of whether these cognitive impairments are interrelated, or rather, exert a unique effect in depressive disorders (Chapter 7). It is anticipated that therapeutic strategies designed to specifically target *both* of these components of cognitive dysfunction, may lead to the development of improved treatments.

CHAPTER FOUR

Brain stimulation techniques and psychiatric disorders: Alcohol Dependence

4.1 General overview

In the fourth chapter, the second published review titled, *Brain stimulation in the study and treatment of addiction,* is presented. The review begins with a brief introduction into the neurobiology of addiction which is placed in the context of the potential effects of brain stimulation on addictive behaviours. Next, the basic mechanisms of Transcranial Magnetic Stimulation (TMS) are described, which then leads into a discussion of how TMS inhibitory paradigms can be used as a research tool to index the pathophysiology of various psychiatric disorders. There follows a review of addiction studies which have administered TMS to assess alterations in cortical excitability associated with substance dependence. The article then outlines how repetitive brain stimulation techniques may be administered as a therapeutic tool. Finally, implications of brain stimulation techniques in the study of addiction are discussed. Following the published article, there is a discussion of the new development of the combined TMS and electroencephalography (TMS-EEG) technique and the utility of administering this technique to provide a measure of cortical excitability within the frontal cortex of an alcohol dependent sample.

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Review

Brain stimulation in the study and treatment of addiction

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ABSTRACT

Addiction is a devastating and chronically relapsing disorder. Repeated drug administration induces neuroadaptations associated with abnormal dopaminergic activity in the mesocorticolimbic circuitry, resulting in altered cortical neurotransmission and excitability. Electrical stimulation of specific brain regions can be used in animal models and humans to induce local activation or disruption of specific circuitries or alter neuronal excitability and cause neuroadaptations. Non-surgical stimulation of specific brain regions in human addicts can be achieved by transcranial magnetic stimulation (TMS). TMS is used for transient stimulation or disruption of neural activity in specific cortical regions, which can be used to assess cortical excitability, and to induce changes in cortical excitability. Moreover, it is suggested that repeated stimulation can cause long-lasting neuroadaptations. Therefore, TMS paradigms were used in some studies to assess the presence of altered cortical excitability associated with chronic drug consumption, while other studies have begun to assess the therapeutic potential of repetitive TMS. Similarly, transcranial direct current stimulation (tDCS) is used to modulate neuronal resting membrane potential in humans and alter cortical excitability. The current review describes how these brain stimulation techniques have recently been used for the study and treatment of addiction in animal models and humans.

Contents

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1. Introduction

One of the most challenging consequences of chronic substance use is the development of dependence. Addiction can be described as a persistent state in which there is diminished capacity to control compulsive drug-seeking, regardless of whether it involves risk of negative consequences (Hyman and Malenka, 2001). To date, available treatment options for addictive behaviors remain limited, and long-term success rates are poor (O'Brien, 2008). The role of the mesolimbic dopaminergic system which includes the ventral tegmental area (VTA) and nucleus accumbens (NAc) has been extensively studied in addiction (Berridge and Robinson, 1998; Kelley and Berridge, 2002; Koob and Nestler, 1997; Robbins and Everitt, 1996). In addition to the acute effect of various drugs of abuse on dopamine release in this system, chronic drug use has been associated with neuroadaptations within several sites in the mesocorticolimbic reward circuitry, including the NAc (ventral striatum), the VTA, the amygdala and the prefrontal cortex (PFC) (Everitt et al., 2008; Hyman and Malenka, 2001; Kalivas and O'Brien, 2007; Robinson and Berridge, 2003; Volkow et al., 2003). These neuroadaptations result in altered dopaminergic activity and cortical excitability (Kalivas and O'Brien, 2007; Kauer and Malenka, 2007; Wise, 1996b), which have been implicated in the persistence of drug-seeking behaviors, increased difficulties regulating drug-seeking behaviors and a heightened likelihood of relapse (Everitt et al., 2008; Jentsch and Taylor, 1999).

Electromagnetic brain stimulation allows modulation of activity in specific brain regions. Recent studies have begun to utilize non-surgical brain stimulation techniques in assessing altered cortical excitability in individuals exposed to addictive drugs in order to further explore the acute and lasting effects of repeated drug use on cortical excitability. Furthermore, several novel studies have begun to assess the potential benefits of brain stimulation in reducing drug craving and associated addictive behaviors. The current review focuses on two non-surgical brain stimulation techniques; Transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). In addition, recent animal model studies, in which brain stimulation approaches were used, are discussed.

TMS is based on inducing brief and strong electric current in a coil placed over the scalp. The rapid change in the current induces a transient, high-intensity magnetic pulse that penetrates through the scalp, skull and meninges to the underlying cortex and generates an electric field that can depolarize cortical neurons beneath the coil (Fitzgerald et al., 2002; Hallett, 2007; Rachid and Bertschy, 2006). TMS can be used to either stimulate or disrupt neural activity in specific cortical regions. In the past, it was very difficult to explore altered cortical excitability in humans. TMS however, is emerging as a promising investigative tool for indexing localized changes in cortical excitability in the brain. Recently, TMS inhibitory paradigms have been applied to examine the effects of drug administration on cortical activity. These studies suggest the presence of altered cortical excitability in the motor and prefrontal cortex of individuals exposed to various addictive drugs.

Repetitive TMS (rTMS) is capable of altering cortical excitability beyond the period of stimulation (Fitzgerald et al., 2006b). Preliminary studies have begun to assess the administration of rTMS as a potential treatment for reducing addictive behaviors. Similarly, tDCS is another non-surgical brain stimulation method capable of altering cortical excitability by modulating neuronal resting membrane potential. Administration of tDCS for an increased duration can result in the prolonged modulation of cortical excitability beyond the period of stimulation (Nitsche and Paulus, 2000, 2001). Both TMS and tDCS induce an electrical field in the cortex which results in neuromodulations. However, while TMS usually involves direct excitation of neurons by induction of action potentials, tDCS utilizes subthreshold fields but much longer pulse durations. In addition, TMS is thought to induce more localized effects. Specific detail of the mechanisms of action of TMS and tDCS will be described later in the review. Recent exploratory studies have sought to explore whether the prolonged effects of rTMS and tDCS can have clinical benefits in reducing craving and addictive behaviors.

The first section of this review provides a brief introduction into the neurobiology of addiction and the potential effect of brain stimulation on addictive behaviors. The second section describes the basic mechanisms of TMS and discusses how TMS inhibitory paradigms can be used to investigate the pathophysiology of addictive behaviors. Then, studies assessing the potential effects of localized brain stimulation treatments on addictive behaviors in animal models and humans (using rTMS) are reviewed. Finally, the mechanisms underlying tDCS are described, and the possibility to utilize this tool in reducing addictive behaviors is examined. In the last section, future directions of localized brain stimulation in addiction studies are discussed.

2. Neurobiology of addiction

2.1. Introduction to addiction

Drug addiction, a chronically relapsing disorder, is characterized by loss of control over drug-seeking and the compulsive desire to procure drugs regardless of aversive consequence (Hyman and Malenka, 2001). Various approaches and extensive research have been conducted to assess the molecular and cellular factors involved in drug administration, and their contribution to the development of addictive behaviors (Everitt et al., 2008; Feltenstein and See, 2008; Kalivas and Volkow, 2005; Lingford-Hughes et al., 2003; Robinson and Berridge, 2003; Wise, 1996b). Neurobiological studies of addiction have established an association between the increase in neuronal activity in the mesocorticolimbic dopamine system and the acute rewarding and reinforcing effects of addictive drugs (Everitt et al., 2008; Feltenstein and See, 2008;

Koob and Nestler, 1997; Wise, 1996b). Stimulant drugs (Chen et al., 2009; Kalivas, 2007; Thomas et al., 2008), such as cocaine and amphetamines induce a direct increase in dopamine levels within the mesocorticolimbic circuitry, while drugs such as nicotine, alcohol, cannabis and opiates increase dopaminergic transmission by acting on the mesocorticolimbic pathways through various intervening receptor systems (Wise, 1996a). In addition to dopamine, major neurotransmitters such as γ-aminobutyric acid (GABA) and glutamate in the brain reward system were shown to play a critical role in addictive behaviors (Enoch, 2008; Filip and Frankowska, 2008; Gass and Olive, 2008; Lingford-Hughes et al., 2003). Within the mesocorticolimbic circuitry, several studies have specifically implicated enhanced glutamate release and glutamate receptors activity (in dopaminergic cells) (Kalivas et al., 2009; Tzschentke and Schmidt, 2003), and alterations in GABA neurotransmission (Enoch, 2008; Filip and Frankowska, 2008), in the development of addictive behaviors. Furthermore, glutamate release from the PFC and amygdala, into the core of the NAc, has also been associated with the persistence of drug-seeking (Kalivas et al., 2009; Tzschentke and Schmidt, 2003).

The mesocorticolimbic circuitry includes dopamine projections from cell bodies in the VTA to limbic structures such as the NAc (Di Chiara, 2002), amygdala (Childress et al., 1999; Meil and See, 1997) and hippocampus (Robbins et al., 2008), and to cortical areas such as the PFC, including the orbitofrontal cortex and anterior cingulate (Goldstein and Volkow, 2002; Jentsch and Taylor, 1999). Chronic drug administration has been proposed to usurp these circuits (which normally subserve processing of natural rewards) and induce long-term neuroadaptations (Hyman et al., 2006; Kauer and Malenka, 2007; Robinson and Berridge, 1993). These neuroadaptations are partly mediated by repeated hyperactivity of dopaminergic transmission (induced by the acute effect of the drug) and result in alterations in cortical neurotransmission and excitability (Wolf et al., 2004).

The NAc, a key component of the mesolimbic system, plays a crucial role in goal directed behaviors (Di Chiara et al., 2004). The NAc forms the ventral components of the striatum and can be divided into two functionally distinct sub-compartments; the shell and core (Di Chiara, 2002). Reciprocal innervations from the NAc *shell* with the VTA, are considered to be critical in influencing motivational salience and responding to novel rewarding stimuli (Ito et al., 2004). The NAc *core*, which is interconnected with the anterior cingulate and the orbitofrontal cortex, is suggested to mediate the expression of learned behaviors, and receives glutamatergic afferents from the PFC (Di Chiara, 2002; Ito et al., 2004), while dopamine release into the core occurs in response to stimuli predicting a motivating event (Cheng et al., 2003). Therefore, the NAc receives information regarding motivationally relevant events (reward opportunities such as evaluating the reinforcing effects of a drug) from the VTA, amygdala, hippocampus and PFC, and responds by providing output to brain circuits which modulate the expression of the behavioral response (i.e. whether to seek or approach the drug) (Robbins and Everitt, 1996). Repeated exposure to addictive drugs is proposed to lead to dysregulation of the mesolimbic circuitry, which could lead to a heightened motivation to consume drugs, and a reduced ability to regulate the behavioral response to drug cues (Di Chiara, 2002; Di Chiara et al., 2004).

In addition to the mesolimbic circuitry, chronic exposure to addictive drugs can result in alterations of frontal cortical areas, including projections from the dorsolateral prefrontal cortex (DLPFC), orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC) (Goldstein and Volkow, 2002; Jentsch and Taylor, 1999). Neuropsychological studies have found that dysfunction within the frontal cortical circuitry translates (behaviorally) to a reduced ability to inhibit prepotent behavioral responses to drug-seeking (Lubman et al., 2004). Neuroimaging studies uncovered abnormalities within frontal brain regions of individuals chronically exposed to addictive drugs (Goldstein and Volkow, 2002). Notably, there were abnormalities within frontal brain regions such as the DLPFC (goal identification and selection) (Wilson et al., 2004), the OFC (decision making, impulsivity and behavioral inhibition) (Dom et al., 2005), and the ACC (assessment of consequences and error detection) (Yücel et al., 2007). Abnormalities within these three PFC-striatothalamic circuits are proposed to play a central role in compulsive drug-seeking and relapse.

Therefore, the neuroadaptations induced in these circuitries by repeated administration of drugs of abuse, and the suggested role of these neuroadaptations in addictive behaviors, highlight the importance of further human studies into the neurophysiological outcomes of such neuroadaptations. In addition, addressing dysregulations in the mesocorticolimbic circuitry may contribute to the design of more effective treatments in reducing behaviors associated with addiction, such as compulsive use, heightened craving, and relapse.

2.2. Addiction and brain stimulation: A brief overview

Brain stimulation techniques in addiction research have been used as an investigative tool to index altered cortical excitability induced by chronic exposure to drugs of abuse. Most of these studies were conducted to assess changes in excitability of the motor cortex (Boutros et al., 2001, 2005; Lang et al., 2008; Sundaresan et al., 2007; Ziemann et al., 1995). In addition, a number of recent studies have begun to assess the effects of addictive drugs on the PFC by combining brain stimulation with EEG techniques (Kahkonen, 2005; Kahkonen et al., 2001, 2003). It is anticipated that utilizing these techniques to measure cortical activity in response to localized stimulation could provide insight into the effect of chronic drug administration on cortical excitability and the pathophysiology of uncontrolled craving.

In addition, *repeated* brain stimulation treatment can modulate cortical excitability (e.g. in the PFC) and thereby alter neuronal activity of circuits associated with drug craving. Therefore, repeated brain stimulation is being evaluated for its potential efficacy in reducing drug craving and associated addictive behaviors. In these studies, brain stimulation techniques were applied to the DLPFC, and their ability to affect drug consumption and craving levels were measured (Amiaz et al., 2009; Camprodon et al., 2007; Eichhammer et al., 2003; Johann et al., 2003; Politi et al., 2008). Overall, it was found that stimulation of the PFC can transiently reduce drug consumption and levels of craving. There are several mechanisms proposed to explain these effects. Firstly, stimulation of the DLPFC can induce release of dopamine in the caudate nucleus (Strafella et al., 2001). Therefore, repeated stimulation may induce neuroadaptations in dopaminergic systems. Moreover, while administration of drugs induces an acute increase in dopamine levels, during withdrawal dopaminergic activity is reduced. Decreased dopaminergic activity has been associated with increased levels of craving and relapse (Diana et al., 1998, 1999, 2006). Therefore, it is possible that even transient increases in dopamine release by brain stimulation may help reduce levels of craving in subjects under these withdrawal conditions (Blum et al., 2008). Secondly, the effects of brain stimulation can extend beyond the directly targeted area, including cross-hemispheric cortical and subcortical activity in remote neural networks connected to the stimulated regions (George et al., 1999). Therefore, given the ability of brain stimulation to modulate cortical excitability, it is possible that these stimulations are able to alter neuroadaptations and synaptic plasticity in the brain reward system. Thirdly, the PFC has been strongly implicated in drug-seeking behaviors. The DLPFC is

proposed to play an executive role in controlled response inhibition, and furthermore, stimulation of the DLPFC could also induce neuromodulations in the OFC and ACC (also implicated in inhibitory control), through its connectivity. Therefore, it is possible that repeated PFC stimulation could lead to improved inhibitory control and thereby reduced levels of drug-seeking.

In summary, brain stimulation techniques are used to index alterations in cortical excitability and could provide further insight into the pathophysiology of addictive behaviors. In addition, repeated brain stimulation may induce neuroadaptations to address abnormalities in regions and circuits that regulate compulsive drug-seeking, craving levels and relapse. The following sections will focus on the basic mechanisms of brain stimulation techniques and explore how they can be used in the study and treatment of addiction.

3. Transcranial magnetic stimulation (TMS) in the study of addiction

3.1. Technical overview of TMS

TMS is a powerful, non-surgical brain stimulation technique and is proving to be valuable for both its research and therapeutic potential within the field of psychiatric medicine (Wagner et al., 2007). TMS administration has a modulatory effect on cortical excitability and is used to facilitate functional brain mapping of cortical regions (Hallett, 2000). To deliver TMS to the brain, a brief electric current passes through a magnetic coil which induces a transient, high-intensity magnetic pulse that penetrates through the scalp, skull and meninges to the underlying cortex. This pulse generates an electric field within the targeted cortical regions that can induce depolarization of superficial cortical neurons (Barker et al., 1985; Rachid and Bertschy, 2006). This results in stimulation or disruption of local neural activity in the region beneath the coil and interconnected areas (Daskalakis et al., 2002; Hallett, 2007) (Fig. 1).

The effect of TMS administration on cortical excitability depends largely on the parameters of stimulation. Variations in stimulation parameters include: orientation of the induced magnetic field, single or repeated stimulation, frequency of stimulation, number of pulses, intensity and site of stimulation (Fitzgerald et al., 2002; Jung et al., 2008; Paus et al., 2001; Wassermann et al., 1998). In addition, a variety of differently shaped magnetic coils have been developed to affect neural activity and excitability in various brain regions. These include: (1) Round coils which are powerful but not focal, (2) Figure-8 coil, consists of two round coils, side by side, which are more focal but superficial, and (3) The newly developed H-coil, with complex windings, which is capable of stimulating deeper structures, without excessive field strengths, but less focal (Daskalakis et al., 2002; Hallett, 2007; Rossini and Rossi, 2007; Wagner et al., 2007; Zangen et al., 2005).

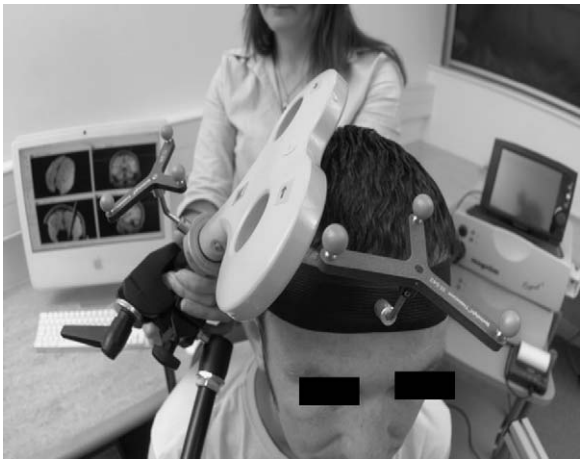

Fig. 1. Transcranial magnetic stimulation (TMS) application using a figure-8 coil over the motor cortex. The TMS figure-8 coil is placed over the subject's right motor cortex using a mechanical coil holder. A brief electric current passes through the magnetic coil which induces a transient magnetic pulse. This pulse penetrates through to the underlying cortex and generates an electric field within the targeted cortical regions which can induce depolarization of superficial cortical neurons and in this case activate muscles of the left hand if the intensity used will be above the motor threshold. Repetitive TMS can result in stimulation and disruption of local neural activity in the region beneath the coil and interconnected areas. Images courtesy of The Magstim Company Limited.

The TMS pulses can also be administered in different patterns (Kobayashi and Pascual-Leone, 2003; Ziemann, 2004). The most common and simple application is single pulse stimulation, in which a single pulse is administered without repetition. To study neural excitability, paired-pulse stimulation is often used, in which two TMS pulses are applied sequentially. Finally to induce longer lasting alterations, facilitation or functional disruptions, rTMS is used, in which trains of several TMS pulses are delivered, using various stimulation patterns (Ziemann, 2004). While the long-lasting neurophysiological effects of rTMS are poorly understood, several studies showed that rTMS can induce significant and long-lasting behavioral alterations, including reduction in craving and consumption of drugs of abuse.

3.2. TMS as a research tool of the pathophysiology of addiction

In the past, it was difficult to measure cortical excitability of the human brain directly. TMS however, is proving to be a useful investigational tool for indexing localized changes in cortical and corticospinal excitability (Cohen et al., 1998; Fitzgerald et al., 2002; Hallett, 2007; Jahanshahi and Rothwell, 2000). Recently, studies have utilized TMS to study cortical excitability and abnormal cortical inhibition (CI) in order to provide new insights into the pathophysiology of various brain disorders. CI refers to a mechanism through which GABA inhibitory interneurons reduce the activity of other local neurons (Daskalakis et al., 2006; Fitzgerald et al., 2006b, 2008). GABA exerts an inhibitory effect on interneuronal activity, while excitatory neurotransmission, which facilitates cortical excitability, is mediated mainly through glutamate. The balance of inhibitory and excitatory neurotransmission is crucial to maintaining the optimal balance of cortical excitability (Torregrossa and Kalivas, 2008). Alterations to the balance of cortical excitability are related to deficits in brain functioning that may result in neurological and psychiatric disorders. In assessing neural excitability and CI, TMS pulses were traditionally administered to the motor and occipital cortex due to the ease at which electromyographic and phosphene activity could be recorded. Although alterations in motor cortex excitability may not be directly related to excitability in the reward circuitry, nevertheless, it can demonstrate how repeated drug use can induce long-lasting effects on neural excitability, and perhaps even used as a diagnostic tool. The new development of a combined TMS-electroencephalography (EEG) tool now allows researchers to utilize TMS paradigms for studies in CI of the DLPFC as well (Daskalakis et al., 2008a,b; Fitzgerald et al., 2008) (Fig. 2).

Recently, TMS has been employed as an investigational tool to examine the effect of exposure to addictive drugs on CI in the cerebral cortex. These studies have assessed cortical excitability across the following drug groups: cocaine (Boutros et al., 2001, 2005; Sundaresan et al., 2007), nicotine (Lang et al., 2008), ecstasy (Oliveri and Calvo, 2003) and ethanol (Conte et al., 2008; Kahkonen, 2005; Kahkonen et al., 2001, 2003; Ziemann et al., 1995). These studies reported altered CI in individuals exposed to addictive drugs, suggesting that abnormal cortical excitability may reflect changes in the brain GABA and glutamate systems. To

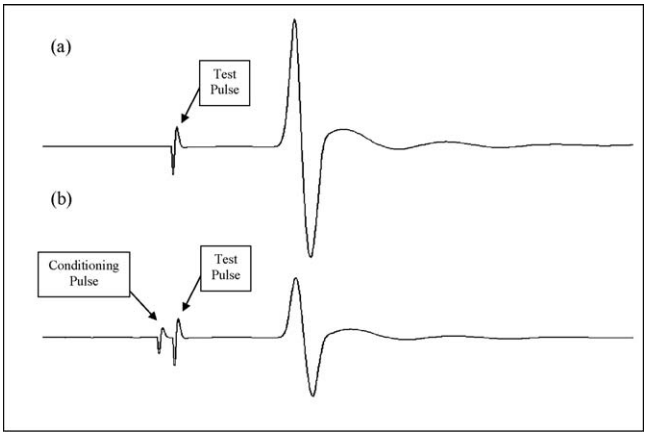

Fig. 2. An illustration of the effects of single and paired-pulse TMS on motor evoked potential (MEP), as measured by surface electromyogram recordings. Surface electromyogram recordings of MEP responses following: (a) a single test pulse and (b) paired-pulse stimulation. The test pulse is preceded by the conditioning pulse, which results in a reduced MEP.

investigate these assumptions, a number of different inhibitory TMS paradigms were applied. The following section begins by outlining the main TMS inhibitory paradigms, followed by a description of recent studies which have utilized these paradigms to index CI in individuals exposed to addictive drugs.

3.2.1. Cortical excitability: TMS paradigms

3.2.1.1. Motor threshold (MT). When a single pulse stimulation of a sufficient strength is applied over the primary cortex, the corticospinal pathway is activated, and the muscles corresponding with the stimulated region contract (i.e. a muscle twitch). These TMS-induced motor responses elicit motor evoked potentials (MEPs) in the contralateral extremity muscles. Electromyogram activity of these MEPs can be recorded and are widely used to measure corticospinal excitability. Motor threshold (MT) is a measure of cortical excitability and refers to the minimum magnetic pulse strength at which a small MEP can be recorded from the target muscle. MT can be measured at rest or throughout active contraction of the target muscle. Therefore, MT provides insight into corticospinal excitability. Furthermore, MT can be influenced by drugs that block voltage gated sodium or calcium channels (Chen et al., 1997; Ziemann et al., 1996a), while no significant effect is observed when exposed to drugs that alter GABA (Ziemann et al., 1996b) or glutamate (Liepert et al., 1997; Ziemann et al., 1998) transmission. Based on these observations, it was suggested that MT strength could reflect ion channel conductivity, and consequently, membrane excitability in pyramidal neurons (Ziemann, 2004; Ziemann et al., 1996c).

3.2.1.2. Motor evoked potential (MEP) amplitude. The amplitude of MEP reflects both the integrity of the corticospinal tract and excitability of the corticospinal system (Rossini and Rossi, 2007). Recruitment curve refers to the increase of MEP amplitude with an increase in TMS intensity. MEP amplitude increases with TMS intensity in a sigmoid fashion (Devanne et al., 1997). At low stimulus intensity, the corticospinal volley which results in the MEP usually consists of one wave. At high stimulus intensity, the corticospinal volley has greater complexity and consists of multiple waves. To explain these observations, several studies (Ziemann, 2004) have suggested that at high stimulus intensity, MEP is modified and influenced by additional processes involving extensive release of neurotransmitters (glutamate and GABA) and modulators of neurotransmission (e.g. dopamine). In addition, an increase in the slope of the recruitment curve has been induced by drugs that increase adrenergic transmission. Conversely, sodium and calcium blockers, and drugs that amplify effects of GABA, were found to decrease that slope. Furthermore, changes in MEP amplitude were reported when there has been no detectable change in MT (Ziemann, 2004). These findings highlight the physiological differences between MT and the MEP amplitude.

3.2.1.3. Cortical silent-period (CSP) duration. CSP is a measure of motor cortical inhibition. Single pulse stimulation elicits a motor response, but also a subsequent duration of suppression of the target muscle, as measured by electromyogram. CSP refers to the pause in ongoing voluntary electromyogram activity induced by TMS. Spinal inhibition has been implicated in the first part of the CSP. However, it is proposed that the latter part of the CSP is caused by cortical inhibition; CSP measured with low stimulus intensity may reflect activation of GABAA receptors, while high range stimulus intensity has been found to be mediated by GABAB receptors (Werhahn et al., 1999).

3.2.1.4. Short-interval intracortical inhibition and intracortical facilitation. Short-interval intracortical inhibition and facilitation are widely used paired-pulse stimulation measurements and reflect the activity of interneurons in the cortex (Chen et al., 1998; Kujirai et al., 1993; Ziemann et al., 1996c). To measure short-interval intracortical inhibition, two pulses are administered in rapid succession; a subthreshold ('conditioning') pulse is administered, then, after a brief inter-stimulus interval (approximately 2–5 ms), a suprathreshold (test) pulse is applied (Kujirai et al., 1993). It is proposed that the subthreshold pulse produces inhibitory post-synaptic potentials, which acts to suppress the amplitude of the MEP elicited by the suprathreshold pulse (Ziemann, 2004). It was suggested that short-interval intracortical inhibition occurs due to activation of intracortical inhibitory neurons influencing excitatory interneurons. Overall, pharmacological studies of short-interval intracortical inhibition (Ziemann et al., 1996a) propose that the inhibitory mechanism of this procedure is associated with neurotransmission activity of the GABAA receptor and regulation of GABAA by the neuromodulating neurotransmitters in the motor cortex.

Measurement of intracortical facilitation follows a similar protocol as short-interval intracortical inhibition, but the inter-stimulus interval is longer, approximately 7–20 ms. When using such lengthened inter-stimulus interval, the subthreshold pulse has an overall facilitatory effect on the supratheshold pulse (Werhahn et al., 1999; Ziemann, 2004). GABA and glutamate are the core neurotransmitters which have been implicated in moderating levels of intracortical facilitation (Chen, 2000, 2004). Therefore, it is thought that short-interval intracortical inhibition and intracortical facilitation measurements provide insight into GABAA and glutamate activity, at least in the motor cortex.

3.2.1.5. Long-interval intracortical inhibition and facilitation. Long-interval intracortical inhibition is assessed in a paired-pulse stimulation protocol by two suprathreshold pulses, with a long inter-stimulus interval (approximately 50–200 ms) between the pulses. This procedure induces a long-lasting cortical inhibition mediated by the GABAB receptor, which is distinct from short-interval intracortical inhibition (Sanger et al., 2001), but similar to CSP (Valls-Solé et al., 1992). Long-interval intracortical facilitation is also induced by paired-pulse stimulation using two suprathreshold pulses, however, it is administered with an inter-stimulus interval of 10–40 ms between the pulses, which results in the facilitation of cortical activity and is proposed to be mediated by glutamatergic mechanisms.

3.3. Addiction: Brain stimulation studies and cortical excitability

Recent studies have applied the abovementioned TMS paradigms to evaluate the presence of altered cortical excitability in individuals exposed to addictive drugs (Barr et al., 2008). The ability of TMS to safely index cortical excitability is proving to be a highly useful research tool, providing evidence for the neurophysiological effects of exposure to addictive drugs on the cerebral cortex. Although these procedures allow measurements of alterations in excitability of the motor cortex and therefore may not reflect the pathophysiology of addiction which is associated with other brain regions, they indicate how repeated drug use induce long-lasting effects on neural excitability and perhaps can also be developed as a diagnostic and research tool (Table 1).

3.3.1. Cortical excitability and cocaine

Chronic cocaine administration has been shown to alter both glutamate and GABA activity within the mesocorticolimbic circuitry (Kalivas, 2007). Boutros et al. (2001) conducted a pilot study to compare the cortical excitability in 10 cocaine-dependent individuals (three weeks post-abstinence) with that of 10 control subjects. Single pulse stimulation was administered to both the left and right motor cortex and MT was measured across the two groups. They found that cocaine-dependent individuals presented with a significantly increased resting MT in both the left and right motor cortex compared to controls. This suggests that chronic cocaine use attenuates cortical excitability and increases cortical inhibition. The authors proposed that the reduction in axonal excitability could reflect long-lasting neuroadaptations in cocaine-dependent individuals to the acute effects of cocaine administration (which usually acts to promote cortical excitability and seizures). Thus, the decreased cortical excitability reflects a compensatory mechanism for the acute effects of repeated cocaine administration (Boutros et al., 2001).

In a replication study, Boutros et al. (2005) compared cortical excitability in 19 cocaine-dependent individuals (three weeks post-abstinence) with that of 12 healthy controls. This time, they applied three different single pulse stimulation TMS measurements to the left and right motor regions; resting MT, active MT and CSP duration. In addition, the researchers administered the Cocaine Experience Questionnaire to assess cocaine-induced psychotic symptoms and the Minnesota Multiphasic Personality Inventory Scales. The cocaine-dependent subjects had a significantly increased resting MT in the right hemisphere, while active MT was increased in both hemispheres. However, no changes in CSP duration were observed. Nevertheless, CSP duration in the right hemisphere was longer in patients with cocaine-induced paranoia when compared to that of subjects without paranoia. Cocaine-dependent subjects presented with elevated scores on several Minnesota Multiphasic Personality Inventory dimensions, however, they did not correlate with the cortical excitability measures (Boutros et al., 2005). Data from this study highlight the presence of decreased cortical excitability in abstinent cocaine-dependent subjects and provide further support for the Boutros et al. (2001) study.

Sundaresan et al. (2007) used both single pulse and paired-pulse stimulation TMS to the left motor cortex to study resting MT, long-interval intracortical inhibition and facilitation in a sample of

Table 1
TMS: studies of cortical excitability in drug addiction.

Study	Substance	Subjects	TMS paradigm	Findings
Boutros et al. (2001)	Cocaine	10 cocaine-dependent individuals (3 weeks post-abstinence) 10 healthy controls	SPS to the left and right motor cortex RMT	↑ RMT
Boutros et al. (2005)	Cocaine	19 cocaine-dependent individuals (3 weeks post-abstinence) 12 healthy controls	SPS to the left and right motor cortex RMT AMT CSP duration	↑ RMT in right hemisphere ↑ AMT in both hemispheres No changes in CSP duration
Sundaresan et al. (2007)	Cocaine	10 cocaine-dependent individuals (3 weeks post-abstinence) 10 healthy controls	SPS to left motor cortex RMT LICI LICF	↑ RMT ↑ LICF No changes in LICI
Lang et al. (2008)	Nicotine	22 chronic smokers 22 healthy controls	SPS and PPS to the motor cortex AMT LICF CSP SAI	↓ AMT ↓ LICF ↑ CSP ↑ SAI
Oliveri and Calvo (2003)	Ecstasy	10 heavy ecstasy users 10 healthy controls	SPS to the occipital cortex PT	↓ PT
Ziemann et al. (1995)	Alcohol	6 healthy volunteers required to consume ethanol	RMT AMT MEP CSP SICI ICF	↑ CSP ↑ SICI ↓ ICF No changes in RMT, AMT, MEP
Kahkonen et al. (2001)	Alcohol	10 healthy volunteers required to consume ethanol	TMS to motor cortex measured through EEG TMS-evoked potentials	↑ Right frontal ↑ Right parietal
Kahkonen et al. (2003)	Alcohol	10 healthy volunteers required to consume ethanol	TMS to PFC measured through EEG TMS-evoked potentials	↓ PFC
Conte et al. (2008)	Alcohol	13 ethanol dependent individuals 10 healthy volunteers required to consume ethanol	MEP CSP SICI ICF	Acute administration: ↑ MEP ↑ CSP ↓ Chronic administration: MEP No changes in CSP

Abbreviations: SPS: single pulse stimulation: RMT: resting motor threshold: AMT: active motor threshold: CSP: cortical silent-period: LICI: long-interval intracortical inhibition: LICF: long-interval intracortical facilitation: PPS: paired-pulse stimulation: SAI: short afferent inhibition: PT: phosphene threshold: MEP: motor evoked potentials: SICI: short-interval intracortical inhibition: ICF: intracortical facilitation: EEG: electroencephalography: PFC: prefrontal Cortex.

10 abstinent cocaine-dependent individuals and 10 healthy controls. Paired-pulse stimulation protocols were administered for their more direct association with glutamate cortical facilitation and GABA inhibition. The authors reported increased resting MT in the cocaine-dependent individuals, thus providing further support for the abovementioned studies. In addition, the abstinent cocaine-dependent individuals presented with increased long-interval intracortical facilitation but normal long-interval intracortical inhibition. Although enhanced long-interval intracortical facilitation reflects increased glutamatergic excitability, the authors suggested that the elevated resting MT may act as a protective mechanism against cocaine-induced cortical excitability and seizures (Sundaresan et al., 2007). Combined, these three studies provide the first evidence of long-lasting decreased cortical excitability in cocaine-dependent individuals post-detoxification.

3.3.2. Cortical excitability and nicotine

A similar study was conducted to examine cortical excitability in a nicotine-dependent population. Both animal and human studies indicate that chronic nicotine use can result in alterations in brain activity and neuronal excitability (Markou, 2008). To study the presence of these neurobiological changes, Lang et al. (2008) assessed cortical excitability in a sample of 22 chronic smokers and 22 healthy controls. They utilized both single pulse and paired-pulse procedures of TMS administration to the motor cortex, testing cortical excitability through measures of CSP, long-interval intracortical facilitation, active MEP and short-latency afferent inhibition. Chronic smokers exhibited prolonged CSP duration and increased short-latency afferent inhibition, which is proposed to rely on the somatosensory induced activity of cholinergic inhibitory circuits. Long-interval intracortical facilitation and active MEP were reduced. Overall, the authors suggested that chronic nicotine use enhanced cortical inhibition. This could be due to the direct effect of nicotine on cholinergic inhibitory circuits and also because chronic nicotine administration can increase inhibitory and decrease facilitatory mechanisms within the motor cortex. Furthermore, the authors suggest that the enhanced inhibitory circuits may provide insight into the pathophysiology underlying behaviors associated with nicotine addiction (Lang et al., 2008). This is the first TMS study assessing cortical excitability in chronic nicotine use and provides support for the presence of altered cortical activity associated with chronic smoking.

3.3.3. Cortical excitability and ecstasy

Chronic ecstasy exposure is associated with alterations in the occipital region of the visual cortex (Chang et al., 2000). Oliveri and Calvo (2003) conducted a preliminary study to explore cortical excitability in 10 heavy ecstasy users and 10 healthy controls. They administered single pulse stimulation TMS over the occipital cortex and measured phosphene threshold. Phosphenes are light perceptions elicited by TMS of the occipital lobe. Phosphene threshold refers to the minimum TMS intensity required to induce phosphenes and is used as a measure of cortical excitability. The authors found phosphene threshold to be lower in ecstasy users compared to controls, and negatively correlated with frequency of ecstasy use. Furthermore, lower phosphene threshold was observed in ecstasy users with hallucinations. This correlation between phosphene threshold and hallucinations supports the association between such hallucinations and local excitability within the visual cortex itself (Oliveri and Calvo, 2003).

3.3.4. Cortical excitability and alcohol

Alcohol has been found to enhance the function of GABA and attenuate the function of glutamate, thus inducing changes in cortical excitability (Enoch, 2008; Gass and Olive, 2008; Lobo and Harris, 2008). Ziemann et al. (1995) conducted the first electrophysiological study on the effect of acute ethanol consumption on cortical excitability within the motor cortex of 6 healthy volunteers. They administered single pulse and paired-pulse TMS to measure resting MT, active MT, MEP amplitude, CSP duration, short-interval intracortical inhibition and intracortical facilitation. Prior to ethanol consumption, focal TMS was applied to the hand area of the left motor cortex and the subjects then participated in a motor function task. Then, subjects were required to consume red wine (0.7 L) and 30 min later, subjects were administered focal TMS and the motor function task again. No changes in MT (active or resting) or MEP amplitude were observed. However, ethanol enhanced short-interval intracortical inhibition and intracortical facilitation. Furthermore, CSP duration was prolonged. This occurred in the absence of altered hand motor function. These findings provide preliminary evidence that acute ethanol administration induces cortical inhibition in the motor cortex (Ziemann et al., 1995).

Kahkonen et al. (2001) also used TMS to examine the effect of acute ethanol administration on cortical excitability in healthy controls. They administered TMS to the left motor cortex of 10 healthy subjects both before and after they ingested a moderate amount of ethanol. Cortical activity was recorded as measured by electroencephalography (EEG). They found that ethanol increased TMS-evoked potentials over right frontal and left parietal areas, with the largest effect in the right prefrontal area. The authors suggest that acute ethanol ingestion may have influenced the functional connectivity between the prefrontal and motor cortices (Kahkonen et al., 2001). In a following study, the same research group tested the effects of acute alcohol administration on cortical excitability in the PFC. Kahkonen et al. (2003) utilized a combined TMS–EEG technique which is capable of recording neural responses to brain stimulation. The TMS–EEG technique was applied to the PFC before and after alcohol consumption. Alcohol reduced TMS-evoked responses in the PFC indicating that acute consumption of alcohol reduces cortical excitability in the PFC (Kahkonen et al., 2003).

Recently Conte et al. (2008) investigated both the acute and chronic effects of ethanol consumption on cortical excitability. Participants consisted of 10 healthy controls who were administered ethanol (24 g for males, 12 g for females), and 13 ethanol dependent subjects, who were not administered ethanol, but rather, assessed for negative blood ethanol levels during the study. All participants received 10 stimuli of 5 Hz rTMS to the motor cortex. The healthy controls were administered rTMS both before and after the consumption of ethanol, while the ethanol dependent subjects were administered the rTMS only once. MEP and CSP duration were measured during the rTMS trains. Short-interval intracortical inhibition and intracortical facilitation were measured in a sub-group of 4 healthy controls and 4 patients, using paired-pulse TMS (in addition to the rTMS). In the healthy controls, both before and after ethanol consumption, rTMS increased MEP and CSP duration, with a further increased CSP duration after ethanol intake. In ethanol dependent participants, the rTMS did not produce normal levels of MEP facilitation (depressed MEP facilitation), and no increase in CSP duration. Thus, the authors found distinct differences in ethanol-induced effects on cortical excitability between the control group and the ethanol dependent group. They postulated that these varying results occurred because acute ethanol intake alters GABA neurotransmission, while chronic ethanol consumption induces long-lasting effects on glutamate neurotransmission (Conte et al., 2008).

3.4. Summary: Brain stimulation to assess cortical excitability in addiction

By utilizing TMS to measure CI, it was found that chronic exposure to various addictive drugs induces alterations in cortical

excitability. Such alterations were demonstrated across the motor cortex, occipital cortex and the PFC. Individuals who are cocaine (Boutros et al., 2001, 2005; Sundaresan et al., 2007) and nicotine-dependent (Lang et al., 2008) presented with decreased excitability in motor cortex. Chronic ecstasy exposure was found to be associated with increased excitability of the visual cortex (Oliveri and Calvo, 2003). Acute alcohol exposure decreased excitability in the motor cortex (Kahkonen et al., 2001; Ziemann et al., 1995) and the PFC (Kahkonen et al., 2003). Moreover, Conte et al. (2008) proposed that while acute ethanol administration seemed to affect GABA neurotransmission, chronic administration appeared to alter the glutamate mechanisms involved in cortical excitability. Although these studies provide support for a relationship between altered cortical excitability and addictive behaviors, there are some potential limitations within the studies which need to be addressed. Firstly, it is difficult to disentangle whether alterations in the corticospinal measures are a direct result of chronic drug administration, or rather, occur due to pre-existing vulnerabilities, or perhaps even a combination of both. In addition, these alterations in cortical excitability could also be exacerbated by poly-substance use and/or a co-morbid psychiatric condition; a thorough screening process should be implemented in future studies. Finally, it is important to note that these exploratory studies consisted of small samples. Nevertheless, it must be appreciated that these studies are highly experimental and provide initial insight, using brain stimulation techniques, into the relationship between administration of addictive drugs and alterations in cortical excitability. Altogether, these findings are important for indexing altered cortical excitability in drug dependent populations and suggest that TMS can be used as an investigative tool to further elucidate the pathophysiology of addiction.

4. Brain stimulation as a therapeutic tool for drug addiction

rTMS can alter excitability in the stimulated cortex, and interconnected brain regions, beyond the period of stimulation (Hallett, 2007; Rossini and Rossi, 2007; Ziemann, 2004). In rTMS, trains of repeated pulses of same stimulus intensity are applied to the cortex. The nature of rTMS-induced effects depends on the number, intensity and frequency of stimulation pulses which can be between 1 and 50 Hz (Wassermann et al., 1998). At a stimulus intensity greater then MT, low-frequency rTMS (approximately 1 Hz) was reported to induce a transient inhibition of cortical excitability (Chen et al., 1997). Conversely, high frequency rTMS (>5 Hz) was reported to transiently enhance cortical excitability (Daskalakis et al., 2006; Fitzgerald et al., 2006b; Pascual-Leone et al., 1994).

Changes in neurotransmission induced by rTMS have been observed in both animal and human studies. Animal studies demonstrated, for example, that rTMS to the frontal regions of rats enhanced release of dopamine in both the mesolimbic and mesostriatal pathways (Kanno et al., 2004; Keck et al., 2002; Zangen and Hyodo, 2002). Strafella et al. (2001) conducted a study in humans, using positron emission tomography (PET) to assess the effects of rTMS on dopamine transmission. They found that rTMS of the PFC induces release of dopamine in the caudate nucleus (Strafella et al., 2001). Thus, rTMS to the PFC appears to have a modulatory effect on the mesolimbic and mesostriatal dopaminergic systems in animals and humans.

The effect of rTMS on dopaminergic neurotransmission and cortical excitability suggests that such a tool can be used in the study and treatment of various neuropsychiatric disorders associated with abnormal dopamine activity and altered cortical excitability, such as depression (Fitzgerald et al., 2003, 2006a, 2007; Kito et al., 2008; Lisanby et al., 2008), obsessive-compulsive disorder (Greenberg et al., 1997, 2000), schizophrenia (Cohen et al., 1999; Jin et al., 2006; Lee et al., 2005; Stanford et al., 2008), food craving (Uher et al., 2005) and drug addiction (Amiaz et al., 2009; Camprodon et al., 2007; Eichhammer et al., 2003; Johann et al., 2003; Politi et al., 2008).

To date, only a small number of animal studies have assessed the utility of brain stimulation as a technique to modulate behavioral and neurochemical alterations induced by chronic drug exposure (Erhardt et al., 2004; Levy et al., 2007). In addition, several human studies have begun to evaluate the effects of rTMS protocols applied to the PFC on drug craving and consumption in nicotine (Amiaz et al., 2009; Eichhammer et al., 2003; Johann et al., 2003) and cocaine (Camprodon et al., 2007; Politi et al., 2008) dependent groups.

4.1. Brain stimulation and addiction in animal studies

Recent animal studies have assessed the efficacy of administering TMS or TMS-like protocols, to frontal brain regions, as a potential non-pharmacological candidate for increasing dopamine levels in the mesocorticolimbic circuitry and altering neuroadaptations induced by chronic drug use. In vivo neurochemical techniques, such as microdialysis, allow investigation of alterations in neurotransmission and neuroadaptations induced by chronic drug administration (reviewed in Torregrossa and Kalivas, 2008). Such investigation across the different brain regions during the different stages (and compared to drug naive animals) can shed light on mechanisms by which brain stimulation can normalize neurochemical and behavioral alterations induced by chronic drug use. The following section reviews animal studies which have utilized neurochemical and behavioral techniques to assess the effects of TMS or TMS-like protocols on addictive behaviors and dopamine or glutamate neurotransmission within reward-related brain regions (Table 2).

Keck et al. (2002) used intracerebral microdialysis to investigate the effects of acute rTMS (20 Hz) to frontal brain regions of adult Wistar rats on dopamine release in the mesolimbic and mesostriatal dopaminergic systems. They found that acute rTMS over left frontal brain regions significantly enhanced dopamine release in both the mesolimbic and mesostriatal pathways. Specifically, rTMS was found to increase the extracellular concentration of dopamine in the dorsal hippocampus, the shell of the NAc and the dorsal striatum (Keck et al., 2002). Based on these findings, the authors suggest that acute rTMS of frontal brain regions has a modulatory effect on the mesolimbic and mesostriatal systems. Zangen and Hyodo (2002) also used intracerebral microdialysis to investigate the neurochemical changes induced by acute rTMS above frontal or caudal brain regions of male Sprague-Dawley rats. Microdialysis samples from the NAc were assessed before, during and after the rTMS session. rTMS over either site increased extracellular levels of dopamine and glutamate in the NAc. The increase in extracellular dopamine levels was greater when stimulation was applied over caudal brain regions (Zangen and Hyodo, 2002).

Kanno et al. (2004) administered acute rTMS (25 Hz) over frontal brain regions of male Wistar rats to evaluate the effects of various rTMS stimulation intensities on extracellular dopamine concentrations. In vivo microdialysis method was used to measure extracellular dopamine and serotonin concentrations in the dorsolateral striatum and PFC before and after rTMS administration. Acute rTMS at stimulus intensity of close to 110% of MT, was found to continuously increase extracellular dopamine concentrations in the rat dorsolateral striatum (Kanno et al., 2004).

The abovementioned studies reported that rTMS is capable of enhancing mesolimbic and mesostriatal dopamine release. These findings are important in aiding our understanding of the potential

Table 2
Animal Studies: Effect of TMS on dopamine and glutamate transmission in the mesocorticolimbic circuitry.

Study	Subject	Type and region of stimulation	Technique of analysis	Findings
Keck et al. (2002)	Adult Wistar rats	Acute rTMS (20 Hz) to the frontal brain regions	Microdialysis	rTMS of left frontal brain increased release patterns of DA in both mesolimbic and meostriatal pathways
Zangen and Hyodo (2002)	Male Sprague-Dawley rats	Acute rTMS (20 Hz) to the frontal and caudal cortex	Microdialysis	rTMS of both frontal and caudal cortex increased extracellular levels of DA and GLU in NAc
Erhardt et al. (2004)	Morphine-sensitized male Sprague-Dawley rats	Acute rTMS (20 Hz) to the left frontal cortex	Microdialysis	rTMS of left frontal cortex enhanced DA in shell region of NAc. DA release patent higher in morphine-abstinent rats compared to controls
Kanno et al. (2004)	Male Wistar rats	Acute rTMS (25 Hz) to the dorsolateral striatum	Microdialysis	rTMS of the dorsal regions, at stimulus intensity of 110% of MT, continuously increased extracellular DA concentration
Levy et al. (2007)	Male Sprague-Dawley Rats pretreated with cocaine or sucrose	ICES (20 Hz or 100 Hz) to the PFC and lateral hypothalamus	Immunohistochemistry	ICES to PFC and lateral hypothalamus reduced cocaine seeking behaviors but not sucrose. Stimulation of PFC reduced cocaine seeking and motivation,increasing GLuR1 in NAc. Stimulation of lateral hypothalamus reduced cocaine cue-induced behaviors, reducing GLuR1 in VTA

Abbreviations: DA: dopamine: GLU: glutamate: NAc: nucleus accumbens: MT: motor threshold: ICES: intracranial electrical stimulation: PFC: prefrontal cortex: GluR1: subunits 1 of the AMAP receptor: VTA: ventral tegmental area.

use of TMS in the development of novel non-pharmacological treatments for drug addiction. The following studies examined the effects of acute repetitive brain stimulation administered to the frontal cortex of rats pretreated with morphine (Erhardt et al., 2004) or cocaine (Levy et al., 2007).

Erhardt et al. (2004) focused on the potential of rTMS as a technique to modulate the dysregulated dopamine activity observed during withdrawal in morphine-sensitized male Sprague-Dawley rats. They used intracerebral microdialysis to assess the effects of acute rTMS (20 Hz) to the left frontal cortex on dopamine release in the NAc of rats during morphine abstinence. rTMS enhanced dopamine release in the NAc shell in both the morphine-abstinent and the drug naive control rats. Furthermore, dopamine release was significantly higher in the morphine-abstinent rats than in the controls, indicating alterations in dopaminergic neurotransmission after chronic morphine administration (Erhardt et al., 2004). Given that rTMS can modulate dysregulated dopamine release in the mesolimbic dopaminergic system during abstinence from drugs, the authors suggest that TMS could prove to be a promising therapeutic tool for the reduction of clinical symptoms associated with drug withdrawal and addictive behaviors.

A recent study by Levy et al. (2007) evaluated the effects of repeated intracranial electrical stimulation (ICES) administration to the PFC or the lateral hypothalamus on neuroadaptations and behaviors associated with cocaine addiction. They administered 10 daily sessions of high frequency stimulation (20 Hz or 100 Hz) to these regions of rats pretreated by self-administration of either cocaine or sucrose. They assessed whether this form of repeated brain stimulation affected cocaine addiction associated behaviors and neuroadaptations. Repeated brain stimulation sessions using rTMS-like treatment patterns (10 daily sessions, each daily session consisted high frequency trains for 30 min) to either the lateral hypothalamus or the PFC affected cocaine addiction-related behaviors, but had no affect on sucrose self-administration. Repeated stimulation to the median forebrain bundle at the lateral hypothalamus (which is thought to induce a generalized activation of the reward circuitry) reduced cocaine cue-induced drug-seeking, and GluR1 levels in the VTA, which contrasts with the up-regulation of GluR1 levels induced by repeated cocaine administration. However, the psychomotor response to cocaine was increased and the motivation for cocaine consumption was not affected. On the other hand, repeated PFC stimulation reduced not only cocaine seeking, but also motivation for cocaine consumption and the psychomotor response to cocaine. In addition, the PFC stimulation treatment increased GluR1 levels in the NAc (core and shell), which contrasts the reduced levels of GluR1 after repeated cocaine exposure (Levy et al., 2007).

These studies demonstrated that rTMS to frontal brain regions was able to enhance dopamine release in both the mesolimbic and mesostriatal pathways (Kanno et al., 2004; Keck et al., 2002; Zangen and Hyodo, 2002). Furthermore, there were promising results from the studies conducted in rats pretreated with morphine or cocaine on the potential of repetitive brain stimulation to increase dopamine and glutamate release in frontal brains regions, affect neuroadaptations induced by chronic drug use, and reduce behaviors associated with drug-seeking. These findings support the proposal that repetitive stimulation of the PFC could be further developed as an effective tool for the treatment of addictive behaviors (Erhardt et al., 2004; Levy et al., 2007). However, it is important to note that the comparison between human and animal rTMS is complicated. It is not possible to make direct comparison between animal TMS or ICES studies and human TMS studies because the distribution of the induced electric field is different. The difference in brain size makes it very difficult to translate the details of stimulation parameters from animals to humans. The size of the scalp has a critical effect on the distribution of the electric field and therefore on the size of the stimulated region. Given the several technical limitations (such as diameter of the coil wire and heating), there are no TMS coils that can induce localized stimulation in rodents that can be directly translated to the human case. Nevertheless, the animal studies allow a better controlled evaluation of brain stimulation effects on addictive behaviors and neuroplasticity. To study the effect of localized stimulation using TMS-like patterns of stimulation, it is necessary to insert electrodes into specific brain regions of rodents (e.g. Levy et al., 2007), but it is not possible to make a clear comparison between stimulation intensities.

While bearing these limitations in mind, the animal studies suggest mechanisms by which repetitive stimulation of the PFC can affect addictive behaviors and support the proposal that such an approach could become a novel strategy for the treatment of addiction (Erhardt et al., 2004; Levy et al., 2007).

4.2. rTMS: Human studies

Recent studies have begun to assess the effects of rTMS on addictive behaviors in humans. As previously described, repeated

drug exposure can induce long-term neuronal adaptations in several systems. These neuroadaptations are partly associated with altered dopamine activity in the mesocorticolimbic circuitry (Hyman et al., 2006; Vanderschuren and Kalivas, 2000) and resulted in altered glutamate neurotransmission (Wolf et al., 2004) and cortical excitability. Given that rTMS can affect cortical excitability and induce enhanced dopamine release in the mesolimbic dopaminergic system, as detailed above, it is thought that repeated application of rTMS can affect neuroadaptations induced by repeated drug use. Moreover, rTMS can disrupt neuronal activity and therefore induce at least acute effects on circuitries mediating various behaviors. Therefore, repeated sessions of rTMS of the PFC are suggested to reduce drug craving, drug-seeking and eventually drug consumption and relapse (Amiaz et al., 2009). The following section describes the recent studies which have begun to explore the therapeutic potential of high frequency rTMS to the PFC in reducing addictive behaviors within substance dependent populations (Table 3).

4.2.1. rTMS and nicotine

In a set of exploratory studies into the effects of brain stimulation on nicotine consumption, Eichhammer et al. (2003) and Johann et al. (2003) investigated whether high frequency rTMS of frontal brain regions could decrease nicotine-seeking related behaviors. Chronic nicotine exposure results in altered dopamine activity in the reward system and dopamine levels are reduced during withdrawal. Therefore, the researchers proposed that rTMS-induced modulation of dopaminergic neurotransmission could result in a reduction in nicotine craving and consumption. In a pilot study, Johann et al. (2003) investigated whether rTMS to the DLPFC could modulate levels of tobacco craving. Eleven tobacco dependent individuals were recruited and assigned either active or sham rTMS over the left DLPFC at 90% of MT. Craving levels were assessed using a visual analogue scale (VAS) both 30 min prior to, and following, the rTMS treatment. Participants who received the high frequency rTMS reported decreased levels of tobacco craving when compared to the sham group (Johann et al., 2003).

Following this pilot study, Eichhammer et al. (2003) conducted another study of rTMS and nicotine consumption. Participants consisted of 14 treatment-seeking heavy smokers. All participants were required to abstain from smoking 12 h before the rTMS sessions. The study was conducted as a double-blind crossover trial. In a randomized order, each participant received 2 active trials and 2 sham stimulation sessions over 4 consecutive days. Participants received high frequency (20 Hz) rTMS to the left DLPFC, the stimulation was administered at 90% of MT. Level of craving was measured by a VAS which was administered at baseline and 30 min after the rTMS treatment. Cigarette consumption was assessed by the number of cigarettes smoked in 6 h following treatment. The findings were that high frequency rTMS of left DLPFC reduced cigarette consumption, but craving levels remained unchanged. The authors have suggested that the evaluation of craving may have not been sensitive enough and that the sample size was probably too small to detect alterations in craving (Eichhammer et al., 2003). Regardless, based on these findings, the authors propose that high frequency rTMS could have potential therapeutic value as a treatment for craving (Johann et al., 2003) and smoking cessation (Eichhammer et al., 2003).

Amiaz et al. (2009) were also interested in the effects of high frequency rTMS over the left DLPFC on cigarette consumption and craving. The researchers expanded on the previous two studies by assessing whether exposure to smoking cues (prior to the stimulation) could modulate the effect of rTMS. They postulated that in addition to the effect of rTMS on dopamine transmission and cortical excitability, rTMS over the PFC may disrupt craving-related circuitries and that this effect would be prominent when rTMS is applied immediately after activation of such circuitry by smoking cues. Forty-eight nicotine-dependent individuals were recruited for the study. Participants were randomly divided into four experimental groups; active TMS with smoking cues, active TMS with neutral cues, sham TMS with smoking cues and sham

Table 3
Studies on the effects of TMS or tDCS on craving and addictive behaviors in humans.

Study	Substance	Subjects	Brain stimulation technique and parameters	Assessment	Findings
Johann et al. (2003)	Nicotine	11 tobacco dependent individuals	Single session of high frequency rTMS to the DLPFC at 90% of MT	VAS (craving levels)	rTMS reduced reported levels of tobacco craving
Eichhammer et al. (2003)	Nicotine	14 treatment-seeking heavy smokers	Single session of high frequency rTMS (20 Hz) to the DLPFC at 90% of MT	VAS (craving levels) Cigarettes smoked following TMS (cigarette consumption)	High frequency rTMS DLPFC reduced cigarette consumption Craving levels did not change
Amiaz et al. (2008)	Nicotine	48 nicotine-dependent individuals	Ten daily sessions of high frequency rTMS (10 Hz) to the DLPFC at 100% of MT	VAS (craving levels) Cigarettes smoked following TMS (cigarette consumption)	High frequency rTMS DLPFC reduced cigarette consumption Cue-induced craving was reduced
Camprodon et al. (2007)	Cocaine	6 cocaine-dependents males	Two sessions of high frequency rTMS (10 Hz) to right and left DLPFC at 90% of MT	VAS (craving levels) assessed at 3 time points	High frequency rTMS to right DLPFC and not left DLPFC reduced cocaine craving
Politi et al. (2008)	Cocaine	36 cocaine-dependent individuals post-detoxification	10 daily sessions of high frequency (15 Hz) rTMS to the left DLPFC at 100% of MT	Clinical evaluation of symptoms associated with craving.	High frequency rTMS to the left DLPFC reduced cocaine cravings gradually throughout sessions
Fregni et al. (2008a)	Nicotine	24 chronic smokers	Single session of anodal 2 mA tDCS stimulation of either left DLPFC, right DLPFC, or sham, for 20 min	VAS (craving levels) VAS (mood levels)	tDCS of DLPFC temporarily reduced general and cue-induced nicotine craving. No mood changes
Boggio et al. (2008b)	Alcohol	13 alcohol-dependent individuals enrolled in rehabilitation program and abstinent for min of 10 days	Single session of anodal 2 mA tDCS stimulation of either left DLPFC, right DLPFC, or sham, for 20 min	VAS (craving levels) VAS (mood levels)	tDCS of DLPFC temporarily reduced alcohol craving and blocked the effects of alcohol cues on craving levels. No mood changes

Abbreviations: DLPFC: dorsolateral prefrontal cortex: MT: motor threshold: VAS: visual analogue scale: mA: milliampere.

TMS with neutral cues. Ten daily sessions of high frequency (10 Hz) rTMS at 100% of MT were administered in an attempt to induce long-lasting effects. Prior to the rTMS, participants were exposed to either smoking or neutral visual cues. VAS was used to evaluate levels of nicotine craving before and after the presentation of the smoking or the neutral cues and after rTMS administration. Before the first and the 10th treatment, the cotinine (a metabolite of nicotine) urine levels were measured, and participants were administered standard questionnaires on nicotine consumption, craving and dependence. After the 10 daily rTMS sessions, participants received maintenance sessions every week during the following month. Overall, results from this study suggested that high frequency rTMS over the DLPFC reduced cigarette consumption and nicotine dependence. In addition, the rTMS blocked craving induced by smoking cues. However, the effect tended to dissipate after the 10 daily sessions and the reduction in cigarette consumption was not significant 6 months after treatment termination (Amiaz et al., 2009).

These three studies demonstrate that high frequency rTMS of the DLPFC can attenuate nicotine consumption (Amiaz et al., 2009; Eichhammer et al., 2003) and craving (Johann et al., 2003). However, the significance and duration of these effects are limited and further investigation is required to identify the appropriate stimulation parameters and targets needed to enhance the effectiveness of such treatment.

4.2.2. rTMS and cocaine

A number of studies into cocaine addiction have implicated the DLPFC (among other regions) in the neurobiology of craving (Wilson et al., 2004). Camprodon et al. (2007) conducted a preliminary study to investigate whether a single session of high frequency rTMS over either the right or the left DLPFC could reduce cocaine craving. The participants recruited consisted of 6 males diagnosed with cocaine dependence. Participants were administered two sessions of high frequency (10 Hz) rTMS at 90% of MT, once over the right, and once over the left DLPFC, with a week break between the two sessions. The order of stimulation was randomized and counterbalanced across the patients. Craving was assessed using a set of VAS at three time-points: 10 min before rTMS, immediately after and 4 h post-rTMS. The authors found that a single session of high frequency rTMS to the right DLPFC, but not the left DLPFC, reduced cocaine craving. However, the authors pointed to the need of further studies with a larger sample size and repeated daily sessions (Camprodon et al., 2007).

Indeed, Politi et al. (2008) studied the effect of 10 daily sessions of high frequency (15 Hz) rTMS over the left DLPFC at 100% of MT on cocaine cravings. Participants recruited consisted of 36 subjects diagnosed with cocaine dependence post-detoxification. The participants underwent daily clinical evaluation of symptoms associated with cocaine craving. The authors found that the daily sessions of high frequency rTMS to the left DLPFC reduced cocaine craving. It is important to note that the cocaine cravings reduced *gradually* throughout the sessions (Politi et al., 2008). Therefore, using different paradigms and assessment tools, Camprodon et al. (2007) and Politi et al. (2008) suggest that rTMS over the DLPFC can potentially provide an effective therapeutic intervention for cocaine craving and dependence, however, further research is required into the optimal stimulation patterns and exact brain region to be stimulated.

4.3. Summary: rTMS and addiction

Overall, the alterations in cortical excitability studied by TMS paradigms and the effects of rTMS sessions on drug craving and consumption provide evidence and support for further brain stimulation studies in the field of addiction research. These studies show that high frequency rTMS over the DLPFC can reduce craving and consumption in both nicotine and cocaine-dependent populations. It is anticipated that these findings will translate across the spectrum of various addictions. However, it is important to note that all of these studies were exploratory in nature and consist of relatively small sample sizes and none of them demonstrated complete abstinence from substance use. Furthermore, in the cocaine craving study, there was a discrepancy in the laterality of the findings. Studies into the appropriate target of magnetic stimulation, intensity, frequency and length of treatment are required to optimize the use of rTMS for addiction treatment and research.

4.4. Safety of TMS

TMS and rTMS have been strictly monitored for safety issues (Levkovitz et al., 2007; Machii et al., 2006). When TMS guidelines (Wassermann, 1998) are followed, single pulses or low frequency appears to carry little risk beyond occasionally causing local discomfort at the site of stimulation or a transient headache in susceptible subjects. No short or long-term sequelae have been described in safety studies in which single TMS pulses were used in adult subjects (Anand and Hotson, 2002). Although rare, the main risk of rTMS is the induction of seizures. Seizures have been reported in less than 0.1% of the subjects following rTMS, in most cases when high frequency and intensity were used in patients taking medications that lower the seizure threshold (Tassinari et al., 2003). Therefore, caution should be used when using high frequency and high-intensity rTMS in alcoholics, cocaine or amphetamine users. Long-term effects of repeated rTMS sessions are as yet unknown. When given within recommended guidelines, the overall safety profile of rTMS is good, and supports its further development as a clinical treatment (Levkovitz et al., 2007; Loo et al., 2008).

5. Transcranial direct current stimulation (tDCS) and addiction

5.1. Introduction to tDCS

tDCS is a non-invasive, painless and safe brain stimulation method capable of *modulating* cortical excitability. Investigation into the action of brief polarising currents applied to the surface of the brain of rats and cats began in the 1960s. Application of these currents to the motor cortex induced changes in cortical evoked potentials and intracellular recorded activity (Purpura and McMurtry, 1965), and prolonged changes in synaptic excitability (Bindman et al., 1964). At the same time, a small number of psychiatric studies of tDCS in major depression and schizophrenia were conducted; however, mixed outcomes were reported. These discrepancies in the psychiatric studies have now been attributed to variations in methodology (Lolas, 1977). Thus, despite the promising results from the animal studies, research into this technique was largely abandoned by the 1970s and was not translated into clinical research (Priori, 2003). Recently however, the potential of direct current stimulation as a tool to induce long-lasting changes in cortical excitability has inspired renewed research interest.

5.2. Technical overview of tDCS

The DC stimulation protocol was revised and improved by applying a stronger current, approximately 1 mA, via a larger pad of electrodes of 35 cm^2, placed on the scalp. When applying the DC stimulation using these revised parameters, tDCS was found to be capable of safely modulating cortical excitability of the human cerebral cortex (Nitsche and Paulus, 2000) and these alterations in

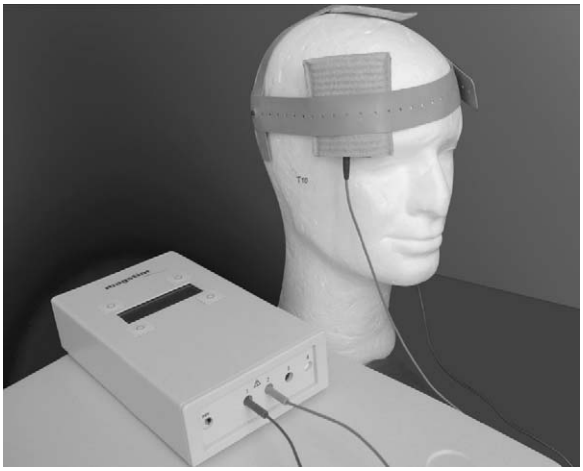

Fig. 3. Example of transcranial direct current stimulation (tDCS) application. For tDCS administration, two 35 cm2 sponge surface electrodes (anode and cathode) are fixed to the subject's head. A weak constant electrical current of approximately 1 mA is generated by the tDCS stimulator and is delivered via the two electrodes. The current flows between the anode and the cathode and results in the modulation of spontaneous neural activity. Images courtesy of The Magstim Company Limited.

excitability could persist beyond the period of stimulation (Nitsche and Paulus, 2001). During tDCS, a weak constant electric current is delivered via two surface electrodes (one the anode, and the other, the cathode) placed on the scalp; the current penetrates the skull and flows through the cerebral cortex (Fig. 3).

Administration of tDCS results in the *modulation* of spontaneous brain activity, and this occurs due to subthreshold modulation of neuronal resting membrane potential. The nature of these modulations is dependent on duration, strength and stimulation polarity; anodal tDCS is thought to cause neuronal depolarisation, thus enhancing cortical excitability, whereas cathodal stimulation is proposed to hyperpolarise neurons, causing a reduction in excitability (Nitsche et al., 2003c, 2005; Nitsche and Paulus, 2000, 2001). Pharmacological studies exploring the direct effects of tDCS on cortical excitability found that voltage-sensitive ion channel blockers can prevent the effects of tDCS, thus highlighting the role of membrane depolarization in modifying cortical excitability (Nitsche et al., 2003b).

Furthermore, increased tDCS duration (i.e. 9 min) results in stimulation after-effects which persist even an hour beyond the period of stimulation (Nitsche and Paulus, 2000, 2001). Pharmacological studies have explored the mechanisms underlying these prolonged effects and found that blocking NMDA (glutamate) receptors suppressed post-stimulation anodal and cathodal after-effects (Liebetanz et al., 2002; Nitsche et al., 2003b), while sodium channel blockers interfered with the anodal effects. tDCS was also found to induce dopaminergic modulation through cortical stimulation (Nitsche et al., 2006). Based on these findings, it was suggested that a combination of glutamatergic mechanisms and changes in membrane potentials are required for DC-induced after-effects (Liebetanz et al., 2002). Thus, tDCS is emerging as a promising tool in brain research, neurology and psychiatry due to its capability to directly modulate cortical excitability, and its potential to induce long-lasting effects.

5.3. Previous tDCS studies

Similar to TMS, many of the initial tDCS studies examined effects of this procedure on the motor cortex by TMS (Baudewig et al., 2001; Lang et al., 2005; Nitsche et al., 2003a, 2005; Nitsche and Paulus, 2000; Rosenkranz et al., 2000) and the visual cortex (Antal et al., 2001, 2003, 2004; Antal and Paulus, 2008) due to the ease in which TMS-evoked MEPs and phosphenes can be measured. Recently however, investigators have begun to assess the neuromodulating effects of tDCS applied to frontal regions, such as the DLPFC, in assessing cognition (Bermpohl et al., 2005; Boggio et al., 2007; Fregni et al., 2006b; Kincses et al., 2004), memory (Fregni et al., 2005; Sparing and Mottaghy, 2008) and impulsivity (Fecteau et al., 2007a,b). In these studies, the quantifiable outcomes of tDCS have been scaled according to behavioral measures. A number of studies have also been designed to assess the therapeutic efficacy of tDCS-induced neuroplasticity in patients with neurological or psychiatric disorders (Fregni and Pascual-Leone, 2007).

In psychiatry, researchers have begun to assess effects of tDCS on the cognitive and clinical aspects of depression (Boggio et al., 2007, 2008a; Fregni et al., 2006a,b), food craving (Fregni et al., 2008b) and drug addiction (Boggio et al., 2008b; Fregni et al., 2008a). Overall, these studies suggest that tDCS is a promising tool for modulating cortical excitability and encourage future research into potential clinical benefits of the prolonged effects of tDCS.

5.4. tDCS: Human studies

Recently, the potential for tDCS-induced modulations of cortical excitability to affect addictive behaviors has been explored. It was proposed that tDCS-induced increases in cortical excitability of the DLPFC in substance dependent populations, would reduce drug craving. Two preliminary tDCS studies, explored this possibility in chronic cigarette smokers (Fregni et al., 2008a) and alcohol-dependent subjects (Boggio et al., 2008b).

5.4.1. tDCS and nicotine

Enhanced activity in the DLPFC has been strongly implicated in the process of craving for nicotine (McBride et al., 2006). Fregni et al. (2008a) hypothesized that tDCS treatment that would increase DLPFC activity could eventually result in a reduction in nicotine craving. Twenty-four subjects who were currently smoking 15 cigarettes or more for at least 1 year were recruited. In this randomized, double-blind, sham-controlled crossover study, participants received three different types of tDCS; sham tDCS, anodal tDCS of the left DLPFC, and anodal tDCS of the right DLPFC. Participants were required to abstain from smoking for at least 1 h and 30 min before the experiment. Prior to the tDCS, participants completed both a VAS to evaluate mood and a nicotine-based VAS to measure craving levels; these craving levels were assessed both before and after exposure to smoking cues. Then, participants underwent tDCS treatment that consisted of a constant current of 2 mA intensity for 20 min. They were then again required to complete a measure of mood and craving levels. Finally, participants were exposed to the nicotine cues for a second time, and craving levels were assessed again (Fregni et al., 2008a).

The authors found that smoking craving increased after exposure to the smoking cues. The tDCS treatment however, temporarily reduced both general and smoking-cue induced nicotine craving. No significant mood changes were induced by the tDCS treatment. Based on these findings, the investigators suggested that tDCS can reduce craving and encouraged further studies of consecutive sessions of tDCS to the DLPFC in a nicotine-dependent population to assess the potential of tDCS as a treatment for nicotine addiction.

5.4.2. tDCS and alcohol

Alcohol dependence is also associated with altered activity in the DLPFC, therefore, the same research group (Boggio et al., 2008b) used tDCS to explore whether modulation of cortical excitability within this brain region could reduce alcohol craving.

Participants recruited consisted of 13 patients diagnosed with alcohol dependence, who were enrolled in a rehabilitation program and were abstinent for a minimum of 10 days. A randomized, double-blind, sham controlled crossover study was conducted in which participants received 3 forms of bilateral tDCS of the DLPFC: (1) Active anodal left/cathodal right tDCS, (2) Active anodal right/cathodal left tDCS and (3) Sham stimulation of DLPFC. The design of this research is similar to the previously described nicotine study (Fregni et al., 2008a). Participants were administered the following: an alcohol urge questionnaire to assess levels of craving and a VAS for mood domains. The participants were then exposed to alcohol cues (a video which presented alcohol consumption in a positive way) and their craving levels were assessed again. The tDCS treatment was then administered at a constant current of 2 mA for 20 min. Then, participants were assessed again for changes in craving levels or mood, and any tDCS side-effects. Finally, alcohol cues were presented again and craving levels or mood changes were assessed. The authors found that both of the active tDCS conditions significantly decreased alcohol craving, when compared with the sham condition. Furthermore, after active tDCS treatment to the DLPFC, alcohol craving was not enhanced by alcohol cues. The authors suggest that when alcohol-dependent individuals are abstinent from alcohol, DLPFC activity is decreased and upon exposure to alcohol cues, there is a response in the mesolimbic pathways, which induces an increase in DLPFC activity, which in turn, may play a role in generating drug-seeking behavior. Therefore, if the tDCS interferes with activity in the DLPFC, it may have a modulatory effect on the occurrence of these events, which could reduce the strong craving for alcohol consumption. Thus, based on the previous two studies, the authors propose that tDCS might prove to be an effective method for reducing craving levels and should be assessed for its potential benefit in a clinical setting.

5.5. Summary: tDCS and addiction

Transient anodal stimulation of the DLPFC temporarily reduced general and smoking-cue induced nicotine craving (Fregni et al., 2008a) and alcohol craving (Boggio et al., 2008b). These original studies had a small sample sizes and did not include neutral cue control groups. Future studies should address these limitations. Additionally, studies that will utilize several consecutive sessions of tDCS might be needed to evaluate potential longer lasting therapeutic effects of tDCS in addicted populations. In addition, to date, there are no documented animal studies which assessed the effects of tDCS on addictive behaviors or neuroadaptations induced by chronic drug use. Nevertheless, results from these initial human studies are promising. Further investigation may translate into a simple, affordable method of reducing addictive behaviors within clinical settings.

5.6. Safety of tDCS

Safety studies of tDCS suggest that under tDCS parameters used in current studies, the method is a safe and painless. These include neuropsychological (Iyer et al., 2005), EEG (Iyer et al., 2005), magnetic resonance imaging (MRI) (Nitsche et al., 2004) and brain metabolites (Nitsche and Paulus, 2001) studies. Gandiga et al. (2006) evaluated the effects of tDCS and sham stimulations on healthy and stroke patients. They were interested in assessing whether there were any adverse effects such as fatigue or discomfort. The participants could not distinguish between the sham or active conditions and no major adverse effects were reported (Gandiga et al., 2006). These findings were supported by Poreisz et al. (2007) in a safety study evaluating potential adverse effects over 567 tDCS sessions applied over motor and non-motor regions. They reported that only minor adverse effects, such as mild tingling sensation, were noted when the present tDCS safety guidelines were adhered to Poreisz et al. (2007). Therefore, the administration of tDCS in substance dependent populations appears to be both safe and warranted.

6. Future studies

Until today, most of the TMS studies evaluating effects of drugs of abuse on neuronal excitability were based on responses of the motor cortex to single pulse or paired-pulse stimulation. However, in order to evaluate the effects of acute and chronic exposure to drugs of abuse on excitability of other brain regions, such as the prefrontal cortex (Kahkonen et al., 2003), more studies combining TMS with EEG (Daskalakis et al., 2008a,b; Fitzgerald et al., 2008) or imaging techniques such as fMRI or PET, are required. In addition, responses to PFC stimulation induced by TMS or tDCS can be measured within reward-related brain regions by fMRI or PET (Bestmann et al., 2008; Siebner et al., 2009). The measurements of local and remote effects of TMS or tDCS can be used to study the effects of various drugs of abuse on neuronal excitability and a comparison between healthy and addicted subjects may lead to fundamental understanding of the neuroadaptations induced by such drugs in humans. These studies would lay the basis for therapeutic brain stimulation interventions aimed to normalize circuitries affected in addicted subjects.

Additionally, rTMS has shown some clinical effectiveness within a number of neuropsychiatric populations. Nevertheless, there is only a limited understanding of the mechanisms of action underlying TMS and its effects of cortical and subcortical networks (Bestmann et al., 2008; Ridding and Rothwell, 2007). Very few studies thus far have utilized a combination of TMS and imaging techniques, and these studies did not assess the long-term effects of rTMS. Traditionally, MEP's or phosphenes were used to evaluate the effects of TMS on the cortex and physiological alterations were studied mainly by stimulation of the hand motor area and the recording of MEP's in the contralateral hand muscle. Although many studies demonstrate the ability of TMS to affect behavior and even suggest the functional contribution of certain cortical areas to different aspects of behavior, these studies cannot determine the exact mechanisms involved in the TMS-induced effects on behavior. Future studies, such as TMS combined with neuroimaging techniques (as mentioned above), are required to identify the effects of TMS not only within the targeted site, but also the remote interconnected neural networks (Bestmann et al., 2008; Ridding and Rothwell, 2007).

It would also be necessary to identify the optimal parameters of stimulation in TMS and tDCS studies for the most effective and safe treatment of drug craving and relapse. Different TMS coil configurations, such as deeper stimulation, which could more directly affect reward-related circuitries, may expand opportunities in both basic studies on the effects of drugs of abuse on neuronal excitability and clinical studies aiming to attenuate craving and relapse. In tDCS, different electrode distribution and sizes should be explored (Boggio et al., 2008b). In addition, future studies should also explore the potential efficacy of co-administering current addiction medications alongside brain stimulation treatments. Finally, given the critical interaction between brain stimulation and cognitive activation revealed in recent studies (e.g. Amiaz et al., 2009), it is possible that a combination of cognitive behavioral therapies and brain stimulation would produce a promising clinical outcome.

7. Conclusion

In summary, repeated drug administration is associated with modified dopamine activity and neuroadaptations within the

mesocorticolimbic circuitry. Electromagnetic brain stimulation techniques, TMS and tDCS, are capable of externally modulating cortical activity. TMS inhibitory paradigms were administered as an investigative tool to index the pathophysiology of addiction in human subjects. This technique uncovered altered cortical excitability in the motor, prefrontal and occipital cortex of individuals exposed to addictive drugs. The longer lasting effects of rTMS and tDCS in substance dependent populations were also explored. Administration of rTMS to frontal brain regions in both animal and human studies enhanced dopamine release in the mesocorticolimbic circuitry. Animal studies indicate the potential of brain stimulation in attenuating addictive behaviors. Application of rTMS to the DLPFC within substance dependent populations transiently reduced levels of craving and consumption of addictive substances. Anodal tDCS administered to the DLPFC was also found to attenuate levels of cue-induced cravings. Overall, these studies support the development of electromagnetic brain stimulation as an investigative technique to index abnormal neuronal excitability associated with chronic drug administration, and furthermore, as a potential therapeutic tool to reduce addictive behaviors.

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4.2.1. Recent advances of brain stimulation techniques

Since the publication of the review titled, *Brain stimulation in the study and treatment of addiction,* there have been significant technical advances in TMS techniques, such as the development of the combined TMS-EEG technique (Daskalakis et al., 2012; Rogasch and Fitzgerald, 2012). Therefore, the next section expands on the brain stimulation techniques presented in the review article, and provides a detailed description of the combined TMS-EEG technique and its potential use in psychiatric medicine. This technique is particularly relevant to the current thesis, as combined TMS-EEG was applied as a research tool to assess alterations of cortical excitability within the frontal cortex of alcohol dependent patients post-detoxification.

4.2.2. Transcranial Magnetic Stimulation - Electroencephalography (TMS -EEG) as an investigative tool for Alcohol Dependence

Alcohol, a central nervous system depressant (Addolorato et al., 2012), has widespread effects on multiple neurotransmitter systems within the brain, including disruption of the delicate balance between inhibitory and excitatory neurotransmitters within the mesocorticolimbic circuitry (De Witte, 1996; Morikawa, 2010; Spanagel, 2009). Neuromolecular models suggest that acute alcohol exposure facilitates γ-aminobutyric acid (GABA) inhibitory neurotransmission (Cui et al., 2012; Enoch, 2008; Filip and Frankowska, 2008; Lobo and Harris, 2008; Weiner and Valenzuela, 2006), and suppresses glutamate (GLU) release and glutamate receptor activity (in dopaminergic cells) (Duncan and Lawrence, 2012; Gass and Olive, 2008; Kalivas, 2009; Kalivas et al., 2009); this results in an overall dampening of cortical excitability. With repeated alcohol exposure, the brain attempts to restore equilibrium in neuronal cell function (Tambour and Quertemont, 2007) by opposing the inhibitory effect of acute alcohol administration (Alfonso-Loeches and Guerri, 2011; Kalivas, 2009; Kalivas et al., 2009; Pulvirenti and Diana, 2001; Van Den Oever et al.,

2012). This leads to the suppression of GABAergic neurotransmission (Addolorato et al., 2012; Enoch, 2008; Filip and Frankowska, 2008; Lobo and Harris, 2008) and the facilitation of GLU excitatory neurotransmission (Duncan and Lawrence, 2012; Gass and Olive, 2008; Olive et al., 2012; Tzschentke and Schmidt, 2003). Thus, alterations of cortical inhibition (CI), the neurophysiological mechanism by which cortical GABA inhibitory interneurons selectively suppress the activity of other neurons in the cortex, is thought to be central to the pathophysiology of Alcohol Dependence (AD) (Diana, 2003). However, despite neuromolecular and preclinical evidence of these compensatory mechanisms, direct evidence of these cortical alterations within the mesocorticolimbic 'addiction' circuitry of the human brain is lacking.

Application of TMS (Barker et al., 1985; Cohen et al., 1998; Hallett, 2000) is emerging as a promising investigative tool for indexing CI of the cortex within the human brain. With respect to alcohol, only a small number of studies have previously employed these TMS techniques to characterize the effects of acute and chronic ethanol exposure on localized changes in CI (for a review, see Feil and Zangen, 2010). Acute alcohol administration was found to potentiate GABAergic inhibitory mechanisms in the motor cortex (Conte et al., 2008; Ziemann et al., 1995), decrease cortical excitability in the prefrontal circuitry (Kahkonen et al., 2003), and influence functional connectivity between the motor and prefrontal cortices (Kahkonen et al., 2001; Kähkönen and Wilenius, 2007). In terms of chronic alcohol consumption, clinical populations with AD (Conte et al., 2008), including those experiencing alcohol withdrawal (Nardone et al., 2010), showed evidence of altered motor cortical activity. Thus, these TMS paradigms are providing important information regarding altered CI within the human cortex. However, these studies were largely confined to measuring CI of the motor cortex, as measuring CI from other brain regions, such as the mesocorticolimbic 'addiction' circuitry, was technically difficult. Therefore, although these

studies provide initial evidence of cortical alterations within the motor cortex, they were unable to directly ascertain CI within the mesocorticolimbic 'addiction' system.

The newly developed combined TMS-EEG technique (Daskalakis et al., 2012; Rogasch and Fitzgerald, 2012) is capable of directly recording CI from the prefrontal cortex (Daskalakis et al., 2008; Farzan et al., 2010; Fitzgerald et al., 2008). Direct measurement of CI of the prefrontal cortex is possible through delivery of the paired pulse TMS paradigm known as long interval CI (LICI) (Valls-Solé et al., 1992) to the dorsolateral prefrontal cortex. LICI involves stimulation of the cortex with a suprathreshold conditioning stimulus 50- 150 milliseconds prior to the suprathreshold test stimulus; this results in suppressed cortical evoked activity by approximately 30% (Daskalakis et al., 2008). Several studies suggest that LICI relates to inhibitory activity at the $GABA_B$ receptor (McDonnell et al., 2006; Sanger et al., 2001), and thus, LICI of the prefrontal cortex may reflect $GABA_B$ receptor inhibitory neurotransmission within the frontal circuitry. Therefore, the newly developed TMS-EEG technique allows researchers for the first time to directly index altered GABAergic neurotransmission within the prefrontal cortex of alcohol dependent patients. So far, there have been no reported studies which have used TMS-EEG within alcohol dependent populations. The current thesis provides the first application of the TMS-EEG technique to evaluate altered cortical excitability within the frontal cortex of patients diagnosed with AD post-detoxification (described further in Chapter 10).

4.3. General summary

TMS is emerging as a promising research and therapeutic technique for addictive disorders. The newly developed TMS-EEG technique allows researchers to safely and non-invasively index cortical activity within the frontal brain regions. Therefore, the new TMS-EEG technology provides researchers with the tools to examine the involvement of the frontal circuitry (from neurotransmitter systems level) in AD. To date, there have been no previously

published studies which have utilized the combined TMS-EEG technique to directly index cortical alterations within dependent populations. Therefore, the current thesis provides the first application of the TMS-EEG technique to directly index cortical alterations within the frontal cortices of patients with AD (Chapter 10).

CHAPTER FIVE

Brain stimulation techniques and psychiatric disorders: Major Depressive Disorder

5.1. General overview

In the current chapter, the clinical and cognitive effects of administering TMS techniques within Major Depressive Disorder (MDD) populations are examined. The published review (Feil and Zangen, 2010) in Chapter 4 provides a detailed overview of the basic mechanisms underlying repetitive brain stimulation techniques; therefore, this chapter does not revisit the technical description of TMS, but rather, places these stimulation techniques in the context of current MDD research. There follows an introduction to the newly developed deep Transcranial Magnetic Stimulation (deepTMS) technique. The present chapter describes the mechanisms underlying deepTMS and reviews previous deepTMS depression studies. Finally, implications of delivery of frontal deepTMS in improving cognitive symptoms of depression are discussed.

5.2. Brain stimulation as a therapeutic tool for Major Depressive Disorder

Application of repetitive transcranial magnetic stimulation (rTMS) is emerging as a promising non-invasive and safe technique for minimizing clinical symptoms of treatment resistant depression (TRD) (Fitzgerald and Daskalakis, 2011; George et al., 2005; Loo et al., 2008; O'Reardon et al., 2007). Brain imaging studies in depressed patients have consistently located hypoactivity within the prefrontal cortex (Drevets, 2000; Fitzgerald et al., 2006) and neural abnormalities within the mesolimbic dopaminergic pathway (Drevets et al., 2008; Mayberg, 1997, 2003a; Mayberg et al., 1999; Nestler and Carlezon Jr, 2006). Therefore, application of rTMS, which is capable of altering neuronal activity within the hypoactive frontal brain regions (Hallett, 2000, 2007; Rachid and Bertschy, 2006), appears to elicit an anti-depressant effect within depressive populations. Consistent with the cerebral asymmetry of the frontal cortex in affective disorders (Bajwa et al., 2008; Garcia-Toro et al., 2001),

patients with MDD tend to show improved treatment response to high frequency (5-10Hz) rTMS to the left prefrontal cortex (PFC) and low frequency (1Hz) rTMS to the right PFC (Fitzgerald and Daskalakis, 2011). Standard TMS methodologies commonly utilize the figure-8 coil for delivery of stimulations, thus enabling direct stimulation of superficial cortical areas to a depth of approximately 1 to 2.5cm from the scalp (Roth et al., 2007; Zangen et al., 2005). The capability of the standard rTMS to stimulate the frontal regions of depressive patients (Drevets, 2001; Drevets et al., 2008; Fitzgerald et al., 2006; Krishnan and Nestler, 2008; Maletic et al., 2007) has promising clinical implications for the treatment of clinical symptoms of depression. The efficacy of these standard TMS techniques have been examined by both large multi-site trials (George et al., 2010; O'Reardon et al., 2007) and meta-analyses (Dell'Osso et al., 2011; Slotema et al., 2010), and they reported that current rTMS methodologies elicit moderate anti-depressant effects relative to a sham condition.

5.2.1. Deep Transcranial Magnetic Stimulation and Major Depressive Disorder

Recently, to improve the clinical efficacy of rTMS treatments, a novel coil designed to stimulate deeper cortical regions was developed (for a technical review, see Bersani et al., 2012). The newly developed H-coil (Zangen et al., 2005) is capable of modulating cortical excitability of deeper neural circuits up to a maximum depth of 6cm (Roth et al., 2007; Zangen et al., 2005), thus enabling direct stimulation of deeper brain regions, such as the mesocorticolimbic circuitry (Mayberg, 1997, 2003a, 2006; Nestler and Carlezon Jr, 2006) which is implicated in the pathophysiology of depression. Therefore, the deep TMS (deepTMS) H-coil, which has been shown to be a safe and effective procedure (Zangen et al., 2005), is currently being investigated as a treatment alternative for TRD (Bersani et al., 2013; Minichino et al., 2012). To date, only six studies have examined the clinical efficacy of deepTMS in the treatment of MDD (Isserles et al., 2011; Levkovitz et al., 2009; Levkovitz et al., 2011; Rosenberg et al., 2011; Rosenberg et al., 2010a; Rosenberg et al., 2010b). The stimulations which will be described in these deepTMS studies were administered to the left prefrontal cortex (Harel et al., 2011; Isserles et al., 2011; Levkovitz et al., 2009; Levkovitz et

al., 2011; Rosenberg et al., 2010; Rosenberg et al., 2011) and the bilateral prefrontal cortex (Levkovitz et al., 2009; Levkovitz et al., 2011).

The first deepTMS and depression study was conducted by Levkovitz et al (2009). They investigated both the antidepressant and cognitive effects elicited by a four week trial of high frequency (20Hz) repetitive deepTMS over the frontal cortex of sixty-five depressive patients who were resistant to anti-depressant medications. Different treatment parameters, such as stimulation intensity and laterality, were evaluated. The authors found that high frequency deepTMS treatment with the H-coil yielded high response and remission rates. In addition to the attenuated depressive symptoms, there were notable improvements across several cognitive domains. Data from this study were revisited by Levkovitz et al (2011) to evaluate the effects of frontal deepTMS on apathy and other depression-related symptoms. In this retrospective analysis they noted that the patients for whom apathy reached remission, depressive symptoms were also attenuated. However, for those patients whose apathy did not reach remission, depressive symptoms remained consistent. This all suggests that frontal deepTMS affects both apathy and depression similarly, while also providing initial evidence of the interplay between apathy, depressive symptoms and the efficacy of frontal deepTMS.

Rosenberg et al (2010a) also explored the efficacy of deepTMS in patients with resistant depression, however, this time, in patients who were previously administered (and resistant to) electroconvulsive therapy (ECT). Six patients participated in a trial of frontal deepTMS administered at high frequency (20Hz) over four weeks (20 sessions). Two of the patients who were resistant to ECT responded to the treatment, with one of the patients achieving full remission. Thus, a sub-group of MDD patients who are resistant to ECT may indeed respond to deepTMS. The efficacy of the deepTMS H-coil in treatment of resistant major depression was further assessed by Rosenberg et al (2010b) across seven participants diagnosed with MDD, after failing to respond to at least two trials with anti-depressant medication. Out of the seven participants, only five completed the four week trial (20 sessions) of high frequency (20Hz) deepTMS. Among these five participants, one attained remission, three patients

presented with a reduction of more than 50% on the Hamilton Depression Rating scale (HDRS), and one patient achieved a partial response. The final two patients dropped out; one due to lack of response, and the other due to insomnia. Despite the small sample size, this study provided further support for the antidepressant effect of deepTMS. To build on these findings, Rosenberg et al (2011) assessed the efficacy of a second anti-depressant course of deepTMS in eight MDD patients who had previously responded promisingly to deepTMS but had relapsed within one year of the treatment. These eight participants were again treated with four weeks (20 sessions) of frontal high frequency (20Hz) deepTMS. Similar to the first course of deepTMS treatment, there was evidence of significantly improved depressive symptoms, although the magnitude of response was smaller than observed after the first course of treatment. Therefore, the authors suggest that participants who respond to the initial deepTMS treatment are likely to respond again; however, the reduction in magnitude of response may be suggestive of a deepTMS tolerance effect.

Following this, Isserles et al (2011) assessed the value of utilizing deepTMS as an adjunct to anti-depressants in treating patients with MDD. In addition, they evaluated the effect of cognitive-emotional reactivation on the clinical outcome of deepTMS treatment. Fifty-seven patients diagnosed with MDD, and resistant to at least two anti-depressant medications, were recruited for the study. Participants were administered four weeks (20 sessions) of frontal high frequency (20Hz) deepTMS, followed by a maintenance stage of four weekly sessions. Participants were divided into three groups: one group received no cognitive-emotional reactivation (25 participants), one group was assigned to positive (17 participants), and another negative (15 participants) cognitive-emotional reactivation prior and throughout treatment. Overall, the findings were very supportive of deepTMS in treating patients with MDD. Thus twenty-one out of the forty-six patients that completed at least ten stimulation sessions achieved treatment response, with thirteen patients achieving remission by the end of

the daily treatments. It was noted, however, that patients in the negative cognitive-emotional reactivation group presented with reduced treatment improvements. Thus, the authors suggest that negative cognitive-emotional reactivation can disrupt the therapeutic utility of deepTMS.

When combined, these preliminary studies suggest that deepTMS is emerging as a promising treatment possibility for the reduction of clinical symptoms of depression. However, these promising results must be examined with a degree of caution, as only a limited number of studies have been conducted, and these studies consisted of considerably small sample sizes. Thus, further studies are required to replicate these studies within larger samples.

5.2.2. *Brain stimulation and cognitive symptoms of Major Depressive Disorder*

Although MDD is primarily a mood disorder, cognitive dysfunction remains a prevalent feature of the disorder (Austin et al., 2001; Elliott et al., 2002; Rogers et al., 2004). Negative automatic thoughts, attentional difficulties and altered emotion-regulation are thought to be critical in the onset, maintenance and recurrence of depressive symptoms (Beck et al., 1979; Clark et al., 2009; Gotlib and Joormann, 2010; Joormann, 2010; Joormann and Gotlib, 2010; Joormann et al., 2007; Paelecke-Habermann et al., 2005; Ravnkilde et al., 2002). Neuroimaging studies of MDD patients demonstrate hypoactivity within the prefrontal cortex (Drevets, 1999, 2000; Fitzgerald et al., 2006), and altered neural activity within the fronto-limbic circuitry (Drevets et al., 2008; Mayberg, 2003b, 2006; Mayberg et al., 1997; Nestler and Carlezon Jr, 2006); causing disruption of the same circuitry recruited for cognitive processing (Blasi et al., 2006; Chambers et al., 2009; Garavan et al., 2002; Miller and Cohen, 2001). This all suggests an intricate relationship between cognitive deficits and the inability to recover from depressive disorders (Baune et al., 2010; Jaeger et al., 2006; Roiser et al., 2012).

Application of rTMS to the frontal regions of patients with MDD is thought to attenuate clinical symptoms of depression; however, these frontal stimulations are likely to also have a concurrent effect on frontally-mediated cognitive function in depressive populations. Surprising though, only a limited number of studies have directly examined this potential effect. To date, TMS research has been largely focused on identifying optimal clinical outcome (George et al., 2005), rather than exploring the underlying effects on cognitive symptoms of depression (Demirtas-Tatlidede et al., 2013; Guse et al., 2010; Hoy et al., 2012). However, although the cognitive effects are not the primary focus of TMS studies, clinical trials of rTMS in depressive samples commonly include a measure of cognitive function to monitor the safety and potential side-effects of brain stimulation techniques (Demirtas-Tatlidede et al., 2013; Guse et al., 2010; Hoy et al., 2012). Overall, these assessments have asserted that non-invasive rTMS techniques do not induce cognitive deterioration (Avery et al., 1999; Avery et al., 2006; Harel et al., 2011; Hoy et al., 2012), but rather, the opposite effect, with a number of MDD participants demonstrating cognitive improvement when frontal stimulations via the figure-8 coil are applied (Fabre et al., 2004; Fitzgerald et al., 2009; Holtzheimer et al., 2010; Höppner et al., 2003; Kuroda et al., 2006; Leyman et al., 2011; Martis et al., 2003; Moser et al., 2002; O'Connor et al., 2003; O'Connor et al., 2005; Padberg et al., 1999; Schulze-Rauschenbach et al., 2005; Schutter et al., 2010; Shajahan et al., 2002; Triggs et al., 1999; Vanderhasselt et al., 2009). Moreover, these cognitive improvements tended to occur within patients who were clinically responsive to rTMS (Loo et al., 2008).

With respect to deepTMS, although repetitive high frequency frontal deepTMS of MDD patients resulted in promising clinical improvement (Isserles et al., 2011; Levkovitz et al., 2009; Levkovitz et al., 2011; Rosenberg et al., 2011; Rosenberg et al., 2010a; Rosenberg et al., 2010b), only a small number of these studies examined change in cognitive functioning

(Isserles et al., 2011; Levkovitz et al., 2009; Levkovitz et al., 2011). Thus far, deepTMS studies found that long-term administration of high frequency rTMS resulted in significant improvement in sustained attention (Levkovitz et al., 2009), which was supported by a second study which indicated a similar trend, though not significant, towards improved attention (Isserles et al., 2011), cognitive planning (Levkovitz et al., 2009), and in treatment responders, information processing (Isserles et al., 2011). Therefore, when combined, these studies suggest that frontal rTMS may induce beneficial cognitive changes in depressive patients, and these effects may impact on treatment response.

5.3. General Summary

Brain stimulation techniques are emerging as effective tools in reducing clinical symptoms of depression. Recent development of a new brain stimulation technique, deepTMS, allows the non-invasive and safe stimulation of deeper cortical regions. It is believed that stimulation of deeper cortical regions, such as the fronto-limbic circuitry, may more effectively improve clinical symptoms of depression. So far, research into the clinical efficacy of the deepTMS has been promising; however, it is still in its early stages and requires further evaluation. DeepTMS applied to the frontal regions of patients with MDD is thought to attenuate clinical symptoms of depression; notably though, these frontal stimulations are also targeting the neural structures which are thought to subserve cognitive function in depressive patients. Therefore, it seems highly possible that delivery of frontal TMS will have an effect on both clinical symptoms and cognitive function in depressive populations. However, surprisingly, very few studies have directly assessed the cognitive efficacy of administering frontal deepTMS in depressive populations, or whether cognitive changes may be associated with a clinical response to TMS treatment. Therefore, the current thesis provides the first direct evaluation of the efficacy of administering deepTMS to the frontal regions in reducing

cognitive symptoms of depression. There follows an examination of whether cognitive factors are predictive of clinical response to TMS treatment (Chapter 8).

CHAPTER SIX

Overview and Introduction to experimental chapters

In everyday situations, many mental representations are simultaneously active, and the intact ability to select and integrate appropriate representations, while inhibiting inappropriate representations, is essential to the basic control of behaviours and thoughts. Recent studies have suggested that the inability to inhibit inappropriate representations reflects dysfunction of the frontostriatal circuitry, and may be closely related to core features of a number of psychiatric disorders. In the current review, the presence of these cognitive inhibitory impairments and related frontostriatal dysfunction were examined across two debilitating psychiatric disorders: Major Depressive Disorder (MDD) and Alcohol Dependence (AD).

In terms of MDD, although it is primarily a mood disorder, cognitive impairment is a defining feature of the disorder. More specifically, the increased difficulty *inhibiting* intrusive negative representations has been found to perpetuate depressive symptoms. Likewise, with regards to AD, a debilitating characteristic of the disorder is the patient's diminished capacity to *inhibit* the compulsive urge to consume alcohol regardless of aversive consequences. Therefore, impaired inhibitory function relates to key symptoms of MDD and AD, an observation supported by neuroimaging studies which have identified alterations within the frontostriatal circuitry, the same brain circuitry which is recruited for these cognitive inhibitory processes.

However, across both disorders, the specific nature of the processes underlying these cognitive inhibitory impairments, and the involvement of the related frontostriatal dysfunction, remains largely unknown. Therefore, the broad purpose of the current thesis is to explore the nature of cognitive impairment and frontostriatal dysfunction across patients with MDD and AD. Further insight into the nature of these deficits and related circuitry could contribute to the development of improved screening and treatment models.

The current thesis aims to:

1. Examine the presence of cognitive deficits and cognitive biases in a sample of severely depressed patients. There follows an evaluation of whether these cognitive components are interrelated, or rather, exert a unique effect on patients with MDD.
2. Assess whether delivery of frontal deep Transcranial Magnetic Stimulation (deepTMS), which stimulates deeper fronto-limbic cortical regions, can elicit improved cognition function in patients with severe depression.
3. Explore the presence of frontally-mediated cognitive inhibitory impairments in patients diagnosed with AD post-detoxification. There follows an examination of whether these cognitive impairments relate to craving, and whether they improve following abstinence.
4. Administer the combined Transcranial Magnetic Stimulation and Electroencephalography (TMS-EEG) technique to ascertain whether patients diagnosed with alcohol dependence post-detoxification exhibit altered cortical excitability within the frontal and motor cortices.

To address these research objectives, the experimental studies to follow are:

Experimental Study One: Impaired cognitive inhibition, attentional control and emotional biases in patients with severe depression.

Experimental Study Two: Effects of repetitive deep transcranial magnetic stimulation of the frontal regions on neurocognition in severely depressed patients.

Experimental Study Three: Frontally-mediated cognitive deficits, craving and cognitive recovery among alcohol dependent individuals following detoxification.

Experimental Study Four: Cortical Inhibition within Motor and Frontal Regions in Alcohol Dependence: A TMS-EEG study.

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CHAPTER SEVEN

Study One: *Impaired cognitive inhibition, attentional control and emotional biases in patients with severe depression*

7.1. Introductory Comments

Depressive disorders are characterized by difficulty in disengaging from negative stimuli and suppressing negative thoughts. Study One was designed to examine the nature of these cognitive inhibitory impairments within a depressive population. Researchers have identified two major components of cognitive inhibitory dysfunction in depressive disorders: 1. *Cognitive biases* which are reflected by regulatory impairments which are specific to emotion-regulation, and 2. *Cognitive deficits* which are represented by generalized cognitive inhibitory deficits. Traditionally, researchers placed primary focus on emotion-related cognitive biases; however, only recently, researchers have begun to examine the dysfunction of the cognitive mechanisms underpinning the processing of neutral stimuli (i.e. generalised cognitive deficits) within depressive disorders. Surprisingly, there have been very few attempts to integrate these separate lines of research. Therefore, Study One sought to expand on these previous studies and examine whether both components of cognitive inhibitory impairment (cognitive biases and cognitive deficits) are present within a severely depressed population. There follows an evaluation of whether cognitive biases and deficits are indeed independent, or rather, exert an interrelated effect within the depressive population.

The following study is presented according to the manuscript version which has been submitted to a scientific journal and is currently under peer-review. The format of the paper is designed according the journal specifications. This includes referring to the patients as suffering from Treatment Resistant Depression (based on a psychiatrist's clinical diagnosis),

and the graphical representation of the data (i.e. having the error bars representing +/- 2 standard errors).

7.2. Paper Under Review

Impaired cognitive inhibition, attentional control and emotional biases in patients with severe depression

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ABSTRACT

Background: Separate lines of research have identified two key components of cognitive dysfunction in depressive disorders: 1. *Cognitive deficits* which are indexed by generalised impairments in cognitive and attentional control and 2. *Cognitive biases* which are characterized by impaired affective processing and emotion regulation. However, few studies have explored the unique contribution of these neurocognitive impairments, or whether these cognitive impairments are interrelated or exert separate effects, within a severely depressed population.

Methods: Twenty-five patients clinically-diagnosed with Treatment Resistant Depression (TRD) and 26 healthy matched control subjects (CS) were recruited. The Sustained Attention to Response Task (SART) measured cognitive inhibition and sustained attention (cognitive deficits). The Emotional Stroop (ES) evaluated an attentional bias for negative stimuli (cognitive biases).

Results: On the SART, TRD individuals made more commission and omission errors, and greater oscillations in performance variability. On the ES, the TRD group presented with a significant attentional bias for negative stimuli. There was no evidence of a relationship between cognitive deficits and cognitive biases.

Conclusion: Individuals with clinically-diagnosed TRD exhibited impairment in both cognitive deficits and cognitive biases. They found it difficult to flexibly adjust behaviours and direct attention towards non-depressive task-related objectives, and showed dysregulated processing of negative stimuli. These cognitive impairments were not interrelated and exerted independent effects. These findings reinforce the need for screening and treatment strategies which address both aspects of these cognitive impairments in depressive disorders.

1. Introduction

Major Depressive Disorder (MDD) is a severe and disabling psychiatric disorder characterized by a wide range of heterogeneous clinical features. Even after adequate anti-depressant therapy, almost one-third of patients with MDD remain symptomatic and can be classified as having Treatment Resistant Depression (TRD) (Fava, 2003; Malhi et al., 2005). TRD is associated with poorer clinical outcome, reduced quality of life and increased mortality (Dunner et al., 2006; Fekadu et al., 2009; Fekadu et al., 2011). Although TRD is primarily a mood disorder, cognitive impairment is a highly prevalent feature (Clark et al., 2009; Gotlib and Joormann, 2010; Joormann, 2010; Joormann et al., 2007). Research has begun to focus on the cognitive aspects of depression to accurately characterise the neuropsychological symptoms associated with depressive disorders.

Separate lines of research have identified two core components of cognitive dysfunction in depressive disorders (Joormann et al., 2007; Murrough et al., 2011): 1. *Cognitive deficits* which are characterized by *generalised* executive deficits in cognitive and attentional control (Chamberlain and Sakakian, 2006; Clark et al., 2009; Desseilles et al., 2009; West et al., 2010), and 2. *Cognitive biases* which are classified as impairments *specific* to processing affective information and emotion regulation (Goeleven et al., 2006; Gotlib et al., 2004; Joormann, 2010). These cognitive processes rely on the integrity of the fronto-limbic-parietal circuitry (Blasi et al., 2006; Chambers et al., 2009; Garavan et al., 2002; Miller and Cohen, 2001); the same circuitry implicated in the presence (Brody et al., 2001; Davidson et al., 2002b; Mayberg et al., 1999), persistence (Drevets et al., 2008), and degree of treatment response (Kumari et al., 2003; Langenecker et al., 2007; Mayberg, 1997; Pizzagalli et al., 2001; Pizzagalli, 2011) in depressive disorders. Thus, the presence of these cognitive deficits

and biases may be inextricably linked with a compromised ability to recover from depressive disorders (Baune et al., 2010; Jaeger et al., 2006).

Although previous studies have focused on cognitive impairments related to processing of negative material in MDD, very few studies have delineated the cognitive inhibitory mechanisms required for the processing of neutral stimuli (i.e. cognitive deficits) and emotional stimuli (i.e. cognitive biases) (De Lissnyder et al., 2012; Joormann, 2010). In addition, there has been limited research into how these cognitive deficits and cognitive biases influence each other, and subsequently, how they may relate to the symptoms of depression (Murrough et al., 2011). Our main objectives were to investigate the presence of both generalised cognitive deficits and cognitive biases in depressive disorders, followed by an assessment of whether these neurocognitive impairments are interrelated, or rather, whether they operate independently for those with MDD.

1.1. *Cognitive deficits*

Cognitive deficits are reflected by *generalised* dysfunction of both cognitive and attentional control, and rely on the fronto-parietal circuitry (Sturm and Willmes, 2001), the same circuitry affected in non-remitting depression (De Raedt and Koster, 2010; Kumari et al., 2003; Leung et al., 2009; Li et al., 2010; Vasic et al., 2008). Cognitive control refers to the ability to flexibly adapt one's thoughts and behaviours towards a current goal (Blasi et al., 2006; Miller and Cohen, 2001; Ridderinkhof et al., 2004). A critical element of cognitive control is the capacity to suppress responses to prepotent yet inappropriate representations (Houghton and Tipper, 1996). Individuals with depressive disorders exhibit difficulties overriding automatic responses, particularly to negative representations, which lead to and exacerbate depressive-related behaviours (Beck et al., 1979). Although previous studies have identified a variety of generalised executive and working memory impairments associated

with MDD (Austin et al., 2001; Rogers et al., 2004), only limited evidence has been presented of cognitive control impairments when processing neutral information (Joormann et al., 2007). To assess cognitive deficits, our study specifically focused on cognitive inhibitory mechanisms, and the difficulty suppressing a prepotent response to a neutral stimulus, within a MDD population.

Reduced attentional control is also a principal feature of the executive control system (Maclean et al., 2009). Consistent with the clinical diagnosis of MDD, which includes "an impaired ability to think or concentrate" (DSM-IV-TR, American Psychiatric Association., 2000), attention deficits appear to be a core feature of depressive disorders (Levin et al., 2007; Ravnkilde et al., 2002). A small number of behavioural studies have revealed the presence of impaired sustained (Cornblatt et al., 1989; Mialet et al., 1996; Ravnkilde et al., 2002), divided (Vasic et al., 2008) and visual (Li et al., 2010) attention in MD. Additionally, attentional deficits were found to correlate with increased depressive symptoms (Paelecke-Habermann et al., 2005), and frontal morphological anomalies (Li et al., 2010; Vasic et al., 2008) in patients with non-remitting depression. However, thus far, across depressive disorders, attentional deficits have only been assessed by a small number of studies. Therefore, to investigate the presence of generalised cognitive deficits (inhibitory and attentional) within a MDD population, our study administered the sustained attention to response task (SART) to patients with clinically diagnosed treatment-resistant depression (TRD).

1.2. The Sustained Attention to Response Task

The SART (Robertson et al., 1997) measures cognitive and attentional control (Molenberghs et al., 2009) and relies on activation of the fronto-parietal regions (Bellgrove et al., 2004; Braet et al., 2009; Breckel et al., 2011; Fassbender et al., 2004; Garavan et al., 2003; Hester

et al., 2004; MacDonald et al., 2009; Manly et al., 2003; O'Connor et al., 2004; Prado et al., 2011; Rueckert and Grafman, 1996; Stuss et al., 2003). Participants are required to frequently respond to *non-target* neutral stimuli (Go response), and withhold responses to randomly distributed rare *target* stimuli (No/Go response). Due to the unpredictable nature of the SART, every stimulus needs to be efficiently processed and identified, and when a 'No/Go' stimulus appears, there is a response conflict between the prepared 'Go' response and withholding the 'No/Go' response (O'Connell et al., 2008). Errors of commission (responding when you should withhold) reflect both impaired inhibitory control (Helton et al., 2009; Johnson et al., 2007a; Johnson et al., 2007b; O'Connell et al., 2008; O'Connell et al., 2009) and compromised sustained attention (Braver et al., 2003; Molenberghs et al., 2009; Robertson et al., 1997). Conversely, errors of omission and individual variations in response time (performance variability) on the SART are associated with difficulty maintaining endogenous attention (MacDonald et al., 2009; Smallwood and Schooler, 2006) and disengagement from task objectives (Cheyne et al., 2009; Johnson et al., 2007b; Sturm and Willmes, 2001).

Previously, assessment of the SART revealed cognitive deficits across various psychiatric populations (Bellgrove et al., 2004; Bellgrove et al., 2006; Johnson et al., 2007a; McAvinue et al., 2005; Molenberghs et al., 2009; Robertson et al., 1997). To date however, only two studies have administered the SART to explore the association between cognitive deficits and depressive symptoms (Farrin et al., 2003; Kim et al., 2008) and they reported mixed findings. Notably, these studies were conducted within non-clinical populations. Therefore, the present study administered the SART within a clinical population; we anticipated that the SART would be a sensitive and robust measure to index frontally-mediated cognitive deficits within depressive disorders.

1.3. Cognitive biases

In depressive disorders, emotion regulation is impaired, and results in a diminished ability to process negative information (Goeleven et al., 2006; Gotlib et al., 2005; Joormann, 2004). Clinically, dysregulation of affective processing is manifested as a reduced ability to inhibit negative automatic thoughts, pervasive rumination about negative events, and difficulties disengaging from negative material (Eugène et al., 2010; Gotlib and Joormann, 2010; Joormann et al., 2007; Koster et al., 2011; Koster et al., 2005; Watkins, 2008). Evidence from neuroimaging studies implicates the limbic-frontal circuitry in the regulation of emotional behaviour (Phillips, 2003; Phillips et al., 2003a, b), the same brain networks implicated in the pathophysiology of mood disorders (Drevets et al., 2008; Mayberg et al., 1997). These studies focus largely on the frontal regions and the anterior cingulate cortex (ACC) as the mediator for the integration of emotional information and the ability to self-regulate (Davidson et al., 2002a; Davidson et al., 2002b; Disner et al., 2011; Mayberg, 1997; Pizzagalli et al., 2001; Pizzagalli, 2011). The same region has also been implicated in the processing of negative thoughts (Eugène et al., 2010), and the extent of response to treatment (Mayberg et al., 1997; Mayberg et al., 1999; Pizzagalli, 2011), in depressive disorders. Emotion-regulatory deficits are proposed to contribute to the maintenance and exacerbation of depressive symptoms (Berman et al., 2011), leading to a compromised ability to functionally recover from MDD (Baune et al., 2010; Jaeger et al., 2006; Langenecker et al., 2007). Therefore, to assess the presence of cognitive biases within a MDD population, our study administered the emotional stroop (ES) to TRD patients.

1.3. The Emotional Stroop

The ES (Gotlib & McCann, 1984), a modified version of the original Stroop task (Stroop, 1935), assesses the processing of emotionally salient stimuli and attentional bias toward negative words (Williams et al., 1996). Participants are presented with depression-related and

neutral words in varying colours, and are instructed to name the ink colour of words, while ignoring their semantics. The *interference effect* occurs when emotional saliency distracts from the task objectives, resulting in increased response latency in naming the ink colours associated with depression-related words. Individuals with MD generally show this interference effect; i.e. a slower response latency for depression-related words (Dai and Feng, 2011; George et al., 1997; Mitterschiffthaler et al., 2008). Additionally, neuroimaging studies have implicated the critical involvement of frontal (Elliott et al., 2002), parietal (Dai and Feng, 2011; McNeely et al., 2008) and in particular the ACC (Eugène et al., 2010) activation in the automatic processing of negative words. In the current study, we administered the ES to further explore the presence of emotion regulatory bias in patients with severe depression.

Our study had three major objectives: (i) Assess cognitive deficits within a MDD population via administration of the SART. (ii) Investigate the presence of cognitive bias within a depressive population through administration of the ES. (iii) Evaluate whether cognitive deficits and cognitive biases are indeed interrelated constructs, or whether they operate independently within the MDD population.

2. Methods

The current study was part of a larger clinical study (clinicaltrials.gov, NCT00460902 and NCT00577070), approved by institutional and national review boards (IRB) committees. The study was conducted in collaboration with the Department of Psychiatry, Hadassah-Hebrew University Medical Center, Jerusalem, Beer-Ya'acov Mental Health Centre, Beer-Ya'acov and Shalvata Mental Health Center, Hod Hasharon, Israel. Active enrolment ran from July 2008 through April 2009. Consenting patients signed a detailed informed consent form prior to study enrolment; they were informed that participation was voluntary, and they could withdraw at any time without prejudice.

2.1. Participants

2.1.1. Treatment Resistant Depression Sample:

Twenty-five patients with TRD were tested. The screening procedure included a psychiatric and medical interview, conducted by a psychiatric clinician, to determine suitability. Main criteria included: a clinical diagnosis of non-psychotic Major Depression Disorder in patients who did not respond to at least two antidepressant medications provided in appropriate doses and duration in the current episode (thus being classified as TRD), and no coexisting DSM-IV axis I or major axis II disorder. Patients also completed the Hamilton depression rating scale (HDRS) (Hamilton, 1960), a 24-item clinical interview, and those with a HDRS score > 21, and aged 18-65years, were recruited for the study. In addition, as a secondary measure, patients were administered the Beck Depression Inventory (BDI) (Beck et al., 1961), a 21-item self-report measure for depression severity. For the study, no change was made to antidepressant treatment, with only limited use of hypnotic or anxiolytic medication (up to 2mg/day lorazepam or equivalent) for treatment-emergent insomnia or anxiety.

2.1.2. Healthy Control Sample:

Twenty-six healthy CS , without any current or previous major medical/psychiatric illness, were recruited through local advertisements and posters, and paid 100NIS (approx $30 US) to participate in the study (covering travel costs and time taken to participate). At screening, CS were required to complete a general demographic questionnaire, plus the BDI to screen for potential confounding levels of depressive symptoms (any BDI scores ≥ 9 were excluded from the study). Relevant demographic and participant characteristics are summarized in Table 1.

Insert Table 1.

The two groups did not differ in terms of age ($p = 0.093$), gender ($p = 0.68$) and years of education ($p = 0.18$). As expected, there was a significant difference in BDI between TRD ($M = 32$, $SD = 8.5$) and CS ($M= 1.7$, $SD = 2.2$), $F(1,49) = 308.81$, $p < 0.0005$.

2.2. Procedure

Following screening, cognitive performance was evaluated by two computerized cognitive tasks using E-prime V1 technology (Psychology Software Tools): the Sustained Attention to Response Task (SART) (Robertson et al., 1997) and Emotional Stroop (Gotlib and McCann, 1984). Participants were seated in a quiet, well-lit room, 30cm from the 17 inch computer screen. The task instructions were presented in Hebrew on the computer screen prior to the initiation of each task. Each task began with a short practice task to confirm that the participants understood the task requirements. All participants were native speakers of Hebrew.

2.3. Neuropsychological assessment

2.3.1. Sustained Attention to Response Task (SART)

In the SART, participants were asked to respond quickly and accurately to the presentation of single digits (1 to 9) with a button press, with the exception of the number ‘3’ (Robertson et al., 1997). The stimuli was presented in a random order in a block of 297 trials, with 33 possible no-go (number 3) responses. Each stimulus was presented for 150ms, with varying inter-stimulus interval (ISI) durations (1000ms, 1500ms and 1250ms) randomly distributed throughout the session (Bonnefond et al., 2010; Dockree et al., 2005). The variable ISI was

used to minimize speed accuracy trade-offs. Prior to recording, participants were administered an 18 trial demonstration sequence. Participants were informed that speed of response and accuracy were of equal importance. Reaction time (SART RT), commission errors, performance variability, and omission errors were recorded.

2.3.2. Emotional Stroop

Participants had to identify, as quickly as possible, the ink colour of stimulus words (neutral and emotional stimuli) presented in varying colours (red, blue, green and yellow). Neutral stimuli were the Hebrew equivalents of the words *branch, centre, ruins (i.e. ancient ruins), send* and *wagon*. Emotional stimuli were the Hebrew equivalents of the words *suffer, weep, hurt, doom* and *worry.* Stimuli words and procedure were based on previous studies (Chajut et al., 2010; McKenna and Sharma, 1995). In each trial, a single-colour word was presented at the centre of the computer screen for 450ms, with a maximum ISI of 2000ms. When the word stimuli appeared, participants had to press one of four specified buttons on the keyboard (corresponding to the colour of the word). The names of the colours were printed onto keys on the keyboard (i for red, j for yellow, l for blue and m for green). When the participant pressed the correct key, reaction time was recorded, and the next stimulus appeared. Presentation of word stimuli was divided into blocks; consisting of 40 trials of neutral stimuli (4 colours X 5 neutral words X 2 repetitions) followed by 40 trials of emotional stimuli (4 colours X 5 emotional words X 2 repetitions). All participants ran through four blocks (neutral, emotional, neutral, emotional), adding to 160 trials. Within each block, the word stimuli were presented in a random order. Prior to the experimental session, participants completed a demonstration (12 single-stimuli trials) in which XXXX was randomly presented in the four colours. Mean reaction times for each condition over the 160 trials were calculated.

2.4. Data analysis

Comparability of TRD patients and CS was assessed using χ^2- tests for categorical and T-tests for continuous variables (see Table 1.). Stem-plots located extreme outliers (> +/- 2.5 standard deviations (SD)), and outliers were brought to within 2.5 SD of the mean. For all data which met assumptions of normality, tests were run at an alpha level of 0.05. There were no significant violations of homogeneity of regression. In a few cases, there were violations of unequal variance (Levene's statistic found to be significant); for those specific cases, to address violations, statistics were run at a more conservative alpha level of 0.025. Pearson's correlation examined potential associations between SART variables, ES variables, and BDI scores within groups.

One-way ANOVA assessed group differences on the SART (reaction time, performance variability and omission errors). Due to the significant correlation between commission errors and SART RT, an ANCOVA (controlling for SART RT as a covariate) explored group differences for commission errors. In the ES, the interference effect was calculated by subtracting the mean neutral word reaction time from the mean emotional word reaction time for each participant (see Table 3.). A one-way ANOVA assessed group differences in Interference Effect. All data analyses were performed using SPSS for Windows, version 15.

3. Results

3.1. Sustained Attention to Response Task performance

Significant differences were observed in performance on the SART between the TRD and matched CS, especially in the number of commission and omission errors and performance variability as detailed below (Figure 1).

Insert Figure 1.

The TRD group (M= 9.16, SD=6.79) made significantly more commission errors (failure to stop on a no-go trial) than CS (M= 6.23, SD=3.08), F (1, 48) = 7.07, p= 0.01. No significant differences were found for SART RT between TRD (M= 423ms, SD=63ms) and CS (M= 413ms, SD=59ms), F (1, 49) = 0.32, p= 0.57. The performance variability measure calculates the standard deviation of the RTs on correct response trials (Go-trials) divided by the mean RT of each subject. The TRD group (M= 0.26, SD=0.06) presented with a significantly greater co-efficient of performance variability than CS (M= 0.23, SD=0.03), F (1, 49) = 5.61, p= 0.02. The TRD group (M= 11.00, SD=11.09) also made significantly more errors of omission (failure to make a response on a go-trial) than CS (M=3.69, SD=2.80), F (1, 49) = 10.58, p= 0.002 (Table 2).

Insert Table 2.

3.2 Correlational data for the SART

Pearson correlation identified significant negative correlations between commission errors and SART RT across both TRD (r = -0.593, n = 25, p = 0.002, two-tailed) and CS (r = -0.428, n = 26, p = 0.029, two-tailed). In addition, significant positive correlations were found between commission errors and performance variability in TRD (r = 0.554, n = 25, p = 0.004, two-tailed) but not the CS group. Performance variability was also found to positively

correlate with omission errors across both TRD ($r = 0.421$, $n = 25$, $p = 0.036$, two-tailed) and CS ($r = 0.4$, $n = 26$, $p = 0.043$, two-tailed). No further significant correlations were identified.

3.3. Emotional Stroop task performance

A significantly slower response latency for depression-related words (i.e. increased interference effect) was observed in the TRD group compared to CS (Figure 2).

Insert Figure 2.

There was a significantly larger interference effect for the TRD group ($M= 100.75$, $SD=77.23$) compared to CS ($M= -20.63$, $SD=40.67$), $F (1, 48) = 49.433$, $p<0.0005$ (Table 3.).

Insert Table 3.

3.2.1. Correlational data for the ES

No significant correlations were observed between demographic, clinical and cognitive variables (SART and ES cognitive variables).

4. Discussion

The present study provided evidence of both cognitive deficits and biases in the TRD group relative to CS. Regarding cognitive deficits, depressive patients showed significant impairment in cognitive inhibition (commission errors), as well as a diminished ability to maintain endogenous attention (performance variability), and a reduced capability to remain vigilant to task demands (omission and commission errors). In terms of cognitive bias,

depressive patients exhibited enhanced processing of negative words (greater interference effect) relative to controls who failed to show such a pattern. Finally, there was no significant evidence of a relationship between cognitive deficits and cognitive biases.

4.1. Cognitive deficits

The TRD group exhibited difficulty discriminating between conflicting response possibilities, and a reduced capacity to suppress an automatic response to the 'No/Go' target in the SART, resulting in commission errors. Commission errors reflect deficits in both cognitive inhibition (Helton et al., 2009) and attentional control (Robertson et al., 1997). Cognitive inhibitory dysfunction (Helton et al., 2009) refers to a diminished ability to overcome a habitual response and suppress a prepotent reaction to an inappropriate stimulus (Chambers et al., 2006). Only the TRD group exhibited significant problems in inhibiting a response when exposed to the 'No/Go' target. Difficulties inhibiting perseverative tendencies may relate to deficient mechanisms underlying the inhibition of inappropriate stimuli (i.e. negative stimuli), which could possibly contribute to problems suppressing ruminative thoughts, leading to intensified depressive symptoms (Davis and Nolen-Hoeksema, 2000; Nolen-Hoeksema, 2000). In terms of attentional control, the repetitive nature of the SART lulls susceptible participants into a non-attentive task-driven response (Fassbender et al., 2004; Robertson et al., 1997). The TRD group found it difficult to continually attend to task objectives, resulting in reduced allocation of attention towards detecting infrequent targets (Braver et al., 2003; Manly et al., 2003; Molenberghs et al., 2009). A recent study (Smallwood et al., 2009) explored the association between increased commission errors and 'mind-wandering'; attention was withdrawn from relevant sensory input when individuals focused on self-directed thoughts. The TRD group were possibly distracted by self-relevant thoughts, and had

difficulties inhibiting inappropriate (i.e. depressive) thoughts, which led to problems identifying the 'No/Go' stimuli.

Our study also revealed no significant differences in SART RT between TRD and CS. This finding is important, as it highlights that the poor performance in commission and omission errors, and response variability, does not reflect a reduction in motivation nor difficulty following task instructions, but rather supports the contention that poor performance reflects difficulties in cognitive and attentional control. Additionally, we revealed a negative relationship between SART RT and commission errors across both groups, indicating a speed-accuracy trade-off (Helton et al., 2009). Participants were instructed to respond as quickly and accurately as possible, and therefore, strategic planning was involved in modulating speed of response against the perceived efficacy of successfully inhibiting an inappropriate response (Manly et al., 1999).

In the traditional vigilance studies (Warm et al., 2008), errors of *omission* were of primary interest (Davies and Parasuraman, 1982; Mackworth, 1948). Recent studies have also administered the SART to measure difficulties in maintaining attentional control (Braet et al., 2009; Cheyne et al., 2009; Helton et al., 2011; Manly et al., 2003; Stuss et al., 2003): whereby performance variability represents difficulties maintaining endogenous attention (Carriere et al., 2010; Cheyne et al., 2009; Johnson et al., 2007a; Molenberghs et al., 2009), while errors of omission relate to extent of attentional disengagement (Manly et al., 2003; O'Connor et al., 2004). In the present study, individuals with TRD displayed greater performance variability relative to CS. While performance variability was traditionally ignored as 'noise' within cognitive experimental paradigms, emerging research suggests that these variations index an important cognitive process (Bellgrove et al., 2004; Ode et al., 2011) subserved by frontal neural mechanisms (Prado et al., 2011; Stuss et al., 2003). For

example, Bellgrove et al (2004) found that response variability predicted inhibitory success on a go-no/go task, and was correlated with task-related frontal brain activation. Prado and colleagues (2011) found that oscillations in response variability were associated with anomalous functional connectivity between ACC and fronto-parietal brain regions. Our study is the first to administer the SART and reveal increased response variability within a clinically-diagnosed TRD population, providing preliminary evidence of frontally-mediated difficulties in maintaining endogenous attention in these patients, and demonstrating the sensitivity of SART to these deficits. Interestingly, in the TRD (but not the CS) group, response variability was also associated with an increased number of commission errors. Heightened distractibility led to a reduced ability to inhibit a motor response initiated at the presentation of unexpected visual stimuli (Dockree et al., 2005; Robertson et al., 1997). Thus, the TRD group exhibited a poor attentional capacity, and an automaticity of response, which led to an increase in commission errors.

The TRD group also made a greater number of omission errors, which reflects an inability to remain vigilant and a diminished ability to maintain goal-directed attentional control (Cheyne et al., 2009; Molenberghs et al., 2009; O'Connell et al., 2008). These findings support earlier studies of impaired attention control in MDD (Cornblatt et al., 1989; Mialet et al., 1996; Ravnkilde et al., 2002) and non-remitting depression (Li et al., 2010; Paelecke-Habermann et al., 2005; Vasic et al., 2008).

Only two studies have examined the relationship between SART variables and depressive symptoms (Farrin et al., 2003; Kim et al., 2008). Kim et al (2008) used positron-emission tomography (PET), and an affective version of the SART, to investigate attentional difficulties; they found that correct response rate (inversely proportional to the measure of omission errors) was significantly lower in the depressed sub-group (compared to healthy

controls), and correlated with prefrontal hypoactivity and depressive symptoms. However, they did not identify any significant differences in number of commission errors. Conversely, Farrin et al (2003) found association between depressive symptoms and increased commission errors, however, observed no significant differences on the attentional constructs. These studies however, were both conducted within non-clinical populations, and indexed level of depression according to self-reported depressive symptoms, and results, therefore, may not reflect the neurocognitive deficits located within a clinical population. Our study is the first to administer the SART within a clinically-diagnosed TRD group, and use this task to successfully identify significant cognitive inhibitory and attentional impairment between individuals with depressive symptoms and matched controls. In the current study, we found that individuals with clinically-diagnosed TRD exhibited difficulties in remaining vigilant and a diminished ability to maintain goal-directed attentional control.

Our study also demonstrated a positive relationship between response variability and errors of omission across both groups, suggesting that when participants are distracted, they are more likely to disengage from the task objectives. In the TRD group only, participants displayed enhanced levels of distractibility (i.e. performance variability), which was correlated with a significantly reduced ability to remain vigilant (omission errors).

Therefore, in summary, we found that depressive patients were characterized by generalised cognitive deficits. Difficulties sustaining and flexibly directing attention relate to an inability to divert attention from depression-related thoughts, and remain focused on positive goal-directed objectives. These cognitive deficits contribute to the persistence of depressive symptoms (Baune et al., 2010), and reduced levels of clinical recovery (Jaeger et al., 2006), posing a serious challenge to the development of effective treatment strategies.

4.2. Cognitive biases

Cognitive theorists propose that preferential processing of negative stimuli (i.e. interference effect) facilitates negative thoughts, which intensifies depressive symptoms, and contributes to the maintenance, and recurrence, of depressive episodes (Beck et al., 1979). In the current study, the TRD group revealed a significant interference effect for depression-related words relative to neutral words; no such valence effect was observed in the CS group. Our findings corroborate previous behavioural studies (Gotlib and McCann, 1984; Lim and Kim, 2005; McNeil et al., 1999) which administered the ES within depressed populations, and consistently observed a prolonged response latency for negative words, and difficulty disengaging from emotional stimuli.

The ES has also been administered to explore the relationship between cognitive bias, depressive symptoms, and dysfunction of the frontal-parietal circuitry (George et al., 1997; McNeely et al., 2008). Mitterschiffthaler et al (2008) reported greater response latencies for the negative word condition, which correlated with greater engagement of the rostral ACC and precuneus in MD. Dai and Feng (2011) found that individuals with MD had a higher interference effect for negative material, and these deficits were accompanied by alterations in parietal regions. These studies provide evidence of cognitive bias to emotional stimuli in MD, and the efficacy of the ES in activating the fronto-limbic-parietal networks, the same networks implicated in the persistence of depressive symptoms. In the present study, cognitive bias, the automatic processing of negative stimuli, and deficits in the response processes (De Raedt and Koster, 2010), were clearly demonstrated in depressive patients compared with CS. Difficulty inhibiting negative automatic thoughts and disengaging from negative material is a debilitating feature of depressive disorders, and has a negative impact on clinical recovery (Berman et al., 2011; Nolen-Hoeksema, 2000; Peckham et al., 2010). Thus, it is important to address and characterize these cognitive biases in developing more effective treatment strategies.

4.3. Relationship between cognitive deficits and cognitive biases

Traditionally, cognitive impairments in MDD were thought to largely relate to dysfunction in inhibiting emotional distracting and intrusive thoughts. However, in our study, given the lack of correlational significance between the cognitive variables (i.e. cognitive deficits and cognitive biases), it appears that each of these impairments may provide a unique contribution to the persistence of depressive disorders. Thus, the framework of cognitive impairments in MDD may be more complex than initially perceived; whereby cognitive deficits and biases are possibly underpinned by differing brain mechanisms. It may be worthwhile to develop screening programs to ascertain the separate presence of both cognitive deficits and cognitive biases, and the extent of any possible interactions.

4.3. Limitations

Our study sample was small, and we must be cautious in interpreting the results. In addition, although a formal rating of anti-depressant resistance was not administered in the current study, trained psychiatrists classified patients as TRD; this diagnosis was based on a clinical evaluation of MDD patients who did not respond to at least two anti-depressant medications, of adequate dose and duration, in the current episode. Our research was therefore focused on a TRD population, but further research is required to replicate and generalize these findings more broadly within a MDD population. Finally, anti-depressant medication may have influenced the results. Despite these limitations, our findings contribute to the characterisation of the neurocognitive profile of depressive disorders.

4.4. Conclusion

To conclude, our study revealed evidence of cognitive deficits and cognitive biases in a severely depressed population. In terms of cognitive *deficits*, the depressive group presented with an inability to inhibit inappropriate representations and to direct attention towards goal-

directed behaviour. With regard to cognitive *biases*, the depressive group exhibited a reduced ability to inhibit automatic processing of negative stimuli. Importantly, there was no interactive effect between cognitive deficits and cognitive biases, suggesting that these cognitive constructs may exert separate and independent effects in MDD. Furthermore, both the SART and ES recruit the fronto-limbic-parietal regions, the same regions which are impaired within TRD populations. Therefore, poor performance on these neurocognitive tasks may reflect dysfunction of these brain regions in depressive populations. Thus, our study demonstrates that the SART and ES are sensitive measures of neurocognitive deficits that are suitably able to quantify such impairments within depressed populations. Future studies, which combine neuroimaging techniques and behavioural assessments, are required to provide direct neurobiological evidence of this relationship. Additionally, it is anticipated that implementation of formal cognitive testing, at diagnosis, and throughout treatment, could improve the clinical assessment and management of depressive disorders.

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Table 1. Demographic and clinical data for Treatment Resistant Depression patients (TRD) and Control Subjects (CS).

	TRD **Mean (+/- sd)**	**CS** **Mean (+/- sd)**	**T-test/ Chi-Squared test**	**Significance**
Age, years	44 (8)	39 (12)	P = 0.093	n.s.
Gender ratio (M:F)	(M:12 , F:13)	(M:15, F:11)	P = 0.68	n.s.
Education, years	14.8 (1.7)	15.5 (2)	P= 0.18	n.s.
BDI	32 (8.5)	1.7 (2.2)	P < 0.0005	**

***p*<0.01
n.s. = not significant
BDI = Beck Depression Inventory

Table 2. Performance Means and Standard Deviations on the Sustained Attention to Response Task (SART) variables for Treatment Resistant Depression patients (TRD) and Control Subjects (CS).

SART	**TRD** **Mean (+/- sd)**	**CS** **Mean (+/- sd)**	**T-test**	**Significance**
Reaction time (ms)	427 (65)	413 (59)	P = 0.573	n.s.
Co-efficient of performance variability	0.26 (0.06)	0.23 (0.03)	P = 0.022	*
Commission Errors	9.16 (6.79)	6.23 (3.08)	P = 0.011	*
Omission Errors	11 (11.09)	3.69 (2.8)	P = 0.002	**

**p*<0.05, ***p*<0.01
n.s. = not significant

Table 3. Performance Means and Standard Deviations for Reaction time (ms) on the Emotional Stroop Task for Treatment Resistant Depression patients (TRD) and Control Subjects (CS).

Emotional Stroop Task	**TRD** **Mean (+/- sd)**	**CS** **Mean (+/- sd)**	**T-test**	**Significance**
Emotional Words	633 (158)	419 (107)	P < 0.0005	**
Neutral Words	533 (105)	398 (118)	P < 0.0005	**
Interference Effect	101 (77)	-21 (41)	P < 0.0005	**

***p*<0.01

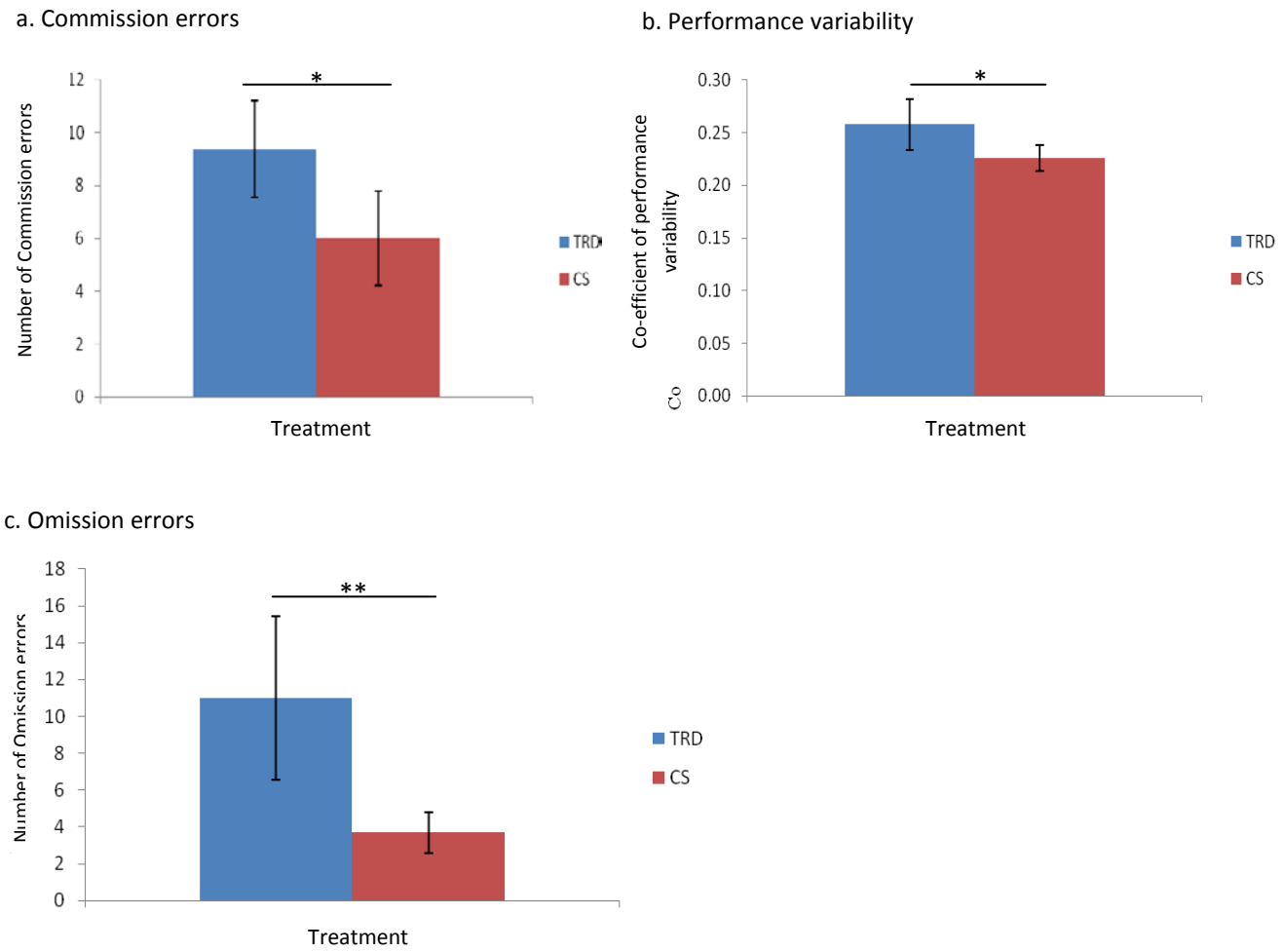

Figure 1. Group performance means of, a) Commission errors (adjusted means) b) Performance variability and c) Omission errors, between Treatment Resistant Depression patients (TRD) and Control Subjects (CS). Error bars are +/- 2 standard errors. *p<0.05, **p<0.01

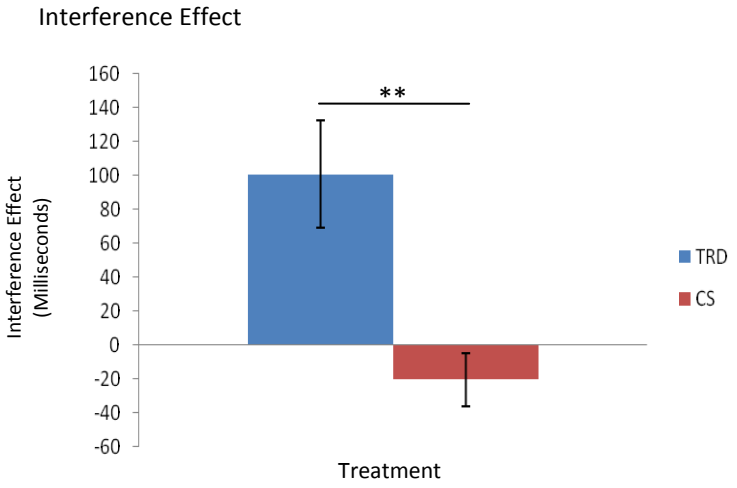

Figure 2. Group performance means of Interference Effect of clinically-diagnosed Treatment Resistant Depression (TRD) and Control Subjects (CS). Error bars are +/- 2 standard errors. **p<0.01

CHAPTER EIGHT

Study Two: *Effects of repetitive deep transcranial magnetic stimulation of the frontal regions on neurocognition in severely depressed patients.*

8.1. Introductory Comments

Once cognitive inhibitory impairments were identified within a depressive population by Study One, the next objective was to examine the involvement of the frontostriatal circuitry in these cognitive symptoms of Major Depressive Disorder (MDD). Therefore, Study Two was designed to explore whether delivery of deep Transcranial Magnetic Stimulation (deepTMS) to the frontal regions of MDD patients would result in improved neurocognitive function. Traditionally, deepTMS (Figure 1.) is applied to the frontal regions of depressive patients as a clinical treatment for depression; however, these frontal stimulations appear to be concomitantly targeting the brain circuitry which subserve various aspects of cognitive function in patients with MDD.

Figure 1. The Deep Transcranial Magnetic Stimulation helmet. An illustration of the H-coil and relevant apparatus used for the administration of deepTMS within clinical trials**.** Images supplied by Brainsway Ltd.

Therefore, Study Two was designed to explore the association between cognitive deficits and depression, and evaluate the involvement of the frontal circuitry in these cognitive symptoms

of depression. The study also examined whether these cognitive features of depression are predictive of clinical response to deepTMS treatment.

The following study is presented according to the manuscript version which is currently under preparation for journal submission.

8.2. Paper Under Preparation

Effects of repetitive deep transcranial magnetic stimulation of the frontal regions on neurocognition in severely depressed patients.

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Abstract

Background: Deep transcranial magnetic stimulation (deepTMS) is emerging as a promising therapeutic tool for Major depressive disorder (MDD). Cognitive dysfunction is a defining characteristic of MDD and has been found to relate to the onset, maintenance and reoccurrence of depressive symptoms. The current study aimed to both explore the relationship between cognitive deficits and depression, and evaluate the efficacy of a clinical trial of repetitive TMS in improving cognitive function within a depressive population. The study also assessed whether the cognitive features of depression are related to treatment response for those with MDD.

Methods: Twenty-one patients with MDD and 26 healthy matched controls (CS) were administered three cognitive tasks at baseline: The Sustained Attention to Response Task, the Emotional Stroop and the Random Number Generation Task. In the patient group, we re-administered these cognitive tasks a further two times to assess the cognitive effects induced by a single session (n=21) and after 4-weeks (n = 13) of high frequency (20Hz) repetitive deepTMS over the prefrontal cortex. Severity of depressive symptoms was measured by the Beck Depression Inventory. The CS were also re-administered the cognitive tasks after 1 day, and 4 weeks, to control for a potential practice effect, but were not administered deepTMS.

Results: The MDD group presented with significant cognitive deficits across the domains of cognitive inhibition, attentional control and emotion-regulation bias at baseline. Both a single session and long term high frequency repetitive deepTMS reduced attentional and cognitive strategy deficits. These short-term improvements were strongly associated with the long-term deepTMS related cognitive improvements. Finally, further analyses identified a number of cognitive factors which are predictive of clinical response.

Conclusion: Long-term treatment of deepTMS is proving to be an effective tool in reducing cognitive symptoms of depression. Additionally, cognitive features of depression are related to treatment efficacy and clinical response. This study contributed to the currently sparse evidence of the cognitive benefits of deepTMS techniques, and of clinical importance was the implication that cognitive symptoms of depression were predictive of treatment response in MDD.

1. Introduction

Major Depressive Disorder (MDD) is a severe and disabling psychiatric disorder characterized by a wide range of heterogeneous clinical features. While MDD is primarily a mood disorder, cognitive dysfunction is emerging as a defining characteristic of the disorder (Austin et al., 2001; Elliott et al., 2002; Rogers et al., 2004). Cognitive models posit that negative automatic thoughts, attentional difficulties and altered emotion-regulation play a central role in the onset, maintenance and recurrence of depressive symptoms (Beck et al., 1979; Clark et al., 2009; Gotlib and Joormann, 2010; Joormann, 2010; Joormann and Gotlib, 2010; Joormann et al., 2007; Paelecke-Habermann et al., 2005; Ravnkilde et al., 2002). Neuroimaging studies implicate hypoactivity within the prefrontal cortex (Drevets, 1999, 2000; Fitzgerald et al., 2006b) and altered neural activity within the fronto-limbic circuitry (Drevets et al., 2008; Mayberg, 2003b, 2006; Mayberg et al., 1997; Nestler and Carlezon Jr, 2006) in the pathophysiology of depressive disorders; the same circuitry proposed to subserve various aspects of cognitive processing (Blasi et al., 2006; Chambers et al., 2009; Garavan et al., 2002; Miller and Cohen, 2001). Therefore, it is not surprising that persistent cognitive deficits relate to the inability to recover from depressive disorders (Baune et al., 2010; Jaeger et al., 2006; Roiser et al., 2012).

Over the last decade, application of neuromodulatory brain stimulation techniques, such as transcranial magnetic stimulation (TMS), has emerged as a promising tool in treating clinical symptoms of treatment resistant depression (TRD) (Fitzgerald and Daskalakis, 2011; George et al., 2005; Loo et al., 2008; O'Reardon et al., 2007). Repetitive transcranial magnetic stimulation (rTMS) involves application of a rapidly time variable magnetic field, delivered via an electromagnetic coil held above the patients' scalp, designed to either stimulate or disrupt neuronal activity in specific cortical regions (Hallett, 2000, 2007; Rachid and Bertschy, 2006). Patients with MDD demonstrate a treatment response to high frequency (5-

10Hz) rTMS to the left prefrontal cortex (PFC) and low frequency (1Hz) rTMS to the right PFC (Fitzgerald and Daskalakis, 2010). This finding is reasonable in the context of an identified cerebral asymmetry of the PFC in affective disorders presenting as reduced excitability in the left DLPFC and increased excitability in the right (Bajwa et al., 2008; Garcia-Toro et al., 2001). Research conducted by large multi-site trials (George et al., 2010; O'Reardon et al., 2007) and confirmed by meta-analyses (Dell'Osso et al., 2011; Slotema et al., 2010) suggest that current TMS methodologies of active rTMS elicit moderate anti-depressant effects relative to a sham condition.

Standard TMS techniques utilize a figure-8 coil which enables direct stimulation of superficial cortical areas to a depth of approximately 1 to 2.5cm from the scalp (Roth et al., 2007; Zangen et al., 2005). Although standard rTMS is capable of stimulating hypoactive frontal regions of depressive patients (Drevets, 2001; Drevets et al., 2008; Fitzgerald et al., 2006b; Krishnan and Nestler, 2008; Maletic et al., 2007), it is unable to stimulate deeper cortical structures, such as the mesocorticolimbic dopaminergic pathway consisting of the nucleus accumbens and the ventral tegmentum area, which are interconnected with both the dorsal and ventral lateral prefrontal cortices (Mayberg, 1997, 2003a, 2006; Nestler and Carlezon Jr, 2006), and which have been implicated in the pathophysiology of depression. These limitations led to the newly developed H-coil (Zangen et al., 2005) which is able to modulate cortical excitability of deeper neural circuits, up to a maximum depth of 6cm (Roth et al., 2007; Zangen et al., 2005) and is currently being evaluated as a treatment alternative for MDD (Bersani et al., 2012; Minichino et al., 2012). The deep TMS (deepTMS) H-coil is designed to enable direct stimulation of deeper brain regions and has been shown to be a safe and effective procedure in treating MDD (Isserles et al., 2011; Levkovitz et al., 2009; Levkovitz et al., 2007; Levkovitz et al., 2011; Rosenberg et al., 2011; Rosenberg et al., 2010a; Rosenberg et al., 2010b).

In addition to its clinical efficacy, it seems likely that these brain stimulation techniques in targeting hypoactivity of the frontal regions could induce changes in cognitive symptoms of depression. Clinical trials designed to evaluate the efficacy of TMS commonly include an assessment of cognitive function to monitor the safety of the technique (Demirtas-Tatlidede et al., 2013; Guse et al., 2010; Hoy et al., 2012). These assessments have established that unlike electroconvulsive therapy, non-invasive rTMS techniques do not induce cognitive deterioration (Avery et al., 1999; Avery et al., 2006; Harel et al., 2011; Hoy et al., 2012), but rather, elicit the opposite effect, with a number of clinical trials presenting evidence of rTMS-related cognitive improvement within depressive populations through administration of stimulation by the figure-8 coil (Fabre et al., 2004; Fitzgerald et al., 2009; Holtzheimer et al., 2010; Höppner et al., 2003; Kuroda et al., 2006; Leyman et al., 2011; Martis et al., 2003; Moser et al., 2002; O'Connor et al., 2003; O'Connor et al., 2005; Padberg et al., 1999; Schulze-Rauschenbach et al., 2005; Schutter et al., 2010; Shajahan et al., 2002; Triggs et al., 1999; Vanderhasselt et al., 2009a). Additionally, these beneficial effects generally occurred within patients who were clinically responsive to rTMS (Loo et al., 2008). Recent studies which have applied repetitive high frequency deepTMS to the frontal regions of TRD patients also observed promising clinical improvement (Harel et al., 2012; Isserles et al., 2011; Levkovitz et al., 2009; Levkovitz et al., 2011; Rosenberg et al., 2011; Rosenberg et al., 2010a; Rosenberg et al., 2010b). However, only a small number of these trials assessed change in cognitive functioning (Harel et al., 2012; Isserles et al., 2011; Levkovitz et al., 2009; Levkovitz et al., 2011), and these findings resulted from side-effect analyses of cognitive data as a measure of safety, while studies designed to specifically assess the effects of rTMS on cognitive function in depressive populations are still lacking.

Given the theoretical relevance of the relationship between cognitive dysfunction and major depression (Austin et al., 2001; Clark et al., 2009; Gotlib and Joormann, 2010; Joormann,

2010; Rogers et al., 2004; Roiser et al., 2012), it is somewhat surprising that this association has only recently attracted research interest (Leyman et al., 2011). Cognitive theories of depression emphasize the role of cognitive dysfunction (Austin et al., 2001; Rogers et al., 2004), attentional deficits (Levin et al., 2007; Li et al., 2010; Paelecke-Habermann et al., 2005; Ravnkilde et al., 2002; Vasic et al., 2008) and biased affective processing (Eugène et al., 2010; Gotlib and Joormann, 2010; Joormann et al., 2007; Koster et al., 2011; Koster et al., 2005; Watkins, 2008) in the development and maintenance of depressive disorders. These cognitive processes recruit the fronto-limbic circuitry (Blasi et al., 2006; Chambers et al., 2009; Garavan et al., 2002; Miller and Cohen, 2001); the same circuitry implicated in the persistence of depressive disorders (Brody et al., 2001; Davidson et al., 2002; Drevets, 1999; Drevets et al., 2008; Mayberg et al., 1999) and degree of treatment response (Kumari et al., 2003; Langenecker et al., 2007; Mayberg, 1997; Pizzagalli et al., 2001; Pizzagalli, 2011). Thus, given that emerging deepTMS techniques target frontal-limbic circuitry, it is highly likely that these treatments are also inducing concomitant changes in cognitive symptoms of depression. Therefore, in the development of the deepTMS technique as treatment for MDD, further evaluation of its effects on cognitive function, and the relationship between these cognitive effects and treatment response, are warranted

The present study had three main objectives. The first objective was to establish the presence of regulative deficits across the domains of cognitive, attentional and affective bias within a MDD population. The second objective was to evaluate whether short-term (a single session) and long-term (19 sessions) of high frequency repetitive deepTMS to the DLPFC could improve these regulatory deficits in MDD patients. The third objective was to examine whether the cognitive symptoms of depression are predictive of clinical response to deepTMS treatment.

2. Methods

The current study was part of a larger clinical study (clinicaltrials.gov, NCT00460902 and NCT00577070), approved by institutional and national review board (IRB) committees. The study was conducted in collaboration with the Department of Psychiatry, Hadassah-Hebrew University Medical Center, Jerusalem, Beer-Ya'acov Mental Health Centre, Beer-Ya'acov and Shalvata Mental Health Center, Hod Hasharon, Israel. Consenting patients signed a detailed informed consent form prior to study enrolment; they were informed that participation was voluntary, and they could withdraw at any time without prejudice. Active enrolment ran from July 2008 through April 2009.

2.1. Participants

2.1.1. Major Depression Sample:

Twenty-one MDD patients were assessed at baseline and completed the short-term component of the study. To determine suitability, the screening procedure included a psychiatric and medical interview conducted by a psychiatric clinician. Main criteria for inclusion: clinical diagnosis of non-psychotic Major Depression Disorder in patients who did not respond to at least two antidepressant medications, provided in appropriate doses and duration, in the current episode, and no coexisting DSM-IV axis I or major axis II disorder. Patients completed the Hamilton depression rating scale (HDRS) (Hamilton, 1960), a 24-item clinical interview, and those with a HDRS score > 21, and aged 18-65years, were recruited for the study. In addition, as a secondary measure, patients were administered the Beck Depression Inventory (BDI) (Beck et al., 1961), a 21-item self-report measure to assess depression severity. A subgroup of 11 MDD patients participated in the long-term component of the study. Throughout the study, no change was made to antidepressant treatment, with

only limited use of hypnotic or anxiolytic medication (up to 2mg/day lorazepam or equivalent) for treatment-emergent insomnia or anxiety.

2.1.2. Healthy Control Sample:

Twenty-six healthy control subjects (CS), without any current or previous major medical/psychiatric illness were recruited through local advertisements and posters, and paid 100NIS (approx $30 US) to participate in the study (covering travel costs and time taken to participate). At screening, CS were required to complete a general demographic questionnaire, as well as the BDI to screen for potential confounding levels of depressive symptoms (any BDI scores ≥ 9 were excluded from the study). Relevant demographic and participant characteristics for MDD and CS are summarized in Table 2.

2.2. Procedure overview

MDD patients were administered basic demographic and depressive symptom (HDRS and BDI) questionnaires at baseline (prior to the initial TMS treatment). These depressive symptoms (BDI) were again assessed immediately prior to the 20^{th} TMS session. In the MDD group, cognitive performance was evaluated at three time-points; baseline, after the first deepTMS session (short-term), and immediately prior to the 20^{th} TMS session (long-term). Throughout the course of the study, patients were under direct monitoring, and any adverse effects or complaints were immediately recorded and responded to by qualified on-site psychiatrists. The control group also completed the basic demographic and depressive symptom (BDI) questionnaires at baseline. Cognitive performance was evaluated at the same three time-points: baseline, one hour after baseline, and one month after baseline (Figure 1.). However, the control group was not administered the deepTMS treatment. Rather, data from the controls were used as a comparative tool to compare the baseline level of cognitive

performance in MDD patients relative to CS, and further, to assess the presence of a practice effect due to repeated administration of the cognitive tasks.

Insert Figure 1.

2.2.1. Baseline

Following baseline screening, cognitive performance for both MDD patients and CS was evaluated by three computerized cognitive tasks using E-prime V1 technology (Psychology Software Tools): the Sustained Attention to Response Task (SART) (Robertson et al., 1997), the Emotional Stroop (Gotlib and McCann, 1984), and the Random Number Generation Task (RNG) (Baddeley, 1966). Participants were seated in a quiet, well-lit room, 30cm from the 17 inch computer screen. Task instructions were presented in Hebrew. Each task began with a short practice task to confirm that the participants understood the task requirements. All participants were native speakers of Hebrew.

2.2.2. Short-term

Following screening and the baseline cognitive evaluation, MDD patients were administered a single treatment of deepTMS. Prior to stimulation, patients were instructed to insert earplugs to prevent any potential adverse effects on hearing. To determine the appropriate stimulation parameters, single pulse stimulation was applied to the motor cortex, and Motor Threshold (MT), the point at which a minimum electric field would induce a noticeable motor response (i.e. twitching of the contralateral finger muscles) in 3 out of 5 trials, was measured. Next, the coil was moved 5.5cm anterior of the motor spot, and placed over the PFC ready for the deepTMS treatment session. The high frequency (20Hz) deepTMS session included administration of 42 trains of pulses, with each train consisting of 40 pulses within 2

seconds at 120% of measured MT intensity, with an inter-train interval of 20 seconds (i.e. 1680 magnetic pulses over 15.5 minutes). These parameters are consistent with previous deepTMS studies in clinically depressed patients (Isserles et al., 2011; Levkovitz et al., 2009; Rosenberg et al., 2011). Immediately following the initial deepTMS session, cognitive short-term performance was re-evaluated through re-administration of the three cognitive tasks (SART, ES, and RNG).

2.2.2. Long-term cognitive evaluation

The long-term trial consisted of five daily stimulation sessions (as described above) per week, over 4 consecutive weeks. MT was measured daily, and the stimulation parameters were administered according to 120% of the daily measured MT. Prior to the 20th deep TMS session, cognitive long-term performance was re-evaluated for the third time through re-administration of the three cognitive tasks (SART, ES and RNG).

2.3. Materials

2.3.1. Deep Transcranial Magnetic Stimulation (DTMS)

The deepTMS stimuli were delivered using the Magstim Super Rapid Stimulator (Magstim, UK). The Magstim stimulator was connected to an extracorporeal device, the novel H-coil, which was positioned on the patients' scalp prior to the stimulation session. The H-coil consists of seven Shelamid 200 copper wires, insulated by two polyester layers, set tangentially to the surface of the scalp (Zangen et al., 2005). The inner frame of the H-coil is flexible to fit the variability in contour of the human scalp. The H1-coil is designed to stimulate deep prefrontal regions; preferentially the left hemisphere (Levkovitz et al., 2007; Roth et al., 2007; Zangen et al., 2005).

2.3.2. Computerized Cognitive Tasks

Sustained Attention to Response Task (SART)

For the SART, participants were asked to respond quickly and accurately to the presentation of single digits (1 to 9) with a button press, with the exception of the number '3' the target stimulus (Robertson et al., 1997). The stimuli appeared in black in the centre of white background, presented in a random order in a block of 297 trials, with 33 possible no-go (number 3) responses. Each stimulus was presented for 150ms, with varying inter-stimulus interval (ISI) durations (1000ms, 1500ms and 1250ms) randomly distributed throughout the session (Bonnefond et al., 2010; Dockree et al., 2005). The variable ISI was used to minimize speed accuracy trade-offs. Prior to recording, participants were administered an 18 trial demonstration sequence, with 2 possible no-go trials presented randomly. Participants were informed that speed of response and accuracy were of equal importance. Reaction time (RT), commission errors, performance variability, and omission errors were recorded.

Emotional Stroop

Participants in this task had to identify, as quickly as possible, the ink colour of stimulus words (neutral and emotional stimuli) presented in varying colours (red, blue, green and yellow). The neutral stimuli were the Hebrew equivalents of the words *branch, centre, ruins (i.e. ancient ruins), send* and *wagon*. The emotional stimuli were the Hebrew equivalents of the words *suffer, weep, hurt, doom* and *worry.* These stimulus words and procedure were based on previous studies (Chajut et al., 2010; McKenna and Sharma, 1995). In each trial, a single-colour word was presented at the centre of the white computer screen for 450ms. Between each word trial, the ISI randomly varied between 1000, 1500 and 2000ms. When the word appeared on the screen, participants had to press, with their right index finger, one of four specified buttons on the keyboard which corresponded to the colour of the word. The names of the colours appeared on keys on the keyboard (i for red, j for yellow, l for blue and m for green), and all other sections of the keyboard were covered with a black material. When the participant pressed the correct key, reaction time was recorded, and after a variable

ISI, the next stimulus appeared. Presentation of word stimuli was divided into blocks (Bar-Haim et al., 2007), consisting of 40 trials of neutral stimuli (4 colours X 5 neutral words X 2 repetitions) followed by 40 trials of emotional stimuli (4 colours X 5 emotional words X 2 repetitions). Within each block, the word stimuli were presented in a random order.

Prior to the experimental session, participants completed a demonstration (12 single-stimuli trials) in which "XXXX" was randomly presented in the four colours, and participants were required to respond to the colours. Following this, in the experimental trials, all participants ran through four blocks (40 neutral trials, 40 emotional trials, 40 neutral trials, 40 emotional trials), resulting in 160 trials. Mean reaction times, for each condition over the 160 trials, were calculated.

Random Number Generation Task

Participants were asked to generate a random sequence of digits. To describe the concept of randomness, the ‘hat’ analogy was used (Baddeley, 1966; Horne et al., 1982). Participants were instructed to imagine that the numbers 0 – 9 are written on pieces of paper, these numbers are placed in a hat, one number is taken out of the hat, they are required to call out that number, and then return the number to the hat. By repeating this process, they will be generating a list of random numbers. All instructions were computerized and participants were instructed to synchronize their verbal response with a pacing black ‘X’ stimulus displayed on the computer screen at a rate of 1 ‘X’ stimulus per second, for a sequence of 20 numbers. The first sequence was conducted as a demonstration trial. Following the demonstration, the experimental trial began and participants were required to generate 5 trials of 20 numbers, thus generating a 100 digit trial. Throughout the task, participants wore a headset with a microphone and verbal responses were recorded through the computer. Executive sub-functions, such as inhibition and deviations from randomness were calculated

according to the indices of random factors (Jahanshahi et al., 2006); and stratified according to the RNG factors relating to repetition, seriation and randomness (described in Table 1).

Insert Table 1.

2.4. Data analysis:

Comparability of MDD patients and controls was assessed using χ^2- tests for categorical and T-tests for continuous variables (Table 1.). Stem-plots located extreme outliers (> +/- 2.5 standard deviations (SD)), and outliers were brought back to 2.5 SD of the mean. For all data which met assumptions of normality, tests were run at an alpha level of 0.05 (two-tailed). In a few cases, there were violations of unequal variance (Levene's statistic found to be significant); for those specific cases, to address violations, statistics were run at a more conservative alpha level of 0.025. There were no significant violations of homogeneity of regression or sphericity. Across the cognitive tasks, mixed model ANOVA was used to analyze both between group differences (between MDD and CS) and within group performance changes over time (between baseline and short-term/long-term).

ANOVA was used for analysis of all baseline cognitive measures. To analyze the SART data, a mixed model ANOVA was used to measure variations in SART RT, performance variability, and omission errors between the groups, and furthermore, changes in performance over time. To control for the covariance of SART RT on measures of commission errors, two one-way between-groups ANCOVAs were used to explore group differences for commission errors. The first ANCOVA examined the difference in number of commission errors for each session (baseline vs short-term/long-term) after adjusting for commission errors at baseline (controlling for SART RT as a covariate). The second ANCOVA assessed whether there was

a difference in commission error performance over time (sessions) between the two groups (again controlling for SART RT as a covariate). Change in number of commission errors was calculated by subtracting the baseline errors score from the session (short term or long term) commission error score. For the ES task, the Interference Effect was calculated by subtracting the mean neutral word reaction time from the mean emotional word reaction time for each participant. A mixed model ANOVA was then used to analyze group differences and performance changes over time. To assess performance on the RNG task, a mixed model ANOVA was used to analyze group differences in performance and changes over time for the indices outlined in Table 3.

Pearson's correlation examined potential associations between basic demographics, cognitive variables (SART, ES and RNG), and BDI scores, within each group separately. Additionally, to explore long term changes in the MDD/depressive group, we investigated whether change in cognitive performance correlated with change in depression (BDI) levels. All data analyses were performed using SPSS for Windows, version 15.

Notably, fewer participants completed the RNG task relative to the SART, since the RNG algorithms can only process data from participants who complete a minimum of 90% of the RNG required responses. Thus data from participants who completed less than 90% of the RNG required responses were excluded (24% of MDD patients and 8% of healthy controls).

3. Results

3.1. Baseline demographics

For all three tasks, there were significant differences at baseline in BDI between the MDD and control groups (Table 2.). The groups did not differ on any of the other demographic variables such as age, gender or education. No significant correlations were observed between SART, ES and RNG cognitive variables. The same analysis was conducted with the long-term cohort only (compared to controls) with the same results.

Insert Table 2.

3.2. Baseline cognitive data across all cognitive tasks

For the SART, the MDD group made significantly more errors of omission than CS, F(1,45) = 9.712, p = 0.003. The MDD group also committed more commission errors than CS, F (1, 44) = 7.41, p= 0.009. While, performance variability was significantly increased in the MDD group relative to CS, F(1,45) = 7.985, p = 0.007 (Table 3.). For the ES, the Interference Effect was larger in the MDD group than CS, F(1,43) = 42.98, p < 0.005 (Table 4). For the RNG, the total count score (i.e. seriation) was significantly increased in the MDD group relative to CS, F(1,38) = 4.24, p = 0.046 (refer to Table 3.).

Insert Table 3.

3.3. Effect of a single session of deepTMS on cognitive performance

For the SART, with regards to omission errors, significant between group, F (1, 45) = 8.5, p = 0.006, and session effects, F (1, 45) = 4.70, p = 0.036 were found. There was also a significant interaction effect, F (1, 45) = 5.41, p= 0.025 (see Figure 2a), such that the MDD group committed more omission errors than the control group at baseline, F (1,45) = 9.712, p = 0.003, but this difference was not significant at session 2, F (1,45) = 2.010, p =0.163 (Table 3.). For the ES, relative to healthy controls, the MDD group had a significantly greater Interference Effect across both sessions compared to controls, F (1, 43) = 31.68, p < 0.005 (Table 3.). A significant interaction was also observed, F (1, 43) = 5.79, p = 0.02

(Figure 2b) suggesting an improvement in the MDD group over time however significant differences were not observed in post hoc tests (Table 3.). For the RNG task, the MDD group had a larger count score than the CS overall, F (1, 38) = 4.968, p = 0.032. A significant interaction session by group effect was also observed, F(1,38) = 5.765, p = 0.021 (Figure 2c), such that the MDD group had a significantly larger count score relative to the control group at baseline, F(1, 38) = 4.241, p = 0.046, but this was not found at session 2 (Table 3.).

Insert Figure 2.

3.4. Effect of long-term treatment of deepTMS on cognitive performance

For the SART, the MDD group committed more omission errors than the control group at baseline F(1, 34) = 11.149, p = 0.002, but this difference was not significant by session 3, F (1, 34) = 5.998, p= 0.02 (Figure 3a). There was a significant improvement observed in the MDD group F(1, 34) = 5.192, p = 0.023, while no such improvement identified in the CS group F(1,44) = 2.609, p = 0.114 (Table 4.). For the RNG, the MDD group demonstrated a higher count score than controls, F (1, 26) = 5.395, p = 0.028 and an improved count score performance from session 1 to session 3 was found overall, F (1,26) = 10.324, p =0.003. There was also a significant group by session interaction effect observed, F (1, 26) = 4.479, p =0.044 (Figure 3b), such that the MDD group had a higher count score at baseline, F (1, 26) = 5.634, p =0.025, but this significant difference was no longer evident at session 3 (Table 4.).

Insert Figure 3.

Insert Table 4.

3.5. Correlational data regarding predictors of long-term cognitive response

For the SART, in the MDD group improvement in omission errors observed after a single session of rTMS positively related to long-term improvement of omission errors ($r = 0.922$, $n = 13$, $p = 0.0005$). With regards to RNG, single session of rTMS-induced changes in total count score positively related to long-term change in count score ($r = 0.922$, $n = 8$, $p = 0.001$).

3.6. Correlational data regarding predictors of clinical response to deepTMS

For the SART, long-term improvement in commission errors positively correlated with improvement in BDI scores ($r = 0.582$, $n = 13$, $p = 0.037$) in the MDD group. With regards to the ES, Interference Effect at baseline positively correlated with improvement in BDI ($r = .585$, $n=13$, $p=0.036$).While, on the RNG, Total Series at baseline negatively correlated with improvement in BDI ($r = -.807$, $n = 8$, $p = 0.015$).

4. Discussion

The present study is the first investigation to focus primarily on the effects of frontal deepTMS in improving cognitive symptoms of depression. To begin, the study presented evidence of regulatory deficits across the domains of cognitive inhibition, attentional control and emotion-processing within the MDD population. Application of a single session and long-term frontal deepTMS were both related to improved attentional control and cognitive strategy in the depressive sample. Moreover, our study identified a strong association between these short-term cognitive change and long-term cognitive improvements. Finally, a number of cognitive factors were found to be predictive of clinical response to deepTMS treatment.

4.1. Cognitive deficits in MDD relative to CS

The MDD group exhibited regulatory deficits across the domains of cognitive inhibition, attentional control and affective processing. Confirming previous studies, on the SART, the MDD group presented with impairments in response inhibition (i.e. increased commission errors) (Farrin et al., 2003) and attentional control (i.e. increased commission errors, omission errors and performance variability) (Kim et al., 2008). On the ES, the MDD group showed a significantly greater interference effect, representing the automatic and preferential processing of negative stimuli and the inability to regulate affective bias (Gotlib and McCann, 1984; Lim and Kim, 2005; McNeil et al., 1999). On the RNG, the MDD group demonstrated heightened difficulties in producing novel responses, while suppressing prepotent responses to the previously learned schemata (i.e. increased seriation) (Horne et al., 1982). These three frontally-mediated cognitive tasks were administered to establish the presence of distinct regulative deficits across the domains of cognitive inhibition, attentional control and emotion-regulation within the MDD population. The next objective is to ascertain whether administration of deepTMS can attenuate these cognitive symptoms of depression.

4.2. Effect of rTMS on cognitive deficits in MDD

The current study then investigated the efficacy of delivering repetitive deepTMS to the frontal regions of MDD patients in improving cognitive symptoms of depression. Both after a single session of rTMS, and long-term administration of rTMS, significant improvement was identified across the domains of attentional control (i.e. omission errors) and cognitive strategies (i.e. seriation) within the MDD group. These improvements are unlikely to be due to a practice effect as the same improvements were not shown by the CS group. By the end of the deepTMS treatment, any significant performance difference between the MDD and CS groups in attentional control and cognitive strategies had dissipated.

Attention deficits, a key feature of depressive disorders (Levin et al., 2007; Ravnkilde et al., 2002) is represented in the clinical diagnosis of MDD as an "impaired ability to think or concentrate" (DSM-IV-TR, American Psychiatric Association., 2000). These debilitating deficits (Cornblatt et al., 1989; Li et al., 2010; Mialet et al., 1996; Ravnkilde et al., 2002; Vasic et al., 2008) relate to heightened depressive symptoms (Paelecke-Habermann et al., 2005) and dysfunction of the frontal cortex (Li et al., 2010; Vasic et al., 2008). Thus, the present study identified the beneficial effect of administering high frequency deepTMS to the frontal regions in improving these attentional deficits within a depressive sample.

Only a small number of studies have previously evaluated the efficacy of frontal rTMS in improving attentional control in depressive samples and their findings were mixed. In terms of standard (i.e. figure-8 coil) TMS studies, a single session of rTMS to the left DLPFC improved attentional control (Shajahan et al., 2002; Vanderhasselt et al., 2009a), with this effect being most evident among treatment responders (Vanderhasselt et al., 2009b). However, further studies did not confirm the efficacy of a single session, but rather, found that long-term administration (i.e. two weeks) of high frequency rTMS treatment induced improved attentional processing of emotional information in treatment responders (Leyman et al., 2011) and levels of concentration (Höppner et al., 2003). With regards to deepTMS studies, one study found that long-term administration of high frequency rTMS resulted in significant improvement in sustained attention (Levkovitz et al., 2009), and this study was supported by a second study which indicated a similar trend, though not significant, towards improved attention (Isserles et al., 2011). Therefore, our study is the first to successfully identify the efficacy of both a single session of deepTMS, and long-term administration of deepTMS, in ameliorating the attentional deficits of depression.

Cognitive strategy deficits relate to increased difficulty producing novel responses, while suppressing prepotent responses to previously learned schemata sets. The presence of these

cognitive deficits within a depressive sample is likely to indicate a compromised ability to develop protective cognitive strategies against depression and to suppress habitual depression-related cognitions. Moreover, cognitive theorists of depression suggest that impaired cognitive strategies (Beck et al., 1979) contribute to the reinforcing and perpetuating nature of depressive symptoms (Davis and Nolen-Hoeksema, 2000; Nolen-Hoeksema, 2000). Previous studies demonstrated that application of rTMS to the frontal regions of healthy controls could influence the processes involved in cognitive strategies on the RNG task (Jahanshahi and Dirnberger, 1999; Jahanshahi et al., 2000; Jahanshahi et al., 1998; Knoch et al., 2005). Thus, in the present study, the beneficial effect of administering rTMS to the frontal regions of a depressive sample in improving these deficits in cognitive strategy was evaluated.

Although rTMS-induced improvements in cognitive strategy have not been specifically assessed within a depressive sample, previous studies have examined more generalized rTMS induced changes executive function in MDD populations. In terms of standard TMS, improved executive function was observed in trials which administered 2-3 weeks of high frequency rTMS to the left DLPFC (Martis et al., 2003; Triggs et al., 1999) and anterior middle frontal gyrus (Moser et al., 2002). While, another study showed that 2 days of high frequency rTMS to the DLPFC resulted in cognitive improvements 6 weeks following stimulation (Holtzheimer et al., 2010). Further preliminary studies reported no adverse rTMS-related change in cognitive function (Avery et al., 1999; Avery et al., 2006), but rather, trends towards cognitive recovery. With respect to deepTMS, long-term administration of frontal rTMS resulted in improved cognitive planning (Levkovitz et al., 2009), and in treatment responders, information processing (Isserles et al., 2011). While at the same time, an additional deepTMS study observed no significant cognitive change in a bipolar depressive group (Harel et al., 2011) . With regards to the mixed findings, across these various studies, a

number of different stimulation paradigms and cognitive tasks to ascertain the safety of the TMS technique were administered. The current study, is the first to implement cognitive testing specific to frontal dysfunction and cognitive symptoms of depression within a depressive sample. As such, the findings from the current study present evidence of the beneficial efficacy of a single session of deepTMS, as well as long-term administration of frontal deepTMS, in restoring cognitive strategy function within a depressive sample.

When combined, our data provides promising support for the efficacy of both short-term and long-term deepTMS in the improvement of attentional and cognitive function within depressive populations. Thus providing preliminary evidence for the proposition that application of deepTMS to stimulate the fronto-limbic circuitry (Drevets et al., 2008; Mayberg, 2003b, 2006; Mayberg et al., 1997; Nestler and Carlezon Jr, 2006), the same circuitry implicated in cognitive dysfunction (Blasi et al., 2006; Chambers et al., 2009; Garavan et al., 2002; Miller and Cohen, 2001), can attenuate certain attentional and cognitive symptoms of depression.

Our data also revealed a strong relationship between the short-term and the long-term rTMS effects on attentional and cognitive deficits. Thus, indicating that a single session of deepTMS may be predictive of long-term cognitive response. It is possible that a single session of high frequency rTMS may induce a short-lasting increase in the release of dopamine within the frontal network (Cho and Strafella, 2009; Strafella et al., 2001) which results in these more immediate cognitive and attentional improvements. While, for long-term treatment, repeated short-lasting increases in excitability (Cho and Strafella, 2009; Strafella et al., 2001) within the deep cortical regions may be associated with long-lasting alterations in neuroplasticity of the frontal regions (Fitzgerald et al., 2006a; Gersner et al., 2011; Pell et al., 2011); thereby resulting in the long-term amelioration of these attentional and cognitive deficits. However, as previously noted, our findings are preliminary and

additional studies are required to further verify the efficacy of deepTMS in reducing cognitive symptoms of depression, and the potential predictive value of short-term deepTMS in determining long-term cognitive response.

4.3. Cognitive factors associated with treatment response

Our final objective was to examine potential cognitive factors associated with clinical response. To date, well-established predictors of treatment response to trials of rTMS are scarce. In the present study, we identified a number of cognitive factors which were associated with deepTMS related improved clinical symptoms. Firstly, enhanced performance on cognitive strategy tasks was related to an improvement in depressive symptoms. Secondly, improvement in the measure of response inhibition and sustained attention (i.e. commission errors) was related to a reduction of depressive symptoms. Thus, when combined, we suggest that depressive patients with an increased ability to generate novel responses (i.e. non-depression related behaviours), maintain focus on non-depression-related thoughts and inhibit prepotent responses (i.e. depression-related cognition) to previous learned schemata may be more receptive to the anti-depressant effects of the trial of deepTMS. At the same time, we found that reduced performance on the emotion-regulatory task (i.e. increased interference effect) at baseline was related to improved depressive symptoms. This data indicated that MDD patients with increased emotional distraction were more amenable to deepTMS induced clinical response; thus, the more unwell the patient at baseline, the greater the response to long-term deepTMS treatment (Bermpohl et al., 2006). Although these findings may appear contradictory, each of the cognitive tasks administered assessed distinct aspects of cognitive functioning. Therefore, the current study provides preliminary evidence regarding potential cognitive predictors of clinical response to deepTMS. These associations also provide support for cognitive theories of depression by

highlighting the intricate relationship between these cognitive factors and depressive symptoms.

4.4. Limitations

Our study sample was small, and we must be cautious in interpreting the results. In addition, in the present study, although no significant correlations between cognitive performance, depressive symptoms and type/dose of medication were identified, it is still possible that anti-depressant medication may have influenced the results. Moreover, even though cognitive functioning was assessed across the three time-points in the CS group to control for a potential practice effect, the present study was unable to evaluate the possible placebo effect of long-term treatment in the MDD sample. This represents a consistent dilemma in the development of psychiatric treatments, as long-term sham treatment may have a detrimental effect on the patients' health. To address this limitation, future studies should consider adding a MDD control group, which does not receive any TMS, but rather participates in the study across the three-time points to gauge a more appropriate MDD practice effect. Despite these limitations, our preliminary findings demonstrate the efficacy of deepTMS in ameliorating cognitive symptoms of depression, and contributes to the cognitive profile of depressive disorders.

4.5. Summary

In conclusion, we have demonstrated that deepTMS is a promising technique for reducing cognitive symptoms of depression. With short-term cognitive change being predictive of long-term cognitive improvement. In addition, we found that cognitive features of depression are predictive of clinical response to deepTMS treatment. Therefore, the present study addressed the scarce amount of research directly focused on the cognitive effects of deepTMS, and provided empirical support for the cognitive benefits of frontal deepTMS

techniques in a depressive sample. Furthermore, we found that cognitive factors were predictive of clinical response to deepTMS; thereby, illustrating the intricate relationship between these cognitive factors and depressive symptoms. Therefore, highlighting the importance of future treatment strategies addressing these cognitive symptoms of depression in improving clinical symptoms of depression.

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Table 1. Definition of indices within the Random Number Generation Task.

Factor	Index Name	Definition
Repetition Measures the number of times an individual repeats the same digit in a successive order.	Total Repetition (TR)	The sum of number of double repetitions (e.g. 4, 4), triple repetitions (e.g. 4,4,4), double digrams (e.g. 1,5,...1,5) and triple digrams (e.g. 1,5,4...1,5,4).
Seriation Measures the number of consecutive digrams. All count/series scores are also calculated according to length of series.	Total Series (TS)	Number of pairs of consecutive digrams (e.g. 4, 5)
	Total Count Score (TCS)	Total count score sums the sequence length of counting in ascending or descending series in steps of 1 (e.g. 1, 2, 3 or 8, 7, 6, 5) and counting in ascending or descending series in steps of 2 (e.g. 2, 4, 6, 8 or 7, 5, 3, 1). In calculating the count scores, the sequence length is squared and then summed together (Jahanshahi et al., 2006).
Randomness	Random Number Index (RNG)	A measure which reflects the difference between the observed and expected probability of all possible number pairs. The higher the reported RNG index, the less random the series.
	Unique Triplets	The number of triplets that are unique are counted. There are 98 (N-2) triplets in a series of 100 responses. The fewer number of unique triplets, the increased tendency to repeat certain runs of digits.

Table 2. Demographic and clinical data for Major Depressive Disorder (MDD) patients and Control Subjects (CS) across the three cognitive tasks.

	MDD Mean (+/- sd)	CS Mean (+/- sd)	T-test/ Chi-Squared test	Significance
SART				
Age, years	44.24 (8.65)	39 (11.74)	p = 0.095	n.s.
Gender ratio (M:F)	10:11	15:11	p =0.491	n.s.
Education, years	15.24 (2.95)	15.85 (3.2)	p = 0.506	n.s.
BDI	31.62 (8.76)	1.69 (2.17)	p < 0.0005	**
ES				
Age, years	44.32 (8.99)	39 (11.74)	p = 0.106	n.s.
Gender ratio (M:F)	10:9	15:11	p = 0.736	n.s.
Education, years	15.16 (3.08)	15.85 (3.2)	p =0.473	n.s.
BDI	32.26 (8.52)	1.69 (2.17)	p < 0.0005	**
RNG				
Age, years	43.88 (9.15)	39.50 (12)	p = 0.225	n.s.
Gender ratio (M:F)	6:10	14:10	p =0.197	n.s.
Education, years	15.06 (3.34)	15.92 (3.31)	p =0.430	n.s.
BDI	32.88 (7.85)	1.58 (2.15)	p < 0.0005	**

***p*<0.01
n.s. = not significant
SART = Sustained Attention to Response Task
ES = Emotional Stroop
RNG = Random Number Generation Task

Table 3. Short-term Performance Means and Standard Deviations for Major Depressive Disorder (MDD) patients and Control Subjects (CS) across the three cognitive tasks.

Cognitive Task	Variables/Indices	*n* MDD	MDD Mean (+/- sd)	*n* CS	CS Mean (+/- sd)
SART					
	Reaction time (ms) Session 1	21	427 (65)	26	413 (57)
	Reaction time (ms) Session 2	21	412 (64)	26	397 (52)
	Performance Variability Session 1	21	0.26 (0.06)	26	0.23 (0.032)
	Performance variability Session 2	21	0.23 (0.05)	26	0.2 (0.039)
	Omission Errors Session 1	21	10 (9.86)	26	3.69 (2.8)
	Omission Errors Session 2	21	5.67 (4.80)	26	3.85 (4.00)
	Commission Errors Session 1	21	9.24 (7.17)	26	6.23 (3.07)
	Commission Errors Session 2	21	9.86 (8.67)	26	5.5 (3.34)
ES					
	Interference Effect Session 1	19	86.32 (68.43)	26	-20.63 (40.67)
	Interference Effect Session 2	19	50.04 (83.42)	26	-7.27 (44.96)
RNG					
	Total Count Score Session 1	16	160.5 (158.01)	24	92.7 (29.86)
	Total Count Score Session 2	16	111 (63.93)	24	85.27 (32.05)
	Total Series Session 1	16	43.44 (16.71)	24	36.83 (9.46)
	Total Series Session 2	16	36.69 (14.89)	24	33.5 (10.58)

n = Number of participants
SART = Sustained Attention to Response Task
ES = Emotional Stroop
RNG = Random Number Generation Task

Table 4. Long-term Performance Means and Standard Deviations for Major Depressive Disorder (MDD) patients and Control Subjects (CS) across the three cognitive tasks.

Cognitive Task	Variables/Indices	*n* MDD	MDD Mean (+/- sd)	*n* CS	CS Mean (+/- sd)
SART					
	Reaction time (ms) Session 1	13	428 (76)	23	411 (60)
	Reaction time (ms) Session 3	13	412 (75)	23	390 (51)
	Performance variability Session 1	13	0.27 (0.06)	23	0.23 (0.03)
	Performance variability Session 3	13	0.23 (0.043)	23	0.19 (0.036)
	Omission Errors Session 1	13	11.85 (11.24)	23	3.7 (2.75)
	Omission Errors Session 3	13	4.15 (1.95)	23	2.28 (3.19)
	Commission Errors Session 1	13	10.23 (8.35)	23	6.22 (3.26)
	Commission Errors Session 3	13	9.77 (8.22)	23	5.57 (4.00)
ES					
	Interference Effect Session 1	13	76.67 (60.60)	24	-19.89 (42.29)
	Interference Effect Session 3	13	75.42 (108.68)	24	-8.58 (41.42)
RNG					
	Total Count Score Session 1	8	182.63 (163.41)	20	94.19 (31.90)
	Total Count Score Session 3	8	81.84 (16.89)	20	73.45 (37.77)
	Total Series Session 1	8	47.5 (16.81)	20	37.8 (9.83)
	Total Series Session 3	8	32.8 (5.50)	20	29.80 (10.81)

n = Number of participants
SART = Sustained Attention to Response Task
ES = Emotional Stroop
RNG = Random Number Generation Task

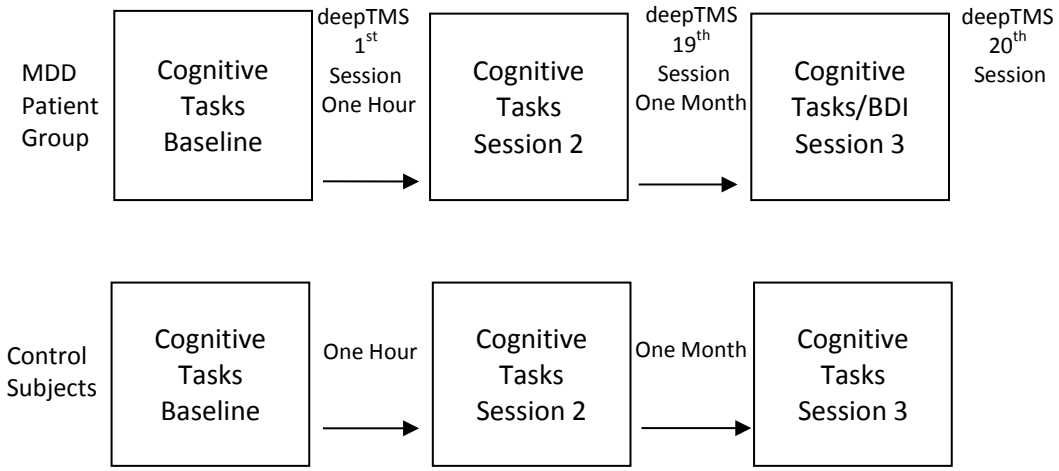

Figure 1. Timeline of the study procedures for the Major Depression Disorder (MDD) patients and the Control Subjects (CS).

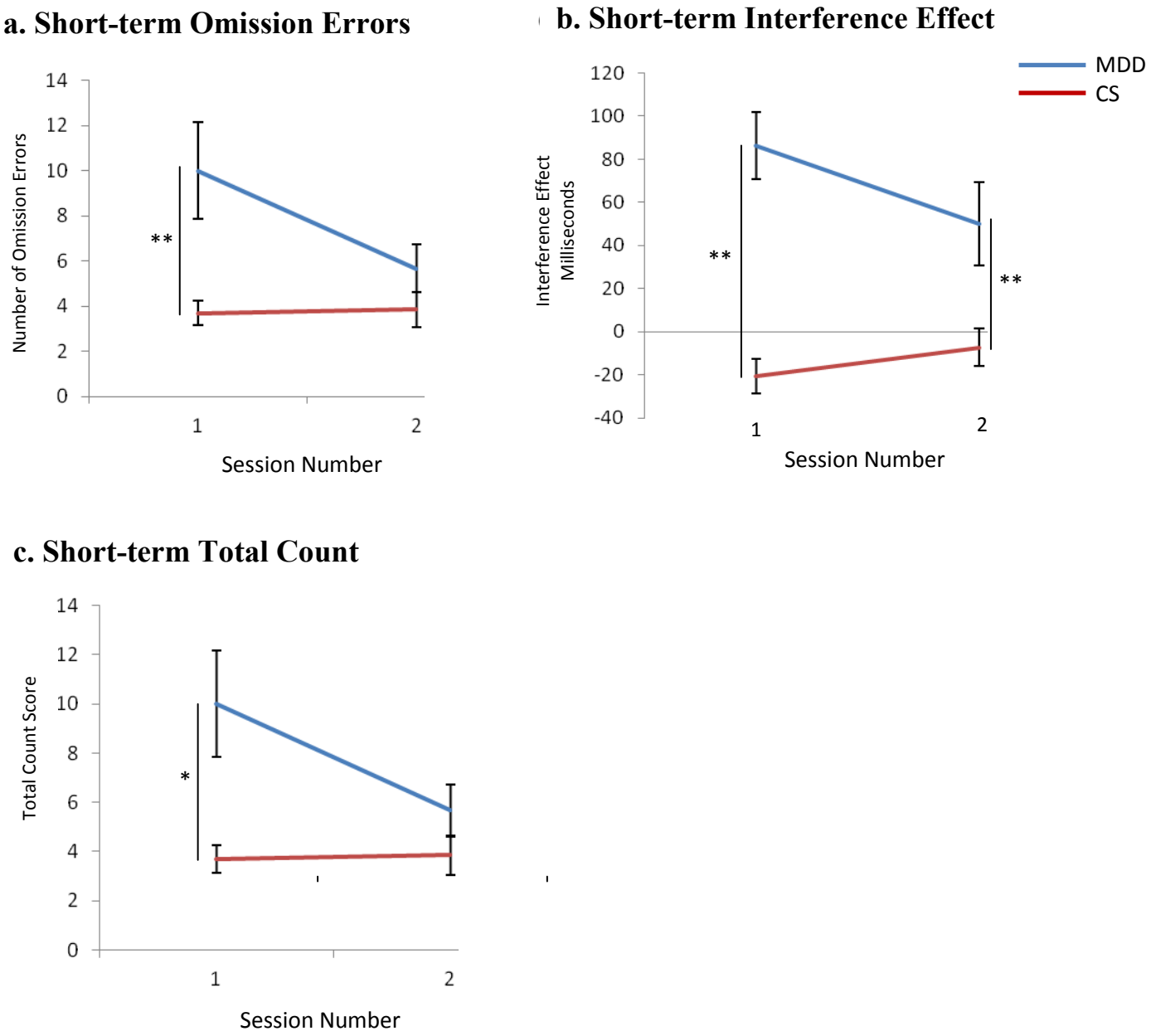

Figure 2. Adjusted group means of, a) Omission errors from the Sustained Attention to Response Task, b) Interference Effect from the Emotional Stroop, and c) Total Count Score from the Random Number Generation Task, across Sessions 1 and 2, for Major Depressive Disorder (MDD) patients and Control Subjects (CS). Error bars are +/- 1 standard errors. The significance differences reported relates to the post hoc analysis of interaction effects, *p<0.05, **p<0.01

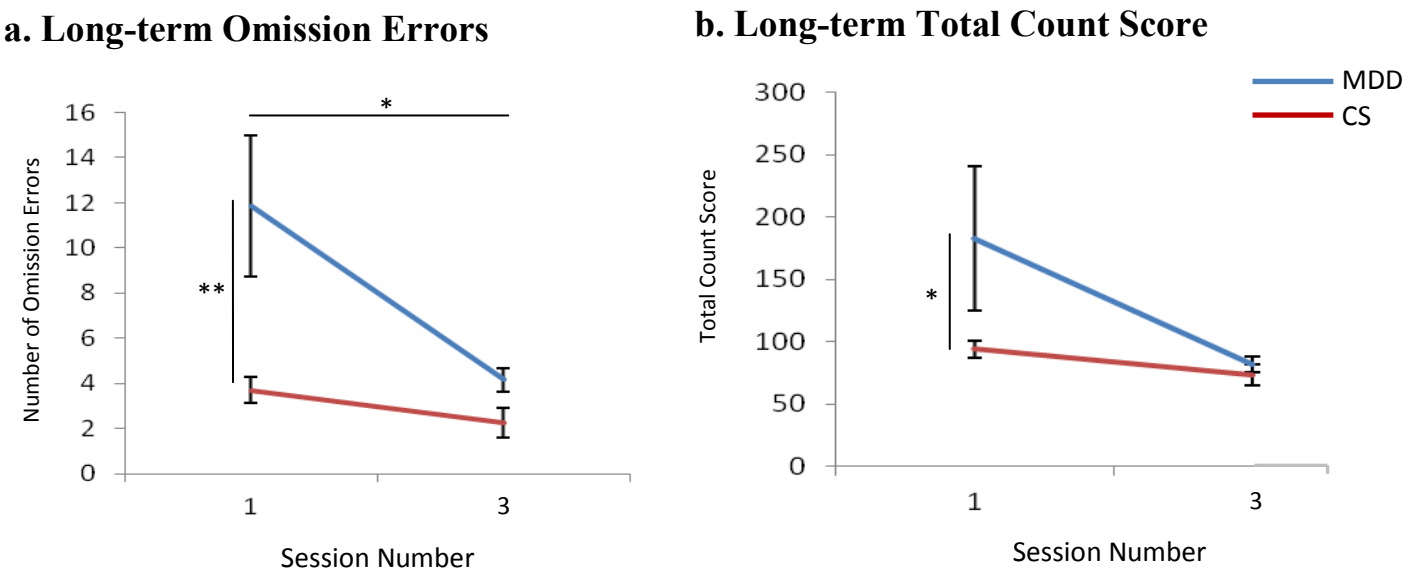

Figure 3. Adjusted group means of, a) Omission errors from the Sustained Attention to Response Task and, b) Total Count Score from the Random Number Generation Task, across Sessions 1 and 3, for Major Depressive Disorder (MDD) patients and Control Subjects (CS). Error bars are +/- 1 standard errors. The significance differences reported relates to the post hoc analysis of interaction effects, *p<0.05, **p<0.01

CHAPTER NINE

Study Three: *Frontally-mediated cognitive deficits, craving and cognitive recovery among alcohol dependent individuals following detoxification*

9.1. Introductory Comments

Alcohol Dependence (AD) is characterized by an impaired ability to regulate the compulsive desire to consume alcohol regardless of associated risk. Recently, addiction theorists have proposed that the inability to suppress these compulsive desires may reflect an underlying cognitive inhibitory deficit. Therefore, Study Three examined the presence of these cognitive inhibitory deficits within an alcohol dependent population post-detoxification. The study then sought to expand on previous studies and explore whether these cognitive inhibitory impairments are related to measures of craving, and furthermore, whether length of abstinence is a marker of cognitive recovery.

The following study is presented according to the manuscript version which has been submitted and is currently under peer-review. The format, style and figures presented within the paper is designed according to the journal specifications.

9.2. Paper Under Review

Frontally-mediated cognitive deficits, craving and cognitive recovery among alcohol dependent individuals following detoxification

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Abstract

Background: Alcohol dependence (AD), a debilitating and chronic relapsing disorder, is associated with neurocognitive impairments that appear to impair the drinker's ability to regulate compulsive urges to consume alcohol. However, few studies have examined how inhibitory deficits are related to craving or whether they improve following abstinence.

Methods: Twenty-four patients with AD were recruited following detoxification, together with 23 healthy controls. Participants were administered the Sustained Attention to Response Task (SART), a measure of response inhibition and sustained attention, and the Random Number Generation (RNG) Task, which assesses executive inhibitory impairments and attentional deficits. Cognitive performance was correlated with clinical measures of AD and duration of abstinence post-detoxification.

Results: On the SART, the AD group demonstrated an increased number of commission errors and slower reaction times (RT). Age was related to reduced commission errors and slower RT in the AD group, while craving was associated with slower RT. On the RNG, the AD group showed excessive repetitions and increased deviations from randomness, with the latter measure associated with duration of alcohol consumption. There was no evidence of a relationship between cognitive performance and duration of abstinence.

Conclusion: AD patients demonstrated neurocognitive impairments across the domains of cognitive inhibition and attentional control. These deficits are related to clinical measures of craving and years of alcohol consumption. Improved cognitive performance was not associated to duration of abstinence, suggesting that these deficits are likely to be enduring. These findings reinforce the need for treatment strategies that specifically target neurocognitive deficits in patients with AD.

Key Words: alcohol dependence, cognitive inhibition, attentional control, craving, cognitive recovery, detoxification

1. Introduction

Alcohol dependence (AD) is a chronic relapsing disorder characterised by impaired control (Hyman and Malenka, 2001) and continued use despite recurrent health, psychological and/or social consequences (DSM-IV-TR, American Psychiatric Association., 2000). A diminished capacity to regulate alcohol consumption, in spite of aversive consequences, remains a critical challenge for the treatment of AD (Noël et al., 2010). Despite a robust literature documenting the neurotoxic effects of alcohol and alcohol-related brain damage (Alfonso-Loeches and Guerri, 2011), the behavioural aspects of impaired control in AD patients without major brain damage require further investigation. Preliminary studies suggest that cognitive inhibitory impairments (Kamarajan et al., 2004; Li et al., 2009; Noël et al., 2007; Rubio et al., 2008), and related frontostriatal dysfunction (Chanraud et al., 2007; Kamarajan et al., 2005; Li et al., 2009; Noël et al., 2001a), are associated with compromised ability to regulate alcohol-seeking behaviours (Stavro et al., 2012). Additionally, these frontally-mediated cognitive deficits persist beyond abstinence (Cohen et al., 1997; Li et al., 2009; Noël et al., 2007), and relate to increased levels of craving (Anton, 2000) and treatment outcomes (Bates et al., 2002; Durazzo et al., 2008; Evren et al., 2012; Noël et al., 2002), including increased vulnerability to relapse (Bowden-Jones et al., 2005; Sorg et al., 2012). Thus, persistence of such inhibitory deficits may be inextricably linked with a compromised ability to recover from AD (Feil et al., 2010; Oscar-Berman and Marinković, 2007).

Growing evidence across various addicted populations, including cocaine (Li et al., 2008; Li et al., 2006), methamphetamine (Baicy and London, 2007; Monterosso et al., 2005), cannabis (Tapert et al., 2007) and opiate users (Verdejo-García et al., 2012; Verdejo-Garcia et al., 2007; Yücel et al., 2007), has demonstrated that substance dependent individuals exhibit diminished executive and inhibitory skills (Feil et al., 2010; Verdejo-García et al., 2008). Similarly for AD, there is a small group of studies demonstrating cognitive inhibitory deficits

following detoxification (Li et al., 2009; Noël et al., 2007). Thus significant errors in response inhibition (Kamarajan et al., 2004; Li et al., 2009; Noël et al., 2007) and attentional control (Noël et al., 2007), related to frontostriatal dysfunction (Kamarajan et al., 2004; Li et al., 2009), were also implicated in the progression from heavy drinking to AD (Rubio et al., 2008); indicating frontally-mediated cognitive inhibitory deficits within AD populations. However, the scope of the literature remains somewhat limited: (i) only a small number of studies have addressed these inhibitory deficits within an AD population, (ii) cognitive inhibitory deficits are proposed to closely relate to levels of craving; however, there is currently minimal empirical support for this relationship, and (iii) although a number of these previous studies were conducted within AD patients post-detoxification, there was no assessment of cognitive recovery following abstinence. As such, our main objectives were to expand upon findings of impaired inhibitory and attentional control in patients with AD, by further investigating whether these deficits relate to clinical measures of craving, and additionally, observe whether a relationship exists between improved neurocognitive function and duration of abstinence.

To assess the presence of inhibitory and attentional deficits within an AD population, we administered two novel cognitive inhibitory tasks. The first, the Sustained Attention to Response Task (SART) (Robertson et al., 1997), was administered to reproduce previous findings regarding inhibitory deficits in AD. The SART (Robertson et al., 1997) provides a frontally-mediated (Braet et al., 2009; Fassbender et al., 2004; Garavan et al., 2003; Hester et al., 2004; Manly et al., 2003; Molenberghs et al., 2009; O'Connell et al., 2009; O'Connor et al., 2004; Rubia et al., 2003) measure of response inhibition (Helton et al., 2009; Johnson et al., 2007b; O'Connell et al., 2008; O'Connell et al., 2009) and sustained attention (Braver et al., 2003; Robertson et al., 1997). Participants maintain exogenous attention and respond to the frequent presentation of a *non-target* neutral stimulus (Go response), while retaining

endogenous attention and withholding responses to the presentation of rare randomly distributed *target* stimuli (No/Go response). Participants commit commission errors when they are unable to effectively suppress their automatic response to the salient, yet inappropriate stimuli (i.e. No/Go response) (O'Connell et al., 2008). Previous studies demonstrate that the SART is a robust and sensitive task which can successfully identify these impairments across a range of clinical populations (Bellgrove et al., 2006; Chan et al., 2011; Chan et al., 2004; Chan et al., 2009; Johnson et al., 2007a; Johnson et al., 2007b; McAvinue et al., 2005; O'Connell et al., 2006; Whyte et al., 2006). To date, the SART has not been administered within an AD population. However, given its sensitivity across a range of clinical studies, we anticipated that it would provide an effective and easy-to-administer cognitive assessment for identification of neurocognitive deficits within an AD population. We predicted that the AD group would exhibit a reduced ability to maintain endogenous attention, and a diminished capacity to inhibit automatic responses to inappropriate stimuli.

The second task, the Random Number Generation Task (RNG: Baddeley 1966), was administered to characterize additional aspects of cognitive inhibition; specifically, the ability to generate a novel response, while also inhibiting habitual responses to previously learned schemata (Jahanshahi et al., 2006; Knoch et al., 2005). The RNG explores the ability to generate random sequences of numbers (Brugger, 1997; Peters et al., 2007). Although the RNG is a procedurally simple task, avoiding deviations from randomness requires a number of complex frontally-mediated executive resources (Dirnberger and Jahanshahi, 2010; Jahanshahi and Dirnberger, 1999; Jahanshahi et al., 2000; Jahanshahi et al., 1998; Jahanshahi et al., 2006; Joppich et al., 2004; Knoch et al., 2005). The executive processes recruited by the RNG engage the supervisory attentional system (Shallice and Burgess, 1998), a limited capacity executive system required to generate strategic and novel responses, suppress automatic responses, and maintain attentional control (as demonstrated by dual-task

paradigms) (Baddeley, 1966; Dirnberger and Jahanshahi, 2010). Poor performance, such as excessive repetition of numbers, counting in series, and producing stereotyped digrams (Ginsburg and Karpiuk, 1994; Towse and Valentine, 1997), results in deviations from randomness (described in table 2).The RNG task has successfully indexed cognitive deficits across a range of clinical populations (Brown et al., 1998; Chan et al., 2011; Dirnberger et al., 2005; Rinehart et al., 2006; Robertson et al., 1996; Salamé and Danion, 2007; Williams et al., 2002). However, it is yet to be administered within an AD population. Therefore we examined whether AD patients presented difficulties producing novel responses, while suppressing habitual responses to previously established schemata. Such problems might relate to a compromised ability to develop adequate alcohol-seeking prevention strategies and to suppress habitual alcohol-seeking behaviours.

Following this, we evaluated whether these neurocognitive deficits were related to heightened levels of craving, a multidimensional construct relating to a compromised ability to regulate drinking behaviours (Anton, 2000). Consistent with the concept of impaired control in addiction, a number of AD studies (Bottlender and Soyka, 2004; Gordon et al., 2006; Kranzler et al., 1999; Roberts et al., 1999; Schmidt et al., 2011) have successfully utilized the obsessive-compulsive drinking scale (OCDS) (Anton et al., 1996), as a clinical measure of obsessive and compulsive craving (Anton, 2000). However surprisingly, there are scarce empirical data regarding the relationship between cognitive inhibitory deficits and heightened craving in AD.

Finally, we assessed whether improved neurocognitive performance was associated with duration of sobriety. Literature assessing this relationship remains limited (for an extensive review, see Stavro et al., 2012). A number of longitudinal studies suggest significant recovery in function across a wide range of cognitive domains, such as, working memory, attention, short-term memory, visuospatial ability (Brandt et al., 1983; Sullivan et al., 2000), over the

first few weeks to one year of abstinence (Crews et al., 2005; Stavro et al., 2012; Sullivan et al., 2000). However, enduring deficits across domains of memory (Brandt et al., 1983) and spatial processing (Fein et al., 2006) have also been reported following long-term abstinence . While impairments in executive performance have been consistently observed across a number of studies assessing short-term abstinence (Chanraud et al., 2007; Davies et al., 2005; Manning et al., 2008; Zinn et al., 2004), as noted by Starvo et al. (2012), there is a dearth of studies regarding long-term abstinence and inhibition/impulsivity in AD.

As such, the current study had three major objectives: (i) Expand on previous AD studies by further characterizing neurocognitive deficits within an AD population via administration of the SART and RNG. (ii) Explore whether the presence of these neurocognitive deficits is related to clinical measures of craving. (iii) Assess whether improved performance on the neurocognitive tasks is associated with duration of abstinence.

2. Methods

The study was approved by the Alfred Hospital Research and Ethics Unit review board committee, and was conducted in collaboration with the Monash Alfred Psychiatry Research Centre and Turning Point Alcohol and Drug Centre. Active enrolment ran from October 2010 through September 2011. Consenting patients signed a detailed informed consent form prior to study enrolment; they were informed that participation was voluntary, and they could withdraw at any time without prejudice.

2.1. Participants

2.1.1. Alcohol Dependent Post-Detoxification Sample:

Twenty-four patients meeting the criteria for DSM IV-TR Alcohol Dependence (AD) (REF) were recruited within 2 years of successful completion of a detoxification program (Range = 5 days - 668 days, Mean = 169 days, SD = 199 days, Median = 66.5). Screening procedure

included a psychiatric history and medical phone interview conducted by a trained research assistant. Participants were recruited through treatment agencies by self or clinician referral. Posters and cards advertising the study were presented at participating centres and offered to detoxification clients who met the study entry criteria. Participants were paid $20 to participate in the study (covering travel costs and time taken to participate), and were aged between 18-60yrs. Alcohol-dependent subjects were required to (1) have a current *Wechsler Test of Adult Reading* score higher than 40, as an indication of no significant intellectual disability; (2) no self-reported drug or alcohol use since completing the detoxification program; and (3) have no current comorbid mental health disorder (including co-morbid depression and polysubstance use). Individuals who had a history of significant head injury, intellectual disability, neurological disease, psychotic symptoms or suicidal ideation, were excluded from the study. Individuals engaging in pharmacotherapy programs were not excluded but type and levels of medication were reported (17% of participants were undergoing Acamprosate or Naltrexone treatment). To account for potential improvements associated with anti-craving pharmacotherapy, medication history was correlated with cognitive measurements; however, no significant relationship was observed. At screening, AD participants completed a general demographic questionnaire.

2.1.2. Healthy Control Sample:

Twenty-three healthy control subjects (CS), without any previous or current history of psychiatric illness, or history of drug or alcohol dependence, were recruited through local advertisements and posters. Participants were aged between 18-60yrs and paid $20 to participate (covering travel costs and time taken to participate). At screening, CS were required to complete a general demographic questionnaire. Relevant demographic and participant characteristics for both AD and CS are summarized in Table 1.

Insert Table 1.

2.2. Clinical Measures

General demographics questionnaire

Screening of participants included basic demographics: gender, age, marital status, country of origin, education, age of first use, age of first treatment, number of detoxifications.

Beck Depression Inventory (BDI)

The BDI, a *self-reported* inventory, measures the severity of depressive symptoms (Beck, 1987) and is widely used in clinical samples and addicted populations.

Wechsler Test of Adult Reading (WTAR)

The WTAR uses a 50-item word list to measure a pre-morbid level of intellectual functioning. The WTAR was administered to evaluate and compare general levels of cognitive functioning (Wechsler, 2001).

2.3. Substance dependence, alcohol use and craving measures

Severity of alcohol dependence questionnaire (SADQ)

A 20-item scale that measures degree of dependence upon alcohol (Stockwell et al., 1979; Stockwell et al., 1994).

Timeline Follow Back (TLFB)

A four week calendar which asks the participant to retrospectively estimate their alcohol consumption over the previous month.

Obsessive Compulsive Drinking Scale (OCDS)

A pencil and paper self-rating questionnaire that assesses overall craving, as well as compulsivity related to craving and drinking behaviour. The OCDS is a good tool for monitoring the severity of substance use and has predictive validity for relapse to drinking (Anton et al., 1996).

2.4. Neuropsychological assessment

2.4.1. Sustained Attention to Response Task (SART)

Participants were asked to respond quickly and accurately to the presentation of single digits (1 to 9) with a button press, with the exception of the number '3', the target stimulus (Robertson et al., 1997). The stimuli appeared in black in the centre of a white background, presented in a random order in a block of 297 trials, with 33 possible no-go (number 3) responses. Each stimulus was presented for 150ms, with varying inter-stimulus interval (ISI) durations (1000ms, 1500ms and 1250ms) randomly distributed throughout the session (Bonnefond et al., 2010; Dockree et al., 2005). The variable ISI was used to minimize speed/accuracy trade-offs. Prior to recording, participants were administered an 18 trial demonstration sequence, with 2 possible no-go trials presented randomly. Participants were informed that speed of response and accuracy were of equal importance. Reaction time (RT), commission errors, performance variability, and omission errors were recorded.

2.4.2.Random Number Generation Task

Participants were asked to generate a random sequence of digits. To describe the concept of randomness, the 'hat' analogy was used (Baddeley, 1966; Horne et al., 1982). Participants are instructed to imagine that the numbers 0 – 9 are written on pieces of paper, these numbers are placed in a hat, one number is taken out of the hat, participants are required to call out that number, and then return the number to the hat. By repeating this process, they will be generating a list of random numbers. All instructions were computerized and participants

were instructed to synchronize their verbal response with a pacing black ‘X’ stimulus displayed on the computer screen at a rate of 1 ‘X’ stimulus per second, for a sequence of 20 numbers. The first sequence was conducted as a demonstration trial. Following the demonstration, the experimental trial began and participants were required to generate 5 trials of 20 numbers, thus generating a 100 digit trial. Throughout the task, participants wore a headset with a microphone and verbal responses were recorded through the computer. Executive processes, such as inhibition and deviations from randomness, were calculated according to the indices of random factors (Jahanshahi et al., 2006), stratified according to the RNG factors relating to repetition, seriation and randomness (see Table 2).

Insert Table 2.

Fewer participants completed the RNG task relative to the SART, since the RNG algorithms can only process data from participants who complete a minimum of 90% of the RNG required responses. Thus data from participants who completed less than 90% of the RNG required responses were excluded.

2.5. Procedure

Following baseline screening and completion of demographic questionnaires, cognitive performance of both AD subjects and CS was evaluated via two computerized cognitive tasks using E-prime V1 technology (Psychology Software Tools): the SART (Robertson et al., 1997), and the RNG (Baddeley, 1966). Participants were seated in a quiet, well-lit room, 30cm from a 17 inch computer screen. Computerized task instructions were presented in English. Each task began with a short demonstration task to ensure that participants understood the task requirements.

2.6. Data analysis

Comparability of AD patients and CS was assessed using χ^2- tests for categorical and t-tests for continuous variables (see Table 1.). Stem-plots located extreme outliers (> +/- 2.5 standard deviations (SD)), and outliers were brought to within 2.5 SD of the mean. For all data meeting assumptions of normality, tests were run at an alpha level of 0.05. There were no significant violations of homogeneity of regression. To address cases of violations of unequal variance (i.e. Levene's statistic found to be significant), statistics were run at a more conservative alpha level of 0.025.

For the SART, an ANCOVA was administered to measure group differences across variables (reaction time, performance variability and omission errors). Across all SART variables, the significant differences in BDI, WTAR and age (near significant) were controlled for as covariates. Performance variability was calculated according to the standard deviation of the RTs on correct response trials (Go-trials) divided by the mean RT of each subject. For number of commission errors, SART RT was also controlled for as a potentially confounding variable. For the RNG analyses, an ANCOVA was also used to evaluate group differences across the RNG indices, with both BDI and WTAR being controlled for as covariates. Pearson's correlation also examined potential associations between cognitive variables (SART and RNG), general demographics, drinking and alcohol questionnaires, as well as BDI scores within groups. All data analyses were performed using SPSS for Windows, version 15.

3. Results

3.1. Sustained Attention to Response Task performance

The AD group exhibited impairments in cognitive inhibition, attention (commission errors) and psychomotor control (SART RT) (Figure 1.).

Insert Figure 1.

The AD group (M= 12.75, SD=6.29) made significantly more commission errors (failure to stop on a no-go trial) than CS (M= 7.7, SD=3.17), F (1, 41) = 5.919, p= 0.019. A significant difference in SART RT was also revealed between AD (M= 373ms, SD=63ms) and CS (M= 359ms, SD=54ms), F (1, 42) = 4.529, p= 0.039. There were no observable differences in performance variability or number of omission errors between the two groups (refer to Table 3).

Insert Table 3.

3.2 Correlational data for the SART

There were significant negative correlations between commission errors and SART RT across both AD (r = -0.655, n = 24, p = 0.001, two-tailed) and CS (r = -0.460, n = 23, p = 0.027, two-tailed) groups. Commission errors negatively correlated with age (r = -0.433, n =24, p = 0.035) in the AD group only. In addition, SART RT positively correlated with age (r = 0.417, n =24, p =0.043) and the OCDS scale (r = 0.424, n =24, p =0.039) in the AD group. Also, increased number of years of alcohol use was positively related to age of participants (r = 0.756, n =24, p < 0.005). No further significant correlations were identified.

3.3. Random Number Generation Task Performance

The AD group presented with a greater number of repetitions and increased departures from randomness (Figure 2).

Insert Figure 2.

In terms of repetition, the AD group (M = 46.87, SD = 4.65) presented with a significantly greater number of total repetitions relative to the CS group (M = 44.29, SD = 4.99), F(1,40) = 4.319, p = 0.044. With regards to departures from randomness, the AD group (M=0.35, SD = 0.05) had a significantly increased response bias index (i.e. a greater RNG ratio), compared to the CS group (M=0.30, SD = 0.04), F(1,40) = 7.404, p =0.01 (Table 4.).

Insert Table 4.

3.2.1. Correlational data for the RNG

Pearson correlation revealed a significant positive relationship between the RNG ratio and years of alcohol use (r = 0.460, n = 23, p = 0.027) in the AD group only. No further significant correlations were identified.

4. Discussion

The current study revealed regulatory deficits in cognitive inhibition and attentional control in the AD group relative to controls. For the SART, the AD group demonstrated a compromised ability to inhibit prepotent responses to inappropriate stimuli (i.e. commission errors) and slower reaction times (RT). In addition, increased age was related to both slower RT, and a reduced number of commission errors, in the AD group only. Slower SART response times were also related to increased clinical symptoms of craving in the AD group only. For the RNG, the AD group exhibited impaired output inhibition and were unable to

successfully suppress previous representations (excessive repetition), as well as demonstrating difficulty inhibiting automatic responses to previously learned schemata (deviations from randomness). Moreover, a relationship between increased deviations from randomness and increased number of years of alcohol consumption (prior to detoxification) was observed. Finally, there was no significant relationship between improved performance on cognitive tasks and duration of abstinence.

The inability to suppress an automatic response to the presentation of inappropriate stimuli on the SART (Braet et al., 2009; Chambers et al., 2006) has been suggested to rely on frontal circuitry (Fassbender et al., 2004; Garavan et al., 2003; Hester et al., 2004; Manly et al., 2003; Molenberghs et al., 2009; O'Connell et al., 2009; O'Connor et al., 2004; Rubia et al., 2003). In the current study, the AD group demonstrated a reduced capacity to discriminate between conflicting response possibilities, and a diminished ability to inhibit their prepotent responses to the 'No/Go' target, resulting in commission errors. These findings are consistent with previous studies that found AD individuals made more errors in response inhibition (Kamarajan et al., 2004; Li et al., 2009; Noël et al., 2007; Rubio et al., 2008), and that these impairments were associated with frontal dysfunction (Chanraud et al., 2007; Kamarajan et al., 2005; Li et al., 2009; Noël et al., 2001a). Thus, the current study provides further neuropsychological evidence of frontally-mediated impairments of response inhibition in AD patients post-detoxification.

With regards to attentional control, the monotonous nature of the SART lulls participants into a disengaged task-driven response mode (Fassbender et al., 2004; Robertson et al., 1997). Thus, the AD group exhibited poor attentional capacity, and an automaticity of response to the infrequent No-Go targets, which contributed to the increase in commission errors. This inability to maintain goal-directed focus may underlie difficulties engaging in non-alcohol

seeking behaviours (Weinstein and Cox, 2006) and continued alcohol consumption (Cox et al., 2002).

Consistent with previous cognitive studies, we also revealed slower RT in the AD group (Cohen et al., 1997; Lawrence et al., 2009; Li et al., 2009; Vivian et al., 1973). RT is a complex measure of information processing, which includes stimulus identification, response selection, and the resulting motor response (Cohen et al., 1997). A recent exploratory study identified that chronic AD patients present with alterations of functional connectivity in the frontal premotor-cerebellar circuitry (Rogers et al., 2012), the same cognitive-motor circuitry required for co-ordinating higher order motor function (Middleton and Strick, 2000; Tekin and Cummings, 2002). Thus, increased RT in the AD group may reflect an interaction between deficits in general cognitive impairment and psychomotor slowing. In addition, these slower RT were associated with clinical measures of craving (i.e. OCDS total) in the AD group. Previous studies have reported that craving levels, as identified by the OCDS, were sensitive to alcoholism severity (Anton et al., 1996), predictive of short-term resumption of drinking outcomes (Kranzler et al., 1999; Roberts et al., 1999), and an increased vulnerability to relapse (Anton et al., 1996; Bottlender and Soyka, 2004; Gordon et al., 2006; Schmidt et al., 2011). Therefore, slower RT may characterize a cognitive-psychomotor cortical impairment specific to AD, and is consistent with previous studies that identified psychomotor slowing is related to severity of AD (Lawrence et al., 2009) and chronic alcohol exposure (De Wilde et al., 2007; Lawrence et al., 2009).

The negative relationship between SART RT and commission errors, across both groups, indicates a speed/accuracy trade-off (Helton et al., 2009). Participants had to respond as quickly and as accurately as possible; thus strategic planning was involved in regulating the speed of response against the perceived utility of successfully suppressing an inappropriate response (Manly et al., 1999). However, the AD group, despite exhibiting a significantly

slower RT relative to controls, still made more errors on tasks of response inhibition and sustained attention, thereby compounding the severity of these cognitive impairments.

Increased age was related to both a reduced number of commission errors, and a slower reaction time, in the AD group only. These results support findings by Carriere et al (2010), whereby SART errors performance declines as a function of age. As individuals age, their strategic responses (i.e. speed-accuracy trade-off) to the SART improve (Carriere et al., 2010). However, in the present study, as expected, age also correlated with years of alcohol use, suggesting that, even with less exposure to alcohol, the younger AD patients presented with greater cognitive impairment. Consequently, and by contrast, there was evidence of compromised strategic planning and cognitive ability in younger AD patients. Recent studies suggest that the younger the age of onset of AD, the greater the likely neurological damage, and impaired cognitive functioning (Chanraud et al., 2007; Hermens et al., 2012). Thus, developmental factors may be involved in the impaired neurocognitive factors associated with AD. Further studies, which assess the developmental impact of alcohol consumption on cognitive function and response inhibition, are warranted.

The RNG task also characterized frontally-mediated cognitive inhibitory deficits in AD patients post-detoxification. Successful performance on the RNG task relies on the recruitment of complex executive processes, such as generation of novel responses, the ability to inhibit automatic responses to previously learned schemata, and the ability to maintain attentional control. The AD group presented with cognitive impairments across two of the major RNG factors: repetition and randomness.

Excessive repetition reflects general deficits in the inhibition of a previous response or representation (Williams et al., 2002). Thus, impairments in inhibiting a previous response, and the inability to generate a novel response, may reflect impaired cognitive flexibility (i.e. the ability to adjust behavioural responses according to goal-related objectives) within the

AD group. Previous studies have also found that AD is characterized by disrupted cognitive flexibility (Fernández-Serrano et al., 2011), and related deficits in frontal lobe functioning (Ratti et al., 2002) that persist following detoxification (Noël et al., 2001b).

Departures from randomness however, relate to an inability to produce a unique sequence of numbers, while inhibiting previously learned schemata or strategies (Jahanshahi et al., 2006; Knoch et al., 2005). The AD group exhibited a significantly impaired ability to generate a random series, and these deficits were associated with increased years of alcohol use. Thus, difficulties generating a novel response could relate to a compromised ability to develop strategies to avoid alcohol-seeking behaviour, while inhibition of responses to learned schemata, could be associated with dysregulated control over previously established (possibly related to years of alcohol use) compulsive responses to alcohol-seeking behaviours.

Finally, we assessed the relationship between neurocognitive recovery and duration of sobriety across all the cognitive and demographic variables, but observed no significant associations. As such, our findings are consistent with previous studies that find executive impairments persist beyond early abstinence (Chanraud et al., 2007; Davies et al., 2005; Manning et al., 2008; Zinn et al., 2004), but they also suggest that these deficits are enduring, and are evident across the first two years of abstinence. The persistence of these executive deficits, and the compromised ability to inhibit the urge to drink, are likely to be associated with reduced treatment success and an increased propensity to relapse (Ihara et al., 2000; Morrison, 2011).

4.1. Limitations

There are a number of potential confounding variables that suggest the results must be interpreted with caution. Firstly, our study sample was small and dependent upon a self-report measure of abstinence, which may have been biased to meet entry requirements of the

study. Notably, there were also significant differences observed on measures of depressive symptoms and WTAR between the groups, despite excluding participants with a history of mental illness or cognitive damage. Although we addressed this limitation statistically, by controlling for these covariates, it represents a significant and consistent difficulty in assessing cognitive function within AD samples. With regards to the WTAR, while the lower score was not low enough to represent intellectual disability, the differences in WTAR score could reflect another component of executive dysfunction in the AD group. Given the cross-sectional nature of the study, it is difficult to ascertain whether the identified frontally-mediated cognitive inhibitory deficits are directly related to chronic alcohol consumption, reflect a pre-existing vulnerability, or are a combination of both (Feil et al., 2010). Finally, although we provided cross-sectional evidence of enduring cognitive deficits, further longitudinal studies are required to confirm these findings. Despite these limitations, our findings provide new evidence regarding the neurocognitive profile of AD patients post-detoxification.

4.4. Conclusion

In summary, the present study addressed its three main objectives: (i) Provided further evidence of impairments in cognitive inhibition and attentional control in an AD population. (ii) Identified an association between clinical measures of craving and general cognitive impairment. (iii) Demonstrated that cognitive performance does not improve with increasing duration of abstinence. Our findings add to the existing literature on cognitive dysfunction in addiction, and highlight the need for interventions that specifically target these neurocognitive deficits, so as to improve treatment outcomes for patients with AD.

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Table 1. Demographic and clinical data for Alcohol-dependent patients (AD) and Control Subjects (CS).

	n AD	AD Mean (+/- sd)	*n* CS	CS Mean (+/- sd)	T-test/ Chi-Squared test	Significance
Sustained Attention to Response Task						
Age, years	24	40 (11)	23	35 (9)	p = 0.067	n.s.
Gender ratio (M:F)	24	11:13	23	11:12	p =0.891	n.s.
BDI	24	16.83 (12.93)	23	2.83 (3.81)	p < 0.005	**
WTAR	24	44.33 (2.79)	23	46.52 (1.50)	p = 0.002	**
SADQ	24	30.96 (14.43)	23	0.83 (2.04)	p < 0.005	**
OCDS	24	27.87 (7.47)	23	1.65 (3.23)	p < 0.005	**
Random Number Generation Task						
Age, years	23	40 (11)	21	34 (9)	p = 0.101	n.s.
Gender ratio (M:F)	23	10:13	21	10:11	p = 0.783	n.s.
BDI	23	16.83 (13.22)	21	3.10 (3.88)	p < 0.005	**
WTAR	23	44.26 (2.83)	21	46.43 (1.54)	p = 0.003	**
SADQ	23	31.45 (14.57)	21	0.90 (2.12)	p < 0.005	**
OCDS	23	28.05 (7.61)	21	1.81 (3.34)	p < 0.005	**

*p<0.05, **p<0.01
n.s. = not significant
BDI = Beck Depression Inventory
WTAR = Wechsler Test of Adult Reading
SADQ = Severity of alcohol dependence questionnaire
OCDS = Obsessive Compulsive Drinking Scale

Table 2. Definition of indices within the Random Number Generation Task.

Factor	Index Name	Definition
Repetition Measures the number of times an individual repeats the same digit in a successive order.	Total Repetition (TR)	The sum of number of double repetitions (e.g. 4, 4), triple repetitions (e.g. 4,4,4), double digrams (e.g. 1,5,...1,5) and triple digrams (e.g. 1,5,4...1,5,4).
Seriation Measures the number of consecutive digrams. All count/series scores are also calculated according to length of series.	Total Series (TS)	Number of pairs of consecutive digrams (e.g. 4, 5)
	Total Count Score (TCS)	Total count score sums the sequence length of counting in ascending or descending series in steps of 1 (e.g. 1, 2, 3 or 8, 7, 6, 5) and counting in ascending or descending series in steps of 2 (e.g. 2, 4, 6, 8 or 7, 5, 3, 1). In calculating the count scores, the sequence length is squared and then summed together (Jahanshahi et al., 2006).
Randomness	Random Number Index (RNI)	A measure which reflects the difference between the observed and expected probability of all possible number pairs. The higher the reported RNI, the less random the series.
	Unique Triplets	The number of triplets that are unique are counted. There are 98 (N-2) triplets in a series of 100 responses. The fewer number of unique triplets, the increased tendency to repeat certain runs of digits.

Table 3. Performance Means and Standard Deviations on the Sustained Attention to Response Task (SART) variables for Alcohol - dependent patients (AD) and Control Subjects (CS).

SART	AD Mean (+/- sd)	CS Mean (+/- sd)	T-test	Significance
Commission Errors	12.75 (6.29)	7.7 (3.17)	p =0.019	*
Reaction time (ms)	373 (63)	359 (54)	p =0.039	*
Performance variability	0.28 (0.11)	0.22 (0.05)	p =0.301	n.s.
Omission Errors	2.75 (2.86)	0.78 (1.13)	p =0.212	n.s.

*p<0.05, n.s. = not significant

Table 4. Performance Means and Standard Deviations for Reaction time (ms) for the Random Generation Number Task (RNG) indices for Alcohol-dependent patients (AD) and Control Subjects (CS).

RNG	AD Mean (+/- sd)	CS Mean (+/- sd)	T-test	Significance
Total Repetition	46.87 (4.65)	44.29 (4.99)	p = 0.044	*
Total Series	33.52 (7.63)	28.76 (6.95)	p = 0.072	n.s.
Total Count Score	71.17 (25.23)	57.62 (17.61)	p = 0.432	n.s.
Random Number Index	0.35 (0.05)	0.30 (0.04)	p = 0.01	*
Unique Triplets	68.74 (7.53)	72.86 (6.15)	p = 0.303	n.s.

*p < 0.05, **p < 0.01
n.s. = not significant

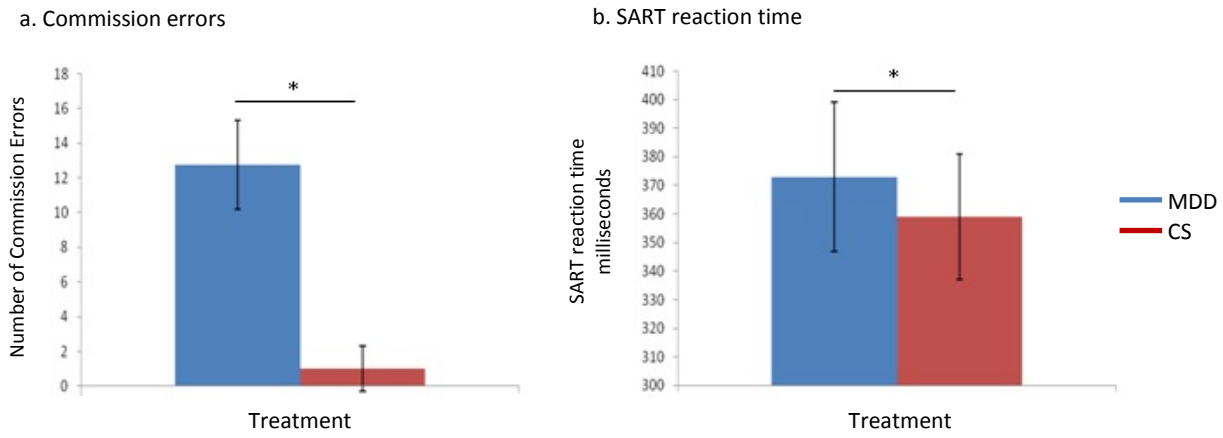

Figure 1. Group adjusted means of a) Commission errors, and b) Sustained Attention to Response Task (SART) reaction time, between Alcohol Dependent post-detoxification (AD) and Control Subjects (CS). Error bars are +/- 2 standard errors. *p<0.05, **p<0.01

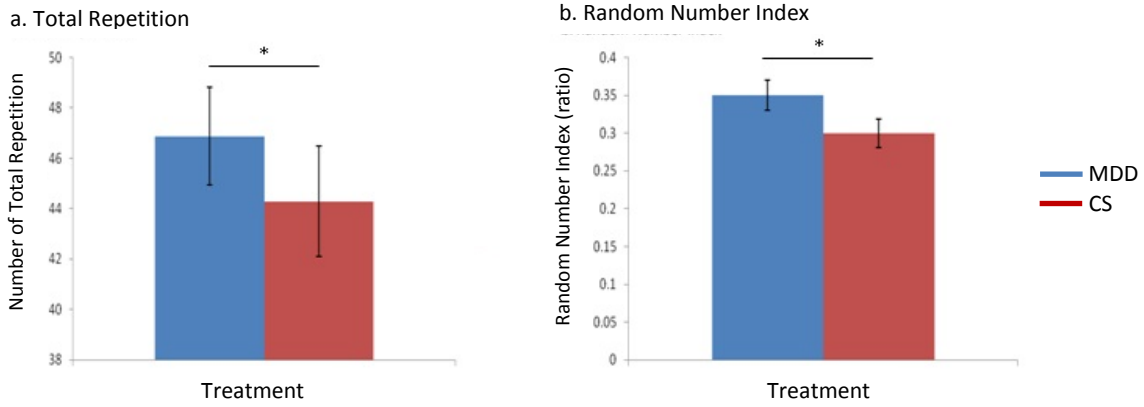

Figure 2. Group adjusted means of a) Total Repetition, and b) Random Number Index, between Alcohol Dependent post-detoxification (AD) and Control Subjects (CS). Error bars are +/- 2 standard errors. *p<0.05, **p<0.01

CHAPTER TEN

Study Four: *Cortical Inhibition within Motor and Frontal Regions in Alcohol Dependence: A TMS-EEG study.*

10.1. Introductory Comments

Once empirical evidence of cognitive inhibitory deficits within the alcohol dependent population was provided by Study Three, the next objective was to examine altered activity within the implicated frontostriatal circuitry in alcohol dependent patients post detoxification. Neuromolecular studies propose that altered cortical excitability within the frontal cortex plays an important role in the pathophysiology of Alcohol Dependence (AD). However, until the recent development of the novel combined Transcranial Magnetic Stimulation-electroencephalography (TMS-EEG) technique (Figure 1.), it was extremely difficult to index alterations within frontal structures.

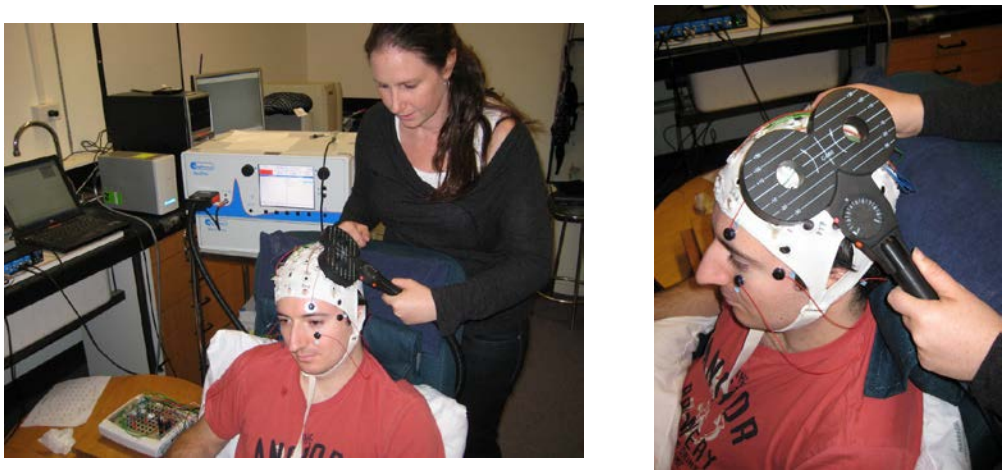

Figure 1. The combined Transcranial Magnetic Stimulation-electroencephalography (TMS-EEG) technique set up. The TMS-EEG set up of the current study; including the figure-8 coil, the EEG system and the MagVenture brain stimulation power source. Images supplied by Monash Alfred Psychiatry Research Centre.

Study Four is particularly innovative in providing the first investigation of altered cortical excitability within the frontal regions of alcohol dependent patients post-detoxification. The primary objective of the study was to apply the novel combined TMS-EEG technique to the frontal regions of alcohol dependent patients, and provide the first measure of altered frontal cortical inhibition within a dependent sample. To index cortical inhibition, a paired-pulse TMS paradigm called long interval cortical inhibition (LICI) is applied to the frontal cortex of alcohol dependent participants, and the neural response is compared to that of a single pulse (Figure 2. provides an example of averaged EEG recordings).

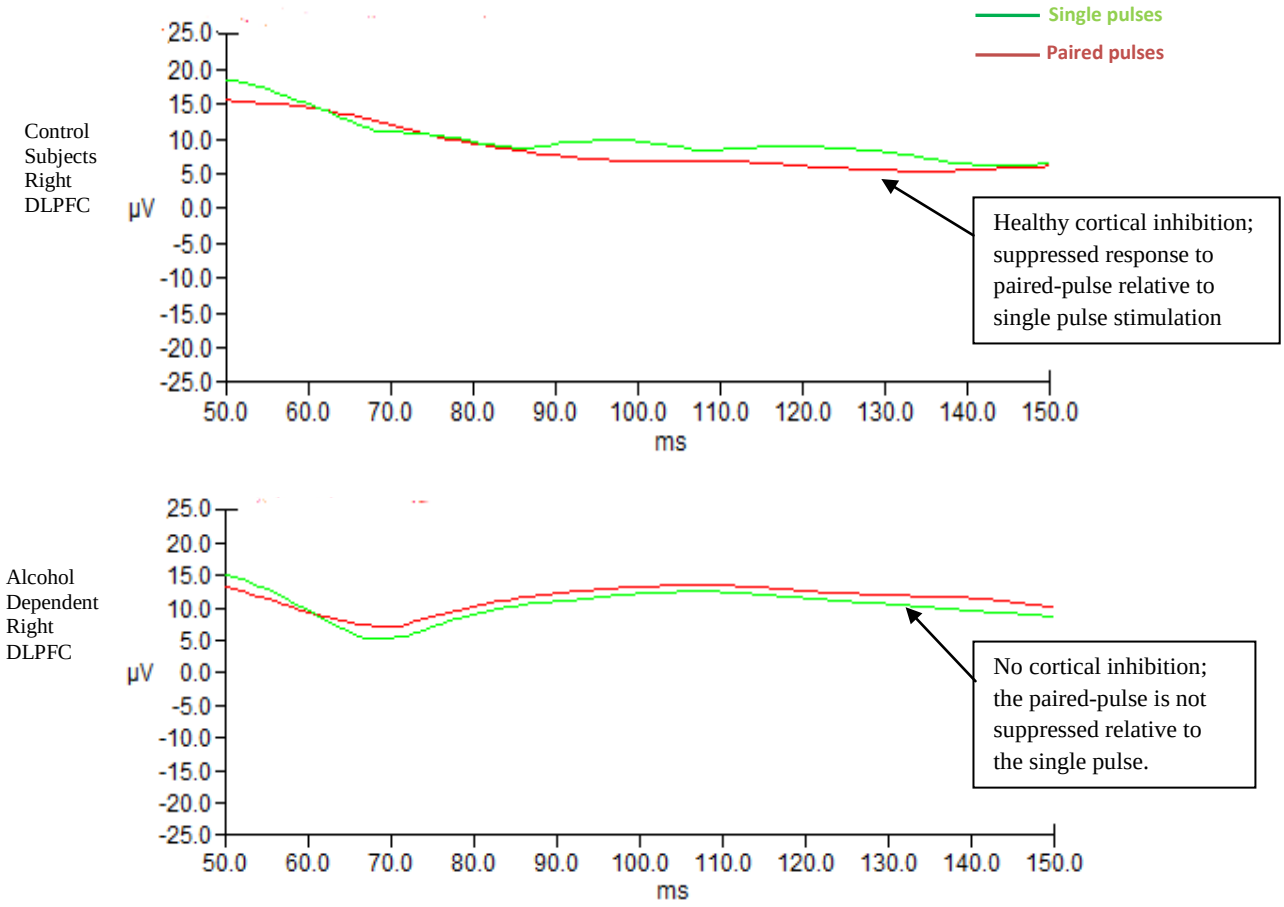

Figure 2. Averaged response to single and paired-pulse stimulations. The averaged single and paired-pulse data in response to TMS administered to the right Dorsolateral Prefrontal Cortex (DLPFC: F4 electrode) in the Control Subjects and the Alcohol Dependent patients. The paired-pulse represents the measure of cortical inhibition via long-interval cortical inhibition (LICI). Cortical inhibition within the healthy brain is demonstrated by a suppressed response to the paired-pulse relative to the single pulse.

Following evaluation of cortical inhibition within the frontal cortex, the secondary objective of the study was to verify previous addiction studies by examining whether AD is also related to altered excitability within the motor cortex. To measure motor cortex excitability, TMS is combined with Electromyography (EMG) recordings to ascertain participants' response to motor TMS-paradigms. In the study, both TMS-inhibitory (i.e. short interval intracortical inhibition, SICI, paradigms; an example is provided in Figure 3.) and facilitatory (i.e. intracortical facilitation, ICF) effects of paired-pulse TMS on motor evoked potentials were examined (the technique is described in detail in Chapter Four of thesis).

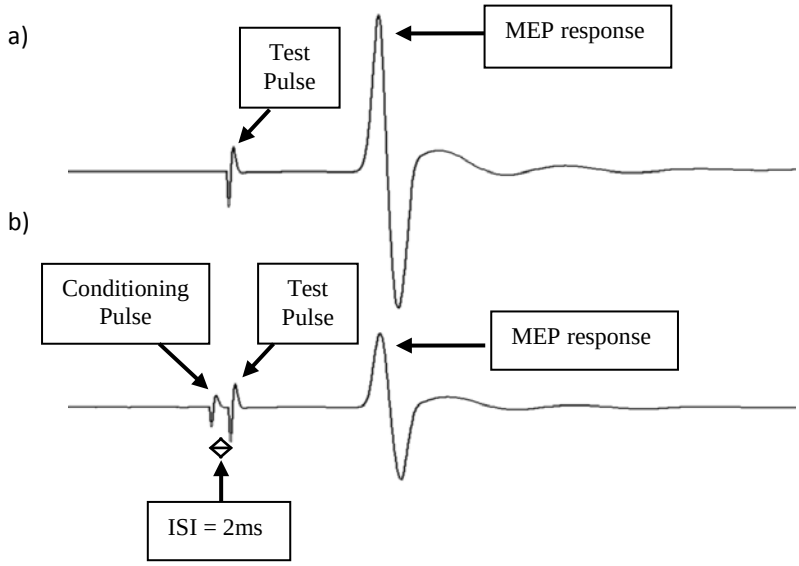

Figure 3. An illustration of the effects of single and paired-pulse TMS on motor evoked potential (MEP), as measured by surface electromyogram (EMG) recordings. Surface EMG recordings of MEP responses following: (a) a single test pulse b) paired-pulse stimulation. The test pulse is preceded by the conditioning pulse, which results in a reduced MEP. This illustration depicts the *suppressed* MEP response which is normally observed in control subjects following administration of short interval intracortical inhibition (SICI) TMS protocols with an inter-stimulus interval (ISI) of 2 milliseconds (ms). For intracortical facilitation, the same protocol is delivered, however with an ISI of 15 ms which facilitates an increased MEP response.

Therefore, the study was designed to investigate the presence of altered cortical inhibition within the frontal cortex of alcohol dependent patients post-detoxification. There follows an examination of whether AD is associated with concomitant changes in excitability within the motor cortex. Insight into disrupted cortical excitability within the frontal and motor cortex should provide critical information regarding the pathophysiology of AD.

The study is presented according to the manuscript version which has been submitted to a scientific journal and is currently under peer-review. The format, style and figures presented within the paper is designed according to the journal specifications.

10.2. Paper Under Review

Cortical Inhibition within Motor and Frontal Regions in Alcohol Dependence: A TMS-EEG study.

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Abstract

Background: Preclinical studies suggest that alterations within the frontal cortex play a critical role in the neurophysiology of alcohol dependence. The combination of transcranial magnetic stimulation and electroencephalography (TMS-EEG) allows a direct assessment of cortical excitability and inhibition within the frontal cortex in human subjects. We report the first application of TMS-EEG to measure these indices within the frontal cortices of patients with alcohol dependence.

Methods: Cortical inhibition was assessed in 12 patients with alcohol dependence and 14 healthy controls through single and paired-pulse transcranial magnetic stimulations (TMS) paradigms delivered to both the frontal and motor cortices. Long interval cortical inhibition (LICI) was used to index inhibition in the frontal cortex. Short interval intracortical inhibition (SICI) and cortical silent period (CSP) was used to index inhibition, while intracortical facilitation (ICF) measured facilitation, in the motor cortex. Cortical excitability was indexed by the resting motor threshold (RMT) and active motor threshold (AMT).

Results: The alcohol dependent group demonstrated deficits in LICI across both the left and right dorsolateral prefrontal cortex relative to healthy controls. The alcohol dependent group also exhibited reduced RMT and AMT. In terms of motor cortex inhibition, there were no significant differences in SICI, ICF or CSP, although increased intra-trial-variability in SICI was observed in the alcohol dependent group.

Findings: The current study provides the first direct evidence of reduced cortical inhibition that is specific to the frontal cortex of patients with alcohol dependence. Our study also revealed evidence of altered cortical excitability in the motor cortex of patients with alcohol dependence; however, the utility of using the motor cortex to index cortical alterations related to alcohol dependence remains unclear. Although these findings are preliminary, they provide

critical neurophysiological evidence of disrupted cortical excitability within the frontal cortex of alcohol dependent patients.

1. Introduction

Alcohol, a central nervous system depressant (Addolorato et al., 2012) has widespread effects across the brain, including alterations in multiple neurotransmitter systems within the mesocorticolimbic circuitry (De Witte, 1996; Morikawa, 2010; Spanagel, 2009). Repeated alcohol exposure induces compensatory neuroadaptations which oppose the inhibitory effect of acute alcohol administration (Alfonso-Loeches and Guerri, 2011; Kalivas, 2009; Kalivas et al., 2009; Pulvirenti and Diana, 2001; Van Den Oever et al., 2012), resulting in the suppression of γ-aminobutyric acid (GABA) inhibitory neurotransmission (Addolorato et al., 2012; Enoch, 2008; Filip and Frankowska, 2008; Lobo and Harris, 2008) and potentiation of glutamate (GLU) excitatory neurotransmission (Duncan and Lawrence, 2012; Gass and Olive, 2008; Olive et al., 2012; Tzschentke and Schmidt, 2003). Altered cortical inhibition (CI), the neurophysiological mechanism by which cortical GABA inhibitory interneurons selectively suppress the activity of other neurons in the cortex, plays a critical role in the development of alcohol dependence (Diana, 2003). However, despite extensive preclinical and neuromolecular evidence of these neuroadaptative changes, supporting human evidence for altered CI within the mesocorticolimbic 'addiction' circuitry in the human brain is lacking.

Advances in brain stimulation techniques have demonstrated that CI of the cortex can be measured through the application of Transcranial Magnetic Stimulation (TMS)(Barker et al., 1985; Cohen et al., 1998; Hallett, 2000). Recently, these TMS techniques have been employed to index the effects of acute ethanol exposure, as well as chronic ethanol consumption on localized changes in CI. Acute alcohol exposure was found to potentiate GABAergic inhibitory mechanisms in the motor cortex (Conte et al., 2008; Ziemann et al., 1995), reduce cortical excitability in the prefrontal circuitry (Kahkonen et al., 2003), and influence functional connectivity between the motor and prefrontal cortices (Kahkonen et al., 2001; Kähkönen and Wilenius, 2007). Further studies have identified altered motor cortical activity in clinical populations with alcohol dependence (Conte et al., 2008), including those

experiencing alcohol withdrawal (Nardone et al., 2010). However, these previous studies were largely confined to measuring CI of the motor cortex, as recording CI from other brain regions, which relate directly to the pathophysiology of dependence, was technically difficult. Therefore, although providing informative evidence of altered activity within the motor cortex, these TMS studies were unable to directly index CI within the mesocorticolimbic system.

Recently, a novel technique, which combines TMS with electroencephalography (TMS-EEG) (Daskalakis et al., 2012; Rogasch and Fitzgerald, 2012), was found to successfully measure CI in the prefrontal cortex (Daskalakis et al., 2008; Farzan et al., 2010; Fitzgerald et al., 2008) through a paired pulse TMS paradigm known as long interval CI (LICI) (Valls-Solé et al., 1992). LICI involves stimulation of the cortex with a suprathreshold conditioning stimulus 50-150ms prior to the suprathreshold test stimulus, resulting in the inhibition of cortical evoked activity by approximately 30% (Daskalakis et al., 2008). A number of studies suggest that LICI relates to activity at the $GABA_B$ receptor (McDonnell et al., 2006; Sanger et al., 2001), thereby allowing researchers, for the first time, to directly probe altered GABAergic neurotransmission within the prefrontal cortex (PFC), a key structure of the mesocorticolimbic 'addiction' circuitry.

The current study utilised these novel TMS inhibitory paradigms to investigate the presence of altered CI within the frontal and motor cortices of patients diagnosed with alcohol dependence. The primary objective of the study was to investigate the presence of altered GABAergic receptor mediated neurotransmission (altered CI) within the frontal cortex of alcohol dependent patients post-detoxification. A secondary objective was to expand previous TMS studies in alcohol dependent populations and investigate whether alcohol dependence was associated with concomitant changes in excitability within the motor cortex.

2. Methods

The study was approved by the Alfred Human Subjects Research and Ethics Committee, and was conducted in collaboration with the Monash Alfred Psychiatry Research Centre and Turning Point Alcohol and Drug Centre. Active enrolment ran from October 2010 through September 2011. Consenting patients signed a detailed informed consent form prior to study enrolment; they were informed that participation was voluntary, and they could withdraw at any time without prejudice.

2.1. Subjects:

2.1.1. Alcohol Dependent Sample:

Twelve patients (mean age = 40.1 years, SD = 13.4 years; 8 males and 4 females) meeting criteria for DSM IV-TR alcohol dependence (DSM-IV-TR, American Psychiatric Association., 2000) were recruited within 2 years of successful completion of a detoxification program. Participants were recruited through treatment agencies by self or clinician referral. Posters and cards advertising the study were presented at participating centres and offered to clients who met the study entry criteria. Exclusion criteria included individuals with head injury, acute medical or physical illness, major depression, epilepsy or history of seizures, metal implants, other drug dependence, engaging in pharmacotherapy programs (including anti-craving or anti-depressant treatment), or reporting psychotic symptoms or suicidal ideation.

2.1.2. Healthy Control Sample:

Fourteen healthy control subjects (mean age = 31.1 years, SD = 5.3 years; 7 males and 7 females), without any previous or current history of psychiatric illness, or alcohol/drug

dependence or abuse, head injury, epilepsy or seizures, were recruited through local advertisements and posters.

All participants were aged between 18-60 yrs and received $40 reimbursement to participate in the study. At screening, participants were required to complete a general demographics questionnaire, the obsessive-drinking scale (OCDS) (Anton et al., 1996) and the severity of alcohol dependence questionnaire (SADQ) (Stockwell et al., 1979) to assess overall craving and degree of dependence on alcohol, the Beck Depression Inventory (BDI) (Beck and Steer, 1987) to measure severity of depressive symptoms and the Wechsler Test of Adult Reading (WTAR) (Wechsler, 2001) to assess pre-morbid level of intellectual functioning; relevant demographic and participant characteristics for both alcohol dependent (AD) and control groups are summarized in Table 1.

Insert Table 1.

2.2. Experimental Design/Procedure:

Active TMS was administered over the left motor cortex (Experiment 1) (always first), the right dorsolateral prefrontal cortex (DLPFC) and the left DLPFC (Experiment 2). The order of left and right DLPFC stimulation was counterbalanced across participants. All subjects participated in both Experiments 1 and 2; however, data from two controls, relating to stimulations to the right DLPFC, were not processed due to excessive movement throughout this measure.

2.2.1. Transcranial Magnetic Stimulation

Biphasic TMS pulses were administered to the cortex using a 7cm figure-of-eight cooled-coil connected to a MagPro R30 stimulator with a MagOption unit (Magventure, Denmark). The coil was held over the scalp, the handle of the TMS coil pointed backward, perpendicularly to the presumed direction of the central sulcus, and angled approximately 45◦ away from the midsagittal line. In Experiment 1, participants were administered a number of motor cortical TMS paradigms as measured by Electromyography (EMG), including: resting motor threshold (RMT), active motor threshold (AMT), 1mV measure (1mV), cortical silent period (CSP), short interval intracortical inhibition (SICI) and intracortical facilitation (ICF). In Experiment 2, participants were administered single and paired-pulse TMS; long-interval cortical inhibition (LICI) of DLPFC electroencephalography (EEG) activity, both in the left DLPFC and right DLPFC, was also examined.

2.3. Motor Cortical TMS Paradigms

2.3.1. Electromyography (EMG)

For all motor cortical TMS parameters and measures, EMG was used to record motor-evoked potentials (MEPs), during stimulation of the left motor cortex, via disposable disc electrodes placed over the contralateral first dorsal interosseous (FDI) muscle. All EMG activity was acquired through Signal software (Cambridge Electronics design, CED Micro 1401 mk II analogue-to-digital converting unit, Cambridge, UK), amplified and filtered (low pass 2kHz, high pass 10 Hz) by a PowerLab/4SP system (AD instruments, Colorado Springs, CO), and stored in a laboratory computer for offline processing.

2.3.2. Measurement of motor cortical inhibition/facilitation

Single-pulse stimulations

At the beginning of each experiment, single pulse stimulation was applied to the motor cortex to determine the RMT. RMT refers to the minimum stimulus intensity required to induce peak-to-peak MEPs > 50 μV of the contralateral FDI muscles in at least 5 out of 10 trials (Rossini et al., 1994). The recorded RMT scores corresponded to 50.67 ± 6.47% of stimulator output in the AD patient group, and 52.79 ± 8.20% of the stimulator output in the control group. Following this, we measured AMT, the minimum stimulation intensity, during FDI muscle contraction, required to produce peak-to-peak MEPs of >100 μV in 3 out 5 consecutive trials. Voluntary muscle contraction was elicited by participants pressing down their index finger against a spring; a press of approximately 20% of maximum voluntary contraction, was maintained throughout delivery of the AMT stimulations. The AMT scores corresponded to 44.08 ± 6.56% of stimulator output in the AD patient group, and 44.64 ± 8.02% of the stimulator output in the control group. Following the assessment of RMT and AMT, the stimulator output intensity was increased to induce peak-to-peak MEPs of approximately 1mV over 10 consecutive trials (i.e. 1mV measure). The 1mV intensity corresponded to 59.92 ± 7.73% of stimulator output in the AD patient group, and 62.43 ± 10.07% of the stimulator output in the control group. The 1mV measure was also determined over the EEG cap and electrodes (i.e. 1mV measure over cap) to provide appropriate stimulation parameters for Experiment 2.

Measurement of motor inhibition/facilitation

To determine CSP, twenty single TMS pulses at 125% of AMT were administered to the motor cortex; during voluntary muscle contraction, the suppression of the FDI muscle was measured via EMG (Cantello et al., 1992). Following this, inter-neuronal activity in the motor cortex was assessed using SICI and ICF paradigms with paired pulse TMS. To obtain a measure of SICI, two pulses were delivered in rapid succession; the subthreshold

conditioning pulse (90% of AMT) was first applied, then occurred a brief inter-stimulus interval (ISI) of 2ms, followed by the suprathreshold test pulse (1mV measure) (Kujirai et al., 1993). For ICF, the same two pulse intensities were administered, but with an increased ISI of 15ms between the pulses. These specific parameters (e.g. TMS intensity, intervals) were determined according to previous clinical studies. Twenty trials of each condition were applied in a random counter-balanced order.

2.3.3. EMG measurement of motor inhibition/facilitation processing

The peak-to-peak amplitudes of MEPs evoked by paired-pulse stimulations were analysed by Signal 3.8 (Cambridge Electronic Design, Cambridge, UK). The CSP duration was measured by calculating the time (ms) from the beginning of the MEP until the end of CSP (i.e. the resumption of tonic activity) (Daskalakis et al., 2003). For SICI and ICF, to assess their inhibitory and facilitatory effects on a *test* pulse, the mean MEP amplitudes were quantified as a percentage relative to the singe pulse measure (i.e. 1mV measure). Therefore, all EMG measures are relative to the single pulse, whereby, a response of 100% reflects no effect of TMS, a response less than 100% refers to an inhibitory effect and a response greater than 100% is suggestive of a facilitatory effect.

2.4. Frontal Cortical TMS Paradigms

2.4.1. Electroencephalography (EEG)

To evaluate TMS induced cortical evoked activity in the frontal regions, EEG recordings were acquired through a Synamps^2 EEG system (Compumedics Neuroscan, Texas, USA). A custom-made 24-channel EEG cap was used to record the cortical signal, and individual electrodes were placed on the outer side of each eye, and above and below the left eye, so as to closely monitor eye movement artefact (Daskalakis et al., 2008). All electrodes (sintered Ag/AgCl: Neuro Prax, Germany) were referenced to an electrode placed posterior to the Cz

electrode. EEG signals were recorded DC at a sampling rate of 20kHz and filtered through a low pass filter of 3500 Hz to minimize TMS-related artefacts, and avoid saturation of amplifiers (Fitzgerald et al., 2008).

To reduce the effect of TMS click-induced auditory activation on the cortical evoked potentials (Paus et al., 2001), white noise (95dB) was played through inserted earphones, from 1 second prior to each TMS pulse, and remained until 1 second after each pulse (Fitzgerald et al., 2008).

2.4.2. Measurement of frontal cortical inhibition

The LICI paradigm involved delivering two suprathreshold pulses: the suprathreshold *conditioning* pulse (1mV measured over cap), then, a long ISI of 100 ms, followed by a suprathreshold *test* pulse (1mV measured over cap). Thus, the conditioning pulse inhibits the MEP produced by the test stimulus (Valls-Solé et al., 1992). The suprathreshold output intensity (i.e. 1mV over the EEG cap) corresponded to 70.09 $\pm$ 5.32% in the AD patient group, and 73.29 $\pm$ 9.29% in the control group. This procedure induces long-lasting cortical inhibition mediated by the $GABA_B$ (McDonnell et al., 2006), and it is suggested that LICI is optimal when the conditioning stimulus precedes the test stimulus by 100-150ms (Sanger et al., 2001). LICI was delivered across both stimulation sites (left and right DLPFC), with 150 stimuli delivered to each site. The stimuli consisted of 75 single pulses (unconditioned *test* stimuli) and 75 paired-pulses (with *conditioned* stimuli followed by *test* stimuli), and were randomly counterbalanced between subjects to prevent order effects.

To assess LICI in the DLPFC, the TMS-coil was placed in a stand, and the coil was set tangentially over the scalp, with stimulations directed between AF3 and F3 for the left DLPFC, and between AF4 and F4 for the right DLPFC. The recording electrode of interest for the left DLPFC was F3, and the right DLPFC was F4, selected to optimally represent

Brodmann areas (BA) 8/9 and 46 within the DLPFC on the medial frontal gyrus (Fitzgerald et al., 2009; Herwig et al., 2003).

2.4.3. EEG data processing

The EEG recordings were processed offline with the commercially available software SCAN 4.3 (Compumedics Neuroscan, Texas, USA). EEG data were down sampled to 1kHz sampling frequency, and fed into an automated eye-blink correction algorithm (Croft et al., 2005) and processed by MATLAB (the MathWorks inc., Natick, MA, USA). The eye-blink corrected data were then segmented into epochs, with respect to the TMS *test* stimulus, such that each epoch included data from 1000ms pre-stimulus baseline and 1047ms post-stimulus activity. Epochs were baseline corrected according to the stimulus condition: single *test* pulses were baseline corrected to 800 ms -150 ms, and paired-pulses were baseline corrected to 900 ms - 260 ms. The baseline corrected data were then further epoched to 25ms pre-stimulus and 1000ms post-stimulus. Following this, the baseline corrected data, which were not contaminated by TMS artefact, were extracted and digitally filtered using a zero-phase shift 1-40Hz band pass filter (48dB/Oct). At this time, epochs were manually reviewed and trials contaminated with muscle activity, movement or TMS artefacts, were excluded from further analysis. Finally, the average signals at each recording site were calculated from the movement-free epochs (approximately 75 trials per subject), average EEG waveforms (area under the curve (AUC)) were then saved as rectified data and imported into SPSS version 17.

2.4.4. EEG data analysis

To obtain a primary measure of LICI, the AUC from averaged-event related potentials (ERPs) were examined. After importing each averaged rectified recording into SPSS via Excel for each subject, the AUC for the time-frame of 50 ms to 150 ms post TMS pulse, for both the single and paired-pulse condition, were averaged separately, and compared across

the left DLPFC and right DLPFC stimulation sites. The first interval (i.e. 50 ms post-stimulus) was chosen as the earliest artefact-free data recorded post-stimulus.

For each subject, EEG inhibition was indexed by measuring the ratio of the AUC of the average paired-pulse potentials (conditioned) over the average single pulse potentials (unconditioned). The measure of LICI was represented by the following equation.

$$\left[1 - \frac{\text{Area under rectified curve (conditioned)}}{\text{Area under rectified curve (unconditioned)}}\right] \times 100 \qquad \text{(A)}$$

Therefore, for the EEG measure, a LICI score of 0 reflects no TMS effect, while a LICI score greater than 0 reflects an inhibitory effect (with 100 being maximum inhibition), and a LICI score less than 0 suggests a facilitatory effect.

2.5. Statistical analysis

For frontal cortical stimulation, two-tailed paired t-tests were performed to assess suppression of the rectified EEG activity in the paired LICI condition compared to the single pulse condition within groups. Analysis of covariance (ANCOVA), while controlling for age, BDI and WTAR, was also administered to calculate group differences in LICI-related measures. For motor cortical stimulations, an ANCOVA, which controlled for age, BDI and WTAR, was used to measure group differences. The group values were reported as mean $\pm$ SD, and tests were run at an alpha level of 0.05. There were no significant violations of homogeneity of regression or unequal variance. All statistical analyses were performed using SPSS version17 (SPSS Inc, Chicago, IL USA).

3. Results

3.1. Frontal-cortical paradigms

3.1.1 Site 1. Left DLPFC

Over the period of 50 ms to 150 ms post-stimulus, there was significant suppression of the rectified EEG activity in the paired LICI condition compared to the single pulse condition (M= 27.30, SD = 32.89, t = 2.953, *df* = 13, p =0.011) in the control group (Table 2). There was no significant LICI-related suppression of the rectified EEG activity in the AD group (M= -22.51, SD = 70.89). The difference between the groups was significant, f (1,21) = 11.683, p = 0.003 (Figure 1 and Figure 2). In addition, no significant differences were revealed between the groups in the single pulse condition, f (1,21) = 0.000, p = 0.984.

Insert Figure 1.

3.2.2. Site 2. Right DLPFC

Over the period of 50-150 ms post-stimulus, there was no significant suppression of the rectified EEG activity in the paired LICI condition compared to the single pulse condition located in either the control or AD group. However, there was a significant difference observed between the AD group (M= -12.98, SD = 73.68) and the control group (M= 16.16, SD = 49.17) in suppression of the rectified EEG activity in the paired LICI condition compared to the single pulse condition, f (1,19) = 9.452, p = 0.006 (Figure 1 and Figure 2). In addition, no significant differences were revealed between the groups in the single pulse condition, f (1,20) = 0.038, p = 0.847.

Insert Table 2.

Insert Figure 2.

3.2. Motor-cortical paradigms

3.2.1. Single-pulse stimulations

The AD group exhibited a significantly lower RMT, $F(1,21) = 9.223$, $p = 0.006$, and a significantly reduced AMT, $F(1,21) = 7.669$, $p = 0.011$, relative to controls (Figure 3). The AD group also presented with a significantly lower 1mV measure, $F(1,21) = 4.812$, $p = 0.04$, as well as a reduced 1mV measure over the EEG cap, $F(1,21) = 5.710$, $p = 0.026$, relative to controls (Table 3).

Insert Figure 3.

3.2.2.Measurement of motor inhibition/facilitation

There were no significant differences between groups on measures of CSP duration, SICI or ICF (Table 3). With regards to SICI, there was evidence of significantly increased SICI intra-variability in the AD ($M= 0.95$, $SD = 0.33$) relative to control group ($M = 0.73$, $SD = 0.21$), $F(1,21) = 4.390$, $p = 0.048$.

Insert Table 3.

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4. Discussion

This is the first electrophysiological study to report alterations in CI across both motor and frontal cortical regions in a clinical sample of patients with alcohol dependence. With regards to frontal excitability, the AD group exhibited reduced LICI in bilateral frontal cortices relative to healthy controls. This suggests that the AD group had deficits in $GABA_B$ receptor mediated inhibitory neurotransmission in both the left and right DLPFC. In terms of motor excitability, the AD group demonstrated increased cortical excitability, as reflected by reductions in RMT, AMT and 1mV threshold. No significant differences in CSP, SICI or ICF were found between groups. However, significantly greater intra-trial-variability in SICI was observed within the AD group.

4.1. Frontal cortical inhibition

The present study provides the first direct measure of altered GABAergic neurotransmission in the left and right frontal regions of patients with alcohol dependence. No significant differences were found between groups in terms of TMS-evoked response to single-pulses. However, there were significant differences in assessment of LICI induced paired-pulse inhibition; the AD group exhibited reduced LICI inhibitory neurotransmission in both the left and right DLPFC. When assessing the motor cortex, a number of studies have suggested that LICI relates to activity at the $GABA_B$ receptor. For example, the $GABA_B$ agonist baclofen potentiates LICI (McDonnell et al., 2006), leading to the proposition that LICI is GABAergic. Additionally, LICI inhibits SICI (Sanger et al., 2001), which is consistent with

in-vivo findings of suppression of $GABA_A$ receptor mediated inhibition by presynaptic $GABA_B$ receptors (Werhahn et al., 1999). Furthermore, a strong relationship between LICI measured with EMG and EEG has also been identified (Farzan et al., 2010). As such, suppressed LICI in the prefrontal cortex in the AD group is likely to reflect reduced $GABA_B$ receptor inhibitory neurotransmission within the frontal regions of patients with alcohol dependence.

As such, our findings provide clinical support for neuromolecular models of alcohol dependence that suggest repeated alcohol use disrupts the delicate balance of cortical excitability. In the current study, we identified the presence of suppressed GABAergic neurotransmission within the mesocorticolimbic circuitry of patients with alcohol dependence (Addolorato et al., 2012; Diana, 2003; Enoch, 2008). Acute alcohol facilitates the GABAergic system by acting through two types of GABA receptors, ionotropic $GABA_A$ and metabotropic $GABA_B$ (Cui et al., 2012; Enoch, 2008; Filip and Frankowska, 2008; Lobo and Harris, 2008; Weiner and Valenzuela, 2006), while also suppressing glutamate release and glutamate receptor activity (in dopaminergic cells) (Duncan and Lawrence, 2012; Gass and Olive, 2008; Kalivas, 2009; Kalivas et al., 2009); resulting in an overall inhibitory effect. After chronic alcohol exposure, the brain attempts to restore equilibrium in neuronal cell function (Tambour and Quertemont, 2007), with neuroadaptations within the mesocorticolimbic circuitry that counteract the effects of acute alcohol (Brodie, 2002; Diana, 2003). This results in the suppression of GABAergic neurotransmission (Addolorato et al., 2012; Diana, 2003; Enoch, 2008) and upregulation of glutamatergic neurotransmission and potentiation of NMDA receptor release (subtype of glutamate receptors) (Gass and Olive, 2008; Kalivas, 2009). Despite promising neuromolecular data regarding these compensatory alterations in cortical excitability, our study is the first to provide direct evidence of these

compensatory mechanisms via suppressed GABAergic neurotransmission within the mesocorticolimbic circuitry of patients with alcohol dependence.

Additionally, the current study specifically targeted cortical alterations within the PFC, a key structure within the mesocorticolimbic circuitry. Neural alterations within the PFC have been consistently implicated in the development and persistence of dependence (Bühler, 2011; Feil et al., 2010; Goldstein and Volkow, 2002; Jentsch and Taylor, 1999; Lubman et al., 2004; Moselhy et al., 2001; Oscar-Berman and Marinković, 2007; Sullivan and Pfefferbaum, 2005). Frontal impairments are associated with poorer treatment outcomes (Durazzo et al., 2008; Noël et al., 2002) and increased vulnerability to relapse (Bowden-Jones et al., 2005; Sorg et al., 2012). Neuroimaging studies have identified morphological evidence of reduced grey and white matter volume (Chanraud et al., 2007; Jang et al., 2007; Makris et al., 2008; Pfefferbaum et al., 1997; Rando et al., 2011; Wobrock et al., 2009), reduced cortical thickness (Fortier et al., 2011), decreased cerebral perfusion (Clark et al., 2007), attenuated cortical activation (Akine et al., 2007; Li et al., 2009) and altered regional cerebral blood flow (Dao-Castellana et al., 1998; Demir et al., 2002; Noël et al., 2001) within the frontal lobes of patients with alcohol dependence (Goldstein and Volkow, 2011; Sullivan and Pfefferbaum, 2005). Our study complements this work by providing direct evidence of altered cortical excitability within the PFC of addicted subjects at a neurotransmitter systems level.

Various treatment agents for alcohol dependence are being developed to target these alterations in GABAergic or glutamatergic neurotransmission; however, current pharmacotherapies provide only moderate clinical success (Addolorato et al., 2012; Tambour and Quertemont, 2007). In terms of direct $GABA_B$ agonists, baclofen (Addolorato et al., 2011; Addolorato et al., 2007; Bucknam, 2007; Colombo et al., 2004; Flannery et al., 2004;

Leggio et al., 2010) or gabapentin (Anton et al., 2009; Anton et al., 2011; Bonnet et al., 1999; Bozikas et al., 2002; Furieri and Nakamura-Palacios, 2007) act by potentiating $GABA_B$ receptors on the cell body of dopamine neurons; designed to restore the balance of cortical excitability within the brain and alleviate symptoms associated with alcohol dependence (Addolorato et al., 2012). These pharmacotherapies however, have been primarily developed based on preclinical models, rather than from direct studies of altered CI in clinical subjects. The present study helps to verify these preclinical studies and demonstrates the role of suppressed GABAergic activity within a clinical alcohol dependent population. In development of improved treatment agents, future pharmacological studies could utilize the frontal TMS-EEG technique to provide a pathophysiological account of how these $GABA_B$ agonists affect the balance of cortical excitability within the frontal cortex, and moreover, assess whether these changes relate to attenuated symptoms of alcohol dependence.

4.2. Motor cortical inhibition

4.2.1. Single-pulse stimulations

The AD group demonstrated significantly reduced RMT, AMT and 1mV thresholds relative to the control group, suggestive of increased excitability within the motor cortex. Our study is the first to identify these reductions in threshold and are consistent with the chronic effects of alcohol on glutamate receptors (Gass and Olive, 2008; Pulvirenti and Diana, 2001); compensatory neuroadaptations counterbalance the acute effects of alcohol exposure, suppress cortical inhibition, and lead to the upregulation of NMDA receptors (Duncan and Lawrence, 2012; Kalivas et al., 2009; Tzschentke and Schmidt, 2003). As such, these reductions in threshold are likely to represent hyper-excitability within the cortex associated with chronic alcohol consumption.

4.2.2. Paired-pulse stimulation

Short interval intracortical inhibition (SICI) is a widely used paired-pulse stimulation measurement which is employed to reflect activity of inter-neurons in the motor cortex (Chen et al., 1998; Kujirai et al., 1993; Ziemann et al., 1996). SICI is proposed to represent $GABA_A$ receptor mediated inhibitory neurotransmission in the motor cortex (Ziemann et al., 1996). Although acute ethanol exposure was found to dose-dependently facilitate SICI, reflecting potentiation of GABAergic neurotransmission within the motor cortex (Ziemann et al., 1995), no observable differences in SICI have been previously identified within alcohol dependent populations (Conte et al., 2008; Nardone et al., 2010).

In the present study, relative to controls, the AD group showed near significant reduced SICI (i.e. lack of inhibition) and significantly increased SICI intra-trial-variability. Therefore, the ability of SICI to identify AD-related cortical alterations from the motor cortex remains unclear. To our best knowledge, there have been no previous reports describing increased SICI intra-trial-variability in alcohol dependent groups. The lack of reported variation may have not been observed, or perhaps, not statistically addressed. Therefore, we advise that future studies, which assess SICI within addiction samples, should also evaluate intra-trial-variability; in a bid to improve our understanding of the SICI measure and its relevance within substance dependent populations.

4.3. Study limitations

Although our study suggests the presence of altered cortical excitability within an alcohol dependent sample, there are several limitations that need to be highlighted. Although we addressed for the following limitations statistically, significant group differences were observed in terms of reported depressive symptoms and WTAR scores. It is important to note that elevated depressive symptoms are common in addicted samples and we excluded any individuals who met clinical criteria for depression. Similarly, with the WTAR, although

there were significant differences between groups, relative to standardized assessment of the WTAR, the alcohol dependent group was well within the normal range of intellectual functioning. In terms of the TMS-EEG technique, although we suggest that inhibition of TMS-induced EEG activity is cortical in nature, other sources, such as the click sound delivered concomitantly with each pulse, may also stimulate the auditory cortex and associated areas. However, previous studies have reported that white noise at 95dB, as we employed, is sufficient to abolish any such effect (Daskalakis et al., 2008). Additionally, although we suggest that LICI is mediated through $GABA_B$ receptors (McDonnell et al., 2006), the potential involvement of additional neurotransmitters cannot be ruled out and requires further assessment. Finally, given the cross-sectional nature of the study, it is difficult to disentangle whether altered cortical excitability is a direct result of chronic alcohol exposure, relates to pre-existing vulnerabilities, or is a combination of both (Feil et al., 2010). Despite these limitations, our study is the first to demonstrate reduced GABAergic neurotransmission within the frontal regions of alcohol dependent individuals. While our study sample was small in size, and the results are therefore preliminary in nature, they provide an initial proof of concept, with further studies required to replicate and extend our findings.

4.4. Summary

We have demonstrated that TMS-EEG is a promising and novel approach to indexing cortical excitability within the frontal cortex of addicted populations. In particular, we found suppressed CI in the frontal cortex and increased cortical excitability within the motor cortex of alcohol dependent patients post-detoxification. Our finding of suppressed GABAergic receptor mediated neurotransmission (altered CI) within the frontal cortex is the first report of altered cortical excitability within the frontal cortex of AD patients. Further research is

required to confirm and extend our findings, as well as assessing the potential role of TMS-EEG in indexing the impact of pharmacotherapy on frontal function across a range of substance dependent populations.

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Table 1. Demographic and clinical data for patients with Alcohol Dependence (AD) and Control Subjects (CS).

	AD Mean (+/- sd)	CS Mean (+/- sd)	T-test/ Chi-Squared test	Significance
Age, years	40 (13)	31 (5)	p = 0.031	*
Gender ratio (M:F)	8:4	7:7	p = 0.453	n.s.
Daily Std Drinks	15.5 (5.20)	0	p = 0.000	**
SADQ	28.7 (11.4)	0.4 (0.8)	p = 0.000	**
OCDtotal	26.4 (9.0)	1.6 (2.2)	p = 0.000	**
WTAR	43.4 (3.0)	46.1 (1.7)	p = 0.010	*
BDI	12.9 (12.3)	1.9 (1.7)	p = 0.003	**

*p<0.05, **p<0.01
n.s. = not significant
SADQ = Severity of alcohol dependence questionnaire
OCDS = Obsessive Compulsive Drinking Scale
WTAR = Wechsler Test of Adult Reading
BDI = Beck Depression Inventory

Table 2. Mean rectified EEG activity following single and paired-pulse for patients with Alcohol Dependence (AD) and Control Subjects (CS).

Condition	*n* (AD)	AD Mean (+/- sd)	*n* (CS)	CS Mean (+/- sd)	T-test	Significance
Left single pulse	12	696.70 (593.90)	14	698.86 (331.98)	p = 0.984	n.s.
% Inhibition left DLPFC	12	-22.51 (70.89)	14	27.30 (32.89)	p = 0.003	**
Right single pulse	12	1208.38 (1377.53)	12	969.99 (708.23)	p = 0.847	n.s.
% Inhibition right DLPFC	12	-12.98 (73.68)	12	16.16 (49.17)	p = 0.006	**

**p<0.01
n.s. = not significant
DLPFC = dorsolateral prefrontal cortex

Table 3. Mean stimulus intensities and motor-evoked MEPS following single and paired-pulse stimulation for patients with Alcohol Dependence (AD) and Control Subjects (CS).

Condition	*n* (AD)	AD Mean (+/- sd)	*n* (CS)	CS Mean (+/- sd)	T-test	Significance
RMT	12	50.67 (6.47)	14	52.79 (8.20)	p = 0.006	**
AMT	12	44.08 (6.56)	14	44.64 (8.02)	p = 0.011	*
1mV measure	12	59.92 (7.73)	14	62.43 (10.07)	p = 0.04	*
CSP	11	117.05 (30.00)	14	113.29 (32.72)	p = 0.969	n.s.
SICI % of SP	12	50.65 (43.44)	14	33.95 (22.03)	p = 0.549	n.s.
SICI variability	12	0.95 (0.33)	14	0.73 (0.21)	p =0.048	*
ICF % of SP	12	97.73 (74.39)	14	142.78 (103.14)	p = 0.753	n.s.
ICF variability	12	0.64 (0.41)	14	0.55 (0.23)	p = 0.456	n.s.
1mV measure over cap	12	70.58 (5.35)	14	73.29 (7.82)	p = 0.026	*

*p<0.05, **p<0.01
n.s. = not significant

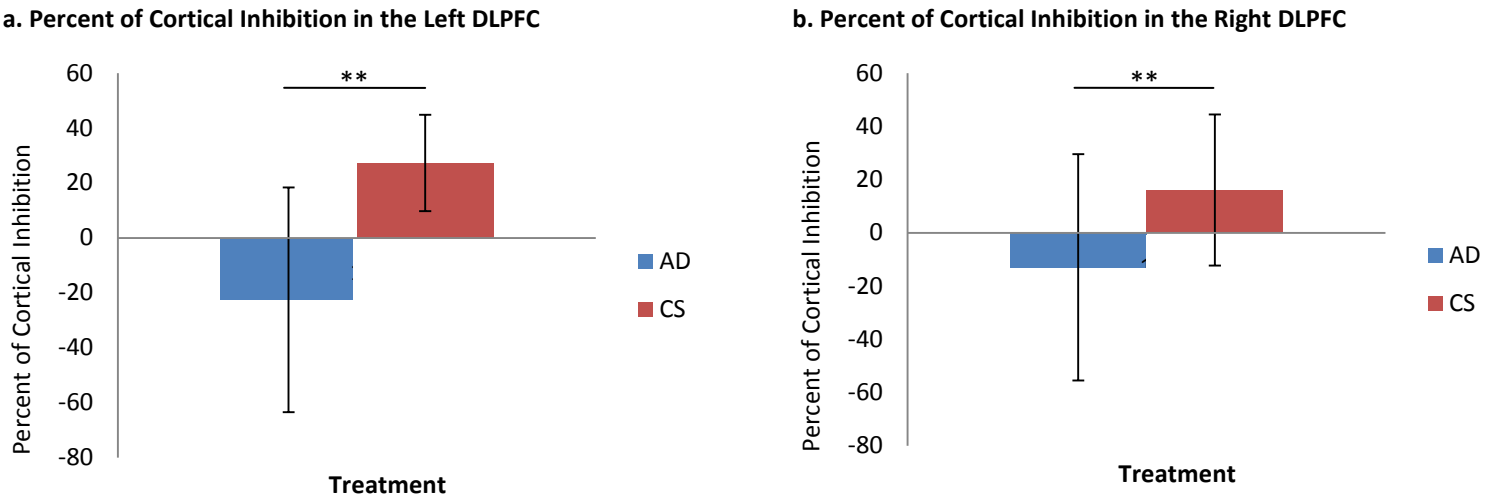

Figure 1. Group adjusted means of a) Percentage of long interval cortical inhibition (LICI) relative to single pulses in the left DLPFC (F3 electrode), b) Percentage of LICI relative to single pulses in the right DLPFC (F4 electrode), between patients with Alcohol Dependence (AD) patients and Control Subjects (CS).
Error bars are +/- 2 standard errors. ***p*<0.01

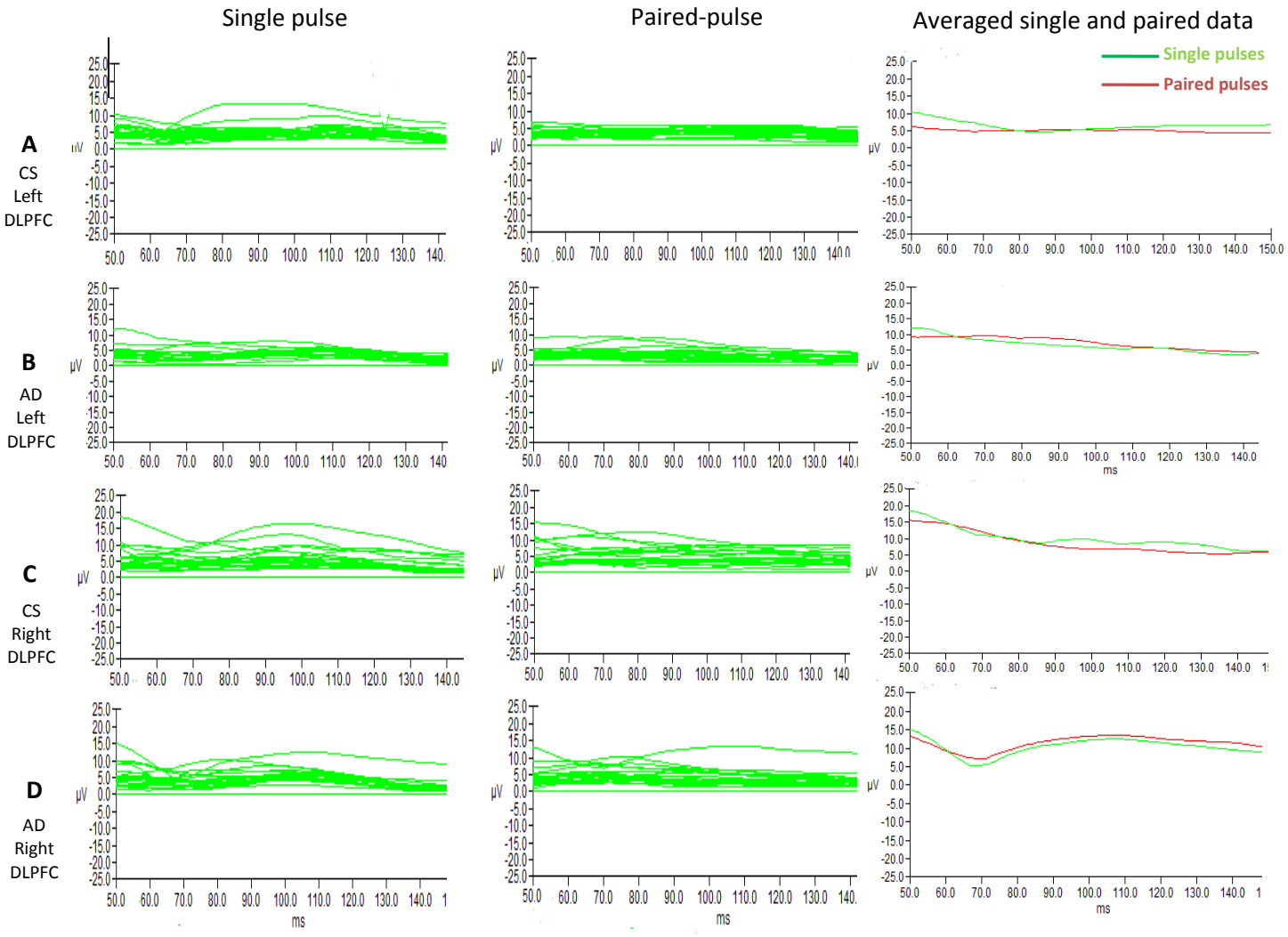

Figure 2. Rectified group mean EEG data between 50 -150ms in response to the long interval cortical inhibition (LICI) paradigm administered to the dorsolateral prefrontal cortex (DLPFC) across Control Subjects (CS) and patients with Alcohol Dependence (AD). (A) Butterfly plot of the mean sweeps evoked with single pulses, paired-pulses and averaged single and paired-pulse data in response to TMS administered to the left DLPFC in CS (F3 electrode), (B) Butterfly plot of the mean sweeps evoked with single pulses, paired-pulses and averaged single and paired-pulse data in response to TMS administered to the left DLPFC in AD group (F3 electrode), (C) Butterfly plot of the mean sweeps evoked with single pulses, paired-pulses and averaged single and paired-pulse data in response to TMS administered to the right DLPFC in CS (F4 electrode), (D) Butterfly plot of the mean sweeps evoked with single pulses, paired-pulses and averaged single and paired-pulse data in response to TMS administered to the right DLPFC in AD group (F4 electrode).

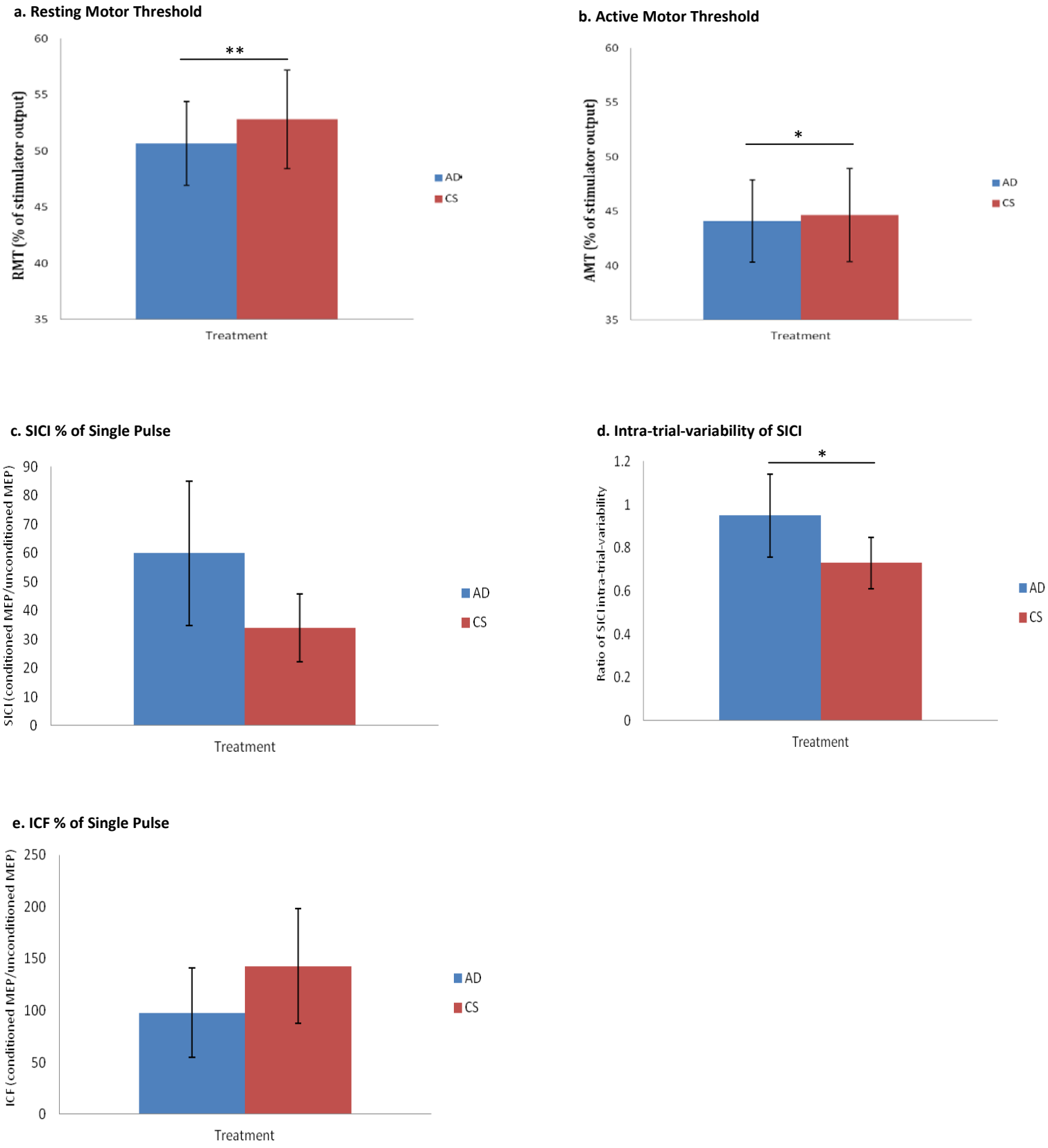

Figure 3. Group adjusted means of a) Resting Motor Threshold, b) Active Motor Threshold, c) Short intracortical inhibition (SICI) of a single pulse, d) Intra-trial-variability on SICI, e) Intracortical facilitation (ICF) of a single pulse, between patients with Alcohol Dependence (AD) and Control Subjects (CS).
Error bars are +/- 2 standard errors. *p<0.05, **p<0.01

CHAPTER ELEVEN

General Discussion

11.1. Summary of Findings

The ability to flexibly adjust one's thoughts and behaviours towards current and relevant objectives is a critical feature of the human cognitive system. Cognitive inhibition refers to the processes required to suppress prepotent yet irrelevant representations. Recent studies suggest that deficits in cognitive inhibition may be closely related to key symptoms of a number of psychiatric disorders. This proposition is supported by brain imaging studies which have shown that these cognitive processes rely on the integrity of the frontostriatal circuitry, the same circuitry disrupted across a number of psychiatric disorders. In the current thesis, the presence of these cognitive inhibitory deficits and the involvement of the frontostriatal circuitry were evaluated across two psychiatric disorders: Major Depressive Disorder (MDD) and Alcohol Dependence (AD). Although these two disorders are characterised by distinctly different clinical symptomotology, the cognitive inhibitory processes, and the involvement of the frontostriatal circuitry in the cognitive symptoms of these disorders, are nevertheless markedly similar. However, the involvement of these frontally-mediated cognitive inhibitory impairments across both depressive and alcohol dependent disorders is not well-established and requires further elucidation. Therefore, the current thesis aimed to (i) provide empirical evidence of cognitive inhibitory deficits across both psychiatric populations, (ii) utilize novel brain stimulation techniques to investigate the involvement of the frontostriatal circuitry, and (iii) explore how these cognitive deficits and frontostriatal dysfunction relate to clinical aspects of these disorders. When combined, the studies confirmed the presence of cognitive inhibitory impairment across both of these disorders, and identified the involvement of the frontostriatal circuitry. A number of equally important conclusions can be drawn from each of the individual studies presented in the

current thesis. Therefore, the next section will provide a brief overview of the conclusions specific to each of the studies. There follows a description of the general limitations which arise from the current research and a proposal of future research possibilities. To conclude the thesis, a concise summary of the thesis findings is presented.

Study One*:* *Cognitive deficits, attentional control and emotional biases in patients with severe depression.*

A critical feature of depressive disorders is the difficulty disengaging from negative stimuli and inhibiting negative thoughts. One of the main findings from Study One was the identification of both cognitive biases (specific to emotion-related stimuli) and cognitive deficits (generalised to neutral stimuli) within a depressive population. Moreover, these cognitive components were not interrelated, but rather appeared to exert an independent effect on the inhibitory processes underlying severe depression. These findings imply that the framework of cognitive inhibitory impairment within depressive disorders is more complex than previously conceptualised. Based on these results, it appears that screening and therapeutic strategies which address *both* of these components of cognitive dysregulation are required to improve our understanding and treatment of Major Depressive Disorder.

Study Two: *Effects of repetitive deep transcranial magnetic stimulation of the frontal regions on neurocognition in severely depressed patients.*

Once these two components of cognitive impairment were identified within the depressive sample, the next study utilized a novel brain stimulation technique to examine the involvement of the frontostriatal circuitry in these cognitive symptoms of depression. Traditionally, Deep Transcranial Magnetic Stimulation (deepTMS) is applied to the frontal regions of depressive patients as a treatment designed to attenuate clinical symptoms of depression; however, these frontal stimulations are also simultaneously targeting the neural

structures (i.e. fronto-limbic circuitry) which subserve cognitive function in depressive patients. Therefore, Study Two examined whether delivery of repetitive frontal deepTMS could improve cognitive function in depressive patients.

A number of important findings were documented in the second study of the thesis. To begin with, both a single session and long-term repetitive frontal deepTMS reduced cognitive impairment across the domains of attentional control and cognitive strategy within the depressive sample. This provided preliminary evidence for the suggestion that application of deepTMS to the fronto-limbic circuitry can improve both cognitive dysfunction and symptoms of depression. In addition, the data also revealed a strong relationship between the short-term and long-term deepTMS effects on cognitive function. Thus, leading to the speculation that a single session of high frequency repetitive frontal deepTMS may induce a short-lasting increase in the release of dopamine within the frontal circuitry, leading to the more immediate cognitive improvements. For long-term treatment, these repeated short-term increases in the release of dopamine within the fronto-limbic circuitry may bring about long-lasting alterations in neuroplasticity of the frontal regions, which could subsequently result in the long-term improvement of cognitive function. Another important finding was the observation that a number of cognitive symptoms of depression were predictive of treatment efficacy and clinical response. In the past there have been very limited findings regarding clinical predictors of repetitive TMS treatment response in depressive disorders. Therefore, these findings provided preliminary evidence of cognitive predictors of clinical response to deepTMS, suggestive of an intricate relationship between cognitive impairment, depressive symptoms and treatment response.

In conclusion, Study Two demonstrated that repetitive deepTMS is a promising tool for reducing cognitive impairments in depressive disorders, and identified the involvement of the fronto-limbic circuitry in the cognitive symptoms of depression. Finally, it showed that

cognitive factors of depression were predictive of clinical response to deepTMS treatment. These findings therefore highlight the importance of future therapeutic strategies targeting these frontally-mediated cognitive features of depression in improving depressive symptoms.

Study Three: *Frontally-mediated cognitive deficits, craving and cognitive recovery among alcohol dependent individuals following detoxification.*

A key feature of AD is the drinker's impaired ability to regulate the compulsive urge to consume alcohol regardless of aversive consequences. Recently, addiction theorists have suggested that the inability to regulate these compulsive urges may relate to an underlying cognitive inhibitory deficit. Therefore, Study Three examined whether cognitive inhibitory deficits were present within an alcohol dependent population post-detoxification. Consistent with the clinical symptoms of regulatory deficits in AD, empirical evidence of general cognitive impairments were identified across the domains of inhibition and attentional control. The study then aimed to further characterize these cognitive impairments by exploring whether these cognitive impairments are related to measures of craving, and furthermore, whether length of abstinence was predictive of cognitive recovery. Certain aspects of cognitive impairment were found to be associated with clinical measures of craving and years of alcohol consumption. However, the duration of abstinence (within the range of 2 years) had no significant influence on cognitive recovery, indicating that these cognitive inhibitory deficits may endure well beyond abstinence. Therefore, the findings from Study Three emphasize the need for therapeutic strategies to target these inhibitory impairments in effectively treating symptoms of alcohol dependence. In addition, these findings suggest that the relationship between cognitive deficits and cognitive correlates of craving should be more closely examined. Finally, the results highlight the importance of addressing these regulatory deficits repeatedly: at screening, throughout treatment, and well beyond abstinence.

Study Four: *Cortical Inhibition in Motor and Frontal Regions in Alcohol Dependence: A TMS-EEG study.*

Once cognitive inhibitory deficits were identified within the alcohol dependent sample, the next objective was to examine alterations within the frontostriatal circuitry in alcohol dependent patients post-detoxification. Preclinical and neuromolecular studies suggest that alterations to the balance of cortical excitability within the frontal cortex play a critical role in the pathophysiology of AD. However, until recently, it was technically difficult to non-invasively assess these alterations within the addiction-related structures of the human brain. The newly developed combined TMS-electroencephalography (TMS-EEG) technique is capable of directly recording cortical excitability from the prefrontal cortex in a non-invasive fashion.

Study Four was a particularly novel and exciting study as it provided the first direct index of cortical inhibition within the frontal regions of alcohol dependent patients post-detoxification. In the study, the combined TMS-EEG technique was applied to the frontal regions of alcohol dependent subjects and cortical inhibition was measured directly from the frontal circuitry. To index cortical inhibition, long interval cortical inhibition (LICI), a paired-pulse TMS paradigm, was applied to the frontal cortex of alcohol dependent participants. The AD group exhibited reduced LICI in bilateral frontal cortices relative to the healthy controls. A number of studies have indicated that LICI reflects activity at the $GABA_B$ receptor. Therefore, Study Four provides the first demonstration of altered $GABA_B$ receptor mediated inhibitory neurotransmission within the prefrontal cortex of AD participants. These results have a number of important implications. Firstly, they provide clinical support for neuromolecular models of AD that suggest chronic alcohol use disrupts the delicate balance of cortical excitability. Secondly, TMS-EEG was delivered to specifically measure cortical alterations within the frontal circuitry, as neural alterations within these frontal regions are consistently

implicated in the development and persistence of dependence. Therefore, this study is the first to provide direct evidence of altered excitability within the frontal cortex of alcohol dependent patients post-detoxification at a neurotransmitter systems level. Thirdly, these findings demonstrate that TMS-EEG is a promising research tool for indexing cortical excitability within the frontal cortex of alcohol dependent populations.

The study was also designed to verify previous addiction studies and investigate whether AD is related to changes in excitability within the motor cortex. Although altered cortical excitability was observed in the motor cortex of patients with AD, our measurements of motor inhibition/facilitation were largely inconclusive. As such, the utility of using these motor measurements to provide an accurate index of cortical alterations specific to AD requires further elucidation.

TMS-EEG is clearly emerging as a promising technique to directly index cortical alterations within the frontal cortex of addicted populations. Study Four provided the first direct evidence of reduced cortical inhibition that is specific to the frontal cortex of patients with AD. Although these findings are preliminary, they provide critical pathophysiological evidence of altered cortical excitability within the frontal cortex of alcohol dependent patients. The study also demonstrated altered cortical excitability in the motor cortex of patients with AD; however, the clinical efficacy of using the motor cortex to index cortical alterations in alcohol dependent patients remains unclear.

11.1.1. Summary of studies

The studies in the current thesis present a number of significant findings which relate to key features of depressive and alcohol dependent disorders. In terms of depression, the first two studies demonstrated the presence of cognitive inhibitory deficits in a depressive population and provided evidence of the involvement of the frontostriatal circuitry in the cognitive

symptoms of depression. With regards to AD, the latter two studies of the thesis demonstrated the enduring nature of these cognitive inhibitory deficits within an alcohol dependent post-detoxification population, and administered TMS-EEG to provide the first index of altered cortical inhibition within the frontal cortex of the alcohol dependent patients. These findings suggest that a critical feature of both disorders is the impaired ability to inhibit and regulate control of basic behaviours and thoughts. In addition, results from these studies strongly implicate the role of the frontostriatal circuitry in these cognitive inhibitory deficits. Therefore, there appears to be a significant overlap in the role of these frontal inhibitory circuits across both disorders. These findings are consistent with the high degree of co-morbidity between AD and MDD in clinical populations (Gilman and Abraham, 2001; Grant and Harford, 1995) and the neurobiological similarities (i.e. the disruption of the fronto-limbic circuitry) between the two disorders.

However, despite these similarities, there are clear differences in how these cognitive symptoms translate into clinical symptoms across the two disorders. Patients with MDD show difficulty disengaging from negative representations and inhibiting negative cognitions, whereas patients with AD present with an impaired ability to inhibit the compulsive urge to consume alcohol despite aversive consequences. Although there is currently very little literature regarding these differences, the following section suggests a number of potential factors which could account for why these frontally-mediated inhibitory impairments translate into significantly different clinical symptoms across the two disorders.

It is possible that the expressions of different clinical symptoms are influenced by the coupling of these frontal inhibitory impairments with disruptions across other separate, yet interconnected, brain regions. For example, in depressive disorders, in addition to the implicated role of the frontostriatal circuitry, there is a large research focus on disruption within the limbic-cortical circuitry (Goldapple et al., 2004; Mayberg, 1997, 2002); the

emotion-regulatory circuitry which includes the hypothalamus, amygdala, hippocampus and the limbic cortex. As such, it seems quite plausible that disruption of both the frontal inhibitory circuitry and the limbic emotion-related circuitry could translate into a difficulty inhibiting emotion-related stimuli and disengaging from negative thoughts. Whereas for alcohol dependent disorders, traditionally addiction research focused on the mesolimbic dopaminergic pathways (Hyman et al., 2006); the neural reward system which includes the ventral tegmental area, nucleus accumbens and the amygdala. Newer addiction models have expanded on this circuitry to include the separate, yet interconnected limbic system and prefrontal cortex. Therefore, it is possible that disruption of the frontal inhibitory circuitry and the mesolimbic 'reward' pathways could translate into uncontrollable cravings for alcohol and dysregulated control over the compulsive desire to drink despite aversive consequences. It is important to note though, that both of these brain structures (i.e. mesocorticolimbic and the limbic-cortical circuitry) are implicated across depressive and alcohol dependent disorders; however, the level of disruption and the involvement of these regions vary across the two disorders.

In support of this concept, a recent review paper examined evidence from a number of structural and functional neuroimaging studies and identified significant neuropathological differences between depressive and alcohol dependent populations (Miguel-Hidalgo and Rajkowska, 2003). Neurophysiological differences between these two disorders has also been identified in prefrontal cell pathology (Miguel-Hidalgo and Rajkowska, 2003) and in the expression of glial and glutamatergic markers (Miguel-Hidalgo et al., 2010). Therefore, although the frontal cortex is deeply involved in both AD and MDD, there appears to be a number of pathophysiological differences between the disorders at the functional, structural and cellular circuit level.

Another possible contributing factor to these differences in expression of clinical symptoms is that the prevalence rates of these two psychiatric disorders differ significantly by gender. Women are far more likely to meet the diagnostic criteria for mood disorders, whereas men are more likely to meet diagnostic criteria for substance use disorders (Kessler et al., 2005; Kessler et al., 1997). It is possible that gender-based expression of the same underlying vulnerability (i.e. cognitive inhibitory deficits) may translate into a significantly different clinical symptomatology.

These are only a select number of many possible factors for the difference in the clinical expression of inhibitory deficits between the two disorders. To date, limited research has been dedicated to the examination of pathophysiological and demographic differences between depressive and alcohol dependent disorders. These possible factors however, highlight the need for further research into the mechanisms underlying the different expression of cognitive inhibitory deficits across various psychiatric populations. However, even though these cognitive impairments translate into different clinical symptoms across the two disorders; the presence of these inhibitory deficits appears to be involved in key symptoms of both disorders.

Therefore, the major research aims of the current thesis were achieved. These studies provided empirical evidence of cognitive inhibitory deficits, and the involvement of the frontostriatal circuitry, across both depressive and alcohol dependent disorders. Thus, the findings from the current thesis provided further insight into cognitive features of these disorders and contributed meaningfully to the current pathophysiological models of AD and MDD. It is hoped that these findings will lead to the development of treatment models which are designed to address these frontally-mediated cognitive deficits, and which may ultimately result in improved treatment efficacy across both disorders.

11.2. General limitations

A number of general limitations need to be considered. With regards to AD, the general limitations relating to substance dependence, cognitive deficits, and frontostriatal dysfunction are explored extensively in Chapter Two over the pages 270-272 of the published review titled, *Addiction, compulsive drug seeking, and the role of frontostriatal mechanisms in regulating inhibitory control*. To avoid repetition, the general limitations relating to AD will not be re-stated here. In addition, the limitations which apply specifically to each of the studies are explored within the experimental chapters, and again will not be repeated here. Instead, the current section will focus on the general limitations associated with experimental research in populations with MDD.

11.2.1. General limitations: Major Depressive Disorder

- **Motivational problems/psychomotor deficits:** An important consideration for the study of cognitive function in depressive populations is the difficulty establishing to what extent the cognitive deficits are caused by motivational problems and psychomotor deficits. Previous studies have suggested that patients with severe depression may have lacked the motivation (Austin et al., 2001; Ravnkilde et al., 2002) and/or may present with psychomotor impairments (Brébion et al., 1997), which could negatively impact on their ability to perform cognitive tasks. The current thesis addressed this potential limitation by measuring the psychomotor speed on the Sustained Attention to Response Task, screening for both motivational problems and psychomotor deficits. In the current thesis, no significant differences in psychomotor speed were identified between the depressive and healthy control groups. Therefore, the MDD group did not appear to exhibit a lack of motivation to complete task requirements, or any evidence of psychomotor deficits. However, it is important for future studies to further explore

the role of motivation and psychomotor deficits in studies of cognitive performance in MDD populations.

- **Definition of Treatment Resistant Depression (TRD):** Despite significant advances in the field of depressive disorders, the diagnosis of treatment resistant depression remains poorly defined (Malhi et al., 2005) and there is no clear consensus regarding the criteria for defining TRD in experimental research trials (Fava, 2003; Souery et al., 2007). In a clinical evaluation, it is common practice for trained psychiatrists to classify as TRD patients who do not respond to at least two anti-depressant medications of appropriate dose and duration in the current episode. This was the clinical diagnosis used for patients recruited in the current thesis. However, given the contentious nature of the definition, in the first study of the thesis (as required by the journal) the participants were classified as TRD but referred to as severely depressed, while in the second study, participants were described as severely depressed (again, according to the journal requirements), rather than classified as TRD.

- **Generalising results across depressive populations:** Another important consideration is that the first two studies of the thesis were conducted within severely depressed patients (see above); replication within a broader depressive sample is required before generalizing the findings to more mildly depressed patients.

- **Anti-depressant medication:** A consistent difficulty across many MDD studies is the high prevalence of anti-depressant medication (Amado-Boccara et al., 1995), which may influence cognitive function. In the current study, although the patients were clinically diagnosed as TRD, a number of patients were prescribed anti-depressant medication which was maintained through the experimental studies.

Unfortunately, the patients in the trial were considered too unwell to remove the anti-depressant medications from their system. To address this limitation, statistical analyses were conducted to assess the potential influence of the anti-depressant drugs on cognitive symptoms of depression and treatment response to brain stimulation techniques. As noted in the experimental chapters, there was no observed effect of the anti-depressant medication on cognition or treatment response. Thus, the influence of the anti-depressants on patients' cognitive function appears to be minimal. However, despite the lack of significant effect observed in the current thesis, the potential effect of these anti-depressant medications on cognitive function warrants serious consideration when reviewing studies relating to cognitive function within a MDD sample.

- **Origins of the cognitive impairment:** Finally, it is difficult to disentangle whether these frontally-mediated cognitive impairments result from a pre-existing vulnerability, or perhaps, depressive disorders lead to or intensify these cognitive impairments. Further longitudinal studies are required to elucidate this chicken-and-egg relationship.

11.3. Future Directions

Despite these limitations, the studies identified a number of unique and important findings regarding cognitive impairment and related frontostriatal dysfunction across both disorders. The following section outlines a number of potential possibilities for future research and treatment.

11.3.1. Future directions: Major Depressive Disorder

- **Delineating cognitive biases and cognitive deficits:** The role of cognitive inhibitory impairment in depressive disorders is gaining increased recognition; however, to date,

there is no clear understanding of the exact cognitive impairments associated with depressive disorders. In the current thesis, the research was focused on providing an improved characterisation of cognitive inhibitory impairments which are present within depressive disorders. Both cognitive biases and cognitive deficits were observed within the depressive sample, and these inhibitory impairments were found to exert an independent effect within depressive disorders. High frequency deepTMS applied to the frontal cortex of the MDD patients was capable of improving a number of cognitive deficits, but had no significant effect on cognitive biases. These preliminary findings provide support for the delineation between cognitive deficits and cognitive biases in depressive disorders, and further suggest that these separate components of cognitive impairment may engage different brain circuitry. Future studies are required to utilize neuroimaging studies to further delineate the similarities and differences in the brain circuitry underlying these two components of cognitive impairment, and whether there are noticeable alterations within the fronto-limbic circuitry following deepTMS. Future treatment strategies which address both the components of cognitive inhibitory impairment, and the related frontostriatal dysfunction, may lead to improved clinical outcome.

- **Repetitive TMS as a cognitive enhancer in psychiatric disorders:** To date, only a limited number of studies have primarily focused on the cognitive enhancing potential of repetitive TMS (rTMS) techniques in psychiatric disorders (Demirtas-Tatlidede et al., 2013). A small number of recent studies (reviewed in Chapter 5) combined with the results from the deepTMS study (i.e. Study Two) provide initial empirical support regarding TMS-induced cognitive improvement within the context of depressive disorders. However, the precise ability of TMS to improve different aspects of cognitive function remains unclear (Moreines et al., 2011). In addition, each of these

preliminary studies used considerably different approaches, including the administration of assorted cognitive tasks, varied diagnoses within the patient groups and markedly different stimulation parameters. Future studies with larger sample sizes are required to verify these promising results. Furthermore, the employment of more consistent experimental methodology is required before reaching definitive conclusions regarding the neurocognitive benefits of administering rTMS to the frontal cortex of depressive patients.

- **Cognitive variables predicting response to repetitive TMS treatment:** Recent studies have examined whether certain features of depressive syndromes can predict a clinical response to rTMS (reviewed by Padberg and George, 2009). An early review of the factors modifying the efficacy of rTMS in the treatment of depression identified no significant outcome predictors (Herrmann and Ebmeier, 2006). Following this review, further studies which utilized the figure 8-coil demonstrated that younger patients (Fregni et al., 2006) with less treatment resistance (Brakemeier et al., 2008; Brakemeier et al., 2007; Fregni et al., 2006), shorter duration of depressive episodes (Brakemeier et al., 2007) and increased sleep disturbances (Brakemeier et al., 2007) were more responsive to rTMS treatment. Overall, it appears that lower level of treatment resistance is the most robust predictor of treatment response to rTMS within a depressive sample. In the current thesis however, a number of baseline cognitive factors were found to predict response to repetitive deepTMS. In addition, deepTMS-induced cognitive improvements were also related to clinical response. These findings provide preliminary evidence of cognitive predictors of treatment response to repetitive deepTMS, and moreover, highlight the intricate relationship between these cognitive predictors, depressive symptoms and treatment response. Future studies should explore the predictive value of cognitive features of depression within a

deepTMS clinical trial, and examine whether these cognitive predictors are applicable within the standard (i.e. figure 8-coil) rTMS clinical trials for depression. Reliable predictors of TMS treatment response will allow improved screening of the individuals which are most suitable for rTMS treatment, and could indicate which patients are more suitable for different approaches to treatment. In addition, future studies should employ a longitudinal design to evaluate whether these cognitive predictors are related to long-term treatment success.

11.3.2. Future directions: Alcohol dependence

- **Long-term cognitive inhibitory deficits in AD:** Literature regarding the relationship between length of sobriety and subsequent improvement in neurocognitive performance remains limited (Stavro et al., 2012). More specifically, there is a dearth of studies regarding long-term abstinence and cognitive inhibitory deficits in alcohol dependent patients. In the current thesis, cognitive inhibitory function within alcohol dependent participants was assessed within a range of 2 years since detoxification. No evidence of a relationship between the length of abstinence and cognitive recovery was identified; this possibly suggests enduring cognitive inhibitory deficits. These findings highlight the importance of further and more extensive longitudinal studies to assess whether cognitive inhibitory recovery is associated with length of abstinence. Moreover, further studies are required to ascertain whether the persistence of these cognitive inhibitory deficits is predictive of increased cravings and relapse. Improved screening of these cognitive inhibitory deficits could contribute to the treatment of alcohol dependence, and potentially predict a vulnerability to relapse.
- **Delicate balance of frontal cortical excitability in alcohol dependence:** Alcohol has widespread effects on multiple neurotransmitter systems within the brain (Addolorato et al., 2012) and plays a critical role in disrupting the delicate balance

between inhibitory and excitatory neurotransmitters within the mesocorticolimbic circuitry (De Witte, 1996; Morikawa, 2010; Spanagel, 2009). Neuromolecular models suggest that chronic alcohol use leads to the inhibition of GABAergic inhibitory neurotransmission (Addolorato et al., 2012; Enoch, 2008; Filip and Frankowska, 2008; Lobo and Harris, 2008), and the potentiation of glutamatergic excitatory neurotransmission (Duncan and Lawrence, 2012; Gass and Olive, 2008; Olive et al., 2012; Tzschentke and Schmidt, 2003). In the current thesis, the novel combined TMS-EEG technique applied a paired pulse TMS paradigm known as long interval cortical inhibition (LICI) (Valls-Solé et al., 1992) to index cortical inhibition in the prefrontal cortex of alcohol dependent patients. A number of recent studies suggest that LICI represents activity at the $GABA_B$ receptor (McDonnell et al., 2006; Sanger et al., 2001), and furthermore, a strong relationship between the LICI measured with electromyography and EEG itself has been identified (Farzan et al., 2010); therefore, this study allowed researchers for the first time to directly examine the possibility of altered GABAergic neurotransmission within the prefrontal cortex of alcohol dependent patients.

To date however, LICI is the only TMS inhibitory paradigm which has been examined and verified when delivering the combined TMS-EEG technique to the frontal regions of the human brain. A number of further inhibitory TMS paradigms could potentially be applied within a frontal TMS-EEG protocol (for a review, see Feil and Zangen, 2010). Such possible TMS inhibitory paradigms include: Long-interval intracortical facilitation which is proposed to be mediated by glutamatergic mechanisms, and short-interval intracortical inhibition is thought to be associated with neurotransmission of the $GABA_A$ receptor and regulation of $GABA_A$ by the neuromodulating neurotransmitters in the cortex. Short-interval intracortical

facilitation is possibly related to alterations of both GABA and glutamate. Therefore, future studies should examine the utility of expanding the use of LICI and establish the value of using further TMS inhibitory paradigms to index altered cortical excitability within the frontal cortex. This could be achieved by examining whether the TMS-paradigm output measured with electromyography is comparable to the conventional EEG-measured output. This would allow researchers to expand on the findings of the TMS-EEG study presented here, and provide a more detailed characterization and profile of altered cortical excitability within the frontal cortex of alcohol dependent patients, specific to alterations both in GABAergic and glutamatergic neurotransmission.

- **TMS-EEG and pharmacotherapy for Alcohol Dependence:** A number of treatment agents for alcohol dependence are currently designed to target alterations in either GABAergic of glutamatergic neurotransmission; however, these pharmacotherapies are considered only moderately successful (Addolorato et al., 2012; Tambour and Quertemont, 2007). For example, direct $GABA_B$ agonists, such as, baclofen (Addolorato et al., 2011; Addolorato et al., 2007; Bucknam, 2007; Colombo et al., 2004; Flannery et al., 2004; Leggio et al., 2010) or gabapentin (Anton et al., 2009; Anton et al., 2011; Bonnet et al., 1999; Bozikas et al., 2002; Furieri and Nakamura-Palacios, 2007) act by potentiating $GABA_B$ receptors on the cell body of dopamine neurons. These $GABA_B$ agonists are designed to attenuate the symptoms of alcohol dependence by reinstating the delicate balance of cortical excitability within the alcohol dependent brain (Addolorato et al., 2012). These pharmacotherapies have been primarily devised according to neuromolecular models of alcohol addiction, rather than clinical studies of altered cortical excitability in the brain of alcohol dependent patients. The findings from TMS-EEG study presented in the current thesis

provide confirmation of these neuromolecular models by identifying the role of suppressed GABAergic activity within a clinical alcohol dependent population. Building on these findings, future pharmacological studies could utilize the TMS-EEG technique to do the following: i) Provide a direct index of how these $GABA_B$ agonists reinstate the balance of cortical excitability within the frontal cortex, (ii) examine whether application of these $GABA_B$ agonists are indeed targeting the optimal neurotransmitter systems, and (iii) assess whether these changes in cortical activity are related to the alleviation of symptoms of alcohol dependence. A better understanding of the mechanisms underlying these pharmacotherapies could lead to improved treatment options.

- **Assessment of cortical inhibition across addictive populations:** Drug addiction is consistently described as a persistent state in which there is a reduced capacity to regulate compulsive drug seeking, regardless of whether it involves risk of aversive consequences. In Chapter Two of the current thesis, the article titled, *Addiction, compulsive drug seeking, and the role of frontostriatal mechanisms in regulating inhibitory control*, describes the pathophysiology of addiction and the proposed involvement of the frontal regions across these various addictive populations (Feil et al., 2010). A small number of exploratory studies have begun to examine whether alterations in cortical excitability are present across a range of addictive populations; however, these cortical alterations were usually measured from the motor or occipital cortex. The relevance of cortical alterations within these peripheral regions within addicted samples is unclear. TMS-EEG, as demonstrated in the current thesis, is emerging as a promising and powerful technique to directly index cortical alterations within the frontal cortex of a range of addicted populations. Therefore, future addiction studies could greatly benefit from applying the same TMS inhibitory

paradigms to the frontal cortex of a range of addictive populations in providing an improved index of the pathophysiology of the disorders, and potentially improving addiction treatments.

11.3.3. Future directions: Frontally-mediated psychiatric disorders

- **Co-morbidity of depressive symptoms and addiction:** The incidence of co-morbidity of depressive disorders and alcohol dependence is remarkably high (Gilman and Abraham, 2001; Kessler et al., 1997; Swendsen and Merikangas, 2000) and is an immense challenge for the clinician treating the patient. There is no consensus in the literature whether to treat depression and alcohol dependence separately (and which diagnosis to treat first), or rather, to address the co-occurance of both, in most effectively treating patients with a dual diagnosis. A large reason for the lack of consensus is that the exact mechanisms underlying the association between depression and alcohol dependence are not well-established. It remains largely unknown whether there exists (i) a causal relationship, (ii) a shared etiology underlying these disorders, or perhaps (iii) a combination of both. In the current thesis, it was proposed that although depressive and alcohol dependent patients present with clinically diverse symptoms, the cognitive inhibitory deficits and the frontostriatal circuitries involved in the cognitive features of these disorders are remarkably similar. Although the studies in the thesis excluded patients with dual diagnosis, it would be beneficial for future studies to examine these shared cognitive inhibitory deficits and the involvement of the frontostriatal circuitry in patients with dual diagnoses. As potentially there exists a shared cognitive deficit which recruits the frontal circuitry in both disorders, it is possible that by adequately addressing these generalized frontally-mediated cognitive inhibitory deficits, there could be improvements in the symptoms associated with both depression and alcohol dependence.

- **DeepTMS and cognitive impairment:** In the current thesis, the cognitive benefits of deepTMS were examined and demonstrated within a depressive population. It is hoped that these findings will act as a precursor to future studies evaluating the efficacy of repetitive TMS techniques in ameliorating cognitive and attentional symptoms across a range of psychiatric disorders. Furthermore, it is possible that somewhere down the track, further research into the beneficial cognitive effects of repetitive TMS could lead to the development of TMS-treatments for other specific disorders which are characterized by cognitive deficits and attentional impairments (such as attention deficit disorder).

11.4. Concluding Statement

Both MDD and AD are devastating disorders which are highly prevalent in our society. Despite extensive research into these debilitating disorders, many of the cognitive and neurobiological aspects of these disorders remain largely unknown. The research conducted in the current thesis sought to expand on previous research, and more accurately to characterize cognitive features of MDD and AD, and to examine the involvement of the frontostriatal circuitry in their pathophysiology. With regards to MDD, the present thesis provided evidence of significant cognitive inhibitory deficits within the depressive population, and through the delivery of the newly developed deepTMS technique, the frontostriatal circuitry was implicated in these cognitive symptoms of depression. In terms of AD, the current thesis further characterized the enduring nature of cognitive inhibitory deficits within an alcohol dependent post-detoxification population, and through administration of the novel TMS-EEG technique, provided the first measure of altered cortical inhibition within the frontal cortex of alcohol dependent patients. The series of studies provided empirical support for the proposition that frontally-mediated cognitive inhibitory deficits are indeed closely related to key symptoms of depressive and alcohol

dependent disorders. In addition, the studies also provided promising support for the utility of brain stimulation techniques in non-invasively identifying alterations within the frontal region of these patient groups. It is hoped that such research will contribute to an improved understanding of the cognitive features of these disorders, and furthermore, will assist in expanding the pathophysiological models of depression and alcohol dependence.

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Appendix I

Chapter Manuscript

Research applications: Addiction

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1. Introduction

Drug dependence is a devastating and chronically relapsing disorder. Repetitive drug administration can lead to the development of psychological addiction; characterized by a diminished ability to regulate the compulsive desire to consume drugs, regardless of the risk of negative consequences (Hyman and Malenka, 2001; Hyman et al., 2006). Neurobiological models of addiction propose that the acute rewarding and reinforcing effects of addictive drugs are associated with dopaminergic increases in the mesocorticolimbic circuitry (Diana, 2011; Everitt et al., 2008; Feltenstein and See, 2008; Koob and Nestler, 1997). Chronic drug administration usurps this reward-related circuitry, inducing long-term neuroadaptations in dopaminergic and glutamatergic transmission and alterations in cortical excitability (Hyman et al., 2006; Kalivas et al., 2009; Kauer and Malenka, 2007; Pulvirenti and Diana, 2001; Robinson and Berridge, 2003; Wolf et al., 2004).

Electromagnetic brain stimulation techniques, such as Transcranial Magnetic Stimulation (TMS) and Transcranial Direct Current Stimulation (tDCS), are capable of safely and non-invasively modulating neural activity within specific brain regions (Hallett, 2000, 2007; Polanía et al., 2011; Wagner et al., 2007). In the past, it was extremely difficult to index the altered cortical excitability associated with exposure to addictive drugs. Recent studies have employed TMS as an investigative tool to measure altered cortical excitability in individuals exposed to drugs of abuse. Thus, providing an initial characterization of the effects of repeated drug use on cortical neurotransmission (Barr et al., 2008; Feil and Zangen, 2010). Additionally, emerging studies have begun to assess the therapeutic potential of administering neuromodulatory brain stimulation techniques, such as repetitive TMS (rTMS) and tDCS, in reducing craving levels and addiction-related behaviours. Therefore, the current chapter is focused on the research application of brain stimulation techniques; firstly, by indexing variations in cortical excitability associated with exposure to drugs of abuse, and secondly, by assessing the therapeutic benefits of administering repeated brain stimulation in attenuating addiction-related behaviours.

The first section of this chapter briefly describes the neurobiology of addiction and the potential effects of brain stimulation techniques on drug seeking behaviours. The following section is divided according to different drugs of abuse, and explores the potential of brain stimulation techniques in the study and treatment of addiction. It provides a review of the emerging studies which assess the application of TMS-inhibitory paradigms to index cortical excitability associated with exposure to addictive drugs. Additionally, the studies which examine the potential efficacy of rTMS or tDCS as a treatment for exposure to these drugs, are evaluated. In the last section, future research directions for the use of brain stimulation techniques in addictive disorders are discussed.

2.1. Brief overview of addiction

Occasional drug use can induce physiological, neurochemical and behavioural changes, and eventually develop to chronic drug use and dependence (Koob and Volkow, 2010; Robinson and Berridge, 2003). Despite extensive studies of molecular and cellular factors involved in drug administration, and the development of drug dependence (Everitt et al., 2008; Feltenstein and See, 2008; Kalivas et al., 2009; Lingford-Hughes et al., 2003; Wise, 1996), there are very few studies characterizing the effect of chronic drug use on electrophysiological changes in the local and systems levels. This highlights the importance of further studies exploring the alterations in neural transmission associated with acute drug exposure, excitability-related neuroadaptations induced by repeated drug use, and the subsequent development of dependence.

Neurobiological models of addiction have established an association between the acute reinforcing effects of drug administration and dopaminergic neurotransmission in the mesocorticolimbic circuitry (Gardner, 2011; Gass and Olive, 2008; Koob and Nestler, 1997; Taber et al., 2012; Wise, 1996). In this circuitry, dopaminergic projections originate in the ventral tegmental area (VTA), and project to limbic structures (i.e. the mesolimbic pathway) and cortical areas (i.e. the mesocortical pathway) (Diana, 2011; Feltenstein and See, 2008; Spanagel and Weiss, 1999). Stimulant drugs, such as amphetamines and cocaine (Baicy and London, 2007; Chang et al., 2007; Ersche and Sahakian,

2007; Kalivas and Hu, 2006), directly increase extracellular dopamine levels by inhibiting dopamine reuptake, or promoting dopamine release within the reward circuitry, while other drugs, such as nicotine, alcohol and cannabis (Koob et al., 1998; Maldonado et al., 2011; Markou, 2008; Tambour and Quertemont, 2007), work indirectly by affecting neurons (GABAergic or glutamatergic) that induce increased dopaminergic neurotransmission through their effect on intervening receptor systems (Wise, 1996). In addition to the key role of dopamine (Diana, 2011), drugs of abuse affect the delicate balance between principal neurotransmitters, γ-aminobutyric acid (GABA), and glutamate (GLU),thereby altering cortical excitability by inducing enhanced glutamate release and glutamate receptor activity (in dopaminergic cells) (Gass and Olive, 2008; Kalivas et al., 2009; Pulvirenti and Diana, 2001; Tzschentke and Schmidt, 2003; Uys and Reissner, 2011; Wolf et al., 2004), or by modulating GABA neurotransmission (Addolorato et al., 2012; Enoch, 2008; Lobo and Harris, 2008).

Repeated drug administration has been proposed to usurp the reward circuitry, inducing long-term neuroadaptations in the mesocorticolimbic circuitry, including the nucleus accumbens (ventral striatum), ventral tegmental area, amygdala and prefrontal cortex (Di Chiara et al., 2004; Feil et al., 2010; Goldstein and Volkow, 2002; Jentsch and Taylor, 1999; Lubman et al., 2004; Robbins et al., 2007; Van Den Oever et al., 2012; Van den Oever et al., 2010). Additionally, these neuradaptations and alterations in cortical excitability are associated with enhanced craving levels, persistent drug seeking, and an increased vulnerability to relapse (Franken, 2003; Franken et al., 2005). Therefore, to develop more effective addiction treatments, it is important to understand the acute effects of drug exposure, which are followed by excitability changes in circuitries involved in the transition to compulsive drug seeking.

Recently, neurobiological studies of addiction have utilized brain stimulation techniques to non-invasively index the effects of acute or repeated drug administration on cortical excitability. Additionally, recent exploratory studies have examined whether the prolonged effects of repeated brain stimulation can have clinical benefits in reducing addiction-related behaviours. The following

section provides a basic overview of the brain stimulation techniques, and their potential research application within the field of addiction medicine.

2.2. Addiction and Brain Stimulation

Electromagnetic brain stimulation can externally modulate cortical excitability within specific brain regions (Hallett, 2000; Rossini and Rossi, 2007; Stagg and Nitsche, 2011). As such, emerging studies are utilizing these techniques to investigate altered cortical excitability in individuals exposed to addictive drugs . Additionally, the potential therapeutic benefits of brain stimulation in reducing drug craving and addiction-related behaviours are being examined. The current chapter is focused on two specific non-surgical brain stimulation techniques: Transcranial magnetic stimulation (TMS) and Transcranial direct current stimulation (tDCS).

TMS is a non-invasive and safe brain stimulation technique, which is gaining widespread support for its research potential, and therapeutic benefits within the field of addiction medicine. To deliver TMS to the brain, a brief and strong electrical pulse of rapidly alternating current passes through a magnetic coil which is placed over the scalp. The rapid change in current induces a transient, high-intensity magnetic pulse that penetrates through the scalp, skull and meninges to the underlying cortex. This pulse generates an electric field within the targeted cortical regions, which can depolarize cortical neurons, and either stimulate or disrupt local neural activity beneath the coil and interconnected areas (Hallett, 2007; Wagner et al., 2007). In the past, it was difficult to directly index cortical excitability in the brain. TMS however, is emerging as a promising investigational tool in the characterization of localized changes in cortical and corticospinal excitability. Recently, TMS-paradigms (refer to Table 1.) have been employed to examine alterations in cortical excitability across the following drug groups: nicotine (Lang et al., 2008; Mostafa, 2009), alcohol (Conte et al., 2008; Kahkonen et al., 2001; Kähkönen and Wilenius, 2007; Kahkonen et al., 2003; Nardone et al., 2010; Ziemann et al., 1995), cocaine (Boutros et al., 2005; Boutros et al., 2001; Gjini et al., 2012; Sundaresan et al., 2007), cannabis (Fitzgerald et al., 2009) and ecstasy (Oliveri and Calvo, 2003).

INSERT Table 1.

In repetitive TMS (rTMS), delivering trains of repeated pulses can disrupt or alter excitability in the stimulated cortex, and interconnected brain regions, beyond the period of stimulation (Daskalakis et al., 2006; Fitzgerald et al., 2006; Gersner et al., 2011; Hallett, 2007; Pell et al., 2011; Rossini and Rossi, 2007; Ziemann, 2004). The nature of TMS-induced effects varies according to the number, intensity and frequency of TMS pulses (Daskalakis et al., 2002; Fitzgerald et al., 2002; Jung et al., 2008; Paus et al., 2001; Pell et al., 2011). Low frequency rTMS (approximately 1Hz) is reported to transiently reduce cortical excitability (Chen et al., 1997), while high frequency rTMS (>5Hz) is proposed to transiently enhance cortical excitability (Daskalakis et al., 2006; Fitzgerald et al., 2006; Pascual-Leone et al., 1994). The ability of rTMS to modulate neurotransmission has been demonstrated by both animal (Funke and Benali, 2011) and human studies (Cho and Strafella, 2009; Strafella et al., 2001). Animal studies found that repeated brain stimulation enhanced dopamine release in both the mesolimbic and mesostriatal pathways (Kanno et al., 2004; Keck et al., 2002; Zangen and Hyodo, 2002). Moreover, repetitive brain stimulation applied to rats pre-treated with morphine (Erhardt et al., 2004) or cocaine (Levy et al., 2007) was also reported to alter dopamine and glutamate neurotransmission, while several sessions of rTMS were found to induce lasting alterations in markers for neuroplasticity (Gersner et al., 2011). These animal studies provide preliminary support for rTMS as a potential non-pharmacological agent capable of changing dopaminergic and glutamatergic neurotransmission in the mesocorticolimbic pathways. These findings in animals are further supported by combined rTMS/PET human studies, whereby high frequency rTMS to the prefrontal cortex was found to induce dopamine release in the caudate nucleus (Strafella et al., 2001) and modulate dopamine release in the ipsilateral anterior cingulate cortex and orbitofrontal cortex (Cho and Strafella, 2009). Therefore, recent studies have examined

the potential efficacy of rTMS-induced modulations in dopaminergic release in reducing drug seeking behaviours across the following drug groups: nicotine (Amiaz et al., 2009; Eichhammer et al., 2003; Johann et al., 2003; Rose et al., 2011), alcohol (De Ridder et al., 2011; Herremans et al., 2012; Höppner et al., 2011; Mishra et al., 2010) and cocaine (Camprodon et al., 2007; Politi et al., 2008). When combined, these studies suggest that rTMS to the DLPFC is a promising tool in the reduction of craving levels and drug consumption.

Transcranial direct current stimulation (tDCS) is capable of altering cortical excitability of the cerebral cortex by subthreshold modulation of neuronal membrane potentials (Nitsche et al., 2003; Nitsche and Paulus, 2000; Polanía et al., 2011). During tDCS, a weak constant current is delivered via two surface electrodes (the anode, and the cathode) placed on the scalp. The current flows between the anode and cathode, penetrating the skull and flowing through the cerebral cortex, resulting in the modulation of spontaneous neural activity. The nature of these modulations on cortical excitability is dependent on duration, strength and stimulation polarity (Nitsche et al., 2005). Anodal tDCS is proposed to induce neuronal depolarization, thus increasing cortical excitability, while cathodal tDCS causes neuronal hyperpolarization, thereby, diminishing cortical excitability (Nitsche and Paulus, 2001; Stagg and Nitsche, 2011). Additionally, a combination of glutamatergic mechanisms, and changes in membrane potentials, have been implicated in the prolonged effects of tDCS on cortical excitability (Liebetanz et al., 2002; Nitsche et al., 2003; Nitsche et al., 2006). Recently, several studies were designed to investigate the potential for tDCS-induced modulations of cortical excitability to reduce craving levels and addiction-related behaviours across various drug groups: nicotine (Boggio et al., 2009; Fregni et al., 2008), alcohol (Boggio et al., 2008) and marijuana (Boggio et al., 2010). These studies suggested that anodal tDCS applied to the DLPFC was capable of reducing craving levels in addicted populations.

The ability of acute or repeated brain stimulation techniques to reduce both craving levels and drug-seeking behaviours may occur due to a number of possibilities (Feil and Zangen, 2010). Firstly, chronic drug exposure repeatedly hyperactivates the dopaminergic pathways (Diana, 2011), while

withdrawal is associated with attenuated dopaminergic activity, and these reductions in dopaminergic activity are associated with heightened levels of craving and relapse (Diana, 1999; Diana et al., 1998; Diana et al., 2006). Therefore, given that both human and animal studies indicate that stimulation over frontal regions can act by releasing dopamine in both the mesolimbic and mesostriatal pathways, it is plausible that transient increases in dopaminergic activity may 'mimic' the drug's action on the mesolimbic pathway, and thus contribute to transient reduction of craving. Secondly, the effects of brain stimulation are proposed to extend beyond the directly targeted brain regions, potentially influencing cross-hemispheric cortical and sub-cortical activity, in more remote brain regions connected to the stimulated region (George et al., 1999). Moreover, repeated sessions can induce lasting neuroplastic alterations and excitability changes (Pell et al., 2011). Therefore, it is possible that repeated stimulation to these frontal regions modulates the neuroadaptations and synaptic plasticity which occur in the mesocorticolimbic reward circuitry. Thirdly, the prefrontal circuitry has been strongly implicated in the processes regulating the compulsive desire to consume drugs (Feil et al., 2010). Therefore, repeated stimulation of the prefrontal cortex could induce neuromodulations, which contribute to the improvement of inhibitory control, and thus reduce drug seeking behaviours. For all of these reasons, it is proposed that brain stimulation techniques, such as rTMS and tDCS, may be able to alter the neuroadaptations in the mesocorticolimbic pathways, and reduce craving levels and addiction-related behaviours.

3. Brain Stimulation and addictive disorders

The following section provides a detailed overview of the recent research application of these brain stimulation techniques across the various drug groups. Within each drug group, we examine the ability of TMS to index cortical excitability and provide evidence of the neurophysiological effects of drug exposure. Following this, we explore the therapeutic potential of rTMS and tDCS techniques in reducing craving levels and addictive behaviours. It is notable though, that many of these preliminary studies consist of small sample sizes, are exploratory in nature, and vary considerably in stimulation parameters. Despite these limitations, these studies provide promising evidence of brain

stimulation as an investigative technique to index abnormal neuronal excitability associated with chronic drug exposure, and even as a potential therapeutic technique for reducing craving and drug-seeking behaviours.

3.1. Brain Stimulation and Nicotine

Nicotine, the key psychotropic agent in tobacco smoke, is a highly addictive psychostimulant (Dani and De Biasi, 2001). Despite the desire of many cigarette smokers to quit smoking, tobacco addiction remains one of the most common, and chronically relapsing, medical conditions. Recent studies have indicated that chronic nicotine use is associated not only with alterations of the nicotinic receptors, but also with GLU (Gass and Olive, 2008) and GABA neurotransmission (Mansvelder et al., 2002; Markou, 2008). Still, emerging research is focused on elucidating the neurobiological substrates underlying nicotine dependence. The following section describes the novel studies which employed brain stimulation techniques to index alterations in cortical excitability associated with chronic nicotine exposure (Lang et al., 2008; Mostafa, 2009), and further, provide a review of studies which administered rTMS (Amiaz et al., 2009; Eichhammer et al., 2003; Johann et al., 2003; Rose et al., 2011) and tDCS (Boggio et al., 2009; Fregni et al., 2008) techniques to investigate whether stimulation to frontal brain regions could reduce nicotine craving and consumption.

3.1.2. Nicotine and Cortical excitability

In a preliminary study, Lang et al (2008) administered TMS to explore the effect of chronic nicotine consumption on cortical excitatory/inhibitory mechanisms in the motor cortex. Single and paired-pulse TMS was delivered to the motor cortex of a sample of 22 chronic smokers and 22 healthy controls, and cortical excitability was measured via Cortical Silent Period (CSP) duration, Long-interval cortical facilitation (LICF), active Motor Evoked Potential (MEP) and short latency afferent inhibition (using combined median nerve stimulation and motor cortex TMS). Compared to healthy controls, chronic smokers displayed prolonged CSP duration and increased short latency afferent inhibition, while LICF and active MEP amplitudes were reduced. Short latency afferent inhibition is

believed to rely on somatosensory induced activity of cholinergic inhibitory circuits, while prolonged CSP is proposed to be mediated by GABAB receptors, and reflects cortical inhibition. The decrease in active MEP represents enhanced inhibition in the motor cortex, and a reduction in LICF, is associated with decreased facilitatory mechanisms within this area. Therefore, it is suggested that chronic nicotine exposure is associated with enhanced cortical inhibition, and reduced cortical excitability. The authors propose that these alterations could occur as a direct effect of nicotine on the cholinergic inhibitory circuits, whereby chronic nicotine may strengthen the cholinergic inhibitory circuits, enhancing inhibitory, and reducing facilitatory, neural mechanisms in the motor cortex. Mostafa et al (2009) expanded on this study by administering single and paired-pulse TMS to investigate the influence of nicotine on cortical inhibition in a sample of 20 chronic smokers compared with 10 matched non-smoking healthy controls. The TMS-paradigms assessments included Motor Threshold (MT), active MEP, Short-interval intracortical inhibition (SICI), Intracortical facilitation (ICF) and CSP. Consistent with Lang et al (2008), they found that CSP was prolonged and that both active MEP amplitude and ICF was significantly reduced in chronic smokers. There were no significant differences in terms of MT and SICI. Similar to Lang et al (2008), the authors suggest that chronic nicotine consumption is associated with enhanced cortical inhibitory, and reduced facilitatory mechanisms within the motor cortex.

3.1.3. Treatment of nicotine with rTMS

Several studies suggest that rTMS-induced modification of dopaminergic neurotransmission or cortical excitability could attenuate nicotine craving and consumption. In a preliminary study, Johann et al (2003) explored the effect of high frequency rTMS applied to the DLPFC in modulating levels of tobacco craving. In their study, 11 tobacco-dependent participants were randomly assigned both active and sham rTMS over the left DLPFC, administered at an intensity of 90% of MT, on consecutive days. A visual analogue scale (VAS) assessed levels of craving 30minutes prior, and following, rTMS treatment. Participants who received active stimulation, reported reduced levels of tobacco craving relative to the sham condition (Johann et al., 2003). Similarly, in a double-blind cross

over trial, Eichhammer et al (2003) administered rTMS to the DLPFC of 14 treatment seeking smokers. They investigated whether high frequency (20Hz) rTMS to the left DLPFC at 90% of MT (1000pulses) per session could reduce cigarette smoking and levels of craving. Participants were randomized to receive a combination of 2 active and 2 sham stimulation sessions over 4 consecutive days. Craving was measured through a visual analogue scale, and assessed both at baseline and re-assessed 30 minutes after rTMS. Number of cigarettes smoked was measured from an ad libitum smoking phase (6 hours) after rTMS, in which the active condition was compared to the sham condition. They found that high frequency rTMS to the left DLPFC lowered number of cigarettes consumed, while changes in craving levels were not observed. The authors propose that the mechanism of rTMS, which involves selective dopamine release to subcortical structures, may mimic nicotine's actions on the mesolimbic pathways, and act by blocking neuronal uptake of dopamine, thus resulting in reduced levels of smoking. Additionally, the authors explain that the measurement of craving levels may have not been sensitive enough, and the sample was perhaps too small to detect changes in craving levels (Eichhammer et al., 2003).

Amiaz et al (2009) expanded on these two studies, and investigated the effects of ten sessions of high frequency rTMS over the left DLPFC, applied over two weeks, in reducing cigarette consumption and craving. They also explored whether exposure to smoking cues prior to rTMS could modify the efficacy of rTMS. Forty-eight nicotine-dependent individuals (> 20 cigarettes daily) were randomized into four experimental groups: Active rTMS with smoking cues, active rTMS with neutral cues, sham rTMS with smoking cues, and sham rTMS with neutral cues. Prior to the rTMS session, smoking or neutral visual cues were presented to the study participants. In the active conditions, participants were administered daily sessions of high frequency (10Hz) rTMS at 100% of MT (1000pulses) to the left DLPFC. Cigarette consumption was indexed by a self-report of number of cigarettes smoked on the previous day and by urine measures of cotinine (metabolite of nicotine) taken prior to the 1st and 10th rTMS treatment session. The Fagerstrom test for Nicotine Dependence was administered to assess levels of dependence, and the Tobacco Craving Questionnaire was used to measure levels

of craving (prior to the 1st and 10th session). Cue-induced levels of craving were assessed by a visual analogue scale prior to, and after, exposure to the smoking or neutral cues, and then re-assessed after the rTMS session. A subsection of subjects then participated in a maintenance phase after the 10 daily sessions. During the first week of maintenance, rTMS or sham stimulation was administered on alternate days, and over the following 3 weeks, one rTMS session was administered per week. Urine samples, nicotine dependence and levels of craving were re-assessed at each maintenance phase. Finally, a follow-up telephone survey was conducted 6 months after treatment for all participants who completed the 10 daily treatment sessions (Amiaz et al., 2009). Consistent with the previous studies, results from this study indicated that high frequency rTMS over the DLPFC attenuates both cigarette craving (Johann et al., 2003) and consumption (Eichhammer et al., 2003). Additionally, cue-induced craving were reduced by active rTMS, as well as general cigarette craving induced by smoking-related stimuli over the 10 days. These findings were further supported by a reduction in both cotinine levels, and self-reported cigarette consumption. The promising effects of rTMS however, seemed to dissipate during the maintenance stage, and there was no observable reduction in cigarette consumption after 6 months (Amiaz et al., 2009). Therefore, when combined, these three studies provide compelling evidence that high frequency rTMS of the DLPFC can transiently reduce nicotine consumption (Amiaz et al., 2009; Eichhammer et al., 2003), general nicotine craving (Johann et al., 2003), and cue-induced craving (Amiaz et al., 2009).

Neuroimaging studies have also revealed the involvement of the superior frontal gyrus (SFG) in cue-induced cigarette smoking (McClernon et al., 2005). Recently, Rose et al., 2011 utilized rTMS to target the SFG in order to further investigate the neural circuitry underlying cue-induced craving. In a repeated measures, counter-balanced design, 15 heavy smokers (15 cigarettes daily) were exposed to three different rTMS conditions, over 3 separate visits: 1. high-frequency (10Hz) to the SFG, 2. low-frequency (1Hz) rTMS to the SFG, and 3. low frequency (1Hz) rTMS to the MT. Prior to each session, participants smoked a cigarette using a controlled puff volume apparatus. One hour later, they were administered rTMS while being exposed to different cue conditions: 1. neutral cues, 2.

smoking cues, and 3. smoking a cigarette (controlled puff volume apparatus). Cigarette craving, as measured by a brief version of the Shiffman-Jarvik, was assessed before and after each cue condition. The data revealed that rTMS over the SFG altered craving for cigarettes. High frequency rTMS *increased* cue-induced craving after the presentation of smoking cues, relative to the low-frequency condition. Interestingly, high-frequency rTMS also *reduced* craving when participants were exposed to neutral cues (relative to the other rTMS conditions). Thus, the authors suggest that the SFG play an important role in modulating (both excitatory and inhibitory) cigarette craving levels (Rose et al., 2011).

3.1.4. Treatment of nicotine with tDCS

Several studies have assessed the potential of tDCS administrated to the DLPFC in attenuating cue-induced nicotine craving. A randomized, double-blind, sham controlled crossover study was designed by Fregni et al (2008) to evaluate whether tDCS administration to the DLPFC could reduce craving levels in 24 heavy smokers (>15 cigarettes daily). Participants were exposed to three different tDCS conditions; sham tDCS, anodal tDCS to the left DLPFC, and anodal tDCS to the right DLPFC. All participants abstained from smoking for a minimum of 1 hour and 30 minutes prior to the session. Craving levels and mood were assessed by two separate visual analogue scales. Cue-provoked craving were induced by two methods. Firstly, exposure to a video which presented smoking cues, and secondly, cigarette manipulation: participants were instructed to open a packet of their preferred brand of cigarette, place the cigarette in their mouth and pretend to light it. Both craving levels and mood were assessed prior to, and after, exposure to smoking cues. This was followed by the tDCS treatment, sham, anodal tDCS to the left DLPFC or anodal tDCS administered to the right DLPFC, using a constant current of 2mA intensity for 20minutes. Levels of craving and mood were re-assessed. Participants were again exposed to the nicotine cues, craving levels and mood were re-evaluated. As expected, smoking craving intensified after exposure to the smoking cues, and tDCS stimulation of the DLPFC, temporarily attenuated both general, and smoking-cue invoked, nicotine craving. There were no observable mood changes throughout the tDCS trial. This

demonstrated that a single session of cortical stimulation with tDCS is capable of reducing cue-induced craving. As such, the authors suggest further investigation into the potential clinical efficacy of consecutive sessions of tDCS in inducing longer-lasting reductions of cigarette craving and consumption (Fregni et al., 2008).

Boggio et al., (2009) addressed this suggestion and investigated the effects of *repeated* tDCS sessions to the left DLPFC in 27 heavy smokers (>10 cigarettes daily). Participants were randomized to receive either active or sham stimulation for 5 consecutive days. Similar to the methodology of Fregni et al (2007), craving levels and mood were assessed at baseline, followed by exposure to smoking cues, and re-assessment of craving levels and mood. Subsequently, stimulation was initiated, and participants in the active condition were administered anodal tDCS to the left DLPFC at a constant current of 2mA for 20 minutes. Craving levels and mood were then re-assessed. Results of this study point towards a cumulative effect of tDCS to the left DLPFC in moderating smoking cue-provoked craving. They found that active tDCS, relative to sham tDCS, was associated with decreased craving levels after exposure to smoking-cues. In addition, over the 5 sessions of stimulation, there was a significant decrease in number of cigarettes smoked in the active group (Boggio et al., 2009).

Therefore, these preliminary studies demonstrated that administration of a single session of tDCS was capable of successfully attenuating craving levels (Fregni et al., 2008), while repeated sessions amplified this effect, and also reduced cigarette consumption (Boggio et al., 2009). The authors propose that anodal tDCS, designed to increase activity in the DLPFC, mimics reward-related activation of the region, thus reducing the levels of craving. Additionally, tDCS modulation of cortical excitability may disrupt the local networks and circuitry involved in craving (Fregni et al., 2008). As such, future studies into the efficacy of tDCS in reducing addiction-related behaviors, and as a potential therapeutic tool, are warranted.

3.1.5. Summary of nicotine and brain stimulation

In summary, these preliminary studies revealed that chronic nicotine use is associated with altered cortical activity, providing evidence of increased cortical inhibition, and reduced facilitatory mechanisms, in the motor cortex (Lang et al., 2008; Mostafa, 2009). The rTMS studies also presented promising results, whereby administration of high frequency rTMS to the left DLPFC attenuated nicotine consumption (Amiaz et al., 2009; Eichhammer et al., 2003), general nicotine craving (Johann et al., 2003) and cue-induced craving (Amiaz et al., 2009). Additionally, a further rTMS study revealed the critical role of the SFG in moderating craving levels (Rose et al., 2011). Further, a single session of tDCS, targeting the DLPFC, reduced craving levels (Fregni et al., 2008), while repeated sessions magnified this effect, and attenuated cigarette consumption (Boggio et al., 2009). Despite the preliminary nature of these studies, and small sample sizes, they provide support for the application of brain stimulation techniques to index cortical excitability alterations associated with chronic nicotine use, and as a potential therapeutic tool.

3.2. *Alcohol and Brain stimulation*

Ethanol, the psychoactive component of alcoholic beverages, is a central nervous system depressant (Addolorato et al., 2012). Multiple neurotransmitters are affected by alcohol, inducing alterations in dopamine, GABAergic, and glutamatergic neurotransmitter systems (Addolorato et al., 2012; Gass and Olive, 2008; Tambour and Quertemont, 2007). Thus, there is a disruption of the delicate balance between excitatory and inhibitory neurotransmitter functions (Mukherjee et al., 2008). Various anti-craving agents for alcohol dependence have been developed, however, they have limited success (Tambour and Quertemont, 2007). Therefore, understanding the neurochemical mechanisms involved in alcohol dependence is highly important and necessary to the development of improved treatments. The following section describes recent studies which utilized TMS-paradigms to examine the influence of acute (Conte et al., 2008; Kahkonen et al., 2001; Kähkönen and Wilenius, 2007; Kahkonen et al., 2003; Ziemann et al., 1995) and chronic (Conte et al., 2008) ethanol consumption on cortical excitability and brain connectivity, as well as alterations in the cortical balance associated with alcohol withdrawal syndrome (Nardone et al., 2010). It is followed by a review of the

preliminary studies which examined the therapeutic potential of targeting the frontal regions with rTMS (De Ridder et al., 2011; Herremans et al., 2012; Höppner et al., 2011; Mishra et al., 2010) and tDCS (Boggio et al., 2008) techniques to reduce levels of alcohol craving.

3.2.2. Alcohol and Cortical excitability

Ziemann et al (1995) pioneered the use of TMS-paradigms to index the direct effects of *acute* ethanol consumption on cortical excitability. Single and paired-pulse TMS was administered to the motor cortex of 6 healthy volunteers: RMT, Active Motor Threshold (AMT), MEP amplitude, CSP duration, SICI, SICF and motor function, were measured at baseline, and again 30minutes after the consumption of red wine (0.7L). Ethanol consumption enhanced SICI, suppressed SICF, and prolonged CSP duration. No observable changes in MT (active or resting), MEP amplitude, or alterations in hand motor function, were reported. Thus, the authors suggest that acute ethanol administration potentiates GABAergic mechanisms, and induces inhibition in the motor cortex. Expanding on this study, Kahkonen et al (2001) combined TMS with electroencephalography (EEG) to explore the influence of acute ethanol consumption on brain connectivity. EEG responses to TMS pulses, administered to the left motor cortex of 10 healthy male subjects, were recorded both before, and after, a dose of 0.8g/kg of ethanol was ingested. Ethanol consumption increased TMS-evoked potentials that are measurable 45ms after stimulation over both the right frontal and left parietal areas, with the greatest effect reported over the right prefrontal area. Thus, the authors propose that acute alcohol ingestion may influence the functional connections between the motor and prefrontal cortices. These data were supported by Kahkonen et al (2007), upon revisiting the data from their Kahkonen et al (2001) study; they revealed that acute alcohol ingestion decreased the TMS-evoked N100 amplitudes (thought to reflect cortical inhibitory processes) at ipsilateral, contralateral and frontal locations. The authors submit that these decreases illustrate the moderating effect of acute alcohol on the cortico-cortical connectivity of the motor cortex. Kahkonen et al (2003), expanded on these studies, and administered the combined TMS and EEG technique to examine the influence of acute alcohol ingestion on cortical excitability in the frontal

cortex. TMS was applied to the left prefrontal cortex of 9 healthy male controls prior to, and 30 minutes after, alcohol consumption (0.8g/kg). TMS-evoked EEG activity was recorded. Acute ethanol decreased TMS-evoked responses in the PFC; thus providing preliminary evidence of the direct effect of acute alcohol ingestion in moderating cortical excitability in the PFC .

Conte et al (2008) built on these earlier studies by utilizing rTMS to investigate both the acute and the chronic effects of ethanol consumption on cortical excitability. Trains of ten stimuli of 5Hz rTMS at an intensity of 120% of RMT were applied to the motor cortex in 10 healthy subjects. The rTMS was applied prior to, and following, acute ethanol consumption (24 grams for males, 12 grams for females). Thirteen ethanol dependent subjects also received 10 stimuli of 5Hz rTMS; however, they received only one session of stimulation, and no ethanol was consumed (negative blood ethanol levels were measured). Across all participants, MEP and CSP duration were measured throughout the rTMS trains. Paired-pulse TMS was then administered to a sub-group of 4 healthy subjects and 4 ethanol dependent subjects and both SICI and ICF were measured. In the healthy controls, rTMS (before and after ethanol consumption) increased both MEP and CSP duration, with a further increased CSP duration after ethanol intake. In the ethanol dependent group, rTMS did not elicit normal levels of MEP facilitation (depressed MEP facilitation), and CSP duration remained unchanged. Thus, the authors propose that there are distinct differences in the acute and chronic effects of ethanol on cortical excitability; acute ethanol intake alters GABA neurotransmission, while chronic ethanol consumption elicits neuroadaptations which act on glutamate neurotransmission.

Following this study, Nardone et al (2010) administered TMS to investigate altered cortical excitability in patients with alcohol withdrawal syndrome. Thirteen patients with alcohol withdrawal syndrome, 12 chronic alcoholics, and 15 matched controls, received single and paired-pulse TMS to the motor cortex. RMT,AMT, CSP duration, SICI and ICF were measured. Next, a single dose of 150mg of glutamatergic antagonist riluzole was administered to a subgroup of 8 alcohol withdrawal syndrome patients, and RMT, AMT, SICI and ICF were re-evaluated. At baseline, they found that IFC was increased in patients with alcohol withdrawal syndrome, compared to chronic alcoholics and

healthy controls, while consumption of the riluzole significantly decreased ICF. No further significant differences were observed. The authors propose that altered glutamatergic receptor function plays a role in the pathogenesis of alcohol withdrawal syndrome, and their findings provide evidence for the potential role of glutamatergic antagonists in treating alcohol withdrawal syndrome.

Thus, preliminary studies indicate that acute ethanol ingestion increases cortical inhibition in both the motor (Conte et al., 2008; Ziemann et al., 1995) and prefrontal circuitry (Kahkonen et al., 2003), and influences functional connections between the motor and prefrontal cortices (Kahkonen et al., 2001; Kähkönen and Wilenius, 2007). Additionally, alterations in GLU neurotransmission have been associated with both chronic alcohol consumption (Conte et al., 2008) and alcohol withdrawal syndrome (Nardone et al., 2010).Therefore, these studies indicate that brain stimulation techniques can successfully index alterations in cortical excitability associated with ethanol exposure. Despite these promising findings, it is notable that these studies are preliminary, and consist of small sample sizes, and as such, further studies are necessary to expand on the neurochemical and electrophysiological mechanisms underlying chronic alcohol consumption and alcohol withdrawal.

3.2.3. Treatment of alcohol with rTMS

Recent studies examined the potential of delivering rTMS to the DLPFC (Herremans et al., 2012; Höppner et al., 2011; Mishra et al., 2010) and medial frontal cortex (De Ridder et al., 2011) in reducing alcohol craving and dependence levels; they appear to report mixed results. Mishra et al (2010) assessed the efficacy of ten sessions of rTMS, administered to the right DLPFC of alcohol-dependent patients, in reducing levels of alcohol-craving. In their study, 45 alcohol dependent patients (10 days post abstinence) received 10 sessions of either active (30 patients) or sham stimulation (15 patients). In the active condition, 20 trains of high frequency (10Hz) rTMS (50 pulses per train, i.e. a total of 1000 pulses) were applied at 110% of MT to the right DLPFC. Severity of alcohol craving was assessed with the Alcohol Craving Questionnaire at three time-points: baseline, immediately after the 10th rTMS session, and 1 month after the 10th rTMS session. Active right

DLPFC rTMS had a significant anti-craving effect in alcohol-dependent patients. Based on these findings, the authors propose that application of rTMS to the right DLPFC modulates altered activity in the reward pathways through activation of the mesocorticolimbic circuitry.

Following this study, De Ridder et al (2011) published a case study describing the effects of rTMS targeting the dorsal ACC in an alcohol-dependent female patient with severe alcohol craving. In a combined rTMS and neuroimaging study, low frequency stimulation (1hz) rTMS was administered through the double-cone stimulation coil to the medial frontal cortex (targeting the dorsal ACC). Stimulation was fixed at 50% of the machine's output intensity, and 600pulses were administered daily (30min session), over a 3 week period. The patient was administered fMRI (while being exposed to alcohol cues/pictures) and EEG sessions across three different time-points: baseline, directly after the rTMS session, and after a reported relapse. Alcohol craving, measured by a visual analogue scale, were recorded daily. After the rTMS sessions, the patient reported reduced symptoms of craving and withdrawal for three months. Levels of craving were related to changes in EEG beta activity, and the connectivity between the dorsal ACC and PCC. These EEG markers for craving however, disappeared with the administration of rTMS. At the same time, fMRI analysis revealed that cue-induced increases in craving (pre-rTMS) activated the frontal and fronto-parietal areas, while post rTMS, these activations were not significant. After the three months though, the patient relapsed, and EEG data revealed that this relapse was related to ACC and PCC activity in the gamma band, while fMRI data found that neural activation in the medial brain structures returned to the initial pre-rTMS state. In response to the relapse, the patient was administered another week of rTMS treatment; however, the patient relapsed again three weeks later, and appeared to be unresponsive to the rTMS treatment. Therefore, this case study provides both clinical and neuroimaging evidence that low frequency rTMS to the medial frontal cortex can reduce symptoms of craving and withdrawal. Future studies in a larger cohort of patients are required to further validate these findings.

Contrary to these promising findings, Hoppner et al (2011) and Herremans et al (2012) reported that rTMS to the left DLPFC (Höppner et al., 2011), and the right DLPFC (Herremans et al., 2012), did not directly reduce alcohol dependence or craving levels. Hoppner et al (2011) explored the effect of high frequency rTMS to the left DLPFC in modulating mood and levels of craving in alcohol-dependent women. Nineteen alcohol-dependent women (14 days post-abstinence) were recruited for the study. Participants received ten sessions of either active (10 patients) or sham stimulation (9 patients). In the active condition, 20 trains using high frequency (20Hz, a total of 1000 pulses) rTMS were applied to the left DLPFC at 90% of MT. Alcohol craving levels were determined by the Obsessive Compulsive drinking scale, while mood ratings were measured by the Hamilton Depression Rating Scale and Beck Depression Inventory. The attentional blink paradigm, with neutral, emotional and alcohol-related stimuli, was also administered to all participants prior to the rTMS, and immediately after the 10th rTMS session. Despite no observable differences in craving or mood between the two groups, the attentional blink was increased for alcohol-related stimuli in the active rTMS group only. Thus, the authors propose that regardless of no significant improvement in craving levels, the data from the attentional blink could have neuropsychological implications for the use of rTMS in altering the prefrontal-amygdala circuitry dysfunction implicated in alcohol dependence.

Herremans et al (2012) explored the effect of a single session of rTMS over the right DLPFC in reducing the levels of craving in alcohol-dependent patients. Thirty-one hospitalized alcohol-dependent patients (abstinent for 14 days), who were recently successfully detoxified through a diazepam substitution scheme, completed the study. Participants were randomized into either the active (15 patients) or sham stimulation condition (16 patients). In the active condition, a single session containing 40 trains of high frequency (20Hz, a total of 1560 pulses) rTMS was applied at 110% of MT to the right DLPFC. Craving was self-rated through the Obsessive-Compulsive Drinking Scale at five time-points: prior to the rTMS session, after the rTMS session, twice from their naturalistic setting (their home over the weekend), and the final rating was complete when patients

returned to the hospital after the weekend. No significant changes in subjective levels of craving were reported. The lack of reported effect of rTMS on craving may have occurred for a number of reasons. Firstly, the administration of a single session of rTMS may have been too short to induce a lasting change in craving. Additionally, all participants were detoxified through a diazepam substitution scheme, which was designed to reduce craving levels upon hospital admission, and which may have influenced the effectiveness of rTMS. The authors propose that further studies, which optimize the rTMS stimulation parameters and deliver repeated sessions of rTMS, may produce more promising results regarding the efficacy of rTMS.

Therefore, although markedly different study designs (i.e. high versus low frequency, varied targets and coil positions), both Mishra et al (2010) and De Ridder et al (2011) present promising data regarding the efficacy of rTMS in attenuating craving levels within alcohol-dependent populations, while later rTMS studies (Herremans et al., 2012; Höppner et al., 2011), did not observe reduction in craving levels. The differential outcomes may have occurred for a number of reasons, firstly, in the Hoppner et al (2011) study, participants were administered rTMS at 90% of MT, relative to the other studies, which administered rTMS at 110% of MT. In the Herremans et al (2012) study, participants were administered only a single session of rTMS, which may not produce a long-lasting effect on craving levels, relative to the other studies where repeated sessions were applied. Finally, across the four studies, the site of stimulation varied between the right DLPFC, the left DLPFC, and the dorsal ACC. Thus, these studies demonstrate the variability and perhaps importance of optimizing stimulation parameters in order to reduce craving levels and drug-seeking behavior.

3.2.4. Treatment of alcohol with tDCS

In a double-blind, sham controlled study, Boggio et al (2008) examined the efficacy of tDCS application to the DLPFC in modulating alcohol craving. Thirteen alcohol-dependent patients enrolled in a rehabilitation program (abstinent for 10 days) were administered three forms of bilateral tDCS to the DLPFC: 1. active anodal left/cathodal right, 2. active anodal right/cathodal left,

and 3. sham stimulation of DLPFC. The stimulation order was randomized and counterbalanced across all participants with a 48hour inter-session interval between treatments. At baseline, craving was assessed by the alcohol urge questionnaire, and mood was measured by a visual analogue scale. Participants were exposed to a video presenting alcohol-related cues, and craving levels were re-assessed. Then, the tDCS treatment was administered to the DLPFC at a constant current of 2mA during a 20minute period. Craving levels and changes in mood were re-assessed. The pre-treatment alcohol cue-exposure technique was repeated, followed by a re-appraisal of craving levels and mood changes. Both conditions of active tDCS applied to the DLPFC (either anodal-left/cathodal-right or anodal-right/cathodal-left) significantly reduced alcohol craving levels. In addition, following active stimulation, alcohol craving was not increased by the presentation of alcohol-related cues. The authors propose that tDCS, externally modulating cortical excitability in the DLPFC, could interfere with the neural response to alcohol-related cues in the reward pathways, and thus, lead to a reduction in alcohol craving. As such, the authors put forward tDCS as a potential efficacious technique for reducing alcohol craving. Further studies are required to replicate these findings, and to evaluate the optimal tDCS stimulation parameters required to induce lasting treatment benefits within clinical settings (Boggio et al., 2008).

3.2.5. Summary of alcohol and brain stimulation

In summary, these experimental studies characterized distinct differences between the acute and chronic effects of ethanol exposure on cortical excitability (Conte et al., 2008). Acute ethanol ingestion increased cortical inhibition in the motor and prefrontal circuitry (Conte et al., 2008; Kahkonen et al., 2003; Ziemann et al., 1995), and altered functional connections between the motor and prefrontal cortices (Kahkonen et al., 2001; Kähkönen and Wilenius, 2007). Neuroadaptations in glutamatergic neurotransmission have been implicated in chronic alcohol exposure (Conte et al., 2008) and alcohol withdrawal syndrome (Nardone et al., 2010). Studies evaluating the potential of rTMS in reducing craving and consumption of alcohol in alcohol-dependent populations, consisted varying stimulation parameters and designs, and reported mixed findings. One study found that

high frequency rTMS to the right DLPFC reduced craving levels (Mishra et al., 2010), while a promising case study found that low frequency rTMS delivered to the medial frontal cortex (targeting the dorsal ACC), reduced alcohol-related symptoms for up to 3months. This case report was confirmed by neuroimaging and clinical data (De Ridder et al., 2011). On the contrary, two studies in which repeated sessions using lower intensity (90% of MT) rTMS was administered to the left DLPFC (Höppner et al., 2011) or a single session using high intensity (110% of MT) rTMS was administered to the right DLPFC (Herremans et al., 2012), did not find reduction in alcohol craving levels. These studies highlight the need for better understanding the outcomes of various stimulation parameters and thereby for optimization of these parameters including frequency, intensity and location in order to successfully reduce craving and addiction-related behaviors. Findings from the tDCS study were promising, and demonstrated the efficacy of tDCS to the DLPFC in attenuating cue-induced alcohol craving. Therefore, although preliminary, these studies provide support for the use of TMS-paradigms to index cortical excitability in alcohol dependent populations, and brain stimulation methods, as a potential therapeutic technique in reducing alcohol-dependence related symptoms.

3.3.1. Cocaine and Brain Stimulation

Cocaine, a short-acting central nervous system stimulant, is a highly reinforcing and addictive drug. Cocaine promotes dopamine transmission by binding to a dopamine transporter, and thus, blocking the synaptic dopamine re-uptake (Kalivas, 2007b), resulting in increased amounts of extracellular dopamine (Kalivas, 2007a; Kalivas and Hu, 2006). Repetitive cocaine administration generates profound addiction in humans, and neurotransmitter systems such as dopamine, GLU and GABA have been implicated in the development of dependence (Uys and Reissner, 2011). To date, there is no approved treatment for cocaine dependence (Karila et al., 2011), however, clinical trials have highlighted glutamate and GABA transmission as potential pharmacological targets (Kalivas, 2007b). Therefore, the next section outlines several studies which utilized TMS-paradigms to index cortical excitability in cocaine-dependent populations (Boutros et al., 2005; Boutros et al., 2001; Gjini et al.,

2012; Sundaresan et al., 2007). There follow two experimental brain stimulation studies which examined the ability of rTMS to the DLPFC to attenuate levels of cocaine craving within cocaine-dependent populations (Camprodon et al., 2007; Politi et al., 2008).

3.3.2. Cocaine and Cortical excitability

The following studies applied TMS-paradigms to index the neurophysiologic effects of repeated cocaine administration on cortical excitability. In a preliminary study, Boutros et al (2001) administered single pulses of TMS over the right and left motor cortex of 10 cocaine-dependent participants (3 weeks post abstinence) and 10 healthy controls. Compared to the healthy controls, RMT was significantly elevated, bilaterally, in the cocaine dependent subjects. The authors propose that attenuated cortical excitability may reflect a 'compensatory' neuro-adaptive response to the effects of repeated cocaine administration (which usually promote cortical excitability and seizure proneness). Further, it is possible that continued cocaine use induces cortical damage which may result in reduced levels of cortical excitability. In a replication study, Boutros et al (2005) assessed cortical excitability in 19 cocaine-dependent subjects (3 weeks post abstinence) relative to 12 healthy controls. Single pulse TMS was delivered over the motor cortex of the participants and RMT, AMT and CSP duration were measured. Additionally, participants completed the Cocaine Experience Questionnaire to provide an index of cocaine-induced psychotic symptoms. Consistent with Boutros et al (2001) findings, cocaine-dependent subjects exhibited increased RMT in the right hemisphere, while AMT was increased bilaterally. Prolonged CSP duration was also present in the right hemisphere of patients with cocaine-induced paranoia compared to subjects without paranoia. As such, these findings provide evidence of the association between repeated cocaine administration, and attenuated cortical excitability. Confirming the findings of Boutros et al (2001), the authors concur that these alterations in cortical excitability may reflect a compensatory mechanism in response to the excitatory and epileptogenic effects of cocaine administration.

Sundaresan et al (2007) expanded on these studies and administered both single and paired-pulse TMS over the left motor cortex of 10 cocaine dependent individuals (3 weeks post abstinence) and 10 healthy controls. Paired pulse stimulation, Long interval cortical inhibition (LICI) and LICF, were administered to provide a more direct investigation of glutamatergic cortical facilitation and GABAergic inhibition. Consistent with Boutros et al (2001) and Boutros et al (2005), the authors reported an increased RMT in the cocaine dependent individuals only. Interestingly though, cocaine-dependent individuals exhibited increased LICF, which reflect increased glutamatergic excitability, but normal LICI. These findings were supported by Gjini et al (2012), where single and paired-pulse TMS was delivered over the motor cortex of 52 abstinent cocaine-dependent subjects (3 weeks post abstinence) and 42 healthy controls. MT, CSP, LICF and LICI were measured. Consistent with the previous study (Sundaresan et al., 2007), the cocaine-dependent group was characterized by increased MT, and increased LICF, while no group differences were identified in LICI (Boutros et al., 2005; Boutros et al., 2001; Sundaresan et al., 2007). Additionally, the authors revealed a prolonged CSP duration in the cocaine-dependent group, which at high range stimulus intensity, is mediated by GABAB receptors, and may further reflect motor cortical inhibition. Across both studies, the authors suggest that heightened GLU activity (LICF) may relate to the increased vulnerability to develop seizures within a cocaine-dependent population, while reductions in axonal activity (increased RMT), and prolonged CSP duration, could reflect a compensatory adaptation to the epileptogenic effects of repeated cocaine administration (Gjini et al., 2012; Sundaresan et al., 2007)**.** Therefore, these studies highlight the complicated nature of cocaine dependence, and present the complex interplay between cortical excitability/inhibitory mechanisms in the motor cortex of cocaine-dependent individuals.

3.3.3. Treatment of cocaine with rTMS

In a randomized cross-over study design, Camprodon et al (2007) investigated whether high frequency rTMS to the right or left DLPFC could reduce cocaine craving in cocaine dependent participants. Two sessions of high frequency (10Hz) rTMS at 90% of MT were administered to the

right or left DLPFC (in random order) of 6 cocaine-dependent males, with an inter-session break of one week. Participants completed a craving visual analogue scale at three time-points: 10minutes before rTMS, immediately following rTMS, and 4 hours after rTMS. High frequency rTMS to the right DLPFC, but not the left DLPFC, transiently reduced cocaine craving. The authors suggest that the effect of stimulation over the right DLPFC, may extend beyond the targeted brain region, and indirectly suppress activity in the left DLPFC. Although the rTMS induced only transient dampening of cocaine craving, the authors propose that longer-lasting effects may result from multiple daily sessions of rTMS (Camprodon et al., 2007). Politi et al (2008) explored whether daily sessions of high frequency rTMS over the left DLPFC could modulate levels of cocaine craving. Ten daily sessions of high frequency (15Hz) rTMS were delivered over the left DLPFC at 100% of MT to 36 cocaine-dependent participants (post-detoxification). Clinical evaluation of symptoms associated with cocaine craving which were assessed daily revealed g*radual* reduction in cocaine craving (Politi et al., 2008).

Therefore, these two exploratory studies provide promising preliminary evidence of the potential therapeutic qualities of rTMS administered to the DLPFC in reducing cocaine craving. Notably though, the discrepant findings regarding the site of stimulation place emphasis on the importance of conducting further research to ascertain the optimal brain stimulation parameters, and regions of stimulation, necessary to reduce cocaine craving in cocaine-dependent populations.

3.3.4. Summary of cocaine and brain stimulation

These preliminary experimental studies provide an initial characterization of the complex nature of cocaine dependence. Cocaine-dependent individuals presented with attenuated cortical excitability (Boutros et al., 2005; Boutros et al., 2001; Gjini et al., 2012; Sundaresan et al., 2007) and increased cortical inhibition (Boutros et al., 2005; Gjini et al., 2012). The alterations in cortical excitability are proposed to reflect a compensatory neuroadaptative response to the excitatory and epileptogenic effects of cocaine administration. Additionally, it is possible that repeated cocaine use caused

cortical damage, resulting in reduced cortical excitability. On the other hand, an increase in GLU excitability was also observed (Gjini et al., 2012; Sundaresan et al., 2007), and proposed to relate to a heightened vulnerability to develop seizures within cocaine-dependent populations. Preliminary studies into the therapeutic potential of brain stimulation techniques found that a single session of rTMS delivered to the right DLPFC, transiently reduced cocaine craving levels (Camprodon et al., 2007), while daily repeated sessions of rTMS to the left DLPFC gradually reduced cocaine-craving (Politi et al., 2008). Therefore, these studies provide promising support for the use of brain stimulation techniques, as an experimental measure to examine alterations in cortical excitability in cocaine-dependent individuals, and as a potential therapeutic tool, in reducing cocaine craving.

3.4.1. Cannabis and Brain Stimulation

The primary psychoactive constituent of Cannabis is Δ^9-tetrahydrocannabinol (THC). Despite being the most widely used illicit psychotropic substance in world, the addictive qualities of THC remain largely unknown (Tanda and Goldberg, 2003). A number of studies have explored the neurochemical mechanisms contributing the cannabinoid addiction (Fattore et al., 2008; Maldonado et al., 2011; Zangen et al., 2006). Cannabis exposure is associated with increases in dopamine neuronal activity by altering the cortical balance of both GABAergic and glutamatergic synaptic transmission (Spiga et al., 2010). The interaction between the endogenous cannabinoid system, and these inhibitory (GABA) and excitatory (GLU) systems are complex and have been poorly addressed by human studies (Fattore et al., 2008; Fitzgerald et al., 2009; Maldonado et al., 2011). Additionally, there is currently no approved pharmacotherapy available to treat cannabis dependence, despite the increasing demand for treatment . The following section describes two innovative studies designed to explore neurochemical mechanisms associated with cannabis dependence. Firstly, an exploratory study designed to index the effect of chronic cannabis use on cortical excitability (Fitzgerald et al., 2009), and secondly, a tDCS study, which examined the influence of brain stimulation on risk-taking and craving levels in chronic marijuana smokers (Boggio et al., 2010).

3.4.2. Cannabis and Cortical excitability

Fitzgerald et al (2009) administered both single and paired-pulsed TMS to assess various parameters of cortical excitability and cortical inhibition within a population of chronic cannabis users. The sample consisted of 25 heavy cannabis users, 17 light cannabis users, and 19 non-using healthy controls. Participants were administered the following TMS-paradigms; RMT, AMT, MEP size, CSP, SICI SICF and LICI. Both of the cannabis using groups (heavy and light use) exhibited a reduction in SICI relative to healthy controls. No further differences in cortical excitability/inhibition were observed. SICI is proposed to be associated with activity at the GABAA receptor and regulation of GABAA by the neuromodulating neurotransmitters in the motor cortex. As such, the authors present the following potential explanations for their results; firstly, the reduction in SICI may directly relate to GABAergic modulation by cannabis, especially given the presence of increased plasma THC levels in high cannabis using participants, and the proposed interaction between cannabis and GABAergic neurotransmission. Secondly, the reduced SICI may also be related to neurobiological adaptations in patients who are regular cannabis users, as evident by the participants who were light cannabis users, who also presented with reduced SICI relative to healthy controls, but had low or non-detectable plasma THC levels. Thirdly, it is possible that the reduction in SICI reflects a pre-existing deficit in SICI, and GABAergic neurotransmission, which may be associated with an increased vulnerability to cannabis use. Therefore, the Fitzgerald et al (2009) study provides promising preliminary insight into the alterations in cortical excitability in heavy cannabis users. Additional studies, designed to further assess the cortical mechanisms associated with chronic cannabis use, are warranted.

3.4.3. Treatment of cannabis with tDCS

Recently, Boggio et al (2010) administered tDCS to assess the effects of brain stimulation on risk-taking and craving in chronic marijuana smokers. In their study, 25 chronic marijuana users (24hours abstinent) were randomly assigned into 3 different conditions: left anodal/right cathodal tDCS of the

DLPFC (8 participants), right anodal/left cathodal tDCS of the DLPFC (9 participants), and sham stimulation (8 participants). In the active conditions, the participants received a constant current of 2mA, and the tDCS began 5minutes prior to the risk-taking task and was delivered throughout the duration of the Risk Task, which lasted 10minutes. Craving levels, as measured by a visual analogue scale, were assessed immediately prior to, and post the stimulation period. Interestingly, the authors discovered that compared with controls (from a previous study), the marijuana users had a lower propensity for risk taking, but risk-taking was increased by both tDCS conditions applied to the DLPFC. The authors suggest that this reveals alterations in the risk-taking neural circuitry of marijuana users, and may reflect a compensatory mechanisms developed against the acute effect of marijuana administration (which induces increases in risk-taking). In addition, they found that the right anodal/left cathodal tDCS condition was associated with reductions in craving for marijuana (Boggio et al., 2010).

3.4.4. Summary of cannabis and brain stimulation

In summary, repeated cannabis use (both heavy and light) was associated with alterations in GABAA activity, and regulation of GABAA by neuromodulating neurotransmitters in the motor cortex (Fitzgerald et al., 2009). The tDCS study found that brain stimulation to the DLPFC can alter the risk-taking circuitry of chronic marijuana users, and reduce the levels of craving for marijuana (Boggio et al., 2010). Therefore, although further research is required to assess the cognitive functions (such as risk taking) involved in chronic marijuana use, the ability of tDCS to transiently reduce craving is encouraging, and may contribute to the development of effective treatments for cannabis/marijuana craving and dependence.

3.5.1. Ecstasy and Brain Stimulation

Ecstasy, otherwise known as 3,4-methylenedioxymethamphetamine (MDMA), from the amphetamine class of drugs, is a psychostimulant and hallucinogenic properties (Büttner, 2011). Acute MDMA consumption induces rapid release of serotonin and dopamine levels, by stimulating

release and inhibiting their re-uptake, in the central nervous system (Chang et al., 2007; Robledo, 2010). Given the hallucinogenic properties of ecstasy, and the reported neurotoxic effects in the occipital cortex, investigation of cortical excitability in the visual cortex may reveal the chronic effects of MDMA use (Bauernfeind et al., 2011; Chang et al., 2000). Therefore, in an innovative study, TMS-paradigms were administered to examine whether repeated ecstasy exposure is related to cortical alterations in the occipital region of the visual cortex (Oliveri and Calvo, 2003).

3.5.2. Ecstasy and Cortical excitability

Oliveri and Calvo (2003) conducted a novel study designed to assess variations in cortical excitability in the visual cortex of ecstasy users. Single-pulse TMS was administered to the occipital cortex and phosphene thresholds were measured across 10 heavy ecstasy users (3 days after last assumption of ecstasy) and 10 healthy controls. Phosphenes are light sensations, produced in the absence of visual stimuli, and can be induced by TMS to the occipital lobe. The phosphene threshold is the minimum TMS intensity necessary to elicit a phosphene light sensation and is used to index cortical excitability. Phosphene thresholds were significantly lower in ecstasy users compared to controls. Additionally, reduced phosphene thresholds in ecstasy users were negatively correlated with frequency of ecstasy use, and positively associated with the presence of visual hallucinations. Thus ecstasy ingestion and visual hallucinations are associated with increased excitability of visual cortical areas, and provide evidence of neurotoxicity.

4. Safety of brain stimulation techniques within addiction populations

Brain stimulation techniques have been strictly monitored for adverse symptoms and safety issues. With regards to TMS, a detailed set of guidelines to monitor the safety of TMS and rTMS have been established (Rachid and Bertschy, 2006; Rossi et al., 2009). There is a potential risk of the induction of a seizure, especially when using high frequencies and high intensities of rTMS. As such, caution should be practiced when using rTMS in drug dependent populations. Particularly within cocaine and ecstasy users, which present with an increased propensity for seizures, or in alcohol withdrawal

patients with a vulnerability to alcohol withdrawal seizures. Thus, it is extremely important for brain stimulation studies to carefully consider the potential interactions between the drug of abuse and brain stimulation. Safety studies of tDCS suggest that under the current stimulation parameters, the method is safe and painless, with only very minor adverse effects reported, such as mild tingling (Poreisz et al., 2007). Therefore, application of tDCS, to substance dependent populations within the current safety guidelines, appears to be safe.

5. Future research applications

Until recently, most of the TMS studies designed to index alterations in cortical excitability associated with drug exposure, administered TMS pulses to the motor cortex. It is important to expand research to assess further regions implicated in the addiction circuitry, such as the prefrontal cortex (Kahkonen et al., 2003). The recent development of a combined TMS-EEG technique (e.g. (Daskalakis et al., 2008; Fitzgerald et al., 2008), allows administration of both single and paired-pulse TMS-paradigms to the frontal regions and measure EEG responses (Rogasch and Fitzgerald, 2012). Additionally, similar to the study of De Ridder et al., (2011), imaging techniques, such fMRI or PET, designed to measure the local and remote effects of brain stimulation, could provide further insight into the neuroadaptations induced by brain stimulation in repeated drug users (Bestmann et al., 2008; Ridding and Rothwell, 2007; Ziemann, 2011). Further, it is necessary to locate the optimal parameters of stimulation (frequency, intensity, site, coil configuration, or electrode distribution) in developing the most effective and safe therapeutic treatment for drug dependence. Finally, future addiction studies should assess the efficacy of administering repeated brain stimulation techniques as an adjunct treatment with current cognitive, and pharmacological, therapies.

6. Conclusion

The current chapter provides promising evidence of the research potential and application of brain stimulation techniques across various drugs of abuse: nicotine, alcohol, cocaine, cannabis and ecstasy. TMS inhibitory paradigms were able to successfully index altered pathophysiology across

the various drug groups. These studies revealed variations in cortical excitability in the motor, prefrontal and occipital cortex of individuals exposed to drugs of abuse. Application of repeated brain stimulation techniques, such as rTMS and tDCS, to frontal brain regions was able to successfully moderate levels of general craving, cue-induced craving and the consumption of addictive drugs. These preliminary studies provide support for administration of brain stimulation techniques as an investigative tool to index altered cortical excitability associated with drug use, and furthermore, for its treatment potential as a clinical tool in reducing addiction-related behaviours.

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Table 1. A brief review of TMS paradigms which index cortical excitability associated with exposure to addictive drugs.

TMS paradigm	Pulse type	Overview
Motor Threshold (MT)	Single Pulse	When a single pulse stimulation of adequate strength is delivered over the primary cortex, the corticospinal pathway is activated, causing the contralateral muscles to contract (i.e. muscle twitch). MT is the lowest intensity of stimulation at which a motor evoked potential can be reliably recorded. MT is proposed to provide a measure of corticospinal excitability.
Motor Evoked potential (MEP) amplitude	Single Pulse	The amplitude of MEP reflects the integrity of the corticospinal tract and corticospinal excitability. At high stimulus intensities, MEP is increased and can be affected by processes involving release of several neurotransmitter or neuromodulator systems (e.g. Glu, GABA, dopamine).
Cortical Silent Period (CSP)	Single Pulse	CSP duration is a measure of cortical inhibition in the motor cortex. Single pulse stimulation elicits a motor response, which is subsequently suppressed by the target muscle, and measured as CSP duration. Low stimulus intensity CSP may reflect activation of GABAA receptors, while high range intensities, are suggested to be mediated by GABAB receptors.
Short-interval intracortical inhibition (SICI) and intracortical faciliation (ICF)	Paired Pulse	Both SICI and ICF reflect activity of interneurons in the cortex. For measures of SICI, paired pulses are administered in rapid succession, a subthreshold pulse is delivered, and after an inter-stimulus interval of 2-5ms, the suprathreshold pulse suppresses the amplitude of the MEP. SICI is associated with neurotransmission of the GABAA receptor and regulation of GABAA by neuromodulators. For measures of ICF, paired pulses are administered in rapid succession, a subthreshold pulse is delivered, and after an inter-stimulus interval of 7-20ms, the suprathreshold pulse has a facilitatory effect. Both GABA and GLU have been implicated in moderating levels of ICF.
Long-interval cortical inhibition (LICI) and Long- interval cortical faciliation (LICF)	Paired Pulse	For measures of LICI, two suprathreshold pulses are delivered, with a long inter-stimulus interval (approx 50-200ms), which induces lasting cortical inhibition mediated by GABAB receptors. For measures of LICF, two suprathreshold pulses are administered, with a shorter inter-stimulus interval (approx 10-40ms), which induces facilitation of cortical activity and is mediated by glutamatergic mechanisms.