EXECUTIVE FUNCTION DEFICITS IN BIPOLAR I DISORDER: ASSOCIATION WITH BRAIN STRUCTURE, ILLNESS PROGRESSION, AND ANTIPSYCHOTIC MEDICATION

by

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B.Sc., University of Alberta, 2009

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF
THE REQUIREMENTS FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY
in
The Faculty of Graduate and Postdoctoral Studies
(Neuroscience)

THE UNIVERSITY OF BRITISH COLUMBIA
(Vancouver)

August 2013

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Abstract

Executive function impairments are a core feature of Bipolar I Disorder (BDI), present not only during acute episodes but also persisting following remission of mood symptoms. Despite advances in knowledge regarding the neural basis of executive functions (EF) in healthy subjects, particularly in regards to the role of the dorsolateral prefrontal cortex (DLPFC) and caudate; research into how changes within these regions contribute to the deficits in BDI is lacking. This thesis explores EF in patients early in the course of illness, examining how impairments evolve with illness progression and how this may relate to neuromorphological changes and naturalistic pharmacological treatment regimes.

The first analysis demonstrates that EF is moderate-severely impaired in patients with BDI even following sustained symptomatic recovery from their first manic episode. Both larger caudate size and treatment with a higher relative dose of an antipsychotic drug predicted the severity of deficits.

Despite receiving ongoing clinical care, half of patients experienced a subsequent hypo/manic and/or depressive episode within one year. While those who remained well did show significant improvements in EF compared to those whose illness progressed, both patient groups still maintained moderate deficits compared to healthy subjects at follow-up. Although not directly associated with cognitive changes, sustained recovery during this time was also associated with reduced grey matter loss (including the left DLPFC) when compared affective recurrence, even after accounting for other clinical or treatment factors.

Maintenance pharmacological treatment with an antipsychotic is commonly used to prevent episode recurrence in BDI. Drugs within this class each show varying affinity to the dopamine D2 receptor (D2R), which plays an important modulatory role in DLPFC and caudate function. Differences in D2R binding have a likely impact on EF, as patients receiving an antipsychotic with high D2R affinity (risperidone) showed larger impairments when compared to those treated with a low affinity drug (quetiapine) or no antipsychotic.

These results demonstrate that illness related structural changes in the DLPFC and caudate are associated with the presence and evolution of executive function deficits in BDI; although the potential confounding effects of antipsychotics which influence functioning in these regions must also be considered.
Preface

This thesis entitled “Executive Function Deficits in Bipolar I Disorder: Association with Brain Structure, Illness Progression, and Antipsychotic Medication” presents research I conducted during my PhD studies at the Department of Neuroscience at the University of British Columbia. I led and performed my PhD research under the supervision of Professor L. N. Yatham, testing hypotheses with clinical, cognitive, and morphological data collected from the Systematic Treatment Optimization Program for Early Mania (STOP-EM; UBC Clinical Ethics Research Board Certificate Number H04-70169).

Accompanying published papers or those in preparation for publication and their associated contributions and collaborations include:

A version of Chapter 2 has been accepted for publication as:
Kozicky J, Ha TH, Bond DJ, Honer WG, Lam RW, Yatham LN. (2013). “Relationship between frontostriatal morphology and executive function deficits in bipolar I disorder following a first manic episode: Data from the Systematic Treatment Optimization Program for Early Mania” Bipolar Disorders; in press.

A version of Chapter 3 is in preparation for journal submission as:
Kozicky J, Bond DJ, Gonzalez M, Torres IJ, Lam RW, Yatham LN. “Grey matter changes in the year following the first manic episode: Association with illness progression”

A version of Chapter 4 has been published as:
Dr.’s Torres, Bond, Honer, Lam, and Yatham were responsible for the design, implementation, and continuation of the STOP-EM program. Dr. Ha assisted in morphometric analysis in Chapter 2, with additional help from Dr. Gonzalez in Chapter 3. Dr. Torres provided supporting statistical and neuropsychological expertise for all analyses. Those named also helped in manuscript revision prior to submission for publication.
# Table of Contents

Abstract ........................................................................................................................................ ii
Preface ........................................................................................................................................ iii
Table of Contents ........................................................................................................................ v
List of Tables ................................................................................................................................ ix
List of Figures ................................................................................................................................. x
Abbreviations ................................................................................................................................. xi
Acknowledgments ............................................................................................................................ xiii
Dedication ........................................................................................................................................ xiv

## Chapter 1

**Introduction and Literature Review** ......................................................................................... 1

1.1 Bipolar Disorder ...................................................................................................................... 1
1.2 Cognitive Impairments in Bipolar I Disorder ........................................................................ 2
1.3 Executive Functions ................................................................................................................. 3
  1.3.1 Working Memory ............................................................................................................... 4
  1.3.2 Set Shifting ....................................................................................................................... 5
  1.3.3 Response Inhibition .......................................................................................................... 5
  1.3.4 Limitations of a Dimensional Approach ......................................................................... 6
1.4 Executive Function Impairments in Bipolar I Disorder ......................................................... 7
  1.4.1 Trait Associated Deficits: Euthymia ............................................................................ 7
  1.4.2 State Associated Deficits: Acute and Subsyndromal Mood Symptoms ................... 10
  1.4.3 Stage Associated Deficits: Illness Risk and Progression ............................................ 12
  1.4.4 Medication Associated Deficits: Antipsychotics ......................................................... 17
1.5 Neural Structures Critical for Executive Functions ............................................................... 20
  1.5.1 Dorsolateral Prefrontal Cortex ...................................................................................... 20
  1.5.2 Cortico-Striatal-Pallidal-Thalamo-Cortical Loops ...................................................... 22
  1.5.3 Caudate .......................................................................................................................... 24
  1.5.4 Other Neural Regions Supporting Executive Functions .......................................... 25
1.6 The Systematic Treatment Optimization Program for Early Mania ..................................... 26
1.7 Thesis Overview ...................................................................................................................... 28
# Chapter 2

## Relationship between Frontostriatal Morphology and Executive Function Deficits in Bipolar I Disorder Immediately Following Recovery from a First Manic Episode

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1 Introduction</td>
<td>30</td>
</tr>
<tr>
<td>2.2 Methods</td>
<td>32</td>
</tr>
<tr>
<td>2.2.1 Study Overview</td>
<td>32</td>
</tr>
<tr>
<td>2.2.2 Participants</td>
<td>32</td>
</tr>
<tr>
<td>2.2.3 Clinical Assessment</td>
<td>33</td>
</tr>
<tr>
<td>2.2.4 Assessment of Executive Function</td>
<td>35</td>
</tr>
<tr>
<td>2.2.5 T1 MR Image Acquisition and Preprocessing</td>
<td>36</td>
</tr>
<tr>
<td>2.2.6 Statistical Analysis</td>
<td>37</td>
</tr>
<tr>
<td>2.3 Results</td>
<td>38</td>
</tr>
<tr>
<td>2.3.1 Demographic and Clinical Features</td>
<td>38</td>
</tr>
<tr>
<td>2.3.2 Comparison of Executive Function Scores between Groups</td>
<td>40</td>
</tr>
<tr>
<td>2.3.3 Volumetric Differences between Groups</td>
<td>41</td>
</tr>
<tr>
<td>2.3.4 Correlations between Executive, Clinical, and Morphometric Variables</td>
<td>41</td>
</tr>
<tr>
<td>2.3.5 Regression Models Predicting Executive Function in Patients</td>
<td>43</td>
</tr>
<tr>
<td>2.4 Discussion</td>
<td>43</td>
</tr>
</tbody>
</table>

# Chapter 3

## Executive Function and Grey Matter Change in the Year Following the First Manic Episode in Bipolar I Disorder: Association with Illness Progression

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1 Introduction</td>
<td>48</td>
</tr>
<tr>
<td>3.2 Methods</td>
<td>50</td>
</tr>
<tr>
<td>3.2.1 Study Overview</td>
<td>50</td>
</tr>
<tr>
<td>3.2.2 Participants</td>
<td>50</td>
</tr>
<tr>
<td>3.2.3 Clinical Assessment</td>
<td>52</td>
</tr>
<tr>
<td>3.2.4 Assessment of Executive Function</td>
<td>52</td>
</tr>
<tr>
<td>3.2.5 T1 MR Image Acquisition and Preprocessing</td>
<td>53</td>
</tr>
<tr>
<td>3.2.6 Statistical Analysis</td>
<td>54</td>
</tr>
<tr>
<td>3.3 Results</td>
<td>55</td>
</tr>
<tr>
<td>3.3.1 Demographic and Clinical Features</td>
<td>55</td>
</tr>
<tr>
<td>3.3.2 Executive Function</td>
<td>57</td>
</tr>
<tr>
<td>3.3.3 Voxel Based Analysis</td>
<td>59</td>
</tr>
<tr>
<td>3.3.4 Correlations with Executive Function</td>
<td>65</td>
</tr>
<tr>
<td>3.4 Discussion</td>
<td>65</td>
</tr>
<tr>
<td>Section</td>
<td>Page</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>Bibliography</td>
<td>105</td>
</tr>
<tr>
<td>Appendix</td>
<td>137</td>
</tr>
<tr>
<td>A. Structural Imaging using Voxel Based Morphometry</td>
<td>137</td>
</tr>
<tr>
<td>A.1 Introduction to the Physics of Structural Magnetic Resonance Imaging</td>
<td>137</td>
</tr>
<tr>
<td>A.2 Overview of Standard Voxel Based Preprocessing and Analysis</td>
<td>137</td>
</tr>
<tr>
<td>A.3 Advanced Voxel Based Tools and Methods</td>
<td>139</td>
</tr>
<tr>
<td>A.4 Validity and Limitations of Voxel Based Morphometry</td>
<td>141</td>
</tr>
</tbody>
</table>
List of Tables

Table 1.1: Proposed Executive Function Dimensions and Associated Cognitive Tests .......... 6
Table 1.2: Effects of Mood Phase, Stage, and Antipsychotic Use on Executive Function in Bipolar Disorder ................................................................. 10
Table 2.1: Baseline Demographic and Clinical Features of Patients and Healthy Subjects .... 39
Table 2.2: Baseline Executive Function z-scores in Patients and Healthy Subjects ............ 40
Table 3.1: Participant Demographics at Baseline and 1 Year Follow-Up .......................... 56
Table 3.2: Clinical and Treatment Features of Patients at Baseline and 1 Year Follow-Up ... 57
Table 3.3: Summary Executive Performance Comparisons between Patients and Healthy Subjects at Baseline and 1 Year Follow-Up ........................................ 57
Table 3.4: Areas of Reduced Grey Matter in Patients vs Healthy Subjects at Baseline and 1 Year Follow-Up .................................................................................. 60
Table 3.5: Areas of Grey Matter Increase in Patients who Remained Well vs Healthy Subjects ........................................................................................................... 64
Table 3.6: Areas of Grey Matter Decrease in Patients who Experienced an Affective Recurrence vs Healthy Subjects ........................................................................... 64
Table 3.7: Areas of Grey Matter Decrease in Patients who Experienced an Affective Recurrence vs Remained Well .............................................................................. 64
Table 3.8: DLPFC Grey Matter Decrease in Patients who Experienced and Affective Recurrence vs Remained well ............................................................................. 65
Table 4.1: Demographic and Clinical Features of Patients Receiving Maintenance Treatment and Healthy Subjects ..................................................................................... 79
Table 4.2: Performance on Executive Function Dimensions in Patients Receiving Maintenance Treatment and Healthy Subjects ........................................................................... 81
List of Figures

Figure 1.1: Schematic Diagram, of the Circuitry and Neurotransmitters of Cortico-Striatal-Pallidal- Thalamo- Cortical Loops .................................................. 23
Figure 2.1: Distribution of Summary Executive z-scores in Patients and Healthy Subjects at Baseline ................................................................. 40
Figure 2.2: Voxelwise Grey Matter Comparison between Patients and Healthy Subjects at Baseline ........................................................................... 41
Figure 2.3: Correlation between Summary Executive Score and Caudate Grey Matter Volume in Patients and Healthy Subjects at Baseline .............................................. 42
Figure 3.1: Summary Executive Performance of Patients and Healthy Subjects at Baseline and 1 Year Follow-Up .......................................................... 59
Figure 3.2: Areas of Significant Grey Matter Loss in Healthy Subjects between Baseline and 1 Year Follow-Up ........................................................................... 61
Figure 3.3: Areas of Significant Grey Matter Loss in Patients who Remained Well between Baseline and 1 Year Follow-Up .................................................................................. 61
Figure 3.4: Areas of Significant Grey Matter Loss in Patients who Experienced an Affective Recurrence vs Healthy Subjects .............................................. 61
Figure 3.5: Areas of Grey Matter Increase in Patients Remained Well vs Healthy Subjects. 63
Figure 3.6: Areas of Grey Matter Decrease in Patients who Experienced an Affective Recurrence vs Healthy Subjects .............................................. 63
Figure 3.7: Areas of Grey Matter Decrease in Patients who Experienced an Affective Recurrence vs Remained Well .................................................. 63
Figure 4.1: Executive Function Performance in Patients Receiving Maintenance Treatment and Healthy Subjects .................................................. 81
Figure 5.1: Proposed Trajectory of Executive Function Deficits in Bipolar I Disorder........ 91
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>3T</td>
<td>3 Tesla</td>
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<tr>
<td>ANCOVA</td>
<td>Analysis of Covariance</td>
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<tr>
<td>ANOVA</td>
<td>Analysis of Variance</td>
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<td>APA</td>
<td>American Psychiatric Association</td>
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<tr>
<td>BA</td>
<td>Brodmann Area</td>
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<tr>
<td>BD</td>
<td>Bipolar Disorder</td>
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<tr>
<td>BDI</td>
<td>Bipolar I Disorder</td>
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<tr>
<td>BDII</td>
<td>Bipolar II Disorder</td>
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<tr>
<td>BPRS</td>
<td>Brief Psychiatric Rating Scale</td>
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<tr>
<td>CANTAB</td>
<td>Cambridge Neuropsychological Test Automated Battery</td>
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<tr>
<td>D₁R</td>
<td>D₁ dopaminergic receptor</td>
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<tr>
<td>D₂R</td>
<td>D₂ dopaminergic receptor</td>
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<tr>
<td>DARTEL</td>
<td>Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra</td>
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<td>DLPFC</td>
<td>Dorsolateral Prefrontal Cortex</td>
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<tr>
<td>DSM-IV-TR</td>
<td>Diagnostic and Statistical Manual of Mental Disorders Version 4 Text Revised</td>
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<td>DSM-V</td>
<td>Diagnostic and Statistical Manual of Mental Disorders Version 5</td>
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<tr>
<td>ePD</td>
<td>Early Parkinson’s Disease</td>
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<td>EPS</td>
<td>Extra-Pyramidal Symptoms</td>
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<td>fMRI</td>
<td>Functional Magnetic Resonance Imaging</td>
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<td>FWHM</td>
<td>Full Width at Half Maximum</td>
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<td>FWE</td>
<td>Familywise Error</td>
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<td>GABA</td>
<td>Gamma AminoButyric Acid</td>
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<td>GAF</td>
<td>Global Assessment of Functioning</td>
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<td>GPe</td>
<td>Globus Pallidus External Segment</td>
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<td>GPi</td>
<td>Globus Pallidus Internal Segment</td>
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<td>HAMD</td>
<td>Hamilton Rating Scale for Depression</td>
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<td>HSCT</td>
<td>Hayling Sentence Completion Test</td>
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<td>HS</td>
<td>Healthy Subjects</td>
</tr>
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<td>ICC</td>
<td>Intraclass Correlation Coefficient</td>
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<tr>
<td>ID/EDS</td>
<td>Intradimensional/ Extradimensional Shift</td>
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<td>IQ</td>
<td>Intelligence Quotient</td>
</tr>
</tbody>
</table>
KBIT  Kaufmann Brief Intelligence Test
MarsBaR  MARSeille Boîte À Région d'Intérêt
MINI  Mini International Neuropsychiatric Interview
MNI  Montreal Neurologic Institute
MR  Magnetic Resonance
MRI  Magnetic Resonance Imaging
NAART  North American Adult Reading Test
PANSS  Positive and Negative Syndrome Scale
PET  Positron Emission Tomography
PFC  Prefrontal Cortex
ROI  Region of Interest
SD  Standard Deviation
SE  Standard Error
sMRI  Structural Magnetic Resonance Imaging
SNC  Substantia Nigra Pars Compacta
SNr  Substantia Nigra Pars Reticulata
SOC  Stockings of Cambridge
SPSS  Statistical Package for the Social Sciences
SSRT  Stop Signal Reaction Test
STOP-EM  Systematic Treatment Optimization Program for Early Mania
STN  Subthalamic Nucleus
SVC  Small Volume Correction
SWM  Spatial Working Memory
T1  Longitudinal Relaxation Time
TE  Time to Echo
TOH  Tower of Hanoi
TOL  Tower of London
TR  Time to Repetition
UBC  University of British Columbia
VBM  Voxel Based Morphometry
WCST  Wisconsin Card Sorting Test
WFU  Wake Forest University School of Medicine
YMRS  Young Mania Rating Scale
Acknowledgments

I could have never done this without the help of so many incredible people.

First and foremost, I would like to thank my supervisor Dr. Lakshmi Yatham for providing me with the amazing opportunity and guidance necessary for the completion of this thesis. I am further indebted to Dr. Ivan Torres for the immeasurable encouragement and advice he afforded me throughout my degree. Dr. Jeremy Seamans and Dr. Alex MacKay also supplied great help for the completion of this work. Outside of my supervisory committee, I have enjoyed the always present administrative and moral support from Nazlin, David, Taj, Cindy, Sylvia, Loretta, and Sharon; along with the many other clinical/research staff at the UBC Mood Disorders Centre. I would also like to acknowledge all the STOP-EM participants whose involvement really made this whole effort possible.

To all of my friends both here in Vancouver and back in Edmonton (including but definitely not limited to CD, JP, DB, GD, EP, JW, CB, EC, DL, MD and AJ); you must know how important you are to me. Your intelligence, wit, and charm are only exceeded by your incredibly good looks. You have sure made my undergraduate training into a truly amazing and inspiring experience.

Finally, I must thank my mother who has always provided me with the support and motivation needed to pursue my education; as well as my siblings Lisa, Sara, and Greg for continually helping me keep perspective on my circumstances and goals.
Chapter 1
Introduction and Literature Review

1.1 Bipolar Disorder

With an estimated lifetime prevalence of 2.4%, over 800,000 Canadians are affected by Bipolar Disorder (BD) (Statistics Canada, 2002). The defining characteristic of BD is one of emotional dysregulation, with sufferers experiencing cyclical fluctuations between the extreme phases of hypo/mania (a distinct period of abnormally elevated, expansive, and/or elevated mood; APA 1994, 2012) and depression (persistently sad, empty, or hopeless mood and/or loss of interest or pleasure; APA 1994, 2012). As a life-long condition with onset frequently in adolescence and young adulthood (65% of patients report a first mood episode before 18 years of age- Perlis et al 2004) individuals with BD can expect to spend at least 20% of their lives experiencing a frank mood exacerbation (Angst & Sellaro 2000) with even more time spent between with milder, though still disabling, subsyndromal symptoms (Huxley & Baldessarini 2007). People living with BD suffer substantial functional impairment- as one of the top 10 causes of disability worldwide its burden outranks all cancers and primary neurologic disorders (e.g. epilepsy and Alzheimer’s disease; Merikangas et al, 2002), with sufferers estimated to be unable to maintain proper work role function over 30% of the time (Judd et al 2008).

The term “Bipolar Disorder” encompasses a spectrum of diagnostic subgroups divided according to the severity of mood elevation experienced during acute episodes (Angst 2007). On this spectrum, Bipolar I Disorder (BDI) is placed at one pole due to the presence of severe manic episodes in which features including inflated self-esteem, decreased need for sleep, pressured speech, racing thoughts, distractibility, psychomotor agitation, and risky behaviour lead to significant functional impairment, include psychotic features, and/or necessitate hospitalization (APA 1994, 2012). At the other end of the spectrum, cyclothymia is characterized by less severe disruptions (most commonly reported symptoms being periods of heightened irritability or aggressiveness, patterns of frequent shifts in interests or plans, episodic promiscuity, and drug or alcohol abuse; Akiskal et al 1977). Bipolar II Disorder
(BDII) sits between the two conditions with hypomanic episodes qualitatively similar to manic periods in BDI that although distinct and observable are not of a sufficient duration or severity to cause significant functional impairment, hospitalization, or psychosis (APA 1994, 2012). As most focus in the field of BD research has been limited to studies focusing specifically on patients with BDI, this will also be the topic of this thesis.

1.2 Cognitive Impairments in Bipolar I Disorder

Along with the hallmark clinical symptoms of mania and depression, individuals with BDI suffer from substantial impairments in cognitive function which persist throughout all mood phases. Subjective difficulties are common, with approximately 80% of patients reporting problems with memory and attention (Goodwin & Jamison 1990). While it has been found that these complaints are associated with deficits in objective measures of these abilities (Arts et al 2011) this relationship has not always been seen (Burdick et al 2005, van der Werf Elderling et al 2011). Noticeable deficits in a variety of neuropsychological tests of memory and attention have also consistently been reported in patients with BDI (Torres et al 2007, Goldberg & Chengappa 2009, Burdick et al 2011) and although not as severe as what seen in individuals with schizophrenia (Krabbendam et al 2005, Daban et al 2006, Schretlen et al 2007), they are still of high clinical relevance: more severe impairments are associated with worse global functioning at time of testing (Martinez-Aran et al 2004, Depp et al 2012) as well as predictive of poor functional recovery (Jaeger et al 2007, Burdick et al 2010, Dickerson et al 2010) and higher rates of episode recurrence (Kam et al 2011) over prospective follow up.

Impairments in cognitive functioning are not merely secondary to mood symptoms: meta-analysis of 28 studies restricted to euthymic patients with BDI found moderate impairments in both verbal memory and attention compared to healthy subjects (d>0.60; Mann-Wrobel et al 2011). Cross sectional studies comparing performance between patients of different mood states only find minimal differences associated with acute episodes, specifically additional memory impairments in depression (Malhi et al 2007) and attentional problems in mania (Gruber et al 2007), with others reporting no significant differences between patients of
different mood states (Bearden et al 2006). Longitudinal studies also show that moderate changes in mood symptoms over follow up do not predict cognitive variability both over short (6, 12, 26 weeks; Depp et al 2012) or intermediate (3 months; Chaves et al 2011) lengths of follow-up, indicating deficits may be a relatively stable state feature. Less severe impairments in verbal memory are also present in unaffected first degree relatives, suggesting that difficulties may in part precede illness onset (Robinson & Ferrier 2006). Function may also deteriorate as the illness progresses: review of cross sectional studies has found a consistent relationship between the number of prior manic episodes and severity of memory problems (Robinson & Ferrier 2006). Similarly, while unaffected relatives of bipolar probands have impairments in attention compared to healthy subjects, deficits are not as severe as those seen in patients (Bora et al 2009), and patients with multiple episodes also have greater impairments compared to those with a single manic episode (Elshahawi et al 2011). Thus cognitive difficulties may be viewed a clinically relevant trait feature resulting from factors of both illness risk and progression.

1.3 Executive Functions

While impairments in memory and attention are of no doubt important symptoms of BDI, cognitive studies in this population are increasing expanding their focus onto another domain: Executive Function. Just as a successful corporation requires executives to oversee business operations, make decisions, and implement plans based on goals and available resources; effective, responsible, and appropriate human conduct is dependent on executive functions in order to orchestrate often complex and extended thoughts or behaviors geared towards a unified goal (Baddeley & Hitch 1974, Lezak 1983, Banich 2004). Patients with acquired brain injury who suffer from dysfunctional executive processes demonstrate a constellation of signs and symptoms that overlap with those witnessed in BDI including variable motivation and affective response, restlessness, perseveration, impulsivity, distractibility, and disinhibition; as well difficulties with planning and decision making (Burgess et al 1996, Simblett & Banich et al 2011). Not only do individuals with BDI demonstrate deficits in a variety of tests of executive function with effect sizes similar to or larger than those for memory and attention (Torres et al 2007, Mann-Wrobel et al 2011),
there are indications that executive impairments are maintained after controlling for differences in attention (Stodart et al 2007, Thompson et al 2009) and may even be a significant contributor to problems in memory (Deckersbach et al 2004). As such, impairments in executive functions can be hypothesized to be a core feature of BDI, critical to the understanding of this complex disease.

Executive Function is a broad, often vague term used to describe a range of abilities that are critical for normal, healthy human conduct, and while description has changed dynamically over recent history (Chan et al 2008) current theories describe key processes as being of cognitive control (Badre 2008, Banich 2009)- allowing individuals to pay attention to, input and maintain necessary information (while suppressing irrelevant processing), retrieve related information from long-term memory, manipulate and integrate pertinent information, then react/ respond accordingly (Funahashi 2001). From a neuropsychological perspective, executive abilities are measured using a wide variety of complex standardized tests with multiple potential conceptualizations possible (Packwood et al 2011). Although the consensus is far from universal, theoretical and experimental evidence supports grouping these skills into overlapping yet still independent dimensions: working memory, set shifting, and response inhibition (Table 1.1). Initial substantiation of these three dimensions was conducted using factor analysis of several both simple and complex cognitive tests (Miyake et al 2000, Lehto et al 2003), and their popular use has been supported through comprehensive review of behavioral data and expert opinion relevant to the concept of cognitive control (Sabb et al 2008). Although most tests traditionally being identified as sensitive to executive functioning employ a combination of different abilities, they can still in part be viewed as belonging to one or more of these categories.

1.3.1 Working Memory

Working memory (also referred to as maintaining & updating) involves the control and manipulation of information held online in mind. Developed from the idea of an immediate memory system for short term storage and processing of goal relevant information during complex cognitive tasks (Baddley & Hitch 1974), it is made up of processes that monitor and
code task-relevant information, and revise it as necessary by replacing old information with new (Morris & Jones 1990, Smith & Jonides 1997, Lehto 1996, Miyake et al 2000). Although this main framework has remained stable with continuing research, further partitioning into subcomponents has also been attempted (reviewed by Baddeley 2012). There are a range of measures judged as belonging to this dimension, with the most commonly investigated in samples with BDI being digitspan backwards/total, visualspan backward/total, letter number sequencing, n-back, and spatial working memory (SWM).

### 1.3.2 Set-Shifting

Set-shifting (also just shifting, attention shifting, task switching, or flexibility) refers to the ability to develop and change mindsets. Measures of these skills require subjects generate and identify concepts, test hypotheses, maintain attention, guide behavior, and when more than one concept is possible to switch sets and inhibit preservation of prior categories (Miyake et al., 2000, Lehto et al 2003, Sabb et al 2008). Tests traditionally belonging to this domain are frequently complex, with skills required also overlapping with other executive or supporting abilities. Examples which are frequently employed in studies of patients with BDI include the wisconson card sorting test (WCST), intradimensional/extradimensional shift test (ID/EDS), trails b, and verbal fluency (semantic or phonemic).

### 1.3.3 Response Inhibition

Response Inhibition (or just inhibition) refers to the ability to deliberately stop dominant, automatic, prepotent, or unwanted responses- whether they be thoughts, actions, or even emotions (Lehto et al 2003, MacLeod 2003, Aron 2007, Sabb et al 2008, Latzman & Markon 2010). Measures often require individuals to resolve a conflict between relevant and irrelevant stimuli and/or to block an incorrect but automatic or perceptually congruent response. Tasks used in BDI which are considered to assess these abilities include the Stroop, the Hayling Sentence Completion Task (HSCT), Go/NoGo, and the stop signal reaction test (SSRT). More complex tasks such as the Tower of London (TOL), Tower of Hanoi (TOH), or Stockings of Cambridge (SOC) can also be considered measures of Response Inhibition,
although they are more commonly described to assess planning ability. Support for inclusion of these measures under the dimension of Response Inhibition comes from a latent variable analysis which found that TOH performance was significantly associated with other measures of this construct (specifically the Stroop, Anti-Saccade, and SSRT), and unrelated to measures of set-shifting and working memory (Miyake et al 2000). Similarly, other authors have also observed that successful performance on these tests frequently requires subjects to inhibit a perceptually congruent response in favor of a more incongruent one (that is, move a ball in the opposite direction of the eventual final position; Morris et al 1997).

### Table 1.1: Proposed Dimensions of Executive Function and Associated Neuropsychological Tests

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<tbody>
<tr>
<td>Working Memory</td>
<td>Digitspan Backward&lt;br&gt;Visualspan Backward&lt;br&gt;Letter Number Sequencing&lt;br&gt;n-Back&lt;br&gt;Spatial Working Memory (SWM)</td>
</tr>
<tr>
<td>Set Shifting</td>
<td>Intradimensional-Extradimensional Shift Test (ID/EDS)&lt;br&gt;Verbal Fluency&lt;br&gt;Trails B&lt;br&gt;Wisconsin Card Sorting Test (WCST)</td>
</tr>
<tr>
<td>Response Inhibition</td>
<td>Stroop&lt;br&gt;Hayling Sentence Completion Task (HSCT)&lt;br&gt;Go/NoGo&lt;br&gt;Stop Signal Reaction Test (SSRT)&lt;br&gt;Tower Planning Tasks (TOL, TOH, SOC)</td>
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#### 1.3.4 Limitations of a Dimensional Approach

Division of these tests into three core executive dimensions can be criticized as being too simplistic, and biased by samples and tests chosen. Indeed, emerging factorial studies of large numbers of frequently complex executive tasks often describe the number of independent dimensions emerging from only two (working memory and set shifting only-Engle & Kane 2004, Huizinga et al 2006, Hull et al 2008) with up to six; each with nuanced and subjective labels (such as prospective working memory, set-shifting and interference management, task analysis, response inhibition, strategy generation and regulation, or self-monitoring and self-maintenance; Testa 2012). These inconsistencies only further demonstrate the fallbacks of current measurement tools and experimental methods- latent
semantic and hierarchical cluster analysis of the 60 most highly cited studies on executive function between 1997 and 2007 identified 50 unique definitions and 18 interrelated factors for 98 different tasks of executive function (Packwood et al 2011). As such, the working memory, response inhibition, and set shifting labels have been emphasized here primarily for their parsimony, and will be used as a crude organizational system rather than a specific or concrete definition as an agreed upon formulation of the latter is not currently available (and is not likely to emerge until more well defined tests are developed; Chan et al 2008).

A further caveat of this presentation is that description is limited to tests which are considered to be “cold” cognitive, mechanistic, or logical executive functions (Grafman & Litvan 1999), which lack the described emotion or motivational aspects of “hot” executive functions such as impulse control, affect regulation, decision making, and risk/reward sensitivity (Ardila 2008, Zald & Andreotti et al 2010). While dysfunction of these abilities are of no doubt high clinical relevance to BDI and are indeed receiving increasing levels of attention (eg Pizzagalli et al 2008, Chandler et al 2009, Roiser et al 2009, Adida et al 2011, Ahn et al 2011) cold abilities have been the subject of vast majority of neuropsychological studies in both healthy and bipolar samples so far.

1.4 Executive Function Impairments in Bipolar I Disorder

1.4.1 Trait Associated Deficits: Euthymia

Investigation of impairments in executive function during periods of episodic remission are important for revealing symptoms that are unaddressed by current therapeutic strategies. Even following recovery of mood symptoms, euthymic patients with BDI demonstrate significant levels of impairment in multiple tests of executive function, including those which test abilities in situations that mimic real life scenarios (O’Shea et al 2010, Torralva 2012). More traditionally used measures also show ecological validity: scores on executive tasks encompassing all three dimensions have been shown to correlate with self or clinician rated measures of quality of life and functioning. Specific measures implicated include the n-back (Simonsen et al 2010, Pattanayak et al 2012); trails b (Brissos et al 2008a, Depp et al
phonemic verbal fluency (Yen et al 2009, Godard et al 2011), WCST (Yen et al 2009); Stroop (Brissos et al 2008; Mur et al 2009, Pattanayak et al 2012), and TOH (Brissos et al 2008). Executive tasks have also been shown to have prognostic use: along with memory measures, baseline letter number and WCST performance predicted 3-month recovery in occupational functioning in 79 patients with BDI after symptomatic recovery from a manic episode (ie after at least six weeks euthymia; Bearden et al 2011). Martinez-Aran et al (2009) also found that in a sample of 35 patients with BDI who had been euthymic for at least 8 weeks prior to neurocognitive testing, baseline digitspan backward and WCST performance accounted for 28% of the variance in overall self-reported functioning after one year follow up. This was also seen in a group (n=32) of individuals with BDI or BDII, with baseline digitspan backwards performance predictive of occupational functioning over four year follow up (Bonnin et al 2010). It should be noted, however, that significant relationships between individual tasks and measures of outcomes varies greatly between studies, and there are multiple instances of negative findings (eg Martinez-Aran et al 2002, 2004; Burdick et al 2010, Dickerson et al 2010, Wingo et al 2010). Despite this, it is generally agreed that along with other cognitive domains it is clinically relevant to assess executive function abilities in patients with BDI following recovery from a mood episode (Iosifescu 2012).

Multiple meta-analyses conducted in the last several years demonstrate that moderate-severe impairments in executive function are a consistent finding among the multitude of studies that compare performance of euthymic patients with BDI to healthy subjects. The most recent (Mann-Wrobel et al 2011) restricted the initially more than 1000 studies identified through Medline and PsycINFO searches of “bipolar, euthymi*, cogni*, neuropsychologi*” to 28 through exclusion of papers that did not include at least three neuropsychological tests, did not include a healthy comparison group or a clear operational definition of euthymia, included subjects over 80 years of age, or did not have sufficient information to calculate an effect size. Specific neuropsychological measures were also only included if they had been used in at least three studies. The 28 resultant tasks were divided into seven domains. Effect sizes adjusted to control for small sample bias (Hedges g) were reported for each domain as well as for every individual measure. Results of this meta-analysis revealed that euthymic
patients with BDI suffer from generalized impairment across cognitive domains (grand mean weighted effect size $g=0.60$). Effect sizes for the three executive domains (and included tests) were: Executive Function $g=0.71$ (WCST categories= 0.56, WCST perseveration= 0.66, trails b=0.80, Stroop color word=0.71, Stroop inhibition=0.88, HSCT time=0.68, HSCT errors=0.63); Working Memory $g=0.60$ (digitspan forward=0.40, digitspan backward=0.81, digits total=0.64, visualspan backward=0.55); fluency $g=0.56$ (phonemic=0.55, semantic=0.58). Consistent with this, the meta-analysis of Bora et al (2009) including 45 studies and 19 measures reported between 1995- October 2007 found the effect sizes of the six executive tasks being 0.86 (trails b), 0.76 (Stroop), 0.75 (digitspan backward), 0.70 (WCST perseveration), 0.66 (WCST categories) and 0.60 (phonemic verbal fluency). This is in accordance with findings by Torres et al (2007), who from a pool of 400 studies gathered from an initial search between 1980 and July 2005 restricted meta-analysis to the 39 papers which contained only patients > 18 years of age who were defined as euthymic and included only cognitive measures used in at least eight other studies. These 15 measures were grouped into 4 domains. Along with several tests of premorbid IQ, attention/processing speed, and memory, 5 tasks were separately classified as belonging to executive/ working memory; all of which showed significant impairments in patients versus controls: digitspan backwards ($g=0.54$), trails b ($g=0.55$), WCST categories ($g=0.69$), phonemic verbal fluency ($g=0.47$), and Stroop interference ($g=0.71$). Two other meta-analyses also demonstrate similar non-specific deficits in executive functioning spanning across multiple tasks of the proposed executive dimensions of working memory, set shifting, and response inhibition (Robinson et al 2006, Arts et al 2008). Focus of more recent investigations has shifted towards the identification of sources of heterogeneity between studies; the potential mediating role of frequently lingering mood symptoms, illness progression, and ongoing pharmacological treatment will be discussed in the following sections. A brief summary of evidence is included in Table 1.2.
Table 1.2: Effects of Mood Phase, Stage, and Antipsychotic Use on Executive Function in Bipolar Disorder

<table>
<thead>
<tr>
<th></th>
<th>Working Memory</th>
<th>Set-Shifting</th>
<th>Response Inhibition</th>
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<tbody>
<tr>
<td>Mood Phase (Section 1.4.2)</td>
<td>No Effect</td>
<td>Verbal fluency more impaired during acute mood episodes</td>
<td>Go/No Go may be more impaired in hypo/mania</td>
</tr>
<tr>
<td>Stage (Section 1.4.3)</td>
<td>Heritable</td>
<td>Heritable</td>
<td>Heritable</td>
</tr>
<tr>
<td></td>
<td>Unimpaired in relatives</td>
<td>Impaired in relatives</td>
<td>Impaired in relatives</td>
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<tr>
<td></td>
<td>Impaired at illness onset</td>
<td>Impaired at illness onset</td>
<td>Impaired at illness onset</td>
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<td></td>
<td>Progressive ?</td>
<td>Progressive ?</td>
<td>Progressive ?</td>
</tr>
<tr>
<td>Antipsychotics (Section 1.4.4)</td>
<td>Negative Effects</td>
<td>Negative Effects</td>
<td>Negative Effects</td>
</tr>
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1.4.2 State Associated Deficits: Acute and Subsyndromal Mood Symptoms

Severity of executive impairments during hospitalization from an acute mood episode have been shown to be an important prognostic indicator of clinical and functional recovery (Malhi et al 2007, Gruber et al 2008, Pogge et al 2008, Levy et al 2011). While it is generally held that executive impairments are more severe during mood episodes than in euthymia, evidence to support this is inconsistent. Studies directly comparing patient groups have yielded mixed results, with some findings supporting the idea that response inhibition and/or set-shifting may be more severely impaired during acute mood states, with working memory consistently unaffected. Ryan et al (2012) investigated executive function between euthymic (n=117), depressed (n=73), and hypomaniac/mixed (n=26) patients with BD and found that hypomaniac/mixed patients had significant deficits in “Inhibitory Control” (Go/NoGo accuracy on inhibitory trials) relative to both depressed and euthymic subjects, although “Processing Speed with Interference Resolution” performance (including Stroop, trails b, and several non-executive tests) was comparable across all mood states, as was “Conceptual Reasoning and Set-Shifting” (includes WCST perseveration) and “Verbal Fluency and Processing Speed” scores. Only one other study has also found a relationship between phase and response inhibition: Stroop scores in patients during manic/mixed episodes (n=15) were lower relative to euthymia (n=15; Dixon et al 2004); this study also found impaired HSCT abilities in depressed subjects (n=15) relative to euthymia. Most other studies have found no differences between hypo/mania or depressed and euthymic patients in response inhibition,
including the Stroop (Martinez-Aran et al 2002, 2004; Malhi et al 2007) and on the SOC (Malhi et al 2007, Maalouf et al 2010) or TOH (Xu et al 2012).

Although there are reports of no differences between symptomatic and euthymic subjects on performance of most set-shifting measures including the trails b and WCST (Martinez-Aran et al 2002, 2004, Malhi et al 2007, Xu et al 2012); impairments in verbal fluency have been seen in depression relative to euthymia (category or phonemic- Martinez-Aran et al 2002, 2004), and mania/mixed episodes relative to euthymia (Martinez-Aran et al 2002, Dixon et al 2004). In a non-independent sample of 25 patients with BDI assessed one or more times across 30 months (n=15 while euthymic, n=14 depressed, n=12 hypomanic), while there was no difference between any patient groups on WCST or trails b, only the depressed group performed worse than healthy subjects (n=25) on phonemic verbal fluency with those who were hypomanic impaired on category verbal fluency (Malhi et al 2007). Meta-analysis of 42 studies of patients with euthymia, 5 with depression, and 13 using mixed or manic samples directly compared functioning between mood states and found that samples of patients in the depressed state had significantly larger effect sizes than those using euthymic patients in phonemic verbal fluency but not trails b, and studies of mixed/manic patients showed comparable effect sizes to euthymic samples in phonemic verbal fluency, WCST perseveration, and trails b (Kurtz & Gerrarty 2009).

Reports on working memory consistently find no difference according to phase. Comparison of performance between euthymic (n=37) and symptomatic (n=43) patients with BDI on a comprehensive neuropsychological battery (Burdick et al 2011) found no significant differences in any cognitive domain, including working memory (letter number sequencing). Yates et al (2011) also found no differences between depressed (n=34) and euthymic (n=31) patients with BD in letter number performance, although only depressed patients demonstrated impairments relative to healthy subjects (n=34). Similar performance between manic/mixed, depressed, and euthymic subjects on digitspan backward has also been seen (Martinez-Aran et al 2002, 2004).
Subsyndromal mood symptoms frequently persist into times of euthymia, and studies statistically correcting for this reduces effect sizes seen versus healthy subjects (Ferrier et al 1999, Clark et al 2002, Thompson et al 2005, Pradhan et al 2008). Significant post-hoc relationships between test performance and residual manic or depressive symptoms, however, are not often reported (Kravariti et al 2012, Lewandowski et al 2011, Hellvin et al 2012). Several longitudinal studies examining the stability of cognitive function have found that patients with BDI have a much higher intra-individual variability in composite cognitive score compared to healthy subjects, but this was not significantly related to variation in co-occurring mood levels throughout multiple testing points over 6 month follow up (Depp et al 2012) or over 1-3 years in subjects who were middle aged or elderly (Depp et al 2008). Consistent with studies of acute patients, in a 3 month follow up of 29 patients with BD, Chaves et al (2012) found a negative relationship between changes in depression and phonemic verbal fluency, but not between manic or depressive symptoms and semantic fluency, trails b, or digitspan backwards. Over 2 year follow up, Arts et al (2011) found levels of psychopathology (manic, depressive, and/or psychotic symptoms) together but not individually related to changes in working memory. These results indicate that acute or subthreshold mood symptoms alone do not account for the severity of executive deficits witnessed in BD. Furthermore, while it is important to both experimentally and statistically control for mood symptoms when examining abilities, the specific relationship between cognitive and affective variability in this disorder is still not yet understood.

1.4.3 Stage Associated Deficits: Illness Risk and Progression

Recent developments have led to conceptualization of BDI as being progressive, with symptoms becoming increasingly more serious and disabling over the natural disease course (reviewed by Vieta et al 2011). According to this hypothesis, over the course of illness acute episodes become more severe and refractory to treatment (Tohen et al 2010, Berk et al 2011), with an increased risk of relapse (Kessing et al 2004) and decreased length and degree of interepisodic recovery (Azorin et al 2011). While not empirically validated, according to this proposed clinical staging model patients with BD transition from early and at risk stages (0) onwards towards mild or non-specific symptoms (1a) or prodromal patterns (1b) which
eventually cumulate into a first depressive or manic episode (2), then onto a subsequent subthreshold (3a), or threshold (3b) relapse and a continuing pattern of recurrence and remission (3c), with the final stage (4) being of an unremitting or treatment refractory course (Berk et al 2007). Although there is little evidence to indicate a relationship between executive functioning and illness stage, theoretical review of overall cognitive functioning in BD posits that impairments may in part precede illness onset (likely as a function of genetic risk), become exacerbated around the time of the first episode, and steadily decline as a function of the number of recurrences with only limited recovery in periods of euthymia (Lewandowski et al 2011). Although there are no prospective studies examining the trajectory of executive impairments over a sufficiently long term follow-up to detect such stage related changes, cross sectional findings in a variety of sample populations provide preliminary support to the hypothesis that executive function is impaired at all illness stages, with some abilities potentially deteriorating over the course of illness.

Twin studies place the heritability estimate of BD upwards of 89% - the highest of any psychiatric disorder (McGuffin et al 2003), and impairments in healthy first degree relatives of patients (Stage 0) are considered to be indicative of a shared genetic risk between illness and executive performance. Genes that have been implicated in BD are also important for executive functions (Savitz et al 2007, de Souza et al 2010, Backlund et al 2011, Kutumbarao et al 2011), and significant heritability estimates of 50-70% for executive test scores have been seen in families with BD- specifically digitspan backward, letter number, trails b, Stroop, as well as phonemic and semantic verbal fluency (Antila et al 2007, Glahn et al 2010). Similarly, meta-analysis of 17 studies of relatives compared to healthy subjects found impaired performance in Stroop, trails b, phonemic verbal fluency, and WCST perseveration of a lesser severity than that seen for bipolar probands, with no significant deficits in WCST categories or digitspan backward (Bora et al 2009). An earlier examination of 14 studies (Arts et a 2008) found healthy first degree relatives had impaired Stroop and trails b but not phonemic verbal fluency, digitspan backward or WCST perseveration or WCST categories compared to healthy subjects. More recently, Schulze et al (2012) found healthy first degree relatives of patients with BDI (n=42) had deficits in response inhibition (HSCT) but not working memory (SWM) or set shifting (ID/EDS) when compared to healthy subjects.
Similarly, impairments in HSCT but not verbal fluency were also seen in the small group of relatives (n=15) examined by Christodoulou et al (2012), and SOC deficits were noticed in 30 siblings of patients with BDI versus healthy subjects (n=30; Kulkarni et al 2010). There have been negative findings in comparative studies of response inhibition, however; Kravariti et al (2009) found no differences in Stroop performance between healthy first degree relatives of patients with BDI (n=45) and healthy subjects (n=45). Familial loading of deficits may not be restricted to this domain either, impairments in trials b and visual span backward have also been found in healthy relatives (Antila et al 2007). As genetically based deficits are expected to co-segregate with risk for disease, even within families (Gottesman & Gould 2003), individuals at highest risk for BD should also have the poorest executive performance. Indeed, Meyer et al (2004) found that 67% offspring of patients with an affective disorder (unipolar depression or BD) who later met criteria for BD in young adulthood were impaired on the WCST in adolescence—compared to only 19% with unipolar depression and 17% with no major mood diagnosis. As there are no studies prospectively examining executive function performance in subjects at genetic (Stage 0) or symptomatic risk (Stage 1) before and after illness onset (Stage 2), the extent to which impairments may precede a diagnosis of BD are yet unknown.

Studies of patients in Stage 2 of the illness are primarily restricted to subjects experiencing or in recovery from their first manic episode. Although depressive episodes frequently precede those of mania, because DSM-IV (APA 1994) and proposed DSM-V (APA 2012) guidelines for BDI require a current or past history of mania, and since criteria for depressive episodes between bipolar and unipolar disorder are identical, individuals with BDI who debut with depression are fated to receive an incorrect diagnosis of major depressive disorder. Although there is a report of executive impairments during a first or second depressive episode in unipolar depression (Gohier et al 2009), this may not persist following symptomatic remission (Kyte et al 2005), and whether severity is related to or a risk factor for a later BD diagnosis is unknown. In contrast, there are several studies examining the severity of executive function in patients surrounding the time of their first manic episode. Zabala et al (2010) found severe impairments in working memory (letter number, digit span backward; mean z score difference vs healthy subjects =0.84) and executive function (trails b, WCST,
semantic and phonemic verbal fluency, Stroop; mean difference=0.90) in subjects with BDI between the ages of 7-17 soon after stabilization of their first psychotic episode (n=19). These deficits were comparable to subjects with a first episode of schizophrenia (n=36) or other psychosis (n=52). This severe, non-specific range of executive impairments has also been seen in similar adult samples; with implicated tests including digitspan backwards, HSCT, and phonemic verbal fluency (Barrett et al 2009). Problems persist following recovery from mood symptoms, Hill et al (2009) found impairments in a composite measure of working memory (digitspan backward, visual span backward, spatial working memory) but not reasoning/flexibility (trails b, cog state set shifting, and penn conditional exclusion task) or processing speed (including category and phonemic verbal fluency, as well as two non-executive measures) in patients with BDI experiencing their first psychotic manic episode (n=22) compared to healthy subjects (n=41) that did not improve more than practice following 6 weeks of treatment. Similarly, Kolur et al (2006) found deficits relative to healthy subjects (n=30) in Stroop, trails b, and WCST in euthymic patients with BDI with no more than two prior affective episodes with less than 5 years duration of illness (n=30).

Although never specifically stated, most studies of executive functions in euthymia and other mood states can be considered to be representative of patients belonging to Stage 3. Cross sectional studies indicate a significant relationship between number of prior episodes and set shifting performance, particularly on the WCST (Denicoff et al 1999, Zubieta et al 2001, Bora et al 2007), although negative findings have been reported for this test (Fleck et al 2008) as well as for verbal fluency (Denicoff et al 1999, Zubieta et al 2001, Cavanagh et al 2002). Although a relationship with prior episodes has also been seen with the Stroop (Rocca et al 2008), there are several negative findings using this test of response inhibition (Denicoff et al 1999, Zubieta et al 2001, Cavanagh et al 2002) as well as with the HSCT (Cavanagh et al 2002, Rocca et al 2008). There are further indications from studies comparing patients with a history of a single vs multiple manic episodes that set shifting impairments may become more severe with episodic recurrence: symptomatic patients who had experienced several past manic episodes (n=26) performed worse than those suffering from a first manic episode (n=19) on phonemic but not category verbal fluency (Lebowitz et al 2001). Similarly, in one comparison of set shifting performance (WCST, trails b) between euthymic
patients with BDI who had recently recovered from their first manic episode (n=50), patients in recovery who had experienced multiple manic episodes (mean(SD)=4.54(2.02); n=50), and healthy subjects (n=50); it was found that although first-episode patients were impaired relative to healthy subjects, those with multiple recurrences had significantly worse functioning compared to both other groups (Elshahawi et al 2011). In another study looking specifically at the WCST, numerical differences between symptomatic patients with multiple past manic episodes (n=34) compared to patients experiencing their first manic episode (n=21) were not significant (Fleck et al 2008). Another comparison of euthymic subjects with BDI with either one (n=24), two (n=27), or three or more (n=47) prior manic episodes found that those with three or more episodes performed worse than those with a single episode on both semantic and phonemic verbal fluency, as well as the Stroop; while those with two episodes were impaired vs the first episode group only on digitspan backwards. Significant differences between the two and three or more episode groups were only found for the Stroop (Lopez-Jamarillo et al 2010). Such stage related deficits have not always been found, however, Hellvin et al (2012) found equivalent WCST as well as Stroop, letter number, and n-back scores between patients receiving treatment for a manic episode who had (n=21) or did not have (n=24) a prior untreated manic episode. Prospective studies longitudinally demonstrating changes in executive performance following multiple affective recurrences are non-existent.

Although there are no studies specifically addressing the hypothesis that executive functions would be more severely affected in subjects with BDI who could be judged to be a Stage 4 (frequent, severe, treatment refractory episodes) there are several that use different criteria to directly compare individuals who were of “good” vs “poor” outcome. Levy et al (2009) found that the duration of hospitalization for an affective episode corresponded with severity of impairments on the Stroop, WCST, phonemic fluency, but not category verbal fluency or trails b at discharge. Furthermore, impairments on these same tests were significantly larger for individuals who were re-hospitalized in the subsequent 3 months (Levy et al 2011). Differences have not always been found, Ferrier et al (1999) divided patients according to recent illness history; there was no difference in digitspan backward, visualspan backward, trails b, phonemic verbal fluency or TOH performance between those deemed of a good (≤ 2
major episodes in previous 5 years, recovery within 12 weeks of specialist referral) versus poor (≥ 3 episodes or ≥ 1 year unremitting illness over past 2 years) outcome. Within the meta-analysis of studies of cognition in euthymic patients with BDI, Mann-Wrobel et al (2011) was also able to compare performance on several executive tests between subjects of a good (no history of psychosis, <2 major affective episodes in the previous 5 years, or high functioning on a clinical global assessment rating) or poor (history of psychosis, >3 episodes in the previous 2 years, or low functioning on the global assessment scale) outcome; and found greater impairments in the poor outcome group on the trails b and WCST categories, but not WCST perseveration nor category or phonemic verbal fluency. These results must be viewed with caution, as none of the individual analyses specifically identified or compared patients according to this clinical staging model.

From these preliminary comparisons, it appears that executive function impairments are present in all stages of BD, which evidence tying each domain with genetic risk. Response inhibition and set-shifting in particular may in part be exacerbated during acute episodes, as well as may get progressively worse over the course of illness. An alternative hypothesis would be that severity of impairments predict rather than precede an unfavorable course. Because there are no studies directly examining how executive function changes prospectively over the course of illness, it is yet unknown which of these two theories is correct. A complex interaction between the two possibilities is likely, as is further influence by another factor: pharmacological intervention.

1.4.4 Medication Associated Deficits: Antipsychotics

While there is a variety of treatment strategies available for BD, their efficacy is still far from satisfactory, particularly in regards to long term prophylaxis (Fountoulakis & Vieta 2008). Even after recovery from an acute manic or depressive episode, patients suffer from high rates of relapse, lingering symptoms, and continued functional impairment. The maintenance phase of treatment in BD begins after two months of sustained recovery from an acute episode and is critical to minimize the frequency, duration, and severity of subsyndromal symptoms, prevent relapse or recurrence; as well as limit further
hospitalizations, morbidity, mortality, and improve functioning and quality of life in sufferers of this chronic condition (Yatham et al 2009). There are a variety of treatment options available with polypharmacy being increasingly utilized (Arvilommi et al 2010). Mood stabilizers (lithium or anticonvulsants such as valproate) are the cornerstone of therapy and antipsychotics (dopamine D2 receptor antagonists; first generation or “typical” such as haloperidol and second generation or “atypical” including risperidone, quetiapine, or olanzapine) are frequently used adjunctively (Bowden 2005).

To date, no randomized controlled designs have been implemented in patients with BDI to specifically test the effects of maintenance treatment on cognitive function. Rather the only available information comes from post-hoc comparisons done in cross sectional studies of patients who are receiving naturalistic treatment, where the effects of prescription bias or pre-existing cognitive differences between groups cannot be ruled out. While in these studies the cognitive impact of the mood stabilizers lithium and valproate appear to be modest and limited to minor effects on memory (Pachet & Wisniewski 2003, Senturk et al 2007, Goswami et al 2009, Wingo et al 2009, Lopez-Jaramillo et al 2010), post-hoc analyses have consistently suggested an association between use of antipsychotics and decreased performance on tests of executive function.

The extent of executive impairments that may be attributable to atypical antipsychotic use is not trivial: in one study of 40 euthymic patients with BDI Jamrozinski et al (2009) found that while those who were not receiving antipsychotics (n=22; medicated on 0-3 other mood stabilizers, antidepressants, or anxiolytics) had normal performance compared to healthy subjects (n=40), those treated with an antipsychotic (n=18; 3 typical, 14 atypical, 1 both; 2-5 total medications) were impaired compared to both groups on German versions of many cognitive tests including those assessing set shifting (trails b, semantic verbal fluency, WCST) and inhibition (TOH). No group differences were seen on phonemic verbal fluency, and working memory was not assessed. In another study, working memory (letter number, digitspan forward) but not set shifting (trails b, semantic verbal fluency) impairments were predicted by antipsychotic use by 51% (94% atypical) of a sample of patients with BDI (n=65; Dittmann et al 2008). In a sample of 43 euthymic patients with BDI, use of
antipsychotics by 51.2% of subjects significantly predicted impaired working memory as well as response inhibition (HSCT, Stroop) and set-shifting (phonemic verbal fluency but not WCST) performance (Donaldson et al 2003, Frangou et al 2005), although neither study compared those receiving typical (n=10) vs atypical (n=12) agents. Although specifics regarding proportions were not provided, another study of 49 subjects with BDI found negative association between antipsychotic use and Stroop, WCST perseveration, but not phonemic verbal fluency or digitspan backward (Savitz et al 2008).

Along with study differences in clinical composition, much of the variability within these findings is likely to be dependent on which antipsychotics are being compared. Reinares et al (2000) found that euthymic subjects with BD receiving long term treatment (>6 months) with risperidone (n=11) performed significantly better on trails b than those on the typical drugs (n=9). There also may be important differences between atypical agents: Torrent et al (2011) divided euthymic patients with BDI in to those receiving quetiapine (n=12), olanzapine (n=26), or risperidone (n=30); and in head to head comparisons found Stroop impairments in those being treated with risperidone vs olanzapine, phonemic verbal fluency deficits in those on olanzapine vs quetiapine; with no differences between patient groups on trails b or WCST. Pretreatment or treatment independent differences in this sample are a likely confound however, as clinical features varied significantly between medication groups.

From the above studies it is clear that antipsychotic agents have an important impact on executive function performance BDI. There is a severe lack of randomized controlled studies examining the efficacy of these agents that also includes measures of cognition; rather all available analyses have been done in the context of naturalistic treatment. Pretreatment differences cannot be ruled out, and are even likely due to clinical heterogeneity. These studies also suffer many other serious methodological limitations, such as restrictions to post-hoc comparisons of larger patient samples that may be either “on” or “off” antipsychotics, with limited effort to separate effects of different agents.
1.5 Neural Structures Critical for Executive Functions

1.5.1: Dorsolateral Prefrontal Cortex

Historically, executive abilities were equated to prefrontal lobe function, often with outright assumptions that the two terms were synonymous (Fuster 1989). While it is clear that other prefrontal regions also play an integral role in cognitive control, aspects of executive function that are best captured by neuropsychological tests stem mainly from the dorsolateral prefrontal cortex (DLPFC; Stuss & Levine 2002). Lesions to this particular area lead to a consistent inability to temporally organize goal directed actions in terms of behaviour, cognition, and language (Fuster 1997, 2002). A meta-analysis of 193 functional magnetic resonance imaging (fMRI) studies of 2,832 healthy subjects during executive function tasks (divided into the dimensions of set-shifting, inhibition, working memory, initiation, planning, and vigilance) confirmed that the DLPFC (BA 9&46; Petrides 2005) is robustly activated across all executive measures when compared to an active control condition (Niendam et al 2012).

Examination of white matter communication pathways in both macaque monkeys (Modha & Singh 2010) and humans (Catani et al 2012) suggest that the prefrontal cortex plays a central role in both integrating and distributing information throughout the brain. Input to the DLPFC from other cortical areas is important to provide up to date neural representations of both the internal and external environment (Funahashi et al 2001, Petrides 2005, Tanji & Hoshi 2008), and direct connections with posterior auditory, visual, and somatosensory association areas allow identification and location of sounds, visual object recognition and localization, localization of our bodies in space, and the perception of pain. Conscious recall of memories may be done through connections with the retrosplenial cortex and parahippocampal gyrus. Communication with the cingulate gyrus provides input regarding error detection, reward anticipation, empathy, and emotion. The orbitofrontal cortex, with linkage to limbic regions provides information on affective value of stimuli, decision making, expectations, and sensitivity to reward and punishment. As well as receiving input from these regions, the DLPFC is able to actively maintain and manipulate information.
received (Wolters & Raffone 2008) and use it to bias processing in posterior regions, promoting or inhibiting functions according to current goal and/or situational contexts (Funahashi 2001, Miller & Cohen 2001, Herd et al 2006). Robust maintenance and stabilization of posterior input is done with the help of dopamine from the mesocortical pathway acting primarily on D₁ receptors (D₁R; Cools & D’Esposito 2011).

There are many indications that the DLPFC may be dysfunctional in BDI. Meta-analysis combining results of 55 fMRI studies in BD found significant hypoactivity in the DLPFC (d=-0.49) that correlated with duration of illness (r=0.49) but not medication or mood symptoms. Larger regions of the PFC were also less activated in patients versus controls, including the superior frontal (d=-1.39), middle frontal (d=-0.95), and inferior frontal gyrus (d=-0.78) as well as the anterior cingulate (d=-0.44). In contrast; posterior cingulate, temporal, parahippocampal, and occipital regions as well as the hippocampus and amygdala were all hyperactive. This meta-analysis included 810 healthy subjects and 774 adults with BD (nmania=149, ndepression=109, neuthymia=348, ncombined=168) and combined results from affective, cognitive (including all three dimensions of executive function), motor, and rest tasks (Kupferschidt et al 2011). Another meta-analysis however, found functional changes only in the ventral prefrontal cortex during either emotional or cognitive tasks (Chen et al 2011). Likewise, morphological studies also show inconsistent results. Meta-analysis of 21 studies of 660 patients and 770 healthy subjects indicates that fronto-insular and anterior cingulate cortices show the most robust volume reductions in BD (Bora et al 2010). Most studies find equivalent DLPFC volumes between patients and healthy subjects (Adler et al 2005, McDonald et al 2005, Chen et al 2007, Scherk et al 2008, Almeida et al 2009, Delaloye et al 2009, Yuksel et al 2012). There is support for the proposition that along with the rest of the PFC, the DLPFC may be structurally normal early in the course of illness (Adler et al 2007, Yatham et al 2007, Perico et al 2011, Watson et al 2012; but also see Janssen et al 2008, de Castro-Manglano et al 2011), with grey matter loss associated with the number of prior episodes (Ekman et al 2010) or acute mood symptoms (Brooks et al 2009). It is also likely that medications also affect structure, with lithium use potentially increasing prefrontal grey matter (Monkul et al 2007). While a post-hoc meta-analysis revealed inconsistent effects of antipsychotics on structure in BD (Hafemen et al 2012), longitudinal
study of first episode schizophrenia hints towards potential degenerative effects (Ho et al 2011). Together, these sources of clinical heterogeneity make interpretations of neuroimaging studies in BD difficult.

1.5.2 Cortico-Striatal-Pallidal-Thalamo-Cortical Loops

Traditionally, it was hypothesized that executive function occurred through hierarchical control of subcortical and posterior structures by the DLPFC and related prefrontal regions, a circuit that is now considered to be far too simplistic (Parvizi 2009). Reviews of basal ganglia function suggest that it is a system which dynamically, adaptively, and selectively gates information flow to and from the prefrontal cortex. According to these models, the PFC maintains many integrated representations simultaneously (such as simple actions, complex behaviours, active memory contents, or cognitive operations; Cohen & Frank 2009). The basal ganglia are believed to continually direct and modulate prefrontal-posterior connectivity, facilitating input to the PFC from some regions while reducing the strength from others. Through complex computational processes within the striatum and rest of the basal ganglia, representations from posterior processes which are more goal relevant or have a higher probability of being correct or rewarded are strengthened or focused on in the PFC, with those which are not being weakened (Hazy et al 2007, Bullock et al 2009, Cohen & Frank 2009, Stocco et al 2009, O’Reilly 2010). The type of processing within a cortical region is dependent on its connections, and it is believed that this is arranged within the PFC on a three-dimensional rostral/caudal (abstract/concrete), medial/lateral (hot/cold), and dorsal/ventral (how/what) axis (O’Reilly 2010); an organization system mirrored in the striatum (Haber et al 2006, Leh et al 2007, Draganski et al 2008). Connections between the prefrontal cortex and striatum can be organized into multiple separate yet integrated cortico-striatal-pallidal-thalamo-cortical loops (Figure 1.1) controlling affect/motivation, motor, and executive functions (Alexander et al 1990, Joel & Weiner 1994, Masterman & Cummins 1997, Utter & Basso 2008, Choi et al 2012).
Figure 1.1: Schematic Diagram of the Circuitry and Neurotransmitters of Cortico-Striatal-Pallidal-Thalamo-Cortical Loops

![Diagram of Circuitry](image)

Abbreviations: D1R: D1 dopamine receptor; D2R: D2 dopamine receptor; GPi: globus pallidus internal segment; GPe: globus pallidus external segment; SNr: substantia nigra pars reticulata; SNc: substantia nigra pars compacta; STN: subthalamic nucleus

Striatal projections from the DLPFC are primarily to the head of the caudate, with some efferents located in the putamen rostral to the anterior commissure, with projections caudal to the anterior commissure confined to the medial and central portion of the caudate with few terminals in the central and caudal putamen (Calzavara et al 2007, Haber et al 2006, Selemon & Goldman-Rakic 1985). Here, DLPFC inputs converge with those originating from other prefrontal areas, as well as parietal, occipital and temporal areas coding for visuospatial, auditory, and mnemonic stimuli. Non-cortical areas projecting to the caudate include the dorsal parafascicular thalamus which receives input from supplementary frontal eye fields, the superior colliculus, and other prefrontal cortical areas. Neuromodulation of the striatum comes primarily through dopamine from the medial substantia nigra pars compacta, although the dorsal raphe and the central midbrain tegmentum also provide serotonergic and noradrenergic input (Cummings 1995).

The striatum is made up of 90-95% medium spiny neurons which use GABA and peptides as neurotransmitters. Two separate pathways exist (Figure 1.1)- the “Go” which sends striatal
inhibitory GABA fibres colocalized with substance P to the dorsomedial globus pallidus internal (GPI) and rostral substantia nigra pars reticula (SNr) which then sends inhibitory GABA projections to the mediodorsal and ventral anterior nuclei of the thalamus, and the “No-Go” pathway which projects from the striatum to the globus pallidus external segment (GPe) using GABA and enkephalin, then to the subthalamic nucleus which transmits excitatory glutamatergic output to the the GPi and SNr which sends inhibitory GABA projections to the mediodorsal, ventral anterior, and ventrolateral thalamus. As the GPi output to the thalamus has a spontaneous rate of discharge resulting in tonic inhibition, activation of the direct pathway results in disinhibition (excitation) of the thalamus while the indirect pathway serves to increase inhibitory output. (Haber et al 1990, Hedreen & DeLong 1991, Lynd-Balta & Haber 1994, Kuo & Carpenter 1973, McFarland & Haber 2000, Middleton & Strick 2002, Selemon & Goldman-Rakic 1990). Output of the ventral anterior thalamus is to motor and premotor areas, while the mediodorsal thalamus connects via excitatory glutamatergic projections to layer IV of the DLPFC (BA 9 & 46) as well as the frontal pole (BA 10), supplementary motor cortex (BA 6), and BA 8 which is involved in planning of complex movement (Ilinsky et al 1985, McFarland & Haber 2002, Strick 1976).

Activation of the Go pathway results in posterior updating of the prefrontal cortex, while the NoGo interrupts communication (Stocco et al 2010). Dopamine modulates both the “Go” and “No-Go” pathways in different ways. D1R are located primarily on “Go” striatal neurons where dopamine from the nigrostriatal pathway enhances signal: noise ratio by increasing the excitability of highly active cells and decreasing firing of those which are less active. In contrast D2 receptors (D2R) are present in the “No-Go” pathway, and dopamine here inhibits neuron firing, independent of activity levels (Frank & O’Reilly 2006).

1.5.3 Caudate

The caudate is acknowledged to play a critical role in the selection and gating of prefrontal cortical connections necessary for working memory (Hazy et al 2007), set shifting (Hikosaka & Isoda 2010, Hazy et al 2007) and inhibition (Isoda & Hikosaka 2011). Along with being consistently activated both within and across all executive dimensions during fMRI studies.
(Niendam et al 2012), injury or disease to this structure also leads to executive impairments parallel to those seen with DLPFC damage (Grahn et al 2008). Meta-analytic connectivity modelling of fMRI studies confirm the caudate’s involvement in a wide cortical and subcortical network; along with the DLPFC multiple prefrontal, sensory, mnemonic, and motor areas were consistently coactivated with the caudate across action, cognitive, emotional and perceptual tasks (Robinson et al 2012).

Along with other parts of the basal ganglia, the caudate is frequently reported to be hyperactive in patients with BDI, with meta-analysis showing over-activation across mood states (Chen et al 2011). Similarly, Kupferschmidt et al (2011) also found moderate hyperactivity \( (d=0.57) \) in adult patients versus healthy subjects, positively associated with both proportion of male subjects \( (d=0.88) \) and manic symptoms \( (d=0.72) \), but not duration of illness, medication, or depressive symptoms. Structural studies are more inconsistent, with reports of volume increases and decreases, amongst many negative results (reviewed by Bonelli et al 2006, Marchand & Yurgelun-Todd 2010). While not universal, research does suggest that the caudate may be larger earlier in the course of illness (Strakowski et al 2002, Wilke et al 2004, Chen et al 2012; Liu et al 2011, but also Watson et al 2012); potentially as a consequence of genetic risk (Noga et al 2001, Hajek et al 2009). Grey matter here also may be lost at an accelerated rate in this disorder (Chen et al 2007), with older adults showing large reductions (Beyer et al 2004, Haller et al 2011). Antipsychotic medication may also play a critical role, although post-hoc comparisons in BD do not indicate any obvious effects (Hafemen et al 2012) studies in schizophrenic populations do suggest that many of these drugs may increase (Massana et al 2005) or decrease (Ebdrup et al 2011) caudate volume.

1.5.4 Other Neural Regions Supporting Executive Functions

The DLPFC, caudate, and rest of the basal ganglia do not work in isolation. Other areas consistently active during executive tests include the frontopolar cortex (BA 10), orbitofrontal cortex (BA 11), dorsal anterior cingulate cortex (BA 32), premotor cortex (BA 6), insula (BA 13), parietal lobe (BA 40, 71), occipital lobe (BA 19), temporal lobe (BA 22, 37), and cerebellum (Niendam et al 2012). While most of these regions can be considered to
play essential supporting roles in early processing of relevant stimuli, the anterior cingulate in particular is associated with higher level functions that also warrant specific mention. With strong connections with the DLPFC, parietal cortex, pre/supplementary motor areas (Devinsky et al 1995), insula (Deen et al 2010) and caudate (Haber & Knutson 2010); the dorsal anterior cingulate is believed to play an evaluative role in executive functions, providing a monitoring and feedback mechanisms to regulate the application of top-down control by the DLPFC (O’Reilly et al 2010). This region also contains both D₁R (Schweimmer & Hauber 2006) and D₂R (Lumme et al 2007), where dopamine from the mesolimbic pathway regulates network activation (Assadi et al 2009). While structural changes in this region and their relationship with will not specifically be examined in this thesis, they are still of high importance to BD. Both functional (Kupferschmidt et al 2011) and structural (Bora et al 2010) abnormalities have been reported in the ACC of patients with BD, with the relationship between volume and WCST performance previously shown to differ between patients and healthy subjects (Zimmerman et al 2006). The orbitofrontal cortex also plays an important role in both cognition and bipolar illness, although abilities ascribed to it more often implicate “hot” or affective/ motivational executive functions not described in this thesis (Rolls & Grabenhorst 2008)

1.6 The Systematic Treatment Optimization Program for Early Mania

Ongoing since 2004, the Systematic Treatment Optimization Program for Early Mania (STOP-EM) is invaluable for describing both trait and stage related impairments that occur through disease progression in BD. As part of regular expert clinical follow-up, the STOP-EM program is a prospective case-control study examining the cognitive and neurobiological changes that occur both immediately following a diagnosis of BD as well as over long term follow up in the context of naturalistic pharmacological treatment. Patients are recruited following clinical recovery from their first manic episode, and along with a complete clinical assessment they undergo a 3 Tesla (3T) T1-weighted structural magnetic resonance imaging (MRI) scan and cognitive testing using a comprehensive neuropsychological battery. Additional optional protocols include genetic and blood biomarker analysis. Follow up visits
are scheduled along regular intervals, with both neurocognitive testing and MRI scans at baseline, 6 months (no MRI), 1,3,5,7,10,13,15, 17 & 20 years.

Initial reports on functional outcomes from the first 53 patients enrolled (Yatham et al 2009) describe this sample as being early in the course of what could potentially be a severe lifelong illness. 88% of these patients were hospitalized, and 68% also presented with psychosis. 58% had a prior episode of depression, and 12% retrospectively reported a history of hypomania. Patients with comorbidities were not excluded, as is often seen in samples with BDI: 54% had a substance use disorder, 20% alcohol abuse, 10% anxiety and 26% with a general medical condition. Most patients were treated with a mood stabilizer (87%) and/or an antipsychotic (77%). Although initially almost 63% met criteria for euthymia (Kauer St-Anna et al 2011) over half experienced a subsequent hypo/manic (24%) or depressive episode (41%) in the following year, with the mean time being well less than 8 months (Yatham et al 2009). Subthreshold depressive symptoms and verbal memory but not executive function scores were predictive of 6 month functional outcome (Torres et al 2011).

Results of cognitive assessment indicated that despite being young, well educated, and of high average premorbid intellectual functioning when compared to matched healthy subjects (n=25), patients (n=45) had moderate to severe impairments in nearly all abilities assessed; with the most severe deficits being seen in the domain of executive functioning (cohen’s d=0.82). Significant deficits in three individual tests were also found (SOC d=0.64, ID/EDS d=0.61, SWM d=0.72), although impairments in phonemic verbal fluency (d=0.23), trails b (d=0.58), Stroop interference (d=0.20) and letter number (d=0.37) did not survive correction for multiple comparisons. Although patients treated with an antipsychotic (n=30) had similar scores to those who were not (n=15), those on valproate (n=20) were impaired compared to those on lithium (n=16). Patients had very minimal subsyndromal mood symptoms, and these did not correlate with performance in executive function. Prior depressive or hypomanic episodes or substance abuse also showed no relationship with executive function (Torres et al 2010). Further investigation also found that executive function was not impaired in patients with a history of childhood trauma (41%) compared to those without (Bucker et al 2012).
Patients with BDI receiving follow-up with STOP-EM who contributed clinical, cognitive, and/or neuromorphological data to this program will be used as the population of interest in research chapters 2, 3 and 4; where further description of relevant protocols will also be provided.

1.7 Thesis Overview

The purpose of this thesis is to describe executive function deficits in BDI and their association with changes in brain structure, illness progression, and antipsychotic treatments. The body of this thesis is comprised of a three research chapters which use data collected from STOP-EM to examine the relationships between executive deficits and structural brain changes immediately following a diagnosis of BDI (Chapter 2) as well as progression in the following year according to clinical outcome (Chapter 3). Chapter 4 examines the impact of different atypical antipsychotics compared to mood stabilizer monotherapy on executive function in the context of naturalistic maintenance therapy.

Chapter 2 examines the association between executive function and brain morphology immediately following recovery from a first manic episode. The relationship between performance of three executive measures and volumetric changes of the DLPFC and caudate were examined. Findings that caudate enlargement rather than DLPFC reductions were related to impairments further emphasize the role of subcortical abnormalities early in the course of BDI, and support hypotheses that prefrontal abnormalities may rather emerge as a consequence of illness progression.

Chapter 3 uses both baseline and 1 year cognitive and neuroimaging data to investigate the differences in longitudinal executive function and grey matter changes in patients who maintain recovery versus experience an affective recurrence in the first year following a diagnosis of BDI. In agreement with theories on longitudinal cognitive progression in BDI, results show that patients who remained well had significantly improved executive function
when compared to those who experienced a subsequent mood episode. Consistent with this, those who remained well also had less prefrontal grey matter loss, including parts of the DLPFC. These results provide the first prospective demonstration of relative preservation of cognitive functions and (prefrontal) grey matter in those with sustained remission versus those who experience affective recurrence, and further suggest that neurobiological changes accompany illness progression BDI.

Chapter 4 examines the differences in executive performance between patients receiving different maintenance treatment regimes. Antipsychotic agents work primarily through antagonism of the D₂ dopaminergic receptor (D₂R), present in high concentrations in the striatum, providing a potential mechanism for the iatrogenic effects seen in patients treated with these drugs. As individual agents used differ primarily in their affinity for the D₂R, it is further likely that their negative impact may depend on relative affinity; with tighter binding drugs having a stronger negative effect. This was tested by comparing individuals receiving naturalistic treatment with either mood stabilizer monotherapy, or combination with a tightly binding drug (risperidone), or a loosely binding one (quetiapine). Consistent with hypotheses, findings show that subjects treated with risperidone had more severe executive impairments than those receiving quetiapine or no antipsychotic.

Finally, Chapter 5 summarizes the thesis and describes results in the context of current theoretical models regarding the pathophysiology in BD.
Chapter 2

Relationship between Frontostriatal Morphology and Executive Function Deficits in Bipolar I Disorder Immediately Following Recovery from a First Manic Episode

2.1 Introduction

Cognitive deficits, particularly in the domain of executive functioning, are a core feature of BDI, present not only during acute manic or depressive episodes but also persisting into periods of remission (Martinez-Aran et al 2004, Torres et al 2007). These skills are important for many aspects of daily life, and even modest impairments can lead to noticeable behavioural difficulties including problems in planning, organization, abstract reasoning, problem solving, and decision making (Burgess & Shallice 1996, Simblett & Batement 2011). Impairments in executive functioning may affect a patient’s ability to work and attend school, function independently at home, or develop and maintain appropriate social relations. As such, it is no surprise that problems in executive functioning are strongly associated with the marked psychosocial impairment present in people with BDI between mood episodes (Wingo et al 2009), a relationship even beyond the influence subsyndromal symptoms (Martinez-Aran et al 2007). This is a critical issue, even early in the course of illness. In the 2 years following syndromal recovery from their first manic or mixed episode less than half of patients return to their premorbid functional status (Tohen et al 2003). At this initial stage of diagnosis there are significant impairments in executive function, with results from the STOP-EM indicating that despite syndromal recovery and continuation of maintenance pharmacological treatment, patients who have recently suffered from their first manic episode still show significant deficits in many tests of executive function (Torres et al 2010). Similarly, Barrett et al (2009) found that after controlling for current intellectual abilities, the severity of executive impairments of patients with BDI experiencing their first episode of mania are similar to that of patients with schizophrenia during onset of psychosis.

As chronic effects of BDI on the presence or severity of executive deficits are still minimal at this point in the disorder, dysfunction is likely more closely related to risk factors associated
with illness expression. Indeed, poor executive function performance may be attributable to environmental factors such as childhood trauma or substance abuse (Savitz et al 2008), or as a consequence of genetic risk. Many of the same genes that have been implicated in BDI are also important for executive functions (Gosso et al 2008, Le-Niculescu et al 2007), with unaffected first degree relatives of patients also showing similar, though less pronounced, impairments (Arts et al 2008, Bora et al 2009). Dysfunctions may become progressively more severe throughout the course of illness (Elshahawi et al 2011); this may be a consequence of neurodegeneration by stress related overload of behavioral and physiological regulatory systems (Kapczinski et al 2008), as many neural regions implicated in executive function are sensitive to their effects (Arnsten 2009).

Prior studies examining the morphological basis for cognitive impairment in samples of patients with BDI have found that the relationship between brain volume and executive abilities differ between patients and controls in several subregions including the DLPFC, anterior cingulate cortex and basal ganglia (Zimmerman et al 2006, Haldane et al 2008, Hartberg et al 2011). However these were conducted in heterogeneous patient samples which included subjects of variable mood states and illness or treatment duration, and focused on regions of interest that were based on areas implicated in the general pathophysiology of BDI rather than executive function per se. Extensive studies in human and non-human cognitive neuroscience indicate that the DLPFC and its connections to the caudate nucleus of the basal ganglia are essential for executive function abilities (O’Reilly et al 2010, Simpson et al 2010). This circuit also shows relevance for the pathophysiology of BDI, potentially underlying not only cognitive deficits but also problems with emotional regulation that define this disorder (Marchand & Yurgelun-Todd 2010, Bennett 2011). Although inconsistent, prior structural imaging studies have found abnormalities in these regions. Caudate enlargements have been observed in adolescents with BDI (Liu et al 2011) and their unaffected relatives (Noga et al 2001), as well as in more heterogeneous samples (Bonnelli et al 2006). Reductions in DLPFC volume have also been found, and may be related to severity of mood symptoms (Brooks et al 2009) or illness progression (Ekman et al 2010).
**Study Hypotheses**

We hypothesized that compared to matched healthy subjects, patients will show significant impairments in executive function, and at this point in the illness caudate enlargements and DLPFC volume reductions would be associated with severity of deficits.

**2.2 Methods**

**2.2.1 Study Overview**

Computerized tests of executive function from the Cambridge Neurocognitive Test Automated Battery (CANTAB) are fairly specific to dysfunction in and between the DLPFC and caudate (Robbins et al 1998, Grahn et al 2008). By comparing performance on these tests to voxel based (Ashburner & Friston 2000) volumetric measures of these regions, this study will examine the relationship between frontostriatal morphology and severity of executive function deficits in BDI. Furthermore, through examination of a sample of patients following remission of their first manic episode, we will be able to minimize the potentially confounding effects of acute mood state, illness duration, or chronic treatment.

**2.2.2 Participants**

Clinically stable patients meeting *DSM-IV-TR* (APA 1994) criteria for BDI were identified through the ongoing STOP-EM at the University of British Columbia (UBC) Hospital and affiliated sites, as well as through community and hospital referrals from physicians and psychiatrists. All patients were diagnosed and identified for inclusion based on a comprehensive clinical assessment by an academic research psychiatrist and confirmed with a structured diagnostic interview (Mini-International Neuropsychiatric Interview; Sheehan et al 1998). Participants were required to be 14-35 years of age, and to be within 3 months of remission from their first manic/mixed episode, where remission was defined as no longer meeting DSM-IV-TR criteria for a manic/mixed episode for two consecutive weeks. Those who had experienced psychotic symptoms during a mood episode or any pre/comorbidities...
were not excluded as long as the primary diagnosis was BDI. Patients received ongoing
naturalistic treatment from psychiatrists with expertise in the management of mood disorders
according to current clinical practice guidelines (Yatham et al 2009).

Of the first 75 patients enrolled in the program, 56 completed a baseline cognitive
assessment and 3T MRI scan. 2 patients were excluded due to large artifacts in the MRI
scan, as were 12 experiencing acute mood symptoms (n=10 depressed, n=2 manic/mixed).
Of the remain 42 patients included in this analysis, 29% had neuroimaging and cognitive
testing done on the same day, for 63% the visits were within 2 weeks of each other, and 79%
a month; with all having both within 10 weeks).

Healthy subjects free of personal or family history of psychiatric illness in their first or
second degree relatives and matched to the patient sample by age, sex, and premorbid
intellectual function were recruited from the community through advertising. Of the first 42
recruited, 38 underwent neurocognitive testing and of those 30 also participated in an MRI
scan. Data from one subject who did not meet inclusion criteria (age 37) was excluded. For
24% of healthy subjects cognitive testing and neuroimaging were done on the same day, 62%
within 2 weeks, 83% in 1 month-and all had both visits done within 12 weeks of each other).

Ethics approval was granted from UBC Clinical Research Ethics Board, and written
informed consent was obtained from all patients and healthy subjects prior to performing any
study procedures.

2.2.3 Clinical Assessment

Several psychiatrist rated symptoms scales were completed by trained research psychiatrists
at the UBC Mood Disorders Centre. The Young Mania Rating Scale (YMRS; Young et al
2000) is a quick and frequently used rating scale to assess mania through clinician
observation and patient self-report (previous 48 hours). It contains a total 11 items; 7 rated on
a scale from 0-4 (4 being most severe; mood, energy, sexual interest, sleep,
language/thought, appearance, insight), with four symptoms given twice the weight (0-8;
irritability, speech, thought content, disruptive/aggressive behavior). The Hamilton Depression Rating Scale 29 item version (HAMD; Hamilton 1960) is a reliable and valid clinical and research tool frequently used to quantify depressive symptoms. Through observation and patient self-report clinicians rate 13 symptoms (mood, work/activities, social withdrawal, hypersomnia, fatigue, guilt, suicide, anxiety (psychic or somatic), hypochondriasis, motor retardation, agitation, and depersonalization) on a scale of 0-4; with 5 scored 0-3 (paranoia, diurnal variation, appetite increase or decrease, carbohydrate craving), and 11 from 0-2 (sexual, somatic (gastrointestinal or general), weight change, insomnia (early, middle, or late), insight, diurnal variation, and obsessions/ compulsions). Additional scales also used include Brief Psychiatric Rating Scale (BPRS; Overall & Gorham 1962) to measure general psychopathology (18 items rated from 1-7), and Positive and Negative Syndrome Scale, Positive Scale (PANSS; Kay et al 1987) to assess psychotic symptoms (7 symptoms rated from 1-7). The Global Assessment of Function (GAF; Hall 1995) was used to quantify clinician judgment of overall psychological, social and occupational functioning; done on a 100 point scale, scores from 0-50 represent severe symptoms or impairment, 51-70 moderate-mild symptoms or impairment, 71-90 transient, minimal, or absent symptoms or impairment; with 91-100 is indicative of ideal health and superior functioning. Further variables collected through patient self-report and hospital records included demographics, premorbid and current occupational functioning, the number of prior depressive episodes, history of psychotic symptoms during a mood episode, time since remission of manic symptoms, age of onset of illness, lifetime substance abuse or dependence, as well as dose and duration of current psychotropic treatment.

Based on both commonly used and recommended criteria (Tohen et al 2009), a cut-off of ≤12 on both the YMRS and HAMD at time closest to cognitive testing was used as the definition of sustained remission for study inclusion (n=42), and ≤7 used to identify a subset (n=29) that was fully euthymic. For 39% of patients, mood rating scales were administered on the same day as cognitive assessment, with 83% within 2 weeks, 90% in 1 month; and all within 2 months.
2.2.4 Assessment of Executive Function

All tests were administered in a quiet testing room following standard procedures. Described measures were included as part of a 2-3 hour neuropsychological battery containing paper and pencil as well as computerized tests spanning several cognitive domains. Three computerized measures from CANTAB were chosen to represent executive function abilities (Robbins et al 1998). Interactive demonstrations can be found with the CANTAB website (http://www.camcog.com/cantab-tests.asp). These tests were chosen based on their established sensitivity to prefrontal and striatal dysfunction (Grahn et al 2008). Internal consistency (Cronbach’s α) between the three measures was 0.70; indicating fair agreement.

*Spatial Working Memory (SWM)* is a self-ordered foraging test which requires examinees to retain spatial information and manipulate it in mind. The goal of this task is to find blue tokens hidden one at a time inside color boxes arranged on a touch computer screen. Once a token has been found, the subject is required to move it to a black column on the right side of the screen and then initiate a new search for subsequent tokens. The key instruction or this task is that once a blue token has been found inside a box, that box will not hide any more tokens. Between search errors are recorded when the subject returns to a box that has previously hidden a token.

*Stockings of Cambridge (SOC)* is a computerized version of the popular TOL or TOH planning tests. Subjects are presented with two combinations of colored balls hanging in pockets, one at the top and one at the bottom of a touch computer screen, and are required to rearrange the balls in the bottom in the same way seen in the top. Scoring is based on the number of arrangement solved in the minimum of number of moves possible.

*Intra-dimensional/Extra-dimensional Shift (IED/EDS)*, as a computerized version of the popular Wisconsin Card Sorting Test, involves a visual discrimination task starting with simple shape discrimination and reversal proceeding through tests of distraction, intradimensional, and then extradimensional target shifting. The extradimensional shift errors
measure will be used to this specifically assesses ability to shift response to the alternative, previously irrelevant stimulus.

Two measures of general intellectual function (IQ) were also included; the North American Adult Reading Test (NAART; Blair & Spreen 1989) uses pronunciation of 61 irregular English words as a quick estimate of premorbid IQ. This index is a reliable and valid measure of verbal intelligence with comparable psychometric properties to other commonly used tests (Uttl 2002). The Kaufman Brief Intelligence Test Full Scale IQ (KBIT) was used to assess current IQ (Kaufman & Kaufman 1990). This test quickly and reliably provides estimates of both verbal and non-verbal abilities.

2.2.5 T1 MR Image Acquisition and Preprocessing

Further information on MR imaging and preprocessing methods can be found in Appendix 1. T1-weighted MR images were acquired on a Philips Achieva 3T scanner (Amsterdam, The Netherlands) using a three-dimensional axial inversion recovery-weighted spoiled gradient recalled sequence and the following parameters: FOV = 25.6 cm, matrix = 256 × 256, isotropic voxels (1 × 1 × 1 mm3), TR/TE = autoset shortest, T/R head coil, flip angle = 8 degrees, and 1 mm thick contiguous 180 slices of the whole brain.

Data was processed and examined using the Statistical Parametric Mapping (SPM8) software (http://www.fil.ion.ucl.ac.uk/spm), where we applied voxel-based morphometry (VBM) implemented in the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm.html). VBM is a sensitive and frequently used tool for assessing localized differences in brain tissue independently of variability in brain shape (Whitwell 2009). T1 images were bias corrected, segmented into grey matter, white matter and cerebrospinal fluid, and applied an affine transformation to Montreal Neurological Institute (MNI) standardized stereotactic space. The affine registered grey and white matter segments were used to create a customized DARTEL template for non-linear warping (Ashburner 2007). Then, each subjects’ original images were normalized using the high dimensional DARTEL algorithm to MNI space. Normalized segmented grey matter images were multiplied by the non-linear components derived from
the normalization matrix in order to preserve actual grey matter values locally (modulation). This allows comparing the absolute volume of tissue corrected for individual brain sizes. The modulated normalized grey matter images with a voxel size of $1.5 \times 1.5 \times 1.5 \, \text{mm}^3$ were smoothed with an 8mm full width at half maximum (FWHM) Gaussian kernel.

### 2.2.6 Statistical Analysis

All data are reported as means and standard deviations (SD). Correlations, regressions, and group comparisons for clinical and cognitive variables were conducted using SPSS 19.0 (SPSS Inc, Chicago, Illinois). Group comparisons on clinical variables were conducted using chi square for categorical and independent samples t-test for continuous variables. To facilitate statistical comparison, antipsychotic doses were standardized according to relative D2R potency by the empirically grounded method proposed by Baitz et al (2012); whereby 1mg of loxapine is equivalent to 0.08mg risperidone, 5.73mg olanzapine, or 8.72mg quetiapine.

All executive raw scores were first adjusted for age, sex, and premorbid intelligence based on CANTAB normative data. Standardized z-scores for each measure were then calculated using the mean and standard deviation from the larger group of healthy subjects who underwent neurocognitive testing but may have not had an MRI scan. Summary executive scores were then calculated using the average standardized z-score of the three tests. This enhanced normalization of the distribution of variables, and allowed for ease of comparison between groups; which was done using independent samples t-test.

Bilateral masks for the DLPFC (Brodmann areas 9 &46; Petrides 2005) and caudate (head/body- the tail was excluded due to its role in sensorimotor rather than executive control (Dreganski et al 2003)) were generated using the WFU PickAtlas toolbox (Maldjian et al 2003). Group grey matter volume contrasts with small volume correction (SVC) were confined to these region of interest (ROI), using a two-sample t-test covarying for age, gender, and total grey matter. We report coordinates which meet a threshold of $p < 0.001$
uncorreted at the voxel level and p < 0.05 family wise error (FWE) corrected at the cluster level.

Separate Pearson correlations for patients and healthy subjects were used to examine the relationship between executive scores and morphological and demographic/clinical variables. For this analysis, grey matter volumes from the four ROIs were extracted from smoothed normalized grey matter images of all subjects using the MarsBar toolbox (Hammers et al 2002). Volumetric or clinical measures which showed at least trend correlation (p<0.1) with the summary executive score were included as predictors in a hierarchical multiple regression, with demographic variables entered in the first step, and clinical and morphological variables added in the second.

2.3 Results

2.3.1 Demographic and Clinical Features

The patient population (n=42) was young (mean (standard deviation)) 22.8(4.6) years, educated 13.4(2.3) years, and displayed average to high average premorbid IQ 106.8(7.2). Patients and the healthy subjects were comparable with regard to age, sex, and premorbid or current intellectual functioning (Table 2.1), although patients had a significantly lower level of educational attainment (t_{69}=-2.32, p<0.05). Patients had been in remission from their first manic episode for 47 (31) days. Overall functioning was only minimally impaired-average Global Assessment of Functioning score was 70(14). Of the 38 patients who were employed or in school prior to onset of the manic episode 60.5% returned to work or school, 31.6% were on sick leave or disability, and the remaining 10.7% were unemployed. All but two healthy subjects were employed or in school, one was on long term disability and the other was unemployed. The proportion of patients currently unemployed or on sick leave/disability was higher in patients than healthy subjects (\chi^2=11.11; df=1; p<0.001)

Patients were early in their course of illness, having experienced an average of 1.2(1.7) prior depressive episodes. Subthreshold symptomatology was low; mean YMRS 0.9 (2.1) and
mean HAM-D 3.7(4.2). 76% patients had history of psychotic symptoms during their first manic episode. 5 patients had a prior history of anxiety (n=4) or ADHD (n=1).

No patients had any exposure to mood stabilizing or antipsychotic treatment prior to their first manic episode; seven had previously been treated with antidepressant(s). At the time of assessment 90.5% of patients were taking pharmacological treatments: 71.4% were receiving combination treatment with an antipsychotic and a mood stabilizer, 11.9% mood stabilizer monotherapy and 7.1% antipsychotic monotherapy. One patient was being treated with an antidepressant. Average duration of current antipsychotic/ mood stabilizing treatment was 6.4(4.2) weeks. Average antipsychotic dose was 17.2(19.4) mg loxapine equivalents. The average dose of lithium and valproate were 909 (154) and 993 (375) mg, respectively.

**Table 2.1: Baseline Demographic and Clinical Features of Patients and Healthy Subjects**

<table>
<thead>
<tr>
<th></th>
<th>Bipolar I Disorder (n=42)</th>
<th>Healthy Subjects (n=29)</th>
<th>T-Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>t (df=69)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>22.8(4.6)</td>
<td>22.4 (3.9)</td>
<td>0.41, NS</td>
</tr>
<tr>
<td>Education</td>
<td>13.4(2.3)</td>
<td>14.7(2.3)</td>
<td>-2.32, p&lt;0.05</td>
</tr>
<tr>
<td>Premorbid Intellectual Function</td>
<td>106.7 (7.2)</td>
<td>107.0 (7.9)</td>
<td>-0.11 NS</td>
</tr>
<tr>
<td>Current Intellectual Function</td>
<td>105.6 (11.1)</td>
<td>109.3 (9.4)</td>
<td>-1.51, NS</td>
</tr>
<tr>
<td>Age of onset^</td>
<td>20.4(5.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of prior depressive episodes</td>
<td>1.2 (1.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAM-D</td>
<td>3.7(4.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>YMRS</td>
<td>0.9 (2.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BPRS</td>
<td>21.4(5.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PANSS</td>
<td>7.5(1.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GAF</td>
<td>69.7 (14.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days in remission from mania</td>
<td>47.4 (30.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weeks on medication</td>
<td>6.4 (4.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antipsychotic dose (mg loxapine)</td>
<td>18.5 (19.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% (n)</td>
<td>% (n)</td>
<td>χ²</td>
<td></td>
</tr>
<tr>
<td>Sex (male)</td>
<td>57.1 (24)</td>
<td>41.4 (12.0)</td>
<td>1.71, NS</td>
</tr>
<tr>
<td>Mood Stabilizer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lithium</td>
<td>40.4(17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Divalproex</td>
<td>45.2(19)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antipsychotic</td>
<td>78.6(33)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td>16.7(7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quetiapine</td>
<td>23.8(10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risperidone</td>
<td>38.1(16)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychosis during Manic Episode</td>
<td>76.2(32)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of Substance Abuse</td>
<td>42.9(18)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NS, non-significant (p>0.05); HAM-D, Hamilton Depression Inventory; YMRS, Young Mania Rating Scale; BPRS, Brief Psychiatric Rating Scale; PANSS, Positive and Negative Syndrome Scale; GAF, Global Assessment of Functioning

^Age of onset=age of first self reported hypo/manic or depressive episode
2.3.2 Comparison of Executive Function Scores between Groups

The distribution of the summary executive score of the two groups is shown in Figure 2.1. Table 2.2 reveals that patients had a significantly lower executive function summary score when compared to healthy subjects ($t_{69}=-4.10$; $p<0.001$). These results were maintained after covarying for education. Significant ($p<0.05$) impairments in the patient group were also seen in all of the three individual measures of executive function. These results were maintained after using the Mann-Whitney U test.

![Figure 2.1: Distribution of Summary Executive z-scores in Patients and Healthy Subjects at Baseline](image)

<table>
<thead>
<tr>
<th></th>
<th>Bipolar I Disorder (n=42)</th>
<th>Healthy Subjects (n=29)</th>
<th>T-Test</th>
<th>Effect Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary Executive Score</td>
<td>-0.73 (1.07)</td>
<td>0.10 (0.63)</td>
<td>$t$ (df= 1.70)</td>
<td>0.97</td>
</tr>
<tr>
<td>SOC problems solved in minimum moves</td>
<td>-0.74 (1.20)</td>
<td>0.21 (0.88)</td>
<td>-3.63 (p&lt;0.001)</td>
<td>0.88</td>
</tr>
<tr>
<td>ID/EDS EDS errors*</td>
<td>-0.70 (1.49)</td>
<td>0.14 (0.86)</td>
<td>-3.01 (p&lt;0.01)</td>
<td>0.69</td>
</tr>
<tr>
<td>SWM between search errors</td>
<td>-0.75 (1.35)</td>
<td>-0.04 (1.09)</td>
<td>-2.42 (p&lt;0.05)</td>
<td>0.58</td>
</tr>
</tbody>
</table>

SOC, stockings of Cambridge; ID/EDS EDS, intradimensional/extradimensional shift extradimensional shift errors; SWM, spatial working memory

*In cases where the EDS stage was not reached, 25 errors was substituted (Robbins et al 1998).
2.3.3 Volumetric Differences between Groups

Patients had increased gray matter volume in the right caudate (Figure 2.2. Cluster size= 169 voxels, p<0.05 corrected; peak voxel MNI coordinates= 18,17,15; t=3.77, p<0.05 corrected). There were no significant grey matter volume differences in the left caudate or right or left DLPFC.

**Figure 2.2: Voxelwise Grey Matter Comparison between Patients and Healthy Subjects at Baseline**

Displayed cluster is significant at peak threshold p<0.001 uncorrected, cluster p<0.05 (FWE-corrected)

2.3.4 Correlations between Executive, Clinical, and Morphometric Variables

In patients, there was a significant negative relationship between summary executive score and both right (r=-0.39, p=0.01) and left (r=- 0.34, p<0.05) caudate volume such that smaller caudate volume was associated with higher executive functioning (Figure 2.3). Specifically, right caudate volume was negatively correlated with SOC (r=-0.35, p<0.05) and SWM (r=-0.39, p<0.05) but not EDS (r=-0.15, p=0.37) performance. Similar correlations were also found for the left caudate: SOC (r=-0.32, p<0.05), SWM (r=-0.29, p=0.06), EDS (r=-0.11, p=0.50). In contrast, executive score did not correlate with right or left DLPFC volume (p>0.15).

Higher executive scores in patients showed a significant relationship with current intellectual functioning (r=0.37, p<0.05), and trend associations with higher premorbid intellectual function (r=0.27, p=0.09) and education (r=0.25, p=0.10). No correlations were seen between executive scores and age, or any illness variables including age of onset, current symptom scores, time since remission or medication dose or duration (all p>0.1).
Because of the potentially confounding effects of subsyndromal mood symptoms on the relationship between cognitive performance and frontostriatal volume, we next specifically examined correlates of executive function in the subgroup of patients (n=29) who met strict criteria for euthymia (HAMD, YMRS ≤7). In this group, a strong relationship with medication emerged, with poor executive performance significantly associated with increased duration of pharmacological treatment (r=−0.55, p<0.01), and higher dose of antipsychotic (r=−0.37, p<0.05). In these subjects, the correlation between right caudate volume and executive score was reduced to trend significance (r=−0.35, p=0.07), and the relationship with left caudate volume was non-significant (r=−0.27, p=0.17). There were no significant relationships between time on medication or antipsychotic dose and caudate volume (p>0.4).

In healthy subjects executive function positively correlated with right (r=0.39, p<0.05) and left (r=0.44, p<0.05) caudate volumes; in contrast to patients with BD the direction of this relationship was such that larger caudate volume was associated with better executive functioning. Specifically, right caudate volume showed a significant relationship with SOC (r=0.46, p<0.05) but not SWM (r=0.30, p=0.11) or EDS (r=0.11, p=0.58). Left caudate volume correlated with SOC (r=0.41, p<0.05), SWM (r=0.36, p=0.05), but not EDS (r=0.11, p=0.56). Executive score did not correlate with age, education, intellectual functioning or DLPFC volume (all p>0.1).

**Figure 2.3: Correlation between Summary Executive Score and Caudate Grey Matter Volume in Patients and Healthy Subjects at Baseline**

![Figure 2.3](image-url)
2.3.5 Regression Models Predicting Executive Function in Patients

In patients, for the first step of a hierarchical regression model current IQ (β=0.42, p=0.01) and education (β=0.08, NS) predicted the executive summary score in patients ($r^2=0.202$, $F=4.57$; df=2.39; p<0.05). Addition of right caudate volume (β=-0.30, p<0.05), duration of pharmacological treatment (β=-0.29, p<0.05) and dose of antipsychotic medication (β=-0.28, p<0.05) significantly improved the model ($\Delta F=4.41$; df=5,36; p=0.01); with the predictive value of current intellectual function (β=0.41, p<0.01) and education (β=0.08, NS) maintained. Together these variables accounted for 43.1% of the variance in executive function.

In the subgroup of patients who met strict criteria for euthymia for the first step of the hierarchical regression model intellectual function (β=0.38, p<0.05) and education (β=0.07, NS) showed trend significant for predicting of executive function ($r^2=0.16$, $F=2.50$; df=2,26 p=0.10). Addition of right caudate volume (β=-0.29, p<0.05), weeks on medication (β=-0.44, p<0.01) and antipsychotic dose (β=-0.37, p<0.01) significantly improved the model ($\Delta F=11.33$; df=5,23; p<0.001), and the predictive value of current intellectual function (β=0.41, p<0.05) but not education (β=0.07, NS) was significant. Together, these variables accounted for 66.1% of the variance in executive function.

2.4 Discussion

Results from this study confirm that patients with BDI who have recently recovered from their first manic episode demonstrate significant impairments in executive function when compared to healthy subjects, further showing that these deficits can be partially attributable to an enlargement of the caudate nucleus. These results are in strong accordance with Hartberg et al (2011) who found that volume of the right putamen, which shows much functional homology with the caudate (Haber et al 2006), was inversely related to the severity of executive (verbal fluency) deficits in a large sample of patients with bipolar spectrum disorder and schizophrenia.
Dysfunction in the caudate and other basal ganglia structures has been implicated in the pathophysiology of BDI for the last 2 decades (Bonnelli et al 2006, Marchand 2010). As part of the striatum- the main input structure of the basal ganglia- the caudate plays a primary role in the funneling and integration of higher order sensory, emotional and cognitive inputs from throughout the brain. Along with the rest of the basal nuclei, it is crucial for selectively gating what information gets updated in the DLPFC where it can be further integrated, maintained and/ or manipulated and used to bias processing in posterior regions (O’Reilly 2010, Simpson etl 2010, Utter & Basso 2008, Badre & D’Esposito 2009). fMRI studies consistently report hyperactivity of the caudate during both emotional and cognitive tasks in this population (Adler et al 2004, Lennox et al 2004, Chen et al 2006), and connectivity between the caudate nucleus and prefrontal cortex is altered in patients with BD when compared to healthy controls (Heng et al 2010, Yeh et al 2010, Pompei et al 2011).

Morphometric studies of the caudate indicate that despite minimal differences in volume between patients with BD and healthy subjects, abnormalities may still have biological significance. While there are several reports of increased caudate volume in patients with BD, most studies have yielded negative results (reviewed by Strakowski et al 2002, Marchand 2010). There is evidence to support that caudate abnormalities may precede onset of BD; in a study of offspring of patients with BD Hajek et al (2009) found a similar magnitude of caudate enlargement as the present analysis. In both unaffected and affected offspring, the maximal effect was found in the anterior portion of the caudate head, an area also linked to neuropsychological dysfunction in treatment naive patients with schizophrenia (Levitt et al 2004).

Genetic risk factors are likely to be at least in part responsible for the association between increased caudate volume and executive deficits in the current sample. Caudate volume is highly heritable, and related to variants in dopamine related functioning including genes coding for the D₂R and the dopamine transporter (Bertolino et al 2009), along with other factors important for dopamine signalling and development (Stein et al 2011). Genetic differences in the D₂R specifically has previously been associated with executive function performance in both healthy subjects (Stelzel et al 2010, Markett et al 2011) and patients
with schizophrenia (Tan et al 2012). Caudate volume has also been found to correlate with D$_2$/D$_3$ receptor binding potential in healthy subjects (Woodward et al 2009). Both D$_2$R and dopamine transporter variants have previously been implicated in risk for BD (Pinsonneault et al 2011, Zhan et al 2011), with PET studies indicating decrease dopamine transporter availability in the caudate of patients with BDI (Anand et al 2011) as well as increased D$_2$R levels in those who have experienced psychotic symptoms (Pearlson et al 1995). The relationship between these genotypes, associated protein expression levels, caudate volume, and executive function performance in BDI has yet to be investigated.

Both dose and duration of antipsychotic treatment further contributed to the extent of executive function impairments, an effect size similar to that of caudate changes. Several post-hoc analyses have indicated a strong negative effect of antipsychotics on executive performance in BDI (Savitz et al 2008, Donaldson et al 2003, Frangou et al 2005, Jamrozinski et al 2009), and iatrogenic effects of antipsychotic treatment on caudate volume also cannot be ruled out. While we did not detect any differences in volume between patients receiving antipsychotics and those who were not, this is likely due to the large variety of treatment combinations and short durations used in this first episode naturalistic design. The only available study of caudate morphology in relation to medication use was done by Hwang et al (2006), who found shape alterations compared to healthy controls were present in the right posterior dorsal and anterior ventral caudate in unmedicated patients, but not patients being treated with lithium, valproate, or atypical antipsychotics.

There have been several studies investigating the effect of atypical antipsychotics on basal ganglia volumes in first episode schizophrenia, most of which have found no effect of these agents on the caudate (Lang et al 2001, Dazzan et al 2005, Tauscher-Wisniewski et al 2005, Glenthoj et al 2007). However, Massana et al (2005) found that treatment with a high dose of risperidone was associated with an increase in caudate volume in initially treatment-naïve patients with schizophrenia, a finding that was attributed to the similarity in pharmacodynamic profiles between risperidone and typical antipsychotics, which do increase caudate volume (Chakos et al 1994). While limited, rodent studies suggest volume increases in the caudate induced by typical antipsychotics are due to neuronal swelling and gliosis, but
are also accompanied by decreases in neuron density (Dean 2006). In contrast, quetiapine may decrease caudate volume in a dose dependent manner (Ebdrup et al 2011), although the potential mechanism by which this may occur is yet unknown. Although there is significant overlap in pathophysiology and treatment between bipolar disorder and schizophrenia, studies in patients with BDI are needed to elucidate the effects of individual antipsychotic agents on basal ganglia shape, structure, and function.

In contrast to findings by Haldane et al (2008) who investigated the relationship between response inhibition and brain volumes in a sample of chronic patients with BDI, we did not find any contribution of DLPFC volumes to executive impairments in this sample. We also did not find any differences in volume in this area between patients and healthy subjects; consistent with other first episode studies from this (Yatham et al 2007) and other research sites (Perico et al 2011). DLPFC volume (Ekman et al 2010), like executive function performance (Elshahawi et al 2011), has shown a negative correlation with number of previous manic episodes; indicating that abnormalities may emerge as a consequence of disease progression. This may be a potential mechanism by which impairments in executive function could be induced or exacerbated throughout the course of illness. Specifically, chronic, maladaptive overload of behavioural and physiological regulatory systems within and between mood episodes (reviewed by Kapczinski et al 2008) can lead to architectural changes in the prefrontal cortex including reduced dendritic length, branching, and spine density which are associated with reduced cognitive functioning in animal models of stress response (Arnsten et al 2009). Further longitudinal studies are needed to explore the rate and cognitive correlates of neurodegeneration in this area, and the impact of both genetic predisposition and pharmacological intervention on a patient’s sensitivity to its effects.

There are several limitations that need to be noted in the interpretation of these results. First, patients examined were all early in the course of illness. As mentioned above, emerging literature on the neurobiology of BDI indicates that many of the morphometric and cognitive abnormalities found at illness onset may progress over time and the relationship between them are likely to also evolve. Patients were treated naturalistically and thus received a variety of combinations of pharmacological treatments, making any conclusions on their
effects tentative and in need of replication. Although a large proportion of subjects were euthymic, many patients did have mild subsyndromal mood symptoms. Although we did not find an obvious relationship between mood and structural or executive changes, we cannot eliminate any contributing effects. Caution also must be taking generalizing findings from these tests to executive abilities in general, as they were chosen based on their specificity for frontostriatal dysfunction (Grahn et al 2008). Furthermore, we only examined the relationship between test scores and DLPFC and caudate volumes—eliminating the opportunity to detect contributions from abnormalities in other brain areas or broader circuits which also could underlie executive functions. These results are consistent with less restrictive analysis from this sample however—when comparing volumes of the entire prefrontal cortex, anterior cingulate cortex, and striatum using voxel based morphometry, patients who demonstrated at least moderate-severe impairments on other tests of executive function (letter number, phonemic verbal fluency, Stroop) showed a trend towards increased in right caudate volume when compared to healthy subjects, a result not shared with patients that had normal executive functioning (Kozicky et al 2012).

In summary, we found increased right caudate volume is a significant predictor of executive function deficits in patients with BDI. Abnormalities in the caudate may reflect vulnerability to BDI as findings in first episode patients exclude much of the impact of chronic illness; however studies combining cognitive and morphological measurements in high risk samples are needed to further explore this possibility. As medication—and in particular typical antipsychotics— may also increase caudate volumes and impact cognitive functioning, studies specifically designed to examine treatment effects, or those restricted to patients who are unmedicated will also be important to clarify these relationships. Longitudinal prospective studies in the current sample should also prove valuable for elucidating the contribution of illness recurrence and chronic antipsychotic treatment on frontostriatal morphology and executive function early in the course of BDI.
Chapter 3

Executive Function and Grey Matter Volume Change in the Year Following a First Manic Episode in Bipolar I Disorder: Association with Illness Progression

3.1 Introduction

BDI is a dynamic illness observed to follow a continually relapsing and remitting course. There is also growing evidence to suggest that this disorder is progressive, whereby each affective recurrence is associated with a subsequent decrease in inter-episodic recovery and functioning, higher rate and severity of relapse, and reduced treatment response (Berk et al 2011). This is a serious issue even early in the course of illness: despite recovering from initial manic symptoms, approximately 50% of patients can be expected to experience a recurrence of a manic and/or depressive episode within the first year of follow up (Strakowski et al 2007). Along with such problems in mood regulation, patients with BDI also experience persistent cognitive impairments. Deficits in executive functioning are of particular concern, as they are of comparable severity to those seen in first episode schizophrenia (Barrett et al 2009) and do not improve with pharmacological treatment (Hill et al 2009). Indeed, the level of dysfunction during periods of euthymia is only modestly less severe than what is seen during acute episodes (Ryan et al 2012), and longitudinal studies consistently show that intra-individual variability in executive function cannot be predicted by changes in mood symptoms (Depp et al 2008, 2012; Arts et al 2011, Chaves et al 2012). Executive function may also decline with illness course; cross sectional studies often report correlations with number of prior episodes, particularly of mania (Robinson & Ferrier et al 2006), with head-to-head comparisons of patients with a single versus multiple prior manic episodes also indicating that deficits progress (Lebowitz et al 2001, Lopez-Jamorillo et al 2010, Elshahawi et al 2011). Despite these reports, there have been no prospective studies examining how executive function changes in relation to clinical outcome, particularly early in the course of illness.
As dysfunction within and between prefrontal and striatal regions are hypothesized to underlie difficulties in both emotional and cognitive regulation in this disorder (Strakowski et al 2012), it would also be critical to understand how structural changes within these regions evolve with illness course. Progression in BDI has been hypothesized to be a consequence of damage to neuronal structure during acute episodes (Post et al 2010), potentially through cumulative overloading of allostatic pathways involved in stress response and adaptation (Kapczinski et al 2008, Berk et al 2011, Brietzke et al 2012). As frontostriatal areas are both critical for a healthy stress response and sensitive to damage from its physiological effects (Arnsten 2009, Dias-Ferreira et al 2009), it can be expected that these regions will also show changes as a consequence of illness progression. Results from meta-analysis of 21 voxel-wise structural imaging studies of whole brain differences in 660 patients and 770 healthy subjects are consistent with this hypothesis; in chronic samples grey matter reductions in the prefrontal cortex and enlargements of the striatum were both associated with longer duration of illness, although specific relationships with number of acute episodes experienced were not found (Bora et al 2010). In other studies, striatal grey matter (particularly the caudate) has been shown to decrease with increased length of illness (Chen et al 2007). There is limited evidence from longitudinal studies to support these cross sectional findings, one small study found that adolescents and young adults with BD (n=10) had significantly greater grey matter loss in parts of the prefrontal cortex over 2 year follow up when compared to healthy subjects (n=8), although the potential effects of episode recurrence were not examined (Kalmar et al 2009). Lisy et al (2011) showed that despite initial decreases in patients (n=58) compared to healthy subjects (n=48), over a 3-34 month scan interval adolescents with BDI showed larger increase in the right basal ganglia (including the striatum) which correlated with the number of intervening depressive episodes. Several studies have also found longitudinal grey matter changes correlating with affective recurrence in other areas- particularly the hippocampus, cerebellum, and anterior cingulate (Moorhead et al 2007, Koo et al 2008); while others have reported no differences relative to healthy subjects (Nakamura et al 2007, de Castro Mangalo et al 2011, Arango et al 2012).
Study Hypotheses

In this analysis, we examined how executive function and grey matter change following a first manic episode in context of natural illness treatment and progression. We hypothesized that patients who experience an affective recurrence during prospective follow up will show a progressive worsening of executive function compared to both those who remain well and healthy subjects. Grey matter was also hypothesized to decline in those who experience a subsequent episode compared to the other groups, with effects to be most apparent in prefrontal and striatal regions.

3.2 Methods

3.2.1 Study Overview

Despite recovery of initial manic symptoms, within 1 year over half of patients receiving longitudinal follow up with STOP-EM experience another mood episode (Yatham et al 2009). This study was undertaken to examine the differences in executive performance from baseline over 1 year follow up in patients who experienced an affective recurrence versus remained well and healthy subjects, and investigate whether this may be accompanied by changes in frontostriatal grey matter over the same time frame. Findings from this study will provide important prospective support to cross sectional reports that suggest affective episodes in BDI are associated with further decline in executive functioning, as well as provide a potential neurostructural basis for this progression. By using patients identified following their first manic episodes confounding effects of prior illness burden, particularly those associated with previous manic episodes, are minimized.

3.2.2 Participants

As described in Chapter 2, clinically stable patients meeting DSM-IV-TR (APA 1994) criteria for BDI were identified through the STOP-EM at the UBC Hospital and affiliated sites, as well as through community and hospital referrals from physicians and psychiatrists. All
patients were diagnosed and identified for inclusion based on a comprehensive clinical assessment by an academic research psychiatrist and confirmed with a structured diagnostic interview (MINI; Sheehan et al 1998). Participants were required to be 14-35 years of age, and to be within 3 months of remission from their first manic/mixed episode, where remission was defined as no longer meeting DSM-IV-TR criteria for two consecutive weeks. Those with any pre/comorbidities were not excluded as long as the primary diagnosis was BDI.

Of the first 75 patients enrolled in the STOP-EM program, 56 underwent the baseline neurocognitive assessment and 3T MRI scan. Of these, 41 also completed the year 1 visit (n=8 withdrew from the study, n=5 missed the 1 year neurocognitive testing and/or MRI scan, and n=2 had artifacts in the MRI scan making the data unusable). 21 experienced an affective recurrence between the two assessments (BD_recurr; n=12 depressive, n=6 hypo/manic, n=3 both a depressive and hypo/manic episode; 67% with one recurrence, 29% with two and 4% with three or more), while 20 remained well (BD_well). Most patients met criteria for syndromal recovery (HAMD, YMRS ≤ 12 closest to time of neurocognitive testing) at both visits (71/76% of BD_recurr and 80/100% for BD_well at baseline and year 1 respectively), and many were also fully euthymic (HAMD, YMRS ≤ 7; 52/62% and 60/90%).

Of the first 41 healthy subjects (HS) meeting inclusion criteria, 24 had matching data available. 5 from the original 29 with complete baseline data withdrew from the study before the year 1 visit. For all participants and time points, 33% had neuroimaging and cognitive testing on the same day, 64% within 2 weeks, 80% within a month; with all within 15 weeks. For 39% of visits, patients had cognitive testing and mood symptoms assessed on the same day, 78% within 2 weeks, and 91% within a month; with all within 16 weeks.

Ethics approval was granted from UBC Clinical Research Ethics Board, and written informed consent was obtained from all patients and healthy subjects prior to performing any study procedures.
3.2.3 Clinical Assessment

Patients received ongoing naturalistic clinical follow up from psychiatrists with expertise in treatment of mood disorders. Clinical assessments according to the STOP-EM protocol and as described in Chapter 2 were scheduled at baseline, 6 month, and year 1 time points; with additional appointments as appropriate (such as during recurrence of mood symptoms). Determination of affective recurrence was done according to DSM-IV-TR criteria and through clinician observation and patient self-report, with additional confirmation as necessary using health records.

3.2.4 Assessment of Executive Function

Cognitive testing was done at baseline, 6 month, and 1 year time points. In addition to the three computerized tests described in Chapter 2 (SWM between errors, ID/EDS EDS errors, SOC problems solved in minimum number of moves), three verbal paper and pencil executive tests were also added to improve reliability and validity to the summary score; letter number sequencing, phonemic verbal fluency, and Stroop. The average z-score from the six tests at baseline and year 1 were used as the executive summary scores. While not ideal (<0.70), agreement across measures was moderate at both baseline (α=0.58) and follow-up (α=0.57). Test-retest reliability in the HS group was also acceptable (mean intraclass correlation (ICC) =0.73). Distribution of the summary score in each group at both time points was approximately normal (Shapiro-Wilk p>0.19).

Letter Number Sequencing: As part of the Wechsler Adult Intelligence Scale this subtest involves the subject being read a randomized, alternating sequence of letters and numbers of increasing length, being asked to reproduce them with numbers in ascending order followed by letters in alphabetical order. Scoring was based on the number of correct sequences recalled, and converted to a z-score based on available norms (Wechsler 1997).

Phonemic Verbal Fluency: For this measure, patients are required to generate as many words as possible beginning with the letters F/A/S, with accompanying instruction not to use proper
nouns or the same word with a different ending; being granted 1 minute for each of the three separate trials (Harrison et al 2000). Scoring was based on the number of words generated, and converted to a z-score based on available norms (Tombaugh et al 1999).

*Stroop*: this task is made up of three 45 second conditions; in the first subjects are required to read a list of colors written as words in black ink (red, green, blue…). In the second they are asked to name the color a series of Xs are printed in. In the third incongruent condition, they have to name the color of the ink that the word is written in rather than the word itself (ex; “red” in blue ink). The interference score was used, calculated from the difference in predicted versus actual responses in the incongruent condition and based on available norms (Stroop 1935, MacLeod 1991, Golden & Freshwater 1992).

### 3.2.5 T1 MR Image Acquisition and Preprocessing

Baseline and 1 year T1 weighted images were acquired as described in Chapter 2, and preprocessed using the longitudinal data algorithm in the VBM8 toolbox developed by Dr. Christian Gaser at the Structural Brain Mapping Group, University of Jena, Germany (http://dbm.neuro.uni-jena.de/vbm8/). More detail has been included in Appendix A.3. Briefly, year 1 images were realigned to those from baseline, with a mean image calculated for each subject. Using this mean image as reference, baseline and follow-up images were realigned again and bias corrected. Parameters for spatial normalization were obtained by segmenting the mean images and then applied to the segmentation of the bias-corrected baseline and 1 year images. The segmented tissue images were again realigned. The final segmented and realigned tissue images were normalized into the MNI space using the DARTEL deformation that had been calculated through the normalization of the mean images. The normalized gray matter images were then smoothed with an 8mm FWHM Gaussian kernel.
3.2.6 Statistical Analysis

All data are reported as means and SD. Correlations, regressions, and group comparisons for clinical and cognitive variables were conducted using SPSS 19.0 (SPSS Inc, Chicago, Illinois). For all results, \( p < 0.05 \) was used as the threshold for statistical significance, with \( p < 0.10 \) also reported as trend differences. Group demographics were examined using ANOVA and comparisons of baseline and year 1 clinical variables between patient groups were conducted using chi square for categorical and independent samples t-test for continuous variables. In two cases (from BD\textsubscript{well}) clinical data was incomplete for the 1 year time point, with missing variables being antipsychotic dose, BPRS, GAF, and PANSS scores. To facilitate statistical comparison, antipsychotic doses were standardized according to relative D\textsubscript{2}R potency whereby 1mg of loxapine is equivalent to 0.08mg risperidone, 5.73mg olanzapine, or 8.72mg quetiapine (Baitz et al 2012).

Group, time, and groupxtime effects for executive performance were examined using repeated measures ANOVA with time (baseline/year 1 summary executive score) as within subject factor and group (BD\textsubscript{recurr}, BD\textsubscript{well}, HS) as the between subject factors. Follow-up contrasts of significant group differences were done using MANOVA, and time effects using paired sample t-tests. All statistical analyses were repeated using age, gender, and premorbid IQ as covariates. Due to a testing error, verbal fluency score for 1 subject (BD\textsubscript{well}) was not available at year 1-the average of the other 5 measures was used instead.

All analysis of MRI data was done using SPM8 (Wellcome Department of Imaging Neuroscience Group, London, UK; http://www.fil.ion.ucl.ac.uk/spm). Cross sectional group contrasts at baseline and year 1 were analyzed using two-sample t-tests. Changes within each group between the two scans were examined using paired sample t-tests. Groupxtime contrasts were examined in with a flexible factorial design with subject, group, and time as factors. For group and groupxtime contrasts; age, gender, and intracranial volume (ICV) were included as covariates.
Whole brain as well as specific analysis of the DLPFC and caudate (created using WFU Pickatlas, as described in Chapter 2) was conducted. Clusters for whole brain analyses were considered significant if extent ≥300 voxels, height threshold p<0.001 uncorrected, and cluster level p<0.05 FWE corrected. In order to identify more localized changes in the DLPFC and caudate small volume correction was used, with clusters considered significant at height threshold p<0.001 uncorrected, and cluster level p<0.05 FWE corrected. Significant clusters were anatomically localized within using the WFU Pickatlas.

Values for average DLPFC and caudate grey matter concentration were extracted for correlation analysis in SPSS using MarsBar (as described in Chapter 2). Relationships with changes in executive performance between baseline and year 1 and changes in mood symptoms, antipsychotic dose, and ROI values were explored using Pearson correlations.

3.3 Results

3.1 Demographic and Clinical Features

All participant groups were well matched (Table 3.1), although on average patients in the BDrecurr group were older than those in other two groups (F=4.00; df=2,62; p<0.05). There were no significant differences in terms of gender, education and premorbid or current intellectual function (all p>0.2). On average, year 1 MRI scans were done 55 weeks after baseline, and not significantly different between groups (p>0.5).

Clinical variables are described in Table 3.2. Patient groups did not differ from each other in baseline or 1 year manic or psychotic symptoms (all p>0.15), although at baseline BDrecurr had a trend for higher general psychiatric symptoms (BPRS, t(39)=−1.97; p=0.06) that was not seen at year 1 (p> 0.15). While not different at baseline, depressive symptoms showed a trend towards being higher in the BDrecurr group at year 1 (t(39)=1.83; p=0.08). While functioning (GAF) was also worse at trend level in the BDrecurr group at baseline (t(39)=−1.97; p=0.06), this reached significance at year 1 (t(37)=−2.44; p<0.05). Patient groups were similar in terms of proportion with past depressive episode(s), or psychotic features during index
manic episode (all $p>0.10$); although $\text{BD}_{\text{recur}}$ had a trend for an older age of onset ($t_{39}=1.73$; $p=0.09$) and higher proportion with substance abuse/dependence ($\chi^2=4.36$; df=1; $p<0.05$).

While pharmacological treatment was similar between groups at baseline (all $p\geq0.1$); there was a trend for more antipsychotic ($\chi^2=3.06$; df=1; $p=0.08$) and antidepressant ($\chi^2=3.49$; df=1; $p=0.07$) use at year 1 by $\text{BD}_{\text{recur}}$.

Table 3.1 Participant Demographics at Baseline and 1 Year Follow-Up

<table>
<thead>
<tr>
<th></th>
<th>$\text{BD}_{\text{recur}}$ (n=21)</th>
<th>$\text{BD}_{\text{well}}$ (n=20)</th>
<th>$\text{HS}$ (n=24)</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Mean(SD)</td>
<td>Mean(SD)</td>
<td>Mean(SD)</td>
<td>$F$ $(p)$</td>
</tr>
<tr>
<td></td>
<td>24.3 (4.3)</td>
<td>21.3 (3.1)</td>
<td>21.6 (3.5)</td>
<td>4.00 (&lt;0.05)</td>
</tr>
<tr>
<td>Education (years)</td>
<td>13.8 (2.1)</td>
<td>13.3 (1.9)</td>
<td>14.4 (2.3)</td>
<td>$\text{BD}<em>{\text{recur}} &lt; \text{BD}</em>{\text{well}}$ (&lt;0.05); $\text{HS}$ (&lt;0.05)</td>
</tr>
<tr>
<td>Premorbid IQ</td>
<td>108.6 (5.0)</td>
<td>107.6 (7.9)</td>
<td>108.1 (6.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Current IQ</td>
<td>105.9 (10.2)</td>
<td>106.3 (9.7)</td>
<td>110.5 (9.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Days between MRI scans</td>
<td>388.5 (39.0)</td>
<td>379.1 (32.4)</td>
<td>378.4 (26.6)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>% (n)</td>
<td>% (n)</td>
<td>% (n)</td>
<td>$\chi^2$ $(p)$</td>
</tr>
<tr>
<td>Sex (Male)</td>
<td>47.6 (10)</td>
<td>50.0 (10)</td>
<td>41.7 (10)</td>
<td>NS</td>
</tr>
</tbody>
</table>

$\text{HS}$: Healthy Subjects; $\text{MRI}$: Magnetic Resonance Imaging; NS: non-significant ($p>0.1$); SD: Standard Deviation
Table 3.2 Clinical and Treatment Features of Patients at Baseline and 1 Year Follow-Up

<table>
<thead>
<tr>
<th></th>
<th>BD&lt;sub&gt;recurr&lt;/sub&gt; (n=21)</th>
<th>BD&lt;sub&gt;well&lt;/sub&gt; (n=20)</th>
<th>t-test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean(SD)</td>
<td>Mean(SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>YMRS</td>
<td>1.9 (4.3)</td>
<td>2.5 (5.9)</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0.9 (1.7)</td>
<td>0.6 (1.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Year 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAMD</td>
<td>9.0 (8.0)</td>
<td>4.6 (6.1)</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>6.1 (7.1)</td>
<td>1.9 (3.2)</td>
<td>B: NS</td>
</tr>
<tr>
<td>Year 1</td>
<td></td>
<td></td>
<td>Y1: 1.83 (0.08)</td>
</tr>
<tr>
<td>PANSS</td>
<td>7.9 (1.8)</td>
<td>7.7 (2.6)</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>7.9 (1.7)</td>
<td>7.0 (0.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Year 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BPRS</td>
<td>25.0 (7.0)</td>
<td>20.6 (4.5)</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>21.4 (4.0)</td>
<td>18.9 (2.6)</td>
<td>B: 1.97 (0.06)</td>
</tr>
<tr>
<td>Year 1</td>
<td></td>
<td></td>
<td>Y1: NS</td>
</tr>
<tr>
<td>GAF</td>
<td>60.8 (13.4)</td>
<td>72.6 (11.7)</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>68.6 (12.0)</td>
<td>80.2 (7.4)</td>
<td>B: -1.97 (0.06)</td>
</tr>
<tr>
<td>Year 1</td>
<td></td>
<td></td>
<td>Y1: -2.44 (&lt;0.05)</td>
</tr>
<tr>
<td>Antipsychotic Dose*</td>
<td>16.6 (21.1)</td>
<td>12.2 (11.7)</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>28.5 (18.2)</td>
<td>15.7 (10.1)</td>
<td>B: -1.71 (0.10)</td>
</tr>
<tr>
<td>Year 1</td>
<td></td>
<td></td>
<td>Y1: NS</td>
</tr>
<tr>
<td>Age of Onset</td>
<td>20.8 (5.6)</td>
<td>18.3 (3.4)</td>
<td>1.73 (0.09)</td>
</tr>
<tr>
<td>% (n)</td>
<td>% (n)</td>
<td>% (n)</td>
<td></td>
</tr>
<tr>
<td>Mood Stabilizer</td>
<td>85.7 (18)</td>
<td>85.7 (18)</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>95.0 (19)</td>
<td>75.0 (15)</td>
<td>NS</td>
</tr>
<tr>
<td>Year 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lithium</td>
<td>57.1 (12)</td>
<td>47.6 (10)</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>35.0 (7)</td>
<td>25.0 (5)</td>
<td>NS</td>
</tr>
<tr>
<td>Year 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valproate</td>
<td>33.3 (7)</td>
<td>42.9 (9)</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>60.0 (12)</td>
<td>55.0 (11)</td>
<td>NS</td>
</tr>
<tr>
<td>Year 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antipsychotic</td>
<td>81.0 (17)</td>
<td>57.1 (12)</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>75.0 (15)</td>
<td>30.0 (6)</td>
<td>B: NS</td>
</tr>
<tr>
<td>Year 1</td>
<td></td>
<td></td>
<td>Y1: 3.06 (0.08)</td>
</tr>
<tr>
<td>Risperidone</td>
<td>42.9 (9)</td>
<td>14.3 (3)</td>
<td></td>
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<tr>
<td>Baseline</td>
<td>40.0 (8)</td>
<td>5.0 (1)</td>
<td>NS</td>
</tr>
<tr>
<td>Year 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td>23.8 (5)</td>
<td>19.0 (4)</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>10.0 (2)</td>
<td>0.0 (0)</td>
<td>B: NS</td>
</tr>
<tr>
<td>Year 1</td>
<td></td>
<td></td>
<td>Y1: 4.22 (&lt;0.05)</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>19.0 (4)</td>
<td>23.8 (5)</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>25.0 (5)</td>
<td>25.0 (5)</td>
<td>NS</td>
</tr>
<tr>
<td>Year 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antidepressant</td>
<td>9.5 (2)</td>
<td>28.9 (6)</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0.0 (0)</td>
<td>5.0 (1)</td>
<td>B: NS</td>
</tr>
<tr>
<td>Year 1</td>
<td></td>
<td></td>
<td>Y1: 3.49 (0.07)</td>
</tr>
<tr>
<td>Past depressive episode</td>
<td>57.1 (12)</td>
<td>50.0 (9)</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>50.0 (9)</td>
<td>50.0 (9)</td>
<td>NS</td>
</tr>
<tr>
<td>Year 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of Psychosis</td>
<td>81.0 (17)</td>
<td>90.0 (18)</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>81.0 (17)</td>
<td>90.0 (18)</td>
<td>NS</td>
</tr>
<tr>
<td>Year 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Substance Abuse/Dependence</td>
<td>57.1 (12)</td>
<td>25.0 (5)</td>
<td>4.36 (&lt;0.05)</td>
</tr>
</tbody>
</table>

* In patients treated with an antipsychotic

YMRS: Young Mania Rating Scale; HAMD: Hamilton Depression Rating Scale; PANSS: Positive and Negative Symptom Scale Positive Symptoms; BPRS: Brief Psychiatric Rating Scale; GAF: Global Assessment of Functioning; B: Baseline assessment; Y1: Year 1 assessment; NS: Non-Significant (p>0.1)

3.3.2 Executive Function

Further description of results can be found in Table 3.3 and Figure 3.1.

Between Group Differences

There were significant differences in executive performance between the three groups (F=5.45; df=2,62; p<0.01). Follow-up contrasts with MANOVA revealed that BD<sub>recurr</sub> were
significantly impaired relative to HS overall (F=3.56; df=1,43; p<0.05); with differences seen at both baseline (F=5.23; df=1,43; p<0.05) and year 1 (F=6.32; df=1,43; p<0.05). Differences at year 1 (F=7.60; df=1,43; p<0.01) but not baseline (F=3.45; df=1,43; p=0.07) remained significant after covarying for age, gender, and premorbid IQ. In contrast, while BD_{well} had lower executive performance than healthy subjects overall (F=8.65; df=1,42; p<0.001); these were apparent only at baseline (F=15.21; df=1,42; p<0.001), with impairments at follow-up reduced to trend level significance (F=2.87; df=1,42; p=0.10). Covarying for age, gender, and premorbid IQ did not change findings. Although there was a trend towards group differences for BD_{well} vs BD_{recur} overall (F=3.05; df=1,39; p=0.06); this was not significant at baseline (F=2.16; df=1,39; p=0.15) or year 1 (F=0.18; df=1,39; p=0.67). While results were maintained after covarying age, gender and premorbid IQ, or substance abuse/dependence; inclusion of antipsychotic dose at baseline eliminated the overall effect (F=1.39; df=1,30; p>0.25).

Within Group Baseline- Year 1 Change

There was a significant effect of time on executive performance across the three groups (F=19.17; df=2,61; p<0.001). Paired sample t-tests indicated that only the BD_{well} group improved between the two time points (t(19)=-6.57; p<0.001). Changes in BD_{recur} and HS were non-significant (all p>0.2).

Group Differences in Longitudinal Performance Change

Mixed models ANOVA revealed a significant group*time interaction (F=4.63; df=2,62 p<0.05). While BD_{recur} had a similar trajectory as HS (F=0.00; df=1,42; p=0.9), BD_{well} had significant performance gains relative to both BD_{recur} (F=5.96; df=1,39; p<0.05) and HS (F=9.90; df=1,42; p<0.01). Covarying for age, gender, and premorbid IQ did not change findings. Differences between BD_{well} and BD_{recur} were maintained after substance abuse/dependence was included as a covariates (F=6.08; df=1,39; p<0.05).
Figure 3.1: Summary Executive Performance of Patients and Healthy Subjects at Baseline and 1 Year Follow-Up

![Graph showing Z-scores for BD Recurrence, BD Well, and HS over Baseline and Year 1.]

Table 3.3: Summary Executive Performance Comparisons between Patients and Healthy Subjects at Baseline and 1 Year Follow-Up

<table>
<thead>
<tr>
<th></th>
<th>Baseline Mean (SD)</th>
<th>Year 1 Mean (SD)</th>
<th>Time F(p)</th>
<th>Contrasts</th>
<th>Group d (p)</th>
<th>Group x Time F (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Baseline</td>
<td>Year 1</td>
</tr>
<tr>
<td>BD_recurr</td>
<td>0.07 (0.53)</td>
<td>0.21 (0.50)</td>
<td>NS</td>
<td>vs BD_well</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>vs HS</td>
<td>.70 (&lt;0.05)</td>
<td>.68 (&lt;0.05)</td>
</tr>
<tr>
<td>BD_well</td>
<td>-0.17 (0.53)</td>
<td>0.28 (0.55)</td>
<td>Improvement (p&lt;0.001)</td>
<td>vs HS</td>
<td>1.16 (&lt;0.001)</td>
<td>0.51 (p=0.1)</td>
</tr>
<tr>
<td>HS</td>
<td>0.43 (0.50)</td>
<td>0.53 (0.43)</td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HS: Healthy Subject; SD: Standard Deviation; NS: non-significant; d: Effect size (cohen’s d)

3.3.3 Voxel Based Analysis

Between Group Grey Matter Differences

Complete description of baseline and 1 year group differences are shown in Table 3.4. At baseline, BD_recurr had less grey matter relative to HS in two clusters: one in the left insula (k=960 voxels, cluster p<0.001 FWE-corrected), and the other in the right medial prefrontal and anterior cingulate cortices (k=456, cluster p<0.001 FWE-corrected). At 1 year follow up, no significant reductions remained. BD_well did not show any significant differences from HS or BD_recurr at any time point. Small volume correction for the DLPFC and caudate did not reveal any further grey matter differences.
Table 3.4: Areas of Reduced Grey Matter in Patients vs Healthy Subjects at Baseline and 1 Year Follow-Up

<table>
<thead>
<tr>
<th>Contrast</th>
<th>Time Point</th>
<th>Voxels</th>
<th>Cluster significance (FWE-corrected)</th>
<th>MNI Coordinates*</th>
<th>Laterality</th>
<th>Talairach Label (Gyrus)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDrecurr &lt; HS</td>
<td>Baseline</td>
<td>960</td>
<td>p&lt;0.001</td>
<td>-36 0 9</td>
<td>Left</td>
<td>Insula</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>-45 -13</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>36 -16 15</td>
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<tr>
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<td>301</td>
<td>p=0.10</td>
<td>-44 -12 4</td>
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<td>Insula</td>
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<tr>
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<td>p=0.10</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>-44 17 1</td>
<td></td>
<td>Inferior Frontal</td>
</tr>
<tr>
<td>Year 1</td>
<td></td>
<td>No Significant Clusters</td>
<td>No Significant Clusters</td>
<td></td>
<td></td>
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<tr>
<td>BDrecurr &lt; BDwell</td>
<td>Baseline</td>
<td>No Significant Clusters</td>
<td>No Significant Clusters</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Year 1</td>
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<td>-50 -57 4</td>
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</table>

BA: Brodmann area; FWE: Familywise error; HS: Healthy Subjects; MNI: Montreal Neurological Institute

* Local maxima more than 8mm apart

**Within Group Grey Matter Change**

Grey matter loss between baseline and year 1 in each group can be found in Figures 3.2-4. Both HS and BD_{recur} showed extensive grey matter loss encompassing much of the cortex. BD_{well} only showed grey matter loss in the right cerebellum (k=561, cluster p<0.05 FWE-corrected). While there were no areas of grey matter gain in HS or BD_{well}, in BD_{recur} increases were found in the left/bilateral cerebellum (k=556, cluster p<0.01 FWE-corrected).

Small volume correction for the DLPFC revealed three clusters where grey matter was lost between baseline and year 1 in HS (Left: k=228, cluster p<0.05 FWE-corrected. Right: k=201, cluster p<0.05 FWE-corrected; k=103, cluster p=0.08 FWE-corrected). Caudate grey matter did not show any significant changes in HS. There were seven clusters in the DLPFC where grey matter was lost in BD_{recur} (Left: k=316, cluster p<0.01 FWE-corrected; k=304, cluster p<0.01 FWE-corrected; k=254, cluster p<0.01 FWE-corrected; k=117, cluster p=0.08 FWE-corrected. Right: k=441, cluster p<0.01 FWE-corrected; k=220, cluster p<0.05 FWE-corrected; k=180, cluster p<0.05 FWE-corrected). Caudate grey matter did not change in BD_{recur}. There was no significant loss or gain in the DLPFC or caudate in BD_{well}. 
Figure 3.2: Areas of Significant Grey Matter Loss in Healthy Subjects between Baseline and 1 Year Follow-Up

Figure 3.3: Areas of Significant Grey Matter Loss in Patients who Experienced an Affective Recurrence between Baseline and 1 Year Follow-Up

Figure 3.4: Areas of Significant Grey Matter Loss in Patients who Remained Well between Baseline and 1 Year Follow-Up

All displayed clusters reach height threshold p<0.001 uncorrected, cluster level p<0.05 FWE corrected. Whole brain clusters also meet extent threshold ≥ 300 voxels.
Group Differences in Longitudinal Grey Matter Change

Further description of whole brain results can be found in Figures 3.5-7 and Tables 3.5-7. BD\textsubscript{well} showed a longitudinal increase in grey matter compared to HS, this included three significant clusters in the left temporo-occipital cortex and left anterior cingulate. In contrast, BD\textsubscript{recur} showed decreases compared to HS in one cluster spanning the lateral middle and inferior frontal gyri. BD\textsubscript{recur} also had significantly greater grey matter loss versus BD\textsubscript{well} in five clusters located bilaterally in the prefrontal cortex, with additional trend differences in the medial prefrontal, superior temporal, and parahippocampal gyri, as well as the thalamus. Covarying for depressive symptoms, substance abuse/ dependence, lithium, or antipsychotic treatment did not eliminate significant findings, rather their inclusion indicated original trend differences in the right temporal lobe as significant.

Description of group\texttimes\textit{time} differences between BD\textsubscript{recur} and BD\textsubscript{well} using small volume correction for the DLPFC can be found in Table 3.8. When small volume correction for the DLPFC was applied, BD\textsubscript{recur} showed significant (left, k=170, cluster p<0.05 FWE-corrected) grey matter loss in the DLPFC relative to BD\textsubscript{well}. Covarying for depressive symptoms (k=170, cluster p<0.05 FWE-corrected), substance abuse/ dependence (k=158, cluster p=0.05 FWE-corrected), lithium (k=190, cluster p<0.05 FWE-corrected), or antipsychotic use (k=144, cluster p=0.07 FWE-corrected) did not eliminate findings. There was no significant difference in longitudinal grey matter change between BD\textsubscript{well} or BD\textsubscript{recur} and HS. No significant clusters emerged for any group\texttimes\textit{time} contrasts when small volume correction was applied to the caudate.
Figure 3.5: Areas of Grey Matter Increase in Patients who Remained Well vs Healthy Subjects

Figure 3.6: Areas of Grey Matter Decrease in Patients who Experienced an Affective Recurrence vs Healthy Subjects

Figure 3.7: Areas of Grey Matter Decrease in Patients who Experienced an Affective Recurrence vs Remained Well

All displayed clusters reach height threshold $p<0.001$ uncorrected, cluster level $p<0.05$ FWE corrected, extent threshold $\geq 300$ voxels.
Table 3.5: Areas of Grey Matter Increase in Patients who Remained Well vs Healthy Subjects

<table>
<thead>
<tr>
<th>Covariates</th>
<th>Voxels</th>
<th>Cluster significance (FWE-corrected)</th>
<th>MNI Coordinates*</th>
<th>Laterality</th>
<th>Talairach Label (Gyrus)</th>
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<tbody>
<tr>
<td>Age</td>
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</tr>
<tr>
<td>Gender</td>
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<td></td>
<td>-15 -10 -20</td>
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<td>Fusiform</td>
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<tr>
<td>ICV</td>
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<td></td>
<td>-17 -21 -23</td>
<td></td>
<td>Parahippocampal</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
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</tr>
<tr>
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<td>p=0.06</td>
<td>9 53 3</td>
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</tr>
</tbody>
</table>

BA: Brodmann area; FWE: Familywise error; MNI: Montreal Neurological Institute; ICV: Intracranial Volume

* Local maxima more than 8mm apart

Table 3.6: Grey Matter Decrease in Patients who Experienced an Affective Recurrence vs Healthy Subjects

<table>
<thead>
<tr>
<th>Covariates</th>
<th>Voxels</th>
<th>Cluster significance (FWE-corrected)</th>
<th>MNI Coordinates*</th>
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<th>Talairach Label (Gyrus)</th>
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<tr>
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<td></td>
<td>-48 39 21</td>
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</tr>
<tr>
<td>ICV</td>
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<td></td>
<td>-42 54 9</td>
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</tbody>
</table>

BA: Brodmann area; FWE: Familywise error; MNI: Montreal Neurological Institute; ICV: Intracranial Volume

* Local maxima more than 8mm apart

Table 3.7: Areas of Grey Matter Decrease in Patients who Experienced an Affective Recurrence vs Remained Well

<table>
<thead>
<tr>
<th>Covariates</th>
<th>Voxels</th>
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<th>Talairach Location (Gyrus)</th>
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<td></td>
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<td></td>
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<td></td>
<td>Precentral</td>
</tr>
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<td></td>
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<td>57 -3 27</td>
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</tr>
<tr>
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<td></td>
<td></td>
<td>14 -2 1 3</td>
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<td>Thalamus</td>
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BA: Brodmann area; FWE: Familywise error; MNI: Montreal Neurological Institute; ICV: Intracranial Volume

* Local maxima more than 8mm apart
Table 3.8: DLPFC Grey Matter Decrease in Patients who Experienced an Affective Recurrence vs Remained Well

<table>
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<tr>
<th>Covariates</th>
<th>Voxels</th>
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<td></td>
<td>-42 38 24</td>
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<tr>
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<td>-47 42 18</td>
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</tr>
</tbody>
</table>

BA: Brodmann area; FWE: Familywise error; MNI: Montreal Neurological Institute; ICV: Intracranial Volume; HAMD: Hamilton Depression Rating Scale
* Local maxima more than 8mm apart

3.3.4 Correlations with Executive Function

Change in executive function did not correlate with change in any symptom rating scales (all p>0.2). Executive change also did not correspond with changes in antipsychotic dose (p>0.4), or with grey matter changes in the DLPFC or caudate (all p>0.4). Results were maintained after covarying for affective recurrence (all p>0.3).

3.4 Discussion

This study demonstrates that patients who maintain syndromal recovery in the year following their first manic episode have improvements in executive function larger than that which could be expected by practice. These results are consistent with hypotheses on the longitudinal course of cognitive functioning in BDI which suggest that trait related deficits are exacerbated during acute episodes, and then slowly recover following symptomatic improvement (Lewandowski et al 2011). This may not be directly a consequence of changes in mood- in the current sample variability in clinical symptoms was unrelated to
improvements in executive performance, results which are consistent with those of Hill et al (2009) who found executive performance did not improve alongside clinical recovery during the initial 6 weeks of treatment of a first psychotic manic episode (Hill et al 2009). During 3 month follow up of a heterogeneous sample of initially symptomatic patients, Chaves et al (2012) also found very minimal association between changes in mood ratings and executive variability. Similarly, Arts et al (2011) showed that while overall symptom levels were negatively associated with executive function; individually neither manic, depressive, nor general psychiatric measures showed any significant relationship with variability in bimonthly performance over 2 year follow up. Together with current results, these studies suggest that while executive functions may at least partially improve with continued clinical recovery, these effects are not merely a consequence of changes in mood symptoms.

While there are several reports of correlations between the number of affective episodes and level of impairments (Robinson & Ferrier 2006, Arts et al 2011), this is the first study comparing trajectories between those who experience a mood episode versus maintain recovery over longitudinal follow up. As expected, performance gains seen in those who remained well were not found in patients who experienced a relapse; suggesting that acute mood episodes do have a negative effect on executive function. Because we did not directly see performance decrease in those who experienced a recurrence when compared to healthy subjects, however, it could still be hypothesized that the effects of a single episode are not severe enough to create noticeable decline. Cross sectional comparisons do indicate that impairments may rather cumulate with multiple rather than a single recurrence (Lopez-Jamorillo et al 2010, Hellvin et al 2012). Furthermore, the combined grouping of patients who experienced either a hypo/manic or a depressive episode may also have limited our ability to detect further impairment relative to healthy subjects: post-hoc correlations between illness characteristics and cognition consistently report a stronger association with the number of prior manic versus depressive episodes (Robinson & Ferrier 2006). As we were underpowered to comparing outcomes of patients who experienced a single depressive (n=9) vs hypo/manic (n=5) episode or multiple recurrences (n=7), further studies are needed to test such hypotheses.
Although we did not find a direct relationship with cognitive changes, neural structures important for executive function were also similarly associated with differences in illness course. Subjects who experienced an affective recurrence had greater grey matter loss than those who remained well in several regions, including the DLPFC, even after accounting for substance abuse/dependence, depressive symptoms, or lithium or antipsychotic treatment. These results can be attributable to both accelerated grey matter loss in those who experienced a subsequent mood episode as well as relative gains in those who maintained recovery, as each patient group showed opposing differences relative to healthy subjects.

There is a wealth of theoretical literature suggesting that neural remodelling (including grey matter loss) may be the mechanism by which affective recurrences lead to a progressive worsening of clinical and functional course (Post et al 2010, Berk et al 2011). A published consensus on the functional neuroanatomy of BDI describes integrative cognitive and emotional control networks involving the prefrontal cortex and basal ganglia being fundamentally disturbed in this illness, with “stably-unstable” functioning during times of euthymia easily disrupted by even minor stress; leading to both inter-episodic affective instability as well as acute mood exacerbations (Strakowski et al 2012). Kapczinski et al (2008) further posits that on a cellular level, overloading of the body’s stress response systems (such as the hypothalamic-pituitary-adrenal axis, circadian rhythm, immune-inflammation, or oxidative stress) during acute episodes induces structural and functional changes that act to sensitize the system to future insult. Indeed, patients of all mood phases have been shown to have higher levels of peripheral markers of oxidative stress and inflammation, as well as decreased antioxidant, anti-inflammatory, and neurotrophic factors compared to healthy subjects; with changes in a similar direction though less severe than patients with sepsis (Kapczinski et al 2010). The prefrontal cortex may be particularly vulnerable to functional and structural damage by these processes (Arnsten et al 2009); preclinical studies in rodents suggest that reduced dendritic arborization in the medial PFC in particular may underly cognitive deficits following prolonged stress (Liston et al 2006), with such remodelling associated with volumetric changes using MRI (Kassem et al 2013). While there is limited empirical support for gross structural changes associated with illness course in BDI (reviewed by Schneider et al 2012), it is believed that manic episodes specifically are
particularly damaging: Ekman et al (2010) found a negative correlation between DLPFC volume and the number of previous manic, but not depressive episodes or duration of illness. The causal and temporal relationship between such mood disturbance, cellular processes, and structural changes however, has yet to be determined.

In contrast to the accelerated grey matter loss in patients who experienced an affective recurrence, we also found that patients who maintained recovery did not show the same age related grey matter loss as healthy subjects; with relative grey matter gains most pronounced in the anterior medial prefrontal and temporo-occipital cortices. These increases are likely to be at least partially attributable to medication use. Current pharmacological strategies used to treat BDI are believed to be protective, potentially even normalizing disease related brain abnormalities (Berk et al 2011). Lithium in particular has correlated with an increase in grey matter in BD, with a recent review of post-hoc comparisons indicating that effects are primarily seen in the limbic regions, particularly the anterior cingulate (Hafemen et al 2012). Furthermore, results from a single randomized controlled trial suggests that total brain grey matter volume gains correspond with clinical response (Lyoo et al 2010). Preclinical studies of the effects of lithium on cell survival indicate that it exerts effects through multiple signalling pathways involved in regulating brain function including those important for cell proliferation, plasticity, and resilience; interacting with multiple neurotransmitter, neurotrophic, inflammatory, and oxidative pathways to potentially prevent deleterious effects of stress on brain structure and function (reviewed by Malhi et al 2013). Because nearly all patients in the current sample were medicated, whether these structural changes can be attributeable to treatment or are rather a part of the natural illness course cannot be known. Further well designed studies specifically examining the effects of medication on brain structure in this population are needed.

The major limitations of this study are direct consequence of the broad, clinically relevant inclusion criteria. In order to ensure generalizability of findings, patients with pre/comorbid diagnoses, acute or subthreshold mood symptoms, or those who had changes in pharmacological treatment over follow up were not excluded. Despite this, patient groups were comparable on most measures at baseline, with the most marked difference being in the
proportion of subjects with co-occurring substance abuse/dependence. Those who experienced an affective recurrence had significantly higher rates versus those who remained well; with cannabis use being particularly elevated (88% of those with substance abuse/dependence). This is a clinically relevant problem, consistently shown to increase risk for affective (particularly manic) recurrence (van Rossum et al 2009, Kazour et al 2011). Although covarying for substance abuse/dependence did not eliminate effects of illness course on cognitive and grey matter trajectories, it is still likely that this comorbidity did play an important role. Although cannabis corresponds with decreased cognitive functioning in schizophrenia, there are suggestions it may improve executive function in BDI (Ringen et al 2011, Braga et al 2012). Cannabis use/abuse may also affect brain structures. For instance, in a study of patients with a first-episode of schizophrenia those who ab/used cannabis had accelerated cortical thinning in the anterior cingulate and DLPFC (Rais et al 2010). Heavy cannabis use has also been inconsistently associated with medial-temporal structural changes in otherwise healthy samples (Lorenzetti et al 2010, Cousijn et al 2012). There have not been any studies specifically examining the effects of cannabis misuse on neural structure in adult bipolar populations.

While both patient groups had comparable treatment characteristics at baseline, there were subtle differences that emerged over naturalistic follow up. While not meeting criteria for statistical significance, patients who remained well were less likely to be on an antipsychotic at follow up. While olanzapine use was specifically lower in this group, risperidone use decreased in both groups over follow up. Numerically, rates of quetiapine prescription were very comparable across groups and time points. While it is likely that antipsychotic use leads to further impairments in executive function (Donaldson et al 2003, Altshuler et al 2004, Frangou et al 2005, Dittmann et al 2007, Jamrozinski et al 2009); we found no relationship between change in dose and variability in executive function. It is likely that individual agents have different impacts on cognition, precluding any overall effects. Changes in antipsychotic treatment may have also confounded structural analyses, although differences between patient groups were maintained after including antipsychotic use or dose as a covariate. Furthermore, there were no morphological differences between those who stayed on (n=15) versus discontinued (n=17) an antipsychotic over follow up, even after
covarying for episode recurrence (not shown). While there are no randomized, controlled studies examining the effects of these drugs on brain structure in BD, recent review of post-hoc studies did not suggest any effects (Hafemen et al 2012). Well designed trials are still needed, however, as prospective studies in first episode schizophrenia do indicate prefrontal grey matter decreases with continued antipsychotic treatment (Ho et al 2011). Although complicated by dose, duration, and differences between individual agents, preclinical studies similarly suggest antipsychotics may affect cell viability through creation of reactive oxygen species or increases in glutamate neurotransmission, or induce apoptosis through mitochondrial respiratory chain inhibition, reduction of neurotrophic factors, or as a byproduct of dopamine depletion (reviewed by Dean 2006).

In summary, we found that sustained recovery in the year following a first manic episode was associated with significant improvements in executive function and reductions in grey matter loss (including the DLPFC) when compared to patients who experience an affective recurrence. These findings support current staging models which describe BDI as a dynamic and neuroprogressive illness, further highlighting the potential benefits of successful early intervention in curtailing the cumulative negative effects of multiple affective episodes. Future studies exploring the impact of manic versus depressive relapses on disease progression and the role of pharmacological treatments are warranted.
Chapter 4

Effects of Adjunctive Risperidone or Quetiapine on Executive Function in Bipolar I Disorder

4.1 Introduction

The effect of medication on cognitive functioning in euthymic patients with BDI has been severely understudied despite the immense implications that this research could have in both the understanding and successful management of this disorder. Combination therapy with a mood stabilizer and an antipsychotic such as risperidone or quetiapine is a frequently employed strategy for treating acute mania, and continuation of a successful regime after mood episode resolution is common. This maintenance phase of treatment in BDI is critical to minimize the frequency, duration, and severity of subsyndromal symptoms; prevent relapse or recurrence, as well as decrease hospitalizations, morbidity, mortality, and improve functioning and quality of life in sufferers of this chronic condition (Yatham et al. 2009). Because of the long term nature of this treatment, side effects and tolerability of medications used also need to be considered.

While the iatrogenic effects of lithium and valproate in this population appear to be modest and limited to effects on memory (Pachet & Wisniewski 2003, Senturk et al. 2007, Goswami et al. 2009, Wingo et al. 2009, Lopez-Jaramillo et al. 2010); as a group, use of antipsychotics may have a more severe impact on cognitive abilities. There is a long history of negative subjective cognitive complaints associated with antipsychotic administration in other populations, this “neuroleptic dysphoria” encompasses feelings of diminished cognitive, affective, and motivation that often leads to drug aversiveness and declines in clinical and functional outcome (Voruganti & Awad, 2004). Although the applicability of self-reported cognitive impairment due to psychotropic medication is limited by its subjective nature (Burdick et al. 2005), it does provide an important starting point to guide standardized, objective, cognitive research. A robust association between use of antipsychotics and decreased performance on tests of executive function involving inhibition (Savitz et al. 2008, Jamrozin斯基 et al. 2009), working memory (Donaldson et al. 2003, Dittmann et al. 2008), and
set-shifting (Savitz et al 2008, Jamrozinski et al 2009, Altschuler et al 2004, Frangou et al 2005) have all been found in post-hoc comparisons of patients receiving naturalistic care; although to date there have been no well designed studies examining the effects of maintenance treatment. Impairments attributed to antipsychotic use are not trivial, Jamrozinski et al (2009) found that when comparing euthymic patients receiving antipsychotics (n=18) to those not (n=22) deficits in executive function for those receiving antipsychotics ranged from $d=0.68-1.39$. Similarly, Frangou et al (2005) found that estimated effect sizes for antipsychotic use on executive function measures between -0.84 and -1.02; an effect even stronger than history of psychosis.

Although relative affinity for the serotonin 5HT-2A receptor may also play a role in the effects of antipsychotics on executive function (Gozzi et al 2010, Tyson et al 2004, 2006); imaging and pharmacological manipulation studies in healthy human subjects indicate the strongest influence is most plausibly through the actions on the $D_2$ dopamine receptor (Arnt & Skarsfeldt 1998, Seeman 2002, Wagner et al 2005). $D_2$ is the only receptor universally occupied at therapeutic doses of all antipsychotics, with efficacy of an agent related to its occupancy in the striatum (Seeman 2002). Although the exact role that dopamine and the $D_2$ receptors play in cognition is unclear, autoradiographic and functional imaging show that they are located in areas heavily implicated in cognitive functioning (Gaspar et al 1995, Khan et al 1998). PET studies in healthy controls have found that $D_2$ binding potential in several regions including the striatum, hippocampus, amygdala, anterior cingulate cortex, and lateral prefrontal cortex correlate with performance on executive function (Aalto et al 2005, Lumme et al 2007, Sawamoto et al 2008, Takahashi et al 2008). Experiments using $D_2$ selective antipsychotic agents in healthy controls have shown that acute administration impairs performance on several aspects of cognitive functioning, although there is a high level of variability between individual studies. Most of the variance between findings has been attributed to tasks used, baseline performance of subjects, and levels of drug occupancy (Mehta et al 2008). Of the cognitive domains examined, executive functioning tests most sensitive to effects of antipsychotics are working memory and set-shifting (Mehta et al 1999, 2004, 2008), with mixed findings in measures of response inhibition (Mehta et al 1999).
The effects of different antipsychotics on executive function may also not be equivocal. While all known antipsychotics bind to the D₂ dopamine receptor with an affinity corresponding with their clinical efficacy, differences in their dissociation rate constants may also result in differences in effects on executive function. This same variability is also likely responsible for disparities between drugs in regards to incidence of extra-pyramidal symptoms (EPS) and hyperprolactemia. According to this theory, classification of drugs as typical (ie having high incidence of hyperprolactemia, EPS, and a negative cognitive profile) verses atypical (low incidence of adverse events) is based on binding relative to dopamine. Agents that bind much less tightly than dopamine to the D₂ receptor (such as clozapine and quetiapine) will dissociate in response to task related surges in dopamine, competitively attenuating physiological signalling. In contrast to this, agents that bind more tightly than dopamine (including haloperidol and risperidone) distort or extinguish dopaminergic transmission (Seeman 2002).

While not universal, most findings in populations with schizophrenia support the idea that antipsychotic drugs with stronger binding to the D₂ receptor will have more negative effects on executive function, with meta-analysis of findings examining cognitive changes after switching from a first generation antipsychotic to a second generation showing that the second generation was associated with improved overall cognitive function; with differences in magnitude of effects between specific second generation agents showing an advantage for quetiapine over risperidone in several cognitive domains (Woodward et al 2005). Extrapolation of these findings to patients with BD must be done with caution because interactions of disease pathology with drug mechanisms can lead to different sensitivities to intended and adverse effects of medication. There is reason to believe that patients with BDI will be more affected by both therapeutic and negative effects: a systematic review has shown that patients with BD both in the manic and depressive phase are more sensitive to EPS from haloperidol as well as the atypical antipsychotics risperidone, aripiprazole, and quetiapine than those with schizophrenia, despite lower doses used to obtain clinical response (Gao et al 2008).
**Study Hypothesis**

Patients treated with risperidone will perform worse than those treated with quetiapine; and these effects would be most strongly seen in working memory and set shifting.

**4.2 Methods**

**4.2.1 Study Overview**

The present study was conducted to examine differences in executive function between euthymic patients with BDI treated with mood stabilizer monotherapy compared to those receiving maintenance treatment with a mood stabilizer plus add on therapy with risperidone or quetiapine, as well as a healthy control group. In order to minimize the effects of subsyndromal symptoms only euthymic patients were included. In order to look more specifically at which abilities may be most impacted, executive tests were broken down into three separate dimensions: working memory, set shifting, and response inhibition. Results from this study will provide important information on the cognitive effects of different treatment regimens used to prevent relapse in BDI.

**4.2.2 Participants**

Patient participants consisted of outpatients meeting DSM-IV-TR criteria for BDI selected from those receiving longitudinal follow up within the Systematic Treatment Optimization for Early Mania (STOP-EM) program at Vancouver Hospital Health Sciences Centre affiliated sites. The patients were recruited from community and hospital referrals from physicians and psychiatrists. The diagnosis of BDI, as well as the presence of comorbid diagnoses, was based on a comprehensive clinical interview by a board certified psychiatrist and confirmed with the Mini International Neuropsychiatric Interview (Sheehan et al 1998).

Description of the full longitudinal study protocol can be found elsewhere (Chapter 2, Chapter 3, Torres et al., 2010). Briefly, patients included in this study were drawn from an
initial pool of participants between the ages of 14-35 who had received baseline cognitive testing within three months of resolution of their first manic/mixed episode, and who may have also received follow up cognitive assessments at multiple points within three years of the initial testing session. Of the 67 patients who have participated in cognitive testing, 47 had at least one session that met the following inclusion criteria: outside of an acute mood episode for at least 4 weeks, receiving continuous pharmacological treatment for more than 8 weeks, and euthymic as determined by mood rating scales HAMD ≤8, and YMRS ≤6. If patients had multiple assessments that satisfied the inclusion criteria the first session was used for analysis. Of the 20 patients who did not meet inclusion, 3 had a recurrence within 8 weeks of the available testing sessions, 8 were not receiving continuous pharmacological treatment, and 9 were not euthymic for any completed assessments. Of the patients meeting inclusion criteria, 15 were treated with risperidone + mood stabilizer, 17 with quetiapine + mood stabilizer, and 15 with mood stabilizer monotherapy.

Healthy subjects (n=28) free of personal or familial history of psychiatric illness in their first or second degree relatives of comparable age, sex, premorbid IQ, and level of educational attainment were recruited from the community through word of mouth and internet advertising. Ethics approval was granted from the UBC Clinical Research Ethics Board, and written informed consent was obtained from all patients and healthy subjects prior to any study procedures taking place.

4.2.3 Clinical Assessment

Sociodemographic and clinical variables were collected as per the protocol of the STOP-EM program and described in Chapters 2 and 3. Patients received naturalistic treatment for BDI from psychiatrists with expertise in the management of mood disorders, and according to clinical practice guidelines (Yatham et al., 2009). The HAMD, YMRS, and PANSS were administered by a trained psychiatrist to assess potential subthreshold symptoms. Additional clinical variables recorded included number and polarity of prior mood episodes, history of psychotic symptoms during a mood episode, duration of illness, age of onset of illness, number of past hospitalizations, and lifetime substance abuse or dependence; and for patients
receiving adjunctive therapy with risperidone or quetiapine the duration and dose. To facilitate statistical comparison, antipsychotic doses were standardized according to the method proposed by Baitz et al (2012); whereby 1mg of loxapine is equivalent to 0.08mg risperidone, 5.73mg olanzapine, or 8.72mg quetiapine.

4.2.4 Assessment of Executive Function

All neuropsychological tests were administered in a quiet testing room following standard procedures. Measures used were part of a 2-3 hour cognitive battery employed in the larger longitudinal study in which assessments occurred every 6 months. IQ measures were only obtained at baseline, whereas all other tests were administered during all time points. Alternate forms of tests were used on an alternating basis for verbal fluency and ID/EDS. Full description of cognitive domains and specific tests employed are provided below:

*Intellectual and Premorbid Intellectual Function:* The North American Adult Reading Test Full Scale IQ (NAART FSIQ) (Blair and Spreen, 1989) was used to measure premorbid IQ, and the Kaufman Brief Intelligence Test (KBIT) IQ composite score (Kaufman and Kaufman 1990) was used to assess intellectual ability.

*Executive Function* was examined separately for each dimension based on previous factor analytic studies in healthy populations (Miyake et al., 2000; Lehto et al., 2003). Measures included standard paper and pencil neuropsychological tests as well as tests from the computerized CANTAB (Robbins et al., 1994). A score for each executive dimension was calculated by averaging the demographically corrected z-scores (obtained from test manuals) for each of the two tests included.

*Response Inhibition* refers to the ability to deliberately inhibit a dominant, automatic, or prepotent response. Choice of measures was based on prior factor analysis (Miyake et al., 2000) and included the Stroop interference score (Golden 1978) and the CANTAB SOC problems solved within the minimum number of moves (Owen et al., 1990). Both of these tasks require the subject to resolve a conflict between relevant and irrelevant
stimuli and to inhibit an incorrect but perceptually congruent response (Goel & Grafman 1995). On the Stroop, subjects are required to name the color of the ink a word is printed in rather than read the word itself (MacLeod 1991). Similarly, within the intermediate planning steps of the SOC subjects are required to move a ball in the opposite direction of the eventual final position (Morris et al 1997).

**Working Memory** involves control and manipulation of information held online, and is made up of processes that monitor and code task-relevant information, and revise it as necessary by replacing old information with new (Miyake et al 2000, Lehto et al 2003). The CANTAB SWM between search errors (Owen et al 1990) has been shown to be a valid measure of this dimension in several neuropsychiatric populations (Fray et al 1996) including BDI (Barrett et al 2008). The Wechsler Adult Intelligence Scale III Letter-Number subtest was also chosen, consistent with proposed neurocognitive batteries for bipolar and schizophrenic populations (Neuchterlein et al 2008, Yatham et al 2010).

**Set-Shifting** refers to the ability to generate and identify concepts, test hypothesis, maintain attention, guide behavior, and when more than one concept is possible, to switch sets and inhibit preservation of prior categories (Miyake et al., 2000; Lehto et al 2003). The first task used to measure this dimension is the CANTAB ID/EDS (Downes et al 1989). The extradimensional shift errors measure will be used as this specifically assesses ability to shift response to an alternative, previously irrelevant stimulus (Robbins et al 1998). The second selected task is Verbal Fluency number of words generated. Its use as a set-shifting measure has been supported by factor analysis (Lehto et al 2003), as optimal performance requires subjects switch between subcategories of words (Troyer et al 1998).

### 4.2.5 Statistical Analysis

All statistical analyses were conducted using SPSS 18.0 (SPSS Inc, Chicago, Illinois). We compared clinical and demographic variables between groups using ANOVA for continuous and chi square for categorical variables. Group differences on neuropsychological measures were assessed using one way ANOVA with follow up Tukey post-hoc comparisons. In
accordance with stated aims, we focused specifically on differences between the risperidone and quetiapine groups.

### 4.3 Results

#### 4.3.1 Demographic and Clinical Features

The patient population (n=47) was young; mean (standard deviation) 23.4 (4.7) years, well-educated with an average of 13.9 (2.4) years, and displayed average to high average IQ 106.9 (7.6). Participants were early in their courses of illness, with an average of 2.8 (2.2) prior mood episodes. Subthreshold symptomatology was low; YMRS 0.6 (1.1) and HAMD 1.7 (2.3), and 85% patients had history of psychotic symptoms during previous mood episodes.

The three different medication groups and the healthy subjects were comparable with regard to major demographic and clinical variables at the time of cognitive testing (Table 4.1). Although non-significant (p=0.35), premorbid IQ in patients treated with risperidone was numerically lower than in the other groups. In terms of pharmacological treatments, equal proportions of patients were treated with lithium and valproate, with one subject in the risperidone group receiving both mood stabilizers. Three patients in the mood stabilizer monotherapy group were concurrently receiving antidepressants (sertraline, fluoxetine, or bupropion). Relative dose was not different between those treated with risperidone or quetiapine (p>0.47). The actual mean doses were 2.08(1.63) mg for risperidone and 160.2(158.1) mg for quetiapine.
Table 4.1: Demographic and Clinical Features of Patients Receiving Maintenance Treatment and Healthy Subjects

<table>
<thead>
<tr>
<th></th>
<th>Risperidone + Mood Stabilizer (n=15)</th>
<th>Quetiapine + Mood Stabilizer (n=17)</th>
<th>Mood Stabilizer Monotherapy (n=15)</th>
<th>Healthy Controls (n=28)</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean(SD)</td>
<td>Mean(SD)</td>
<td>Mean(SD)</td>
<td>Mean(SD)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>22.4 (3.8)</td>
<td>23.5 (5.4)</td>
<td>24.3 (4.6)</td>
<td>23.5 (4.6)</td>
<td>0.43</td>
</tr>
<tr>
<td>Education (years)</td>
<td>13.5 (2.0)</td>
<td>14.8 (2.7)</td>
<td>13.7 (2.7)</td>
<td>14.9 (2.3)</td>
<td>2.44</td>
</tr>
<tr>
<td>Premorbid IQ (NAART)</td>
<td>103.8 (7.8)</td>
<td>108.1 (6.8)</td>
<td>107.4 (7.3)</td>
<td>107.6 (7.7)</td>
<td>1.11</td>
</tr>
<tr>
<td>IQ (K-BIT)</td>
<td>105.3 (9.0)</td>
<td>107.3 (9.9)</td>
<td>105.1 (10.7)</td>
<td>110.4 (9.1)</td>
<td>1.42</td>
</tr>
<tr>
<td>Age of Onset</td>
<td>20.1 (3.2)</td>
<td>21.7 (4.9)</td>
<td>19.0 (7.0)</td>
<td>-</td>
<td>1.07</td>
</tr>
<tr>
<td>Duration of Illness (years)</td>
<td>2.4 (2.3)</td>
<td>2.1 (2.2)</td>
<td>5.1 (5.8)</td>
<td>-</td>
<td>2.88</td>
</tr>
<tr>
<td>Time since first Manic Episode (years)</td>
<td>0.8 (0.9)</td>
<td>0.8 (0.7)</td>
<td>1.1 (0.8)</td>
<td>-</td>
<td>1.65</td>
</tr>
<tr>
<td>Number of Prior Episodes Mania</td>
<td>2.1 (1.5)</td>
<td>3.0 (2.4)</td>
<td>3.1 (2.7)</td>
<td>-</td>
<td>0.88</td>
</tr>
<tr>
<td></td>
<td>Number of Prior Episodes Depression</td>
<td>0.9 (0.5)</td>
<td>1.2 (0.4)</td>
<td>1.1 (0.3)</td>
<td>2.33</td>
</tr>
<tr>
<td></td>
<td>Number of Prior Hospitalizations</td>
<td>1.1 (0.4)</td>
<td>1.3 (0.8)</td>
<td>0.9 (0.6)</td>
<td>1.60</td>
</tr>
<tr>
<td>GAF</td>
<td>77.9 (6.6)</td>
<td>77.9 (8.3)</td>
<td>80.7 (7.8)</td>
<td>-</td>
<td>0.64</td>
</tr>
<tr>
<td>HAMD</td>
<td>1.4 (1.6)</td>
<td>2.6 (2.6)</td>
<td>0.9 (2.3)</td>
<td>-</td>
<td>2.33</td>
</tr>
<tr>
<td>YMRS</td>
<td>0.5 (0.9)</td>
<td>0.9 (1.5)</td>
<td>0.3 (0.7)</td>
<td>-</td>
<td>1.23</td>
</tr>
<tr>
<td>PANSS Positive Scale</td>
<td>7.2 (0.6)</td>
<td>7.0 (0.0)</td>
<td>7.0 (0.0)</td>
<td>-</td>
<td>2.04</td>
</tr>
<tr>
<td>Weeks on Antipsychotic</td>
<td>33.7 (34.6)</td>
<td>34.4 (19.2)</td>
<td>-</td>
<td>-</td>
<td>0.01</td>
</tr>
<tr>
<td>Antipsychotic Dose (mg loxapine)</td>
<td>24.4 (18.4)</td>
<td>19.6 (18.3)</td>
<td>-</td>
<td>-</td>
<td>0.53</td>
</tr>
<tr>
<td>N(%)15</td>
<td>7(46.7)</td>
<td>7(41.1)</td>
<td>8(53.3)</td>
<td>14(50.0)</td>
<td>0.54</td>
</tr>
<tr>
<td>N(%)17</td>
<td>8(53.3)</td>
<td>9(52.9)</td>
<td>7(46.7)</td>
<td>-</td>
<td>0.13</td>
</tr>
<tr>
<td>Sex (Male)</td>
<td>8(53.3)</td>
<td>8(53.3)</td>
<td>13(86.7)</td>
<td>-</td>
<td>0.88</td>
</tr>
<tr>
<td>Mental Stabilizer</td>
<td>8(53.3)</td>
<td>8(53.3)</td>
<td>8(53.3)</td>
<td>-</td>
<td>0.13</td>
</tr>
<tr>
<td>Divalproex</td>
<td>13(66.7)</td>
<td>13(76.4)</td>
<td>11(73.3)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Previous Psychotic Symptoms</td>
<td>13(66.7)</td>
<td>13(76.4)</td>
<td>11(73.3)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>History of Drug Abuse</td>
<td>7(46.7)</td>
<td>8(47.1)</td>
<td>7(46.7)</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

All F and χ² values are non-significant.

NAART, North American Adult Reading Test; KBIT, Kaufman Brief Intelligence Test; GAF, Global Assessment of Functioning; HAMD, Hamilton Depression Inventory; YMRS, Young Mania Rating Scale; BPRS, Brief Psychiatric Rating Scale; PANSS, Positive and Negative Syndrome Scale

4.3.2 Executive Function Performance

All neuropsychological dimensions met assumptions for parametric tests: no cognitive measures showed significant Hartley’s variance ratio (p<0.05), indicating comparable variances across groups. Scores were normally distributed (Shapiro-Wilk p>0.05) except for the patient group treated with quetiapine in measures of set-shifting (W(17)=0.874, p<0.05).
While reliability for working memory was modest (α=0.55), it was poor for both inhibition (α=0.17) and set-shifting (α=0.08). Across groups, there was no significant difference in the proportion of patients receiving alternate forms of Verbal Fluency or ID/EDS (χ²=3.77, df=3; p = 0.29). The proportion of individuals tested at the baseline versus other time points was comparable between the groups (χ² = 6.80, df= 3, p=0.08). Overall, 47% of patients were tested on the same day mood ratings were obtained, 68% within 1 week, and 83% within 2 weeks of mood ratings.

Executive Functioning performance across groups is presented in Table 4.2 and Figure 4.1. One way ANOVA revealed a significant effect of group in working memory (F=3.94, df=3, 71; p<0.05) set-shifting (F=7.08, df= 3, 71; p<0.001), but not response inhibition (F=2.23, df= 3, 71; p=0.09). Post-hoc analysis revealed that those on risperidone performed significantly worse than those treated with quetiapine on set-shifting (Mean Difference=0.74, df=1,30; p<0.05), with a trend towards significant impairments in working memory (Mean Difference=0.81, df= 1,30; p=0.06). Patients on risperidone also performed worse than those receiving mood-stabilizer monotherapy in set-shifting (Mean Difference=0.73, df=1,28; p<0.05). Compared to healthy subjects only patients treated with risperidone showed significant deficits; found in both working memory (Mean Difference=0.88, df=1,41; p<0.05) and set shifting (Mean Difference=1.02, df=1,41; p<0.001). The above analysis was repeated using premorbid IQ as a covariate, and findings remained unchanged.

Relative antipsychotic dose negatively correlated with working memory (r=-0.36, p<0.05) but not set-shifting (r=-0.13, NS) or inhibition (r=-0.29) scores.
Table 4.2: Performance on Executive Function Dimensions in Patients Receiving Maintenance Treatment and Healthy Subjects

<table>
<thead>
<tr>
<th></th>
<th>Risperidone + Mood Stabilizer (n=15)</th>
<th>Quetiapine + Mood Stabilizer (n=17)</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>F</td>
</tr>
<tr>
<td>Inhibition</td>
<td>0.36 (0.74)</td>
<td>0.36 (0.64)</td>
<td>0.51 (0.53)</td>
<td>0.82 (0.77)</td>
<td>2.23</td>
</tr>
<tr>
<td>Stroop Interference</td>
<td>0.47 (0.79)</td>
<td>0.85 (0.47)</td>
<td>0.82 (0.60)</td>
<td>0.71 (0.90)</td>
<td></td>
</tr>
<tr>
<td>SOC Minimum Moves</td>
<td>0.26 (0.99)</td>
<td>-0.12 (1.39)</td>
<td>-0.12 (1.29)</td>
<td>0.93 (1.25)</td>
<td>8.29*</td>
</tr>
<tr>
<td>Working Memory</td>
<td>-0.39 (1.23)</td>
<td>0.41 (0.76)</td>
<td>-0.04 (0.75)</td>
<td>0.49 (0.79)</td>
<td>3.94*</td>
</tr>
<tr>
<td>Letter/Number</td>
<td>-0.31 (0.97)</td>
<td>0.41 (1.21)</td>
<td>0.29 (0.81)</td>
<td>0.58 (1.15)</td>
<td></td>
</tr>
<tr>
<td>SWM Between Errors</td>
<td>-0.47 (1.82)</td>
<td>0.42 (0.78)</td>
<td>-0.36 (1.01)</td>
<td>0.39 (0.74)</td>
<td>7.87*</td>
</tr>
<tr>
<td>Verbal Fluency</td>
<td>-0.69 (1.20)</td>
<td>-0.16 (0.77)</td>
<td>0.25 (1.34)</td>
<td>0.22 (0.97)</td>
<td></td>
</tr>
<tr>
<td>EDS Errors^</td>
<td>-0.60 (1.61)</td>
<td>0.33 (0.67)</td>
<td>-0.09 (1.04)</td>
<td>0.54 (0.17)</td>
<td></td>
</tr>
<tr>
<td>Working Memory</td>
<td>0.08 (0.85)</td>
<td>0.38 (0.52)</td>
<td>7.08***</td>
<td>R+MS&lt;HS*</td>
<td></td>
</tr>
<tr>
<td>SOC Minimum Moves</td>
<td>0.26 (0.99)</td>
<td>0.12 (1.39)</td>
<td>0.93 (1.25)</td>
<td>8.29*</td>
<td></td>
</tr>
<tr>
<td>Set-Shifting</td>
<td>0.10 (0.58)</td>
<td>0.08 (0.52)</td>
<td>2.87*</td>
<td>Q+MS*, X+MS**</td>
<td></td>
</tr>
<tr>
<td>Letter/Number</td>
<td>0.31 (0.97)</td>
<td>0.41 (1.21)</td>
<td>0.29 (0.81)</td>
<td>0.58 (1.15)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>EDS Errors^</td>
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<td>0.33 (0.67)</td>
<td>-0.09 (1.04)</td>
<td>0.54 (0.17)</td>
<td></td>
</tr>
</tbody>
</table>

^ In cases where the EDS stage was not reached, 25 errors was substituted (Robbins et a 1998)
R+MS, Risperidone + Mood Stabilizer; Q+MS, Quetiapine + Mood Stabilizer; X+MS, Mood Stabilizer Monotherapy; HS, Healthy Subjects
SOC, Stockings of Cambridge; SWM, Spatial Working Memory; EDS, Extradimensional Shift
*: p<0.05, **: p<0.01, ***: p<0.001
# Due to non-normal distribution (Shapiro-Wilk p<0.05) Kruskal-Wallis non-parametric test was used for denoted individual measures

Figure 4.1 Executive Function Performance in Patients Receiving Maintenance Treatment and Healthy Subjects

** Between group differences, p<0.01
*** Between group differences, p<0.001
# Superior to Risperidone + Mood Stabilizer, p<0.05
## Superior to Risperidone + Mood Stabilizer, p<0.01
### Superior to Risperidone + Mood Stabilizer, p<0.001


4.4 Discussion

Upon consideration of the importance of executive abilities on functional outcome in bipolar disorder, the importance of choosing medications that do not exacerbate already impaired processes is evident. As the first study to examine differences in neuropsychological function between patients recently diagnosed with BDI who were receiving mood stabilizer monotherapy or adjunctive treatment with risperidone or quetiapine, we found that euthymic patients with BDI receiving risperidone plus a mood stabilizer performed significantly worse than those receiving quetiapine in executive function dimensions of working memory and set shifting. While patients treated with adjunctive quetiapine performed similarly to those on mood stabilizer monotherapy in all dimensions, patients treated with risperidone had comparably worse performance in set shifting.

A single randomized, double blind, crossover study comparing the effects of treatment with risperidone versus quetiapine in euthymic BDI found that initiation of risperidone was associated with better working memory compared to quetiapine, with advantages for quetiapine seen in inhibition; however unlike the current study, this analysis evaluated acute effects within 24 hours following drug initiation. At this point cognitive differences may have been secondary to effects of quetiapine on somnolence- patients treated with risperidone reported more vigor and less fatigue (Harvey et al 2007). Recently, one other analysis has examined differences in cognitive profiles after chronic administration of these agents in euthymic BDI patients. Torrent et al (2011) similarly found that after adjusting for subsyndromal symptoms, naturalistic treatment with risperidone or olanzapine was associated with more impairment than with quetiapine or no antipsychotic. Specifically, this study found that patients on risperidone performed worse than healthy subjects on both verbal fluency and Stroop, while those on olanzapine had impaired performance on verbal fluency, trails B, and digitspan backward. Patients treated with quetiapine or who were unmedicated performed similar to healthy subjects on all measures.

Findings that long term use of risperidone relative to quetiapine is associated with impaired executive functioning may be attributable to the same mechanism that is hypothesized to
underlie differences in incidence and severity of hyperprolactanemia and extrapyramidal side effects between individual antipsychotic agents, namely relative affinity to the D₂ dopaminergic receptor (Arnt & Skarsfeldt 1998, Seeman 2002). While risperidone binds tighter than dopamine (DA) to the D₂ receptor, quetiapine demonstrates a very low affinity. Although both drugs will occupy the same proportion of receptors during basal levels of DA release, during phasic bursts quetiapine will quickly dissociate to allow some of the signal through, then return to basal occupancy levels, resulting in a competitive decrease in DA signalling. Risperidone, in contrast, will dissociate very little from the receptor, extinguishing or distorting physiological signalling, potentially resulting in negative side effects. Agents that show medium binding affinity, such as olanzapine, have intermediate effects which are likely to be dose dependent. This mechanism also may explain the large negative effects of antipsychotics on executive function in patients reported in the Maudsley Bipolar Disorder Project (Donaldson et al 2003, Frangou et al 2005). In these reports, nearly half of the subjects receiving antipsychotics were on typical agents that show affinity to the D₂ receptor even stronger than risperidone. Consistent with this hypothesis, Reinares et al (2000) found that when compared to patients taking the typical drug haloperidol, those treated with risperidone had better cognitive performance, specifically on a measure of set-shifting abilities.

Cognitive models suggest that D₂ receptors play a gating role in the striatum, allowing for flexible updating and manipulation of information held online in the prefrontal cortex; skills important for both working memory and set shifting (Hazy et al 2007). This model has received support from pharmacological studies (Dodds et al 2009). Both too little and too much D₂ activity is likely to impair cognition (Cools & D’Esposito 2011)- selective overexpression of D₂ receptors in the striatum during development in mice results in impairments in working memory and set shifting in the absence of more generalized cognitive deficits. The role of D₂ receptors in executive function is not likely limited to the striatum, however, autoradiographic studies show that D₂ receptors are located in other areas implicated in cognitive functioning including the amygdala, hippocampus, and thalamus (Khan et al 1998), as well as in low levels in the prefrontal and cingulate cortex (Gaspar et al 1995), with binding potentials in these regions also correlating with working memory and set
shifting performance (Aalto et al 2005, Lumme et al 2007, Sawamoto et al 2008, Takahashi et al 2006). The absence of effects between antipsychotic groups in inhibition may be attributed to a more complex role that other neurotransmitters may play in performance of the tasks chosen. While the Stroop test has been previously found to be sensitive to D2 manipulation (Roesch-Ely et al 2005), these effects may have been dampened by concomitant effects of antipsychotics on serotonergic function. Scholes et al (2007) found that while depletion of both the dopamine and serotonin systems individually resulted in decreased Stroop interference, this was not seen when the two systems were simultaneously manipulated. Similarly, although prior investigations have shown that SOC performance is also dependent on D2 receptors (Mehta et al 2003, 2008), these studies used a modified version of the task thus making results not directly comparable. Although D2 receptor availability in the striatum has been found to correlate with performance on the version of the test used in our study, this was only significant for the most difficult problems (Reeves et al 2005). Animal studies of inhibition indicate that while a D2 receptor antagonist alone had no effect, it did attenuate amphetamine and nicotine induced premature responding (van Gaalen et al 2006).

The present study has several limitations. First, the sample size was modest, as a direct consequence of the strict inclusion criteria. Furthermore, although examination of the different effects of these drugs in this sample of euthymic patients early in the course of illness allowed us to minimize the effects of other potentially confounding disease variables on cognitive performance, the generalizeability of these results is unknown; although comparable results in another more heterogenous sample indicates findings may be applicable to a broader population of patients with BDI. Finally, patients were treated naturalistically. Thus, although groups appeared to be very homogenous and well-matched, effects of selection bias cannot be entirely ruled out.

While the present study provides an important indicator of potential differences in cognitive effects of individual antipsychotics, future randomized studies are needed to both confirm findings as well as determine whether the apparent benefit of using a loosely binding drug
(such as quetiapine) is an actual improvement of pretreatment executive impairments, or merely a less negative effect compared to older, tightly binding drugs.
Chapter 5
Summary and Discussion of Research Findings

5.1 Summary of Results

Along with a comprehensive review of previous research on executive function throughout the course and treatment of BDI, and introduction to the cortico-striatal-pallidal-thalamo-cortical circuitry whose dysfunction could potentially underlie impairments; original studies undertaken for this thesis describe executive function deficits and grey matter changes that are present immediately following recovery from a first manic episode and the year following a diagnosis of BDI. Furthermore, results here within indicate that certain medications used to treat and prevent mood symptoms rather than alleviate cognitive difficulties may further exacerbate them.

As hypothesized, we found that patients within 3 months of recovery from their first manic episode showed moderate-severe impairments in executive function (0.5<d<1.0); and that these deficits correlated with larger caudate volumes. Interestingly, while caudate volume was also associated with executive performance in healthy subjects, the direction of this relationship was reversed. Additionally, when patients who were strictly euthymic were considered separately, a strong negative relationship between executive function and antipsychotic dose and treatment duration also emerged. As with other studies of patients early in the course of BD, we did not find any grey matter changes in the DLPFC. Together with IQ and education, caudate volume, standardized antipsychotic dose, and treatment duration predicted over 40% of the variance in executive function in the entire patient sample, and over 65% in the subset that were euthymic.

As with other prospective samples of patients following their first manic episode, rates of episode recurrence over one year follow-up in the STOP-EM sample were high (>50% experienced at least one subsequent hypo/manic or depressive episode within this period), even in the context of ongoing pharmacotherapy. While we originally hypothesized that recurrence during follow-up would be associated with longitudinal declines in executive
function, this was not specifically found. Rather, we saw that patients who remained well during this period showed performance gains greater than both those who experienced a recurrence as well as healthy subjects, although impairments relative to healthy subjects still remained at a moderate severity at follow-up (d=0.51, compared to d=0.68 for those who experienced recurrence of mood symptoms). Surprisingly, executive improvements in those who remained well were also accompanied by reductions in age related grey matter loss, although no obvious relationship between structural and cognitive changes were detected. Consistent with our original hypothesis, we did also see that patients who experienced an affective recurrence over follow-up had accelerated grey matter loss compared to healthy subjects and patients who remained well, with the most extensive differences localized to the lateral PFC, including the DLPFC; although these changes also showed no clear association with executive changes.

As long-term maintenance treatment using combination therapy with a mood stabilizer (such as lithium or valproate) and an antipsychotic agent (including risperidone or quetiapine) is a common therapeutic practice to prevent or reduce the severity of episode recurrence in euthymic patients with BD, it is also important to consider how such strategies may also influence cognitive performance. As previous findings, including those from this sample, have indicated that antipsychotic use in particular may be associated with more extensive cognitive impairments, we compared executive performance between patients receiving monotherapy with a mood stabilizer, or combination treatment with either risperidone or quetiapine. Consistent with the hypothesis that treatment with risperidone in particular (which has a much higher D₂R affinity compared to quetiapine) would be associated with the most severe deficits, we found that those on a mood stabilizer plus risperidone showed the worst performance across all executive dimensions, with significant impairments relative to those on quetiapine or mood stabilizer monotherapy in set-shifting, and deficits in working memory correlating with higher doses of either antipsychotic drug (standardized according to D₂R occupancy levels). These results are consistent with hypotheses that suggest negative side effects of antipsychotic agents are largely attributable to differences in D₂R occupancy.
Together, these results confirm that impairments in executive function are present in patients early in the course of BDI, and that deficits are accompanied by grey matter changes in the caudate and DLPFC. Cognitive and neural changes seen immediately after initial recovery from mania are not static, however, as they were shown to evolve dynamically in a way that differed according to illness progression. Furthermore, treatment with antipsychotic agents which act through D2R to modulate activity of the executive cortico-striatal-thalamo-cortical circuitry (of which the DLPFC and caudate are important members) were also associated executive performance in a manner likely dependent on differences in receptor affinity and binding.

5.2 Evolution of Executive Function Impairments in Bipolar I Disorder

5.2.1 Executive Function Following Recovery from a First Manic Episode

In the current sample, there were large impairments in CANTAB tests of executive functioning in patients with BDI who had achieved sustained syndromal recovery from their first manic episode. Deficits did not correlate with the severity of subsyndromal mood symptoms. While this is the first study looking specifically at impairments in these tests in early stage, euthymic patients; several studies examining more heterogenous or symptomatic samples have yielded inconsistent results. Impairments on ID/EDS have been found in euthymic subjects of various illness stages (Barrett et al 2008, McKirdy et al 2009) including healthy first degree relatives (Clark et al 2005). Smaller studies using euthymic (Olley et al 2005) or symptomatic patients, however, have yielded negative results (Sweeney et al 2000, Roiser et al 2009). The test of spatial working memory is also inconsistently implicated in this illness, with deficits found in large studies of euthymic subjects (Barrett et al 2008, Rybakowski et al 2010) but not in those who are depressed but not medicated (Rosier et al 2009). Although scores were numerically lower, manic patients (n=12) had similar SWM performance as healthy subjects (Badcock et al 2005). Although patients in the current sample were moderate-severely impaired; other than one investigation that showed impairments in siblings of patients, (Kulkarni et al 2010) no studies have found significant

The severity of executive impairments seen following sustained syndromal recovery from a first manic episode may be attributable to multiple genetic, environmental, and illness related factors. Genetic factors in particular are likely to make a substantial contribution to impairments; with the heritability of several executive tasks in bipolar subjects and their families estimated at 50-70% (Antila et al 2007, Glahn et al 2010). Many specific genes have been associated with executive performance in healthy subjects; most of which are involved in dopaminergic neurotransmission within frontostriatal regions, with particular emphasis being on the importance of dopamine receptors (D₁, D₂, D₄), as well as the COMT enzyme which breaks down prefrontal dopamine (Savitz et al 2006), the dopamine transporter which is responsible for dopamine reuptake in the striatum (Barnes et al 2011), and DARPP-32 which is involved in D₁R signalling (Frank & Fossella 2011). While many of these genes have also been implicated in risk for BDI, their role in contributing to executive deficits is unknown. Environmental factors also likely to play a role; childhood trauma has been associated with impaired executive performance in BD (Savitz et al 2008), although this has not been seen in a subset of the same first episode mania sample as used in this thesis (Bucker et al 2012). The severity of deficits witnessed following a first manic episode could also be a secondary consequence of the mood disturbance itself; comparisons of patients with multiple versus single episodes do suggest cumulative effects (Lopez-Jamorillo et al 2010, Elshahawi et al 2011; but also Fleck et al 2008, Hellvin et al 2012); although preliminary studies do suggest that executive and other cognitive impairments are still present prior to a first manic episode (Meyer et al 2004, Olvet al 2010). As there are no prospective studies comparing executive function patients with BDI before and after onset of a first manic episode, it cannot be speculated to what extent deficits seen following at this point of the illness can be attributed to that episode versus premorbid impairments.
5.2.2 Executive Function a Year after a First Manic Episode: Association with Illness Progression

In contrast to original hypotheses, results from longitudinal analysis suggest that affective recurrence in the year following a first manic episode is not associated with noticeable declines in executive functioning. Recurrence may still have a negative impact on executive function however, as subjects in the current sample who experienced a mood episode over follow up did not show the same performance gains as those who remained well. It is likely that the effects of a mood episode is insufficient to lead to further executive impairments (Hellvin et al 2012); and rather declines only occur after accumulation of multiple episodes (Lopez-Jamorillo et al 2010), with grey matter loss seen in the DLPFC and other cortical areas a likely factor underlying these further impairments. As manic episodes in particular may be associated with more extensive cellular (Kapczinski et al 2011) and prefrontal (Ekman et al 2010) changes, it may be also hypothesized that executive function is more sensitive to recurrences of this polarity- a possibility that the current sample was not adequately powered to explore.

Executive function significantly improved in patients who sustained recovery for a full year when compared to both healthy subjects and those who experienced an affective recurrence. This did not show any obvious relationship with changes in mood symptoms. These results are similar to other prospective studies which do not show consistent associations between changes in manic or depressive symptoms and executive performance (Arts et al 2011, Chaves et al 2012), although neither of these studies specifically examined the effects of affective relapse. As sustained recovery was also associated with relative gains in cortical grey matter, this may be a potential mechanism by which executive performance improves; although no relationship between cognitive function and brain structure was detected.

Overall, baseline and longitudinal results are consistent with hypotheses of cognition presented by Lewandowski et al (2011); whereby impairments are present following illness onset, improving with continued symptomatic recovery but not episode recurrence (Figure 5.1). Changes do not seem to be directly associated with reductions in mood symptoms.
Findings from one year follow-up do not support hypotheses that acute episodes specifically lead to further impairments; suggesting that these effects may rather cumulate with multiple episodes, a question that may be addressed with further ongoing prospective study of the current sample. While deficits can be speculated to both precede the first manic episode as well as be exacerbated by it, prospective support comparing patients before and after illness onset is unavailable.

**Figure 5.1 Proposed Trajectory of Executive Function Deficits in Bipolar I Disorder**

![Diagram showing trajectory of executive function deficits in Bipolar I Disorder]

*Modified from Figure 1 in the qualitative review by Lewandowski et al (2011).*

Impairments are present prior to as well as after a first manic episode, with moderate exacerbation and recovery over illness progression.

### 5.2.3 Effects of Maintenance Antipsychotic Treatment on Executive Function

It is unclear as to what extent that treatment with D₂ receptor antagonists may be responsible for the severe impairments in executive function witnessed in first episode mania studies whose populations all have antipsychotic prescription rates between 80-98% (Barrett et al 2009, Zabala et al 2010, Hellvin et al 2012). Even in the current sample, over 75% were being treated with risperidone, olanzapine, or quetiapine at baseline assessment. In Chapter 2, we found that antipsychotic dose (standardized according to D₂ receptor occupancy) was negatively associated with executive function performance, particularly in patients who were euthymic. Although many patients discontinued antipsychotic treatment in the current sample as outlined in Chapter 3, this did not appear to have any influence on longitudinal change in executive function. In Chapter 4, we compared executive functioning between euthymic patients receiving different maintenance treatment regimes. Here we found severe deficits relative to healthy subjects only in patients being treated with risperidone; with the largest effect sizes seen for set shifting (d=1.4 vs 0.51 for quetiapine) and working memory.
(d=0.85 vs 0.10). Although significant group differences were not seen for inhibition, both
groups showed impairments when compared to healthy subjects (0.4<d<0.6). While these
results provide further support to several other cross sectional studies suggesting the negative
effects of antipsychotic treatment in general (Donaldson et al., 2003, Altshuler et al., 2004;
Frangou et al., 2005; Dittmann et al., 2008; Savitz et al., 2008; Jamrozinski et al., 2009),
antipsychotic use is not likely to wholly explain impairments in BDI. Although not
statistically significant, patients receiving mood stabilizer monotherapy still had mild-
moderate deficits compared to healthy subjects in all domains (0.4<d<0.7).

In contrast to the negative association antipsychotics have with cognition in BDI, in
schizophrenic samples treatment with these agents has been shown to lead to improved
function. Differences between individual agents have been receiving the greatest attention
with over 40 published studies comparing drugs available to date. Due to promising results in
initial studies, it became generally held that atypical antipsychotics showed beneficial effects
compared to typical agents (Keefe et al 1999), although methodological weaknesses in early
studies have led to dispute over many findings (Harvey & Keefe 2001). Meta-analysis of
findings examining cognitive changes after switching from typical to atypical drugs found
that the atypical use was associated with improved overall cognitive function, with
differences in magnitude of effects between specific agents showing an advantage for
quetiapine over risperidone and olanzapine in verbal fluency (phonemic and semantic) but
not working memory (Woodward et al 2005).

While antipsychotics such as risperidone and quetiapine exert their actions on a multitude of
receptors involving dopaminergic, serotenergic, noradrenergic, histaminergic, and
cholinergic receptors; the primary mechanism of all these drugs is considered to be through
the dopamine D<sub>2</sub> receptor (Seeman 2002). Along with presence in the prefrontal and anterior
cingulate cortices, amygdala, and hippocampus D<sub>2</sub>R are heavily expressed in the striatum of
the basal ganglia (Piggott et al 1999, Seeman et al 2006). Acting here dopamine decreases
activity of the “NoGo” pathway, allowing posterior inputs to update the prefrontal cortex
(Cohen & Frank 2009). Normally these receptors are activated under both basal and burst
dopaminergic firing, with a significant increase in activity during dopamine dips. By binding
to but not activating D_{2R} during basal and dopamine dips, antipsychotics may then theoretically allow for more NoGo signalling and thus less cortico-cortical communication. During dopamine bursts, however, loosely binding atypical drugs such as quetiapine can dissociate to allow for prefrontal updating, while those like risperidone which bind tightly will maintain their positions (Seeman 2002). This has likely consequences for executive function, as well as affect/motivation and motor control.

5.3 Grey Matter Changes in Bipolar I Disorder: Potential Causes and Consequences for Executive Function

Due to the complex nature of the illness, it is likely that abnormalities in both the DLPFC and caudate (along with other regions) contribute to executive impairments in BDI in a way which evolves over illness progression. Effects of mood state also cannot be ruled out, both mania and depression are associated with changes in dopamine and thus frontostriatal function (Berk et al 2007) that also implicate executive abilities (Chudasama & Robbins 2006, Robbins & Arnsten 2009). Although results are mixed, reviews of functional imaging studies indicate euthymic patients with BDI show functional hypoactivity of the prefrontal cortex (including the DLPFC), with the basal ganglia (including the caudate) being hyperactive (Strakowski 2005, Yurgelun-Todd & Ross 2006, Cerullo et al 2009, Chen et al 2011, Kupferschmidt et al 2011). While it has been suggested that pharmacological treatment may normalize such dysfunction (Phillips et al 2008, Hafemen et al 2012), it should be noted that medication effects have been almost exclusively analyzed using post-hoc comparison of subjects who are medicated versus those who are not.

While functional imaging studies are critical for identifying situation dependent differences in brain activity, sMRI allows for examination of more stable changes in white or grey matter morphology. These anatomical measures are likely indicative of differences in functional activity (Michael et al 2010) as well as other cellular abnormalities like changes in neuronal density (la Fougere et al 2010) or dendrite size (Kassem et al 2012). sMRI also shows behavioural relevance, able to predict healthy inter-individual variability in a wide range of basic and higher cognitive functions (Kanai & Rees 2011).
5.3.1 Caudate

Our baseline analysis of caudate grey matter volume indicated that patients with BDI within 3 months of sustained recovery from their first manic episode have larger right caudate volumes than healthy subjects. Despite the 50% overlap with the patient groups used in the baseline analysis, no grey matter differences in the caudate were found between groups examined for follow-up; this is likely attributable to both sample variability and the use of grey matter density rather than volume in voxel-based analysis (as these two measures are only modestly correlated; data not shown). As the mean effect size difference between groups for caudate volume at baseline was modest (d=0.5), a sample size of 51 in each group would be required to have an 80% chance to detect enlargements. This may be a reason that most studies do not report significant differences in patients compared to healthy subjects (reviewed by Bonelli et al 2006, Marchand & Yurgelin-Todd 2010); as they all include sample sizes well under 42 as used in this thesis. Despite this, it has been asserted that increased grey matter volume in the basal ganglia, including the caudate, may be a potential neuroanatomical risk factor for bipolar disorder (Hajek et al 2005). Findings of increased caudate volumes in healthy first degree relatives (2009) including unaffected twins (Noga et al 2001) suggest that volume increases seen early in the course of illness can at least in part be attributed to genetic risk.

Research in healthy subjects indicates caudate volumes are related to variants in genes critical for dopamine-related functioning including the D2R and dopamine transportor (Bertolino et al 2009) along with other proteins implicated in dopamine signalling and development (Stein et al 2011). Consistent with this, a recent study examining the relationship between brain structure and whole genome analysis of peripheral blood mononuclear cells found that overexpression NR4A2 (involved in differentiation and maintenance of dopaminergic neurons in the ventral tegmental area, as well as control of D2R and dopamine transporter gene expression) positively correlated with caudate volume in unmedicated depressed patients (8 with BD, 21 with unipolar depression; Savitz et al 2013).
Taken together, these results suggest that genetic contributions to increased caudate volume are likely caused by differences in dopamine function, although the cellular correlates of this (ie neuron or glia size or number) is yet unknown. Interestingly, post-mortem studies in schizophrenia which show increased neuron numbers (Beckmann & Lauer 1997) and densities of cortical type synapses (Roberts et al 2005) in the caudate suggest reductions in normal pruning or abnormal sprouting may occur.

At baseline caudate enlargements predicted the severity of executive impairments in patients who were in sustained remission from their first manic episode, with similar results in the subset who had achieved euthymia. This relationship was of a similar magnitude but opposite direction of what was seen in healthy subjects. There is robust evidence indicating that dopamine has a non-linear relationship with executive function, whereby both too little and too much activity is associated with decreased performance (Cools & D’Esposito 2011). Indeed, as caudate volume has been found to correlate with D$_2$/D$_3$ receptor binding potential in healthy subjects (Woodward et al 2009), it may thus be hypothesized that the differences in correlations with caudate volume between patients and healthy subjects may be reflective of D$_2$/D$_3$ receptor levels- with healthy subjects on average being below, and patients above, the maximum or ideal. Consistent with this, analysis of the association between right caudate volume and executive function in the combined patient and healthy subject sample confirms a statistically significant quadratic relationship, where both the smallest and largest caudate volumes are associated with the worst executive score (data not shown).

Although we also did not find any difference in longitudinal grey matter changes in the caudate between patient groups and healthy subjects in Chapter 3, it still may be believed that changes occur with illness progression and that one year follow-up with the current sample size was inadequate to detect differences. Normal aging is consistently associated with decreased caudate (7% loss from the 20s-30s, and 3% from 30s-40s and 40-50s) and putamen (10% and 5% respectively) volumes (Walholvd et al 2011). While caudate volume has been found to negatively correlate with duration of illness in BD (Chen et al 2007), the opposite has been seen for the putamen (Bora et al 2010). A potential cause of these abnormalities and their behavioural effects has been demonstrated in animal models: chronic
stress exposure in rats has been shown to lead to atrophy of the caudate and hypertrophy of the putamen, changes which occurred alongside insensitivity to changes in outcome value and resistance to changes in action-outcome contingency (Dias-Ferriera et al 2009). Indeed, it has been noticed that the relationships between volumes of prefrontal and striatal regions are altered in BD; with a decreased latent structure path from the DLPFC to caudate, but increase from DLPFC to putamen relative to both healthy subjects and unipolar depression (Yeh et al 2010).

5.3.2 DLPFC

As with other studies of patients early in the course of illness (Adler et al 2007, Yatham et al 2007, Perico et al 2011, Watson et al 2012; but also Janssen et al 2008, de Castro-Manglano et al 2011), we did not find that DLPFC grey matter was lower in patients versus healthy subjects at either the baseline or year 1 visit. We did however notice that patients who experienced an affective recurrence between the initial assessment and 1 year follow-up had larger reductions in the DLPFC and surrounding prefrontal areas when compared to those who remained well, with grey matter loss in surrounding prefrontal areas also larger in those who experienced an affective recurrence compared to healthy subjects. Consistent with this, grey matter here (Ekman et al 2010) as well as in other prefrontal regions (Lyoo et al 2004) has previously been found to negatively correlate with the number of prior manic episodes. Affective episodes (and mania in particular) have been shown to be accompanied by dramatic alterations in physiological stress response systems including markers of inflammation, oxidative stress, and neural health (Kapczinski et al 2011); and it is commonly hypothesized that these cellular changes lead to grey matter loss and cognitive decline (Kapczinski et al 2008, Post et al 2010, Berk et al 2011). The role of these processes in contributing to a progressively more dysfunctional stress response and adaptation system is also emphasized.

As prefrontal dendritic remodelling in response to stress has also been shown to correspond with volumetric measures obtained using MRI in rodents (Kassem et al 2013); this is a likely potential mechanism for our findings of cortical grey matter decrease in patients who
experienced an affective recurrence. Animal models of stress (and thus potentially mood episode) induced changes in prefrontal grey matter is mostly confined to reductions in higher order apical (rather than basilar) dendrites of pyramidal neurons (Cook & Wellman 2003, Radley et al 2004); with up to 1/3 of all axospinous synapses being lost following repeated exposure (Radley et al 2006). As these synapses play an important role in integrating relevant input from across the brain, such loss is likely to have significant negative impact on cognition. Although no relationship between prefrontal grey matter loss and executive performance was found in the current sample, stress induced impairments executive function has been found in several studies using rodent models (reviewed by Holmes & Wellman 2009); with specific correlations between dendritic retraction and set-shifting in particular being found (Liston et al 2006).

Progressive prefrontal structural and accompanying behavioural changes may also be expected to occur as a consequence of normal healthy aging, as volumes have been shown to peak in the mid-late twenties and decline over the following decades (Terribilli et al 2011). Indeed, healthy subjects did show 1-2% grey matter loss in the frontal cortex (including the DLPFC) and temporal lobe over 1 year follow up; although loss was both less than what was seen in patients who experienced an affective recurrence (3-5%) and greater than those who remained well (0-+1%). The most likely substrate of age related grey matter changes is neuronal shrinkage, rather than cell loss (Terry et al 1987). In rhesus monkeys, age related decline in volume (as well as synaptic density) in BA 46 has been shown to correlate with impairments in cognitive functioning (Dimutriu et al 2010, Hara et al 2012), with similar results also found in healthy older adults (Head et al 2009).

Relative gains (or reductions in age associated grey matter loss) in patients who remain well are likely biological expressions of continued recovery in this group. Preliminary (n=7) results indicate that patients with BDI who are initially depressed show grey matter gains in the prefrontal and anterior cingulate cortex, as well as superior temporal and lingual gyri once euthymia has been achieved. In contrast, this study also found that remission was associated with grey matter loss in the subgenual cingulate, parahippocampal, and inferior temporal gyri (Brooks et al 2009). In the current sample, while the only grey matter change
associated with one year sustained remission from a first manic episode was grey matter loss in the cerebellum, when compared to healthy subjects longitudinal grey matter gain was seen both in the anterior cingulate and multiple temporal-occipital regions (including those seen to both increase and decrease with symptom improvement in study by Brooks et al). As baseline whole brain analysis of the full STOP-EM sample found grey matter decreases in the anterior cingulate in these subjects (Ha et al, in preparation); grey matter increases in this area in particular is likely to be beneficial. While medication effects are also very likely to contribute to these changes (see next section), it also may be speculated that reversal of damage associated with the first manic episode also occurred. Rodent studies suggest recovery of stress induced dendritic retraction does occur, particularly in young in animals (Bloss et al 2010), with further over expression of proximal dendritic arbors and spine growth also possible (Goldwater et al 2009). Although associations with such changes have yet to be demonstrated in either rodent or human studies, it is still plausible that grey matter gains seen in the current sample underlie improvements in executive function.

5.4 Potential Medication Effects on DLPFC and Caudate Volume

5.4.1 Antipsychotics

The effects of illness risk and course on DLPFC and caudate structure are very likely to be confounded by medication use, but there is a complete absence of well-designed studies examining their effects in this population. As D2R where antipsychotics exert their actions are located primarily in the caudate and surrounding striatum, and heavily influence processing in frontal regions; structural effects here are also likely. Review of post-hoc analyses in BD indicates no effects of these drugs on grey matter volume in any regions (Hafemen et al 2012). While most studies in first episode schizophrenic samples also indicate no effects on caudate volume (Lang et al 2001, Dazzan et al 2005, Tauscher-Wisniewski et al 2005, Glenthoj et al 2007), it could also be suggested that that caudate enlargements occur with risperidone (Massana et al 2005), and decreases with quetiapine (Ebedrup et al 2011); which would be consistent with the effects on executive function seen in Chapter 4. Most studies in first-episode schizophrenia do not find effects of antipsychotics on prefrontal
cortical volume (Leung et al 2011, Radua et al 2012); although Ho et al (2011) did find treatment with typical or atypical drugs was associated with decreased prefrontal volume over an average time frame of 7.2 years. There may be differences between drugs, however; Thompson et al (2009) found that prefrontal grey matter loss seen in those randomized to haloperidol was not found in those treated with olanzapine over 12 month follow-up.

Rodent studies indicate that antipsychotics either increase or decrease cortical expression of many genes and transcripts involved in cell survival, neural plasticity, signal transduction, ionic homeostasis, and metabolism; with effects further complicated by differences between acute and chronic administration, dose, as well as individual agents (Feher et al 2005). In general, drugs which show higher binding to the D$_2$R (haloperidol, as well as higher doses of risperidone) may be hypothesized to show greater negative effects, especially under conditions of chronic administration. As reviewed by Dean et al (2006), striatal changes associated with haloperidol in animal studies include decrease in neuron density and loss of dendritic spines, accompanied by increase in neuron size and gliosis. Changes in the prefrontal cortex may be accompanied by reorganization of layer 6 (containing cortico-thalamic and thalamo-cortical projections), with several studies indicating increases in axodendritic synapses and loss of dendritic spines. A potential mechanism underlying the neurotoxic effects of chronic administration of antipsychotics is through alterations in mitochondrial function: risperidone has been found to decrease complex I activity in the frontal cortex (29%) after 45 days, and striatum after 90 days; while clozapine only decreased activity in the frontal cortex (16%) after 90 days (Maurer & Moller 1997). As even subtle reductions in mitochondrial complex I activity impairs energy metabolism and increases oxidative stress (Davey et al 1998), this may be an important factor underlying grey matter changes following chronic drug administration.

### 5.4.2 Mood Stabilizers: Lithium and Valproate

The effects of mood stabilizers on grey matter also cannot be ignored, with lithium use in particular believed to normalize volume loss in prefrontal and limbic regions (Hafeman et al 2012). Indeed, regardless of clinical outcome most patients received ongoing lithium or
valproate treatment during follow-up; a factor which may have at least partially limited age or disease related grey matter loss, and normalized grey matter reductions found in both patient groups compared to healthy subjects at initial assessment.

Grey matter increases due to lithium and valproate use are likely to be neuroprotective, as preclinical indicates that administration of either of these drugs both reverses and prevents amphetamine induced lipid peroxidation (Frey et al 2006), as well as glutamate induced increases in intracellular free calcium concentration, lipid peroxidation, protein oxidation, DNA fragmentation, and cell death (Shao et al 2005). As both lithium and valproate exert a myriad of effects through multiple signalling pathways, no single biochemical action likely to be responsible for their efficacy. In light of this, activity of these two drugs on the glycogen synthase kinase-3β pathway in particular may play central role (Hu et al 2011), as its activity within the Wnt signalling system has important actions on cell proliferation, differentiation, migration, morphogenesis, and neuroprotection. Through interactions with brain derived neurotrophic factor, these actions may also be implicated in neuronal survival, growth, and repair. Further communication with inflammatory and oxidative stress pathways could also intercept the effects of stress (as well as mood episodes) on progressive cortical grey matter loss. As only 5 subjects in the patient group who remained well over 1 year follow up were not being treated with a mood stabilizer, we were unable to examine whether relative grey matter gains seen could be attributed to their use.

5.5 Study Limitations

While the broad inclusion criteria allowed for the examination a clinically relevant population of patients, the confounding effects of comorbid conditions cannot be excluded. Substance misuse in particular may play an important role, as nearly half of patients reported regular use or abuse of illegal substances (particularly cannabis). This is a common observation in youth and young adults with BD, Dell’Osso et al (2011) found 50% of patients under the age of 30 had a co-occurring substance abuse diagnosis (compared to 28% in those 31-45 and 24% in those over 45). Whether they precede, induce or follow onset of mood symptoms; common thematic reasons for substance abuse in this population include
early experimentation, enjoyment, or as a self-medication or coping strategy to feel normal, manage stress, or to sustain living with serious mental illness (Healey et al 2009). This is a clinically relevant comorbidity associated with poor treatment compliance, longer hospitalizations, shorter remissions, and higher rates of suicide and crime (Jaworski et al 2011). Illicit drug or alcohol misuse is also likely to have a negative impact on executive functioning: a lifetime history of any substance abuse disorder (n=158; 53% only one substance, 47% multiple substances; 82% alcohol, 53% cannabis, 13% cocaine, 13% stimulant, 10% sedative, 13% opiate) in non-manic patients with BD was associated with worse conceptual reasoning and set-shifting (WCST correct and perseveration, Go/NoGo target accuracy), but not inhibitory control (Go/NoGo target response time, inhibitory accuracy), processing speed and interference resolution (trails a, b; digit symbol, Stroop interference, Go/NoGo target response time), or verbal fluency and processing speed (phonemic and semantic verbal fluency, trails b, digit symbol, Stroop word and color) compared to those with no prior substance abuse (n=98); although both groups were impaired relative to healthy subjects (Marshall et al 2012). It is also likely that frontostriatal structure and functioning influence and are influenced by substance abuse, as these circuits are also highly implicated in both craving regulation (Kober et al 2010) and risk taking (Schneider et al 2012). Indeed, functional changes associated with substance abuse severity have been seen in BD; negatively correlating with right dorsal prefrontal activity in response to happy faces, and right caudate activity to neutral faces (Hassel et al 2009). Structural changes are also indicated, patients with BDI with a comorbid alcohol use disorder in remission (mean 6 years) have demonstrated a reduced prefrontal volume compared to those with BDI alone (Nery et al 2011). While no studies have been done in BD, sMRI in patients with schizophrenia show that regular cannabis use is associated with decreased grey matter in many regions including the dorsolateral prefrontal cortex and ventral striatum (James et al 2011). Prospectively, first episode schizophrenia patients who use cannabis showed left DLPFC thinning not seen those who abstained over 5 year follow-up (Rais et al 2010).

Care must also be taken extrapolating findings from the current sample to the general population of first episode mania patients; as with other first episode mania studies STOP-EM recruitment was primarily done through inpatient settings, favoring inclusion of more
severe cases. Many patients with BDI can be expected to experience a first manic episode not requiring hospitalization: Kozloff et al (2010) found that only 56% of youth with self-reported BD (n=191, aged 15-24) accessed mental health services in the year prior to interview. Furthermore, our sample also had high rates of psychosis. Modern views on psychiatric diagnosis suggest that illness exist on a spectrum, and that psychosis in BDI may be a clinical manifestation of high levels of genetic overlap with schizophrenia (Laursen et al 2009, Ivleva et al 2010). Studies utilizing a dimensional approach do indicate that approximately 45% of patients with psychosis have an intermediate presentation between the two prototypical diagnoses (Keshavan et al 2011). Meta-analysis indicates that many aspects of executive function are more severely impaired in patients with BDI who have experienced psychosis (Bora et al 2010); with some studies indicating that psychosis may explain more of the variance in cognition than a bipolar or schizophrenic diagnosis per se (Simonsen et al 2011, Ivleva et al 2012). Brain structure may also be differently affected in patients with BD according to history of psychosis, although this question has not been specifically addressed. The changes seen in frontostriatal grey matter in the current sample may be hypothesized to relate to high incidence of psychosis (and thus presumed similarity to schizophrenia); prior meta-analysis comparing the two illnesses has found robust grey matter reductions only in limbic regions (anterior cingulate and insula) in patients with BDI, with differences in the prefrontal cortex and basal ganglia only in subjects with schizophrenia (Ellison-Wright & Bullmore 2010). Many studies directly comparing diagnostic groups also support this, with bipolar disorder associated with a restricted pattern of structural changes (Rimol et al 2010) even early in the course of illness (Farrow et al 2005, de Castro-Manglano et al 2011).

Along with the clinical characteristics that limit generalizability of findings, the naturalistic nature of the study also warrants consideration. Attrition levels were not negligible and results taken from those who were motivated and clinically stable enough to remain in the study may not represent the larger population. Importantly, choice of pharmacological treatments was based on clinical judgement and patient preference, with drug and dosing changing dynamically throughout the study. While the associations found between
antipsychotic treatment and executive function and brain structure are an important initial step, randomized controlled trials to test these hypotheses are urgently needed.

5.6 Implications for the Neurobiology of Bipolar I Disorder

The consensus model proposing a functional basis for BDI (Strakowski et al 2012) suggests that the primary disturbance in this illness is in mood regulation. It is further posited that this is directly related to inadequate top down regulation of limbic regions (particularly the amygdala) by ventral and medial fronto striatal circuits parallel to and integrated with those described for executive function. A combination between genetic vulnerability and environmental exposure may sensitize these regions, causing them to inappropriately react to stress in a way that causes variable daily dysfunction and eventually cumulates into an acute mood episode. While functioning may recover between episodes, it is believed to do so in a way that is “stably unstable,” becoming subsequently more and more easily disturbed as illness progresses.

Behavioural and structural findings from this population suggest that fronto striatal circuitry is abnormal early in the course of BD. While the primary cause is yet unknown, it is further likely that severity of dysfunction changes dynamically across natural disease course and with pharmacological treatment. Theories on the molecular basis for pathophysiology in BD suggest that acute overload of stress adaptation and regulation pathways occurs during affective episodes, and while partially recovering in euthymia also “scar;” further increasing inter-episodic problems and risk for recurrence (Kapczinski et al 2008). On a systems level, cellular signalling in reaction to acute or chronic stress leads to many functional brain changes transitioning behaviour from slow, thoughtful, flexible, and goal relevant cognitive control to a state of more reflexive, habitual, saliency based emotional responding (Arnsten 2009). Interestingly, fronto striatal systems may be the most sensitive to these processes; being the first to go offline during acute stress conditions, showing further reorganization with chronic exposure (Arnsten 2009, 2010; Dias-Ferreira 2009).
Structurally, it may be that changes in limbic regions including the medial temporal, insular, and/or anterior cingulate cortices, as well as supporting subcortical structures (such as the striatum and basal ganglia) are a consequence of illness risk or expression; with abnormalities spreading to prefrontal areas with disease course and progression. Further examination of the potential mediating effects of a dysfunctional stress response on neural changes in this disorder are needed, as are investigations into strategies by which to intercept or reverse them.
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108


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Appendix

A. Structural imaging using Voxel Based Morphometry

A.1 Introduction to the Physics of Structural Magnetic Resonance Imaging

A magnetic field in a magnetic resonance imaging (MRI) machine is produced by electrons moving in a coiled wire. Within brain tissue are positively charged hydrogen ions that align parallel to the magnetic field inside the scanner (longitudinal plane), rotating in phase at a specific frequency (Lamour’s). When these ions are hit with a pulse at a corresponding radiofrequency they absorb the energy and rotate pointing perpendicularly into the transverse plane. “T1” weighted images can be produced using the rate of time taken to return to 63% of the original longitudinal position (relaxation). Structural scans produce images with signals corresponding to T1 values, with hydrogen ions in fat rich tissue (such as white matter) having shorter times and thus lower intensities than those in more water based tissues which will have higher intensities (grey matter and cerebrospinal fluid). There are several parameters that can be adjusted to maximize signal:noise resolution; for T1 images TR (time to go through the pulse sequence one time) should be short/intermediate and TE (time between the peak of the pulse and when ions rephase) should be kept short. Advanced techniques such as inversion recovery and gradient recalled echo can also be used to suppress unwanted signals and decrease data collection times respectively.

A.2 Overview of Standard Voxel Based Preprocessing and Analysis

Voxel-Based Morphometry (VBM) is an automated technique for comparing local composition of brain tissue, after macroscopic differences in shape and position have been discounted (Ashburner & Friston 2000). While traditional morphometry is a time consuming process requiring experimenters to hand draw regions of interest around large predefined areas, VBM is a quick, comprehensive, unbiased examination of the entire brain which allows users to easily and sensitively detect small localized difference in tissue volume. A summary of the main procedure for standard VBM for grey matter analysis (Ashburner & Friston 2000, Good et al 2001, Mechelli et al 2005, Whitwell 2009) follows:
Spatial normalization of all subject scans to the same stereotactic space

First, all T1-weighted MRI images are registered to the same Montreal Neurological Institute (MNI) template. To do this scans are first matched using a 12 parameter affine transformation, and then estimations to account for global non-linear shape differences are completed.

Segmentation of grey matter, white matter, and cerebrospinal fluid

Voxels are binarized and separated according to tissue type based on a priori tissue probability maps and a posteriori voxel tissue classification models.

Modulation

Because spatial normalization warps individual images to match the size and shape of a template, images at this point (unmodulated) can be thought of as representing the relative amount (or concentration) of a specific tissue class within a region. By multiplying the spatially normalized image by its relative volume before and after spatial normalization, non-linear modulation is done in order to regain information about absolute tissue volumes of different regions, corrected for individual brain sizes.

Smoothing

In this step, the value for each voxel becomes the average of its surrounding voxels (Gaussian kernel, usually between 6-12mm). Smoothing is done to improve normality of data distribution, compensate for the inexact nature of spatial normalization, and reduce the number of statistical tests needed (and thus decrease the extent of necessary correction for multiple comparisons).

Statistical Analysis

Standard parametric tests from the general linear model are employed, correcting for multiple dependent comparisons. Localized differences inferred from F or t tests are mapped onto the brain template with accompanying MNI coordinates. Results can be viewed as clusters with multiple voxels, or as a peak where individual voxels have significantly different signal intensities between groups.
A.3 Advanced Voxel Based Tools and Methods

Optimized VBM

With normalization, the effects of non grey or white matter abnormalities may subsequently confound resulting volume tests. Ventricular size differences between groups may be a particular cause of error. As ventricular enlargements in patients relative to healthy subjects are one of the most robust findings in BDI (Hallahan et al 2011), an optimized VBM procedure is an important strategy to reduce this source of error. With this method, segmentation of tissue types is done first in native space, with normalization to the MNI template done separately for each subclass to derive the optimized normalisation parameters. These parameters are then applied to the original whole brain structural images prior to a final segmentation. Modulation, smoothing, and statistical analysis are identical to those for “standard” VBM.

Customized DARTEL template

DARTEL stands for “Diffeomorphic Anatomical Registration using Exponential Line Algebra” and is a complex statistical method applied during normalization within optimized VBM (Ashburner 2007). Briefly, segmented tissue class images are converted to transformed versions in close alignment with initial tissue probability maps from the MNI template. A mean customized template of all images is calculated, and deformations of individual images to this mean are computed. This procedure is repeated multiple times, with regeneration of the customized template done through applying the inverse of the deformations to the images and averaging. Final warped versions of the images warped are then be generated. This technique greatly improves inter-subject normalization and alignment, boosting confidence that resulting group differences are due to morphometric rather than registration differences (McLaren et al 2010, Takahashi et al 2010).

For further reference, flow charts comparing the processing steps for standard VBM with MNI template, optimized VBM with MNI template, and optimized VBM with custom template (similar to DARTEL) can be found in Senjem et al (2005).
Localization of differences

In order to identify which neural regions voxel wise differences exist in, MNI coordinates can readily be converted to those in the atlas by Talairach and Tournoux using automated programs, and from these anatomic labels can also be easily identified (Lancaster et al 2000). While having undergone improvements since its original presentation (Lacadie et al 2008), this method has been described as an “alluringly easy but bad option,” although better procedures were not specified (Devlin & Poldrack 2007).

Regions of interest analysis

Regions of interest may also be selected for specific a priori examination through creation of “masks” that exclude exterior voxels, limiting the number of comparisons and improving statistical power. These masks can be made for implementation in VBM using the “WFU Pickatlas” toolbox (Maldjian et al 2003) and voxel values within these masks can be extracted to SPSS using “MarsBaR” (Brett et al 2002).

Longitudinal analysis

Longitudinal analysis follows a similar pipeline as described for cross sectional analysis, but is much more complex because of consideration of intra-subject characteristics. Described in more detail by Draganski et al (2004, 2006), a processing algorithm registers both images of each subject to correct for position, but derives normalization estimates from the mean of the baseline and year 1 scan. A freely available program to apply this processing is available from the Structural Brain Mapping Group from the University of Jena, Germany (http://dbm.neuro.uni-jena.de/vbm/). This method does not apply modulation (as the parameters for each subject would be the same for each scan), meaning that the interpretation of group and groupxtime differences are in terms of “concentration” (relative grey/ white matter volume) rather than absolute volume (Dr. Christian Gaser, unpublished communications).
A.4 Validity and Limitations of Voxel Based Morphometry

VBM is frequently used for structural analysis, quickly overtaking the popularity of manual ROI tracing studies. While it may not be a perfect replacement, VBM procedures do show similar accuracy and reliability for detecting both prefrontal (Giuliani et al 2005) and subcortical (Bergouignan et al 2009) differences in psychiatric populations relative to healthy subjects. There have been many criticisms of the validity of techniques and statistics used in VBM (eg Bullmore et al 1999, Worsley et al 1999, Bookstein 2001, Thacker 2004, Whitwell & Jack 2005); addressed largely by Ashburner & Fishburner (2001) and also discussed by Ridgway et al (2008). First of all, as image preprocessing is hugely affected by scanner type and parameters, comparison across research locations should be limited. Furthermore, despite the availability of algorithms to complete preprocessing and analysis, somewhat arbitrary variation in user defined parameters (eg smoothing kernel size, statistical thresholds) can lead to non-trivial differences in results. Other criticisms at the core of this method suggest that limitations are introduced throughout the preprocessing process. First, there is a significant potential for specific pathophysiology in a disease group leading to systematic misregistration and thus misinterpretation of resulting structural changes. There are also problems with tissue classification; many central grey matter structures will have image intensities similar to surrounding white matter and may thus be classified incorrectly as such. Because of binarization, partial volume effects (when a region is both grey and white matter) may also reduce the accuracy of this method. Importantly, because of current spatial normalization limitations, specific localization of changes is relatively imprecise and further limited by the size of the smoothing kernel. It is also important to note that VBM can not address the pathological basis for group effects: while it could be that differences are the result of changes in cellular composition, size, connectivity, or organization; non-MRI methodology is needed to examine this (a feat currently impossible in living, human subjects).