A Randomized, Double-Blind, Placebo-Controlled Clinical Trial Evaluating the Effect of Infliximab on General Cognition in a Population of Depressed Individuals with Bipolar Disorder Type I/II

by

Zihang Pan

A thesis submitted in conformity with the requirements for the degree of Master of Science
Institute of Medical Science
University of Toronto

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2018

Abstract

Aim: To evaluate the efficacy of adjunctive infliximab in mitigating cognitive symptoms in depressed bipolar individuals.

Methods: A randomized, double-blind, placebo-controlled clinical trial was conducted in outpatients between the ages of 18-65. Participants were randomized to receive adjunctive intravenous infliximab (at 5 mg/kg) or placebo (saline) at week 0, 2, and 6. Digit Symbol Substitution Test (DSST) and Rey Auditory Verbal Learning Test (RAVLT) were used to determine cognitive performance. Generalized estimating equations were used to determine significance of between- and within-group effects.
Results: Sixty individuals were enrolled (placebo n=31, infliximab n=29). Despite a significant within-group improvement in cognition from week 0 to week 12, there was no significant difference between infliximab and placebo (p>.05).

Conclusions: Within-group improvement in cognition may be due to mechanisms yet uncharacterized. Inflammatory pathoetiolog of mood disorders provide an impetus to investigate additional anti-inflammatory agents to mitigate transdiagnostic disturbances such as cognitive dysfunction.
Acknowledgments

I want to sincerely thank the patients who participated in this clinical trial. Your valuable time and inputs have made this study possible. It is with my highest honour and privilege to have served you. You have my deepest admiration and respect. I wish you all the best.

The project would not have been possible without the generous financial support of the Stanley Medical Research Institute. From all members of the team, thank you.

I want to thank Dr. Roger S. McIntyre, my supervisor, mentor, and dear friend. I will never forget your generosity and support over the past few years. You are the rock that anchors this lab and the light that leads us forward. Your unwavering passion for our patients is immeasurable. And without your guidance and direction, none of us could achieve what we have accomplished. You have my sincerest gratitude.

Thank you to Dr. Anne Bassett, Dr. George Foussias, and Dr. Walter Swardfager for your invaluable time and guidance throughout this project. Thank you so much for your patience and kindness. It was truly a pleasure having you all onboard my Program Advisory Committee.

I also wish to thank members of our team at the Mood Disorders Psychopharmacology Unit (MDPU), Toronto Western Hospital, University Health Network. Without your expertise and collaboration, I could not imagine where we would be today. Special thanks to Dr. Rodrigo B. Mansur, Mehala Subramaniapillai, Yena Lee, Nicole Carmona, Margarita Shekotikhina, Bernadette DeFreitas, Caroline Park, Hannah Zuckerman, and countless other volunteers. It is my pleasure to have spent the past few years with you. I am fortunate to have made lasting friends throughout this journey. It was truly an unforgettable experience. Thank you all very much!

Special thanks to Jane Lui and your team at the Toronto Western Hospital Clinical Research Pharmacy for the preparation of the Infliximab and placebo intravenous solutions used throughout the study. Special thanks to Arlene for your patience and nursing expertise. It was a pleasure working with you all.
Special thanks to all members of the Stanford team who ran the parallel study in California. It was a pleasure collaborating with you all.

Finally, I would like to thank my family, my mother Biquan Hu and my father Anping Pan. Thank you for sharing all the moments of happiness and joy, and guiding me through moments of uncertainty. Thank you for your unconditional love and unwavering faith. It is a pleasure to have made this journey with you by my side.
Contributions

Dr. Roger S. McIntyre: Directed all aspects of this research study and edited thesis content

Dr. Rodrigo B. Mansur: Assessed patient eligibility for recruitment, assessed patient health and mental status during clinical visits throughout the study

Mehala Subramaniapillai: Coordinated study logistics

Yena Lee: Assisted with patient enrollment and study logistics

Nicole Carmona: Assisted with patient enrollment and study logistics

Margarita Shekotikhina: Assisted with patient enrollment and study logistics

Bernadette DeFreitas: Scheduled patient clinical visits

Dr. Anne Bassett: Served as member of Program Advisory Committee, edited thesis content

Dr. George Foussias: Served as member of Program Advisory Committee, edited thesis content

Dr. Walter Swardfager: Served as member of Program Advisory Committee, edited thesis content
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List of Abbreviations

ACC – Anterior Cingulate Cortex

BD – Bipolar Disorder

BDI – Beck Depression Inventory

BMI – Body Mass Index

CBT – Cognitive Behavioural Therapy

CGI – Clinical Global Impression

CNS – Central Nervous System

COX - Cyclooxygenase

CRP – C-Reactive Protein

CXCL10 – C-X-C Motif Chemokine 10

DSM – Diagnostic and Statistical Manual of Mental Disorders

DSST – Digit Symbol Substitution Test

FDA – US Food and Drug Administration

GLP – Glucagon-Like Peptide

HAMD – Hamilton Depression Rating Scale

ICD – International Statistical Classification of Diseases and Related Health Problems

IL-1β – Interleukin 1 Beta

IL-4 – Interleukin 4

IL-6 – Interleukin 6
MADRS – Montgomery-Asberg Depression Rating Scale

MDD – Major Depressive Disorder

MDE – Major Depressive Episode

NSAIDs – Non-steroidal Anti-inflammatory Drugs

NIMH – National Institute of Mental Health

OFC – Orbitofrontal Cortex

PDQ – Perceived Deficits Questionnaire

RAVLT – Rey Auditory Verbal Learning Test

RDoC – Research Domain Criteria

rTMS – Repetitive Transcranial Magnetic Stimulation

SNP – Single Nucleotide Polymorphism

SNRI – Serotonin and Norepinephrine Reuptake Inhibitor

SSRI – Selective Serotonin Reuptake Inhibitor

sTNFR1 – Soluble Tumor Necrosis Factor Receptor 1

sTNFR2 – Soluble Tumor Necrosis Factor Receptor 2

TNF-α – Tumor Necrosis Factor Alpha

YMRS – Young Mania Rating Scale
Chapter 1
Introduction and Literature Review
1 Introduction and Literature Review

1.1 Bipolar Disorder

1.1.1 Introduction

Bipolar disorder (BD) is a severe, chronic, persistent and progressive mood disorder characterized by episodes of mania, hypomania and depression. Both the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5) and the International Classification of Diseases Tenth Revision (ICD-10) typify bipolar disorder as a prevalent and disabling affective mood disorder associated with significant morbidity and mortality (American Psychiatric Association, 2013; World Health Organization & WHO, 1992).

Bipolar disorder is characterized by fluctuations in mood with periods of mood elevation and depression (Phillips & Kupfer, 2013). Bipolar disorder type I is characterized by the presence of at least one manic episode, with intertwining episodes of depression typical, however not necessary, for diagnosis. Bipolar disorder type II is characterized by at least one hypomanic episode and at least one depressive episode. Both mania and hypomania are episodes of mood elevation. Whether an episode is determined to be manic or hypomanic is based on the degree of mood elevation, the persistence of symptoms and impact on function, with the former more pronounced.

Bipolar disorder affects approximately 1% of the world’s population and represents one of the leading causes of disability worldwide (Alonso et al., 2011). Bipolar disorder type I and type II have aggregated worldwide lifetime prevalence of 0.6% and 0.4% respectively (Merikangas et al., 2011). Bipolar disorder affects individuals irrespective of nationality, ethnicity, and socio-demographic status (Alonso et al., 2011). There is no difference in prevalence between men and women in BD type I; however, BD type II disproportionately affects women (Nivoli et al., 2011). According to one global mental health survey, among psychiatric disorders, BD is ranked second in terms of impairment to occupational function (Alonso et al., 2011). Estimated economic costs due to decreased workplace productivity, impaired cognitive and psychosocial functioning, and direct and indirect health care burden amounts to $202.1 billion in
United States annually (Cloutier, Greene, Guerin, Touya, & Wu, 2018). High rates of psychiatric comorbidity are common in BD, contributing to high levels of chronicity and recurrence (Grande, Berk, Birmaher, & Vieta, 2016).

1.1.2 Mania and Hypomania

Mania and hypomania are episodes of elevated mood and increased motor drive with variance in severity and episode duration. A manic episode is often characterized by significant impairment to social and/or occupational functioning leading to hospital admission (Grande et al., 2016). A hypomanic episode is also characterized by an observable disturbance in function, however, such impairments may not require hospital admission (Grande et al., 2016). Psychotic symptoms in patients with acute mania is common. Delusions, grandiosity, megalomania, risk-taking behaviours, and irritability are also common presentations for both mania and hypomania (Gruenberg, 2008).

The DSM-5 defines a manic episode as persistent mood elevation lasting for at least one week and a hypomanic episode as mood elevation lasting for four consecutive days (American Psychiatric Association, 2013). An episode of mania or hypomania must include sustained abnormal mood plus three additional features from the following: elevated grandiosity, talkativeness, decreased need for sleep, distractibility, flight of ideas, increase in goal-directed activity, and high-risk behaviours (American Psychiatric Association, 2013). A detailed list of diagnostic criteria for mania and hypomania is included in Table 1.

It is important to note that the reliability of a phenomenology-based diagnostic system such as the DSM-5 on the diagnosis of BD have come into question. For example, the requirement of four consecutive days of mood elevation to identify a hypomanic episode is not referenced by specific cut-points in reported data. In addition, in order to qualify for a diagnosis of a manic episode, mood disturbances must be accompanied by an increase in either energy or activity. Patients with mix specifier affective episodes, including, but not limited to, unipolar depression, are insufficiently captured by existing
approaches. Indeed, there may be an underestimation of bipolar symptoms. The BRIDGE study by Angst and colleagues found that 16% of patients diagnosed with major depressive disorder (MDD) met DSM criteria for BD, and an additional 47% met at least one bipolar-specific criteria (Angst et al., 2011). The authors concluded that up to 31% of patients diagnosed with MDD had subthreshold manic or hypomanic symptoms (Angst et al., 2011).

The National Institute of Mental Health (NIMH) Research Domain Criteria (RDoC) is an integrative and domain-based approach to understanding the pathoetiology and phenomenology of mental disorders (Cuthbert, 2014). Currently, five domains (negative valence systems, positive valence systems, cognitive systems, systems for social processes, and arousal regulatory systems) across seven broad units of analysis (genes, molecules, cells, circuits, physiology, behaviour, and self-reports) comprise the key cornerstones of the RDoC matrix (Frank, 2011). The five domains of the RDoC can be further refined into domain-specific constructs (Table 2). For example, negative valence can refer to systems of stress, fear response, aggression; positive valence can refer to systems of reward; cognitive systems can refer to attention, concentration, learning, memory, and cognitive control (Cuthbert & Insel, 2013). Bipolar mania or hypomania can be viewed as conditions that affect one or more of these domains. The RDoC integrate observable behaviours and neurobiological constructs for psychiatric conditions to inform treatment. The RDoC approach, therefore, can be complementary to existing diagnostic systems such as the DSM and ICD.
Table 1. The DSM-5 criteria for manic and major depressive episode

<table>
<thead>
<tr>
<th><strong>Manic or Hypomanic Episode</strong></th>
<th><strong>Major Depressive Episode</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>An episode of mania or hypomania must involve a sustained abnormal mood plus three (3) of the following features present (or four features if the patient’s mood is irritable rather than elevated) to meet DSM-V criteria</td>
<td>A major depressive episode is defined by five (5) or more of the following symptoms, present at the same time, for at least a two-week period. At least one of the symptoms must be either a depressed mood or a loss of interest or pleasure</td>
</tr>
<tr>
<td>Inflated self-esteem or grandiosity</td>
<td>Depressed mood for most of the day, nearly every day</td>
</tr>
<tr>
<td>Increased talkativeness</td>
<td>Markedly reduced interest or pleasure in all, or almost all, of the day’s activities, most of the day, nearly all day</td>
</tr>
<tr>
<td>Decreased need for sleep, e.g. is rested after three hours sleep</td>
<td>Insomnia or hypersomnia, nearly every day</td>
</tr>
<tr>
<td>Easily distracted by unimportant or externally irrelevant stimuli</td>
<td>Feelings of worthlessness or excessive or inappropriate guilt, nearly every day</td>
</tr>
<tr>
<td>Flight of ideas characterized by a nearly continuous flow of accelerated speech, which abruptly shifts from one topic to another</td>
<td>Significant weight loss when not dieting, or weight gain of more than 5% in a month, or a decrease or increase in appetite nearly every day</td>
</tr>
<tr>
<td>An increase in goal-directed activity, e.g. at work, socially or sexually, or restlessness, i.e. purposeless activity such as pacing or holding multiple conversations at once</td>
<td>Psychomotor agitation or retardation nearly every day</td>
</tr>
<tr>
<td>Excessive involvement in high-risk activities, e.g. spending money recklessly,</td>
<td>A decreased ability to think or concentrate, or indecisiveness, nearly</td>
</tr>
<tr>
<td>sexual indiscretion or imprudent investments</td>
<td>every day</td>
</tr>
<tr>
<td>--------------------------------------------</td>
<td>----------</td>
</tr>
<tr>
<td>Recurrent thoughts of death or suicide, or a suicide attempt</td>
<td></td>
</tr>
</tbody>
</table>

| If the patient displays psychotic features or requires hospitalization then the episode is automatically classified as manic | Episodes of major depression may last weeks or even months |
Table 2. The RDoC matrix

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute threat (fear)</td>
<td>Approach motivation</td>
<td>Attention/concentration</td>
<td>Affiliation and attachment</td>
<td>Arousal</td>
</tr>
<tr>
<td>Sustained threat</td>
<td>Initial reward response</td>
<td>Perception</td>
<td>Social communication</td>
<td>Biological rhythms</td>
</tr>
<tr>
<td>Loss</td>
<td>Sustained reward response</td>
<td>Working memory</td>
<td>Perception and understanding of self</td>
<td>Sleep-wake cycle</td>
</tr>
<tr>
<td>Frustrative non-reward</td>
<td>Reward learning</td>
<td>Declarative memory</td>
<td>Perception and understanding of others</td>
<td></td>
</tr>
<tr>
<td>Habit</td>
<td>Language</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cognitive control (executive function)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
1.1.3 Depression

The DSM-5 criteria for depressive episodes are the same for unipolar and bipolar depression. A major depressive episode (MDE) is defined by five or more of the following depressive symptoms presenting for at least a two-week period: depressed mood, anhedonia (lack of interest), insomnia or hypersomnia, feelings of worthlessness, significant weight or appetite disturbance, psychomotor agitation or retardation, difficulties in concentration, and recurrent thoughts of suicide (American Psychiatric Association, 2013; Severus & Bauer, 2013). A detailed list of diagnostic criteria for a major depressive episode is included in Table 1.

There are subtle differences between unipolar and bipolar depression. Bipolar depression often has an earlier age of onset, has more frequent episodes with shorter duration, are more abrupt in onset and offset than unipolar depression, and may have distinct stress and substance misuse triggers (Forty et al., 2008; Ayal Schaffer et al., 2010; Tondo et al., 2010). In addition, atypical symptoms (i.e., insomnia or hypersomnia, fluctuations in mood, weight and appetite instability) are common in bipolar compared to unipolar depression (Akiskal et al., 1995). Comorbid psychotic and psychomotor symptoms are also more prevalent in bipolar depression whereas somatic symptoms are more prevalent in unipolar depression (Perlis et al., 2006). In addition, suicide risk in bipolar depression is high. Approximately 30-50% of individuals diagnosed with bipolar depression attempt suicide at least once in their lifetime (Schaffer et al., 2015). Age of onset, biological sex, severity of depressive episode, medical and psychiatric comorbidity, and substance abuse can all influence the severity of depression in individuals with BD (Grande et al., 2016).

1.1.4 Progression

Bipolar disorder is a chronic and neuroprogressive illness (Berk, 2009). Individuals often cycle between episodes of mania, hypomania, euthymia, subthreshold depression, and major depression. Although individuals with BD often experience periods of remission, recurrence of depressive or manic episodes are frequent. In
particular, functional, cognitive, and physiological decline has been well characterized (Kapczinski et al., 2009).

The notion of BD as a neuroprogressive illness was first described by Kraepelin in 1921. He saw BD as an episodic disorder with clear temporal progression in phenomenology, neurobiology, functional impairment, and treatment response (Kraepelin, 1921). Berk and colleagues later refined a stepwise staging model to identify features and inform treatment (Berk et al., 2017). Stage 0 denotes the earliest stage where individuals with known risks for the development of BD (i.e., genetic susceptibility, substance abuse, childhood trauma, etc.) remain asymptomatic. Stage 1a and 1b comprise the prodromal stages of BD where non-specific and identifiable BD symptoms are present, respectively. Stage 2 marks the first episode of illness and is characterized by the onset of the first episode of mania or hypomania. Stage 3 is illness recurrence and is subdivided into 3a, 3b, and 3c. These substages identify various levels of recurrence, relapse and illness persistence. Stage 4 is the final stage whereby the individual becomes treatment resistant (Berk et al., 2017). Detailed staging characteristics are listed in table 3.

The aforementioned BD staging is closely linked to neuroprogressive functional and cognitive decline, despite individuals having normal or above normal cognition before the onset of illness. Poor performance in executive function and verbal memory have been reported (Bourne et al., 2013). These neurocognitive deficits are progressive across all mood states, including periods of remission and euthymia, and are mediated by illness severity and duration (Bourne et al., 2013). In addition, in the absence of pharmaceutical intervention, functional impairment worsened along with illness progression (Rosa et al., 2012). Individuals with BD also have higher levels of medical comorbidities such as cardiovascular disease, diabetes, and obesity (Fiedorowicz et al., 2008). It is hypothesized that the sensitization to stress and the overburdening of the body’s natural compensatory mechanisms may lead to an increase in allosteric load, which is negatively associated with cognitive and psychosocial functions (Grande et al., 2012). The specific pathoetiological mechanisms underlying neuroprogression in BD is still not understood and represents an area requiring further research. Neurochemical pathways involving oxidative stress, inflammation, cellular metabolism, and hormonal
regulation have been proposed to influence neuroprogression observed in BD (Berk, 2009; Kauer-Sant’Anna et al., 2009).
### Table 3. Bipolar disorder staging and neuroprogression

<table>
<thead>
<tr>
<th>Stage</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>Individuals have known risk factors for BD (i.e., genetic susceptibility, childhood trauma, proximal psychological stress, substance abuse) but no overt bipolar symptoms</td>
</tr>
<tr>
<td>Stage 1a</td>
<td>Presence of mild non-specific symptoms</td>
</tr>
<tr>
<td>Stage 1b</td>
<td>Presence of identifiable BD symptoms</td>
</tr>
<tr>
<td>Stage 2</td>
<td>First episode of mania or hypomania</td>
</tr>
<tr>
<td>Stage 3a</td>
<td>Recurrence of subthreshold symptoms</td>
</tr>
<tr>
<td>Stage 3b</td>
<td>Recurrence of threshold symptoms</td>
</tr>
<tr>
<td>Stage 3c</td>
<td>Persistence relapses</td>
</tr>
<tr>
<td>Stage 4</td>
<td>Treatment resistance and persistent unremitting course</td>
</tr>
</tbody>
</table>
1.1.5 Symptom Management

Antipsychotics and mood stabilizers are the most common acute management strategies for BD. In terms of acute treatment efficacy against bipolar mania, antipsychotics were more efficacious than mood stabilizers, with haloperidol, risperidone, and olanzapine having the most potent effects (Cipriani et al., 2011). With respect to tolerability, risperidone, quetiapine, and olanzapine are optimum. Aripiprazole, valproate, and lithium are also acceptable choices for the acute management of manic symptoms (Yıldız et al., 2015).

In the acute management of depressive symptoms, lamotrigine, lithium, quetiapine, and lurasidone are recommended as first-line treatment agents (Yatham et al., 2018). Supplementation with adjunctive antidepressants such as Selective Serotonin Reuptake Inhibitors (SSRIs) and bupropion have also been recommended (Yatham et al., 2018). Evidence supporting antidepressant use in bipolar depression in terms of efficacy and tolerability is mixed and should be considered as adjunctive therapy in the management of acute depressive symptoms (Pacchiarotti et al., 2013).

Due to the chronic and recurrent nature of BD, the optimum long-term management strategy is early detection and prevention combined with pharmacological, psychosocial, and lifestyle mediation approaches (Grande et al., 2016). In one meta-analysis, lithium was identified as one of the most efficacious treatments for the prevention of both manic and depressive symptoms, despite an elevated risk of hypothyroidism and decreased renal function (Miura et al., 2014). Lithium combined with valproate as well as quetiapine in individuals with good acute response have also shown efficacy in preventing relapse (Miura et al., 2014). It is important to note that the polarity of the individual’s bipolar symptoms can affect treatment approach. If an individual is predominately manic in symptom presentation, long-term management with atypical antipsychotics is warranted; conversely, if the individual has a depressive polarity, then lamotrigine and adjunctive antidepressant therapy may be more efficacious (Grande et al., 2013). Lithium and quetiapine are equally efficacious in the prevention of manic and depressive symptoms (Grande et al., 2013).
Due to the neuroprogressive nature of BD and prominent functional and cognitive decline over the course of illness, therapeutic agents targeting cognition and functional impairment is currently lacking. No Food and Drug Administration (FDA)- or Health Canada-approved pharmacological agents are available to target specific cognitive deficits in BD. Cognitive behavioural therapy (CBT), functional remediation, and psychosocial interventions have shown efficacy in improving function in individuals with BD (Scott et al., 2006). Despite these interventions, there is an urgent unmet need in BD treatment and management, presenting opportunities for novel drug discovery.
1.2 Cognition in Depression

1.2.1 Overview

Bipolar depression is a syndrome of disturbance in mood, energy, metabolism, motivation, and cognition. Many studies in adults with depression have shown that cognitive dysfunction is a powerful predictor of occupational and psychosocial impairment (McIntyre et al., 2013; McIntyre & Lee, 2016; Woo et al., 2016). Indeed, cognitive dysfunction is well established as a core disturbance according to the NIMH RDoC. The RDoC matrix dissects affective mood disorders such as BD and MDD into domains of analysis with the aim of identifying biological underpinnings (i.e., cognitive processes) and predicting treatment outcomes.

A significant subpopulation of individuals with bipolar depression do not achieve functional remission after treatment with multiple FDA-approved pharmacological agents (McIntyre & Lee, 2016). It is important to note that improvements in mood does not necessarily translate into improvements in function. Furthermore, FDA- and Health Canada-approved pharmacological agents targeting cognitive dysfunction are scarce. Hitherto, only two antidepressants (i.e., duloxetine and vortioxetine) have demonstrated direct, independent, and clinically-relevant effects on cognitive dysfunction in adults with MDD (Rosenblat, Kakar, & McIntyre, 2015). The effects of vortioxetine and duloxetine on cognition in adults with BD have not been extensively studied. The persistence of cognitive deficits after remission of depressive symptoms has been shown to contribute to the failure in achieving full functional recovery in MDD and BD (Woo et al., 2016). Vice versa, functional impairments can also contribute to the persistence of cognitive symptoms (Pan, Grovu, et al., 2017).

Domain-specific cognitive deficits in learning and memory, executive function, processing speed, and attention and concentration are highly replicated findings in individuals with MDEs. Moreover, cognitive dysfunction in MDD and BD has been proposed to be an endophenotype that worsens as a function of episode frequency (Pan, Grovu, et al., 2017; Rosenblat, Brietzke, et al., 2015). Other well-characterized symptoms in patients with MDEs include anhedonia and depressed mood. The trifecta
of cognitive dysfunction, anhedonia, and mood disturbance is thought to be critically mediate MDE-related functional disability (Carvalho, Berk, Hyphantis, & McIntyre, 2014; McIntyre et al., 2013). These interconnected domains of depression and cognition continue to contribute to self-perpetuating cycles of illness and impairment.

Multiple neurobiological mechanisms have been proposed to explain the pathoetiology and neuroprogression of cognitive dysfunction observed in individuals with MDEs (McIntyre, Cha, & Soczynska, 2014). Neuroinflammatory pathways are hypothesized to play key roles in the onset of cognitive symptoms in individuals with MDD and BD (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008). Indeed, individuals with inflammatory and metabolic comorbidities are at greater risk of incident mood disorders and cognitive dysfunction (Jantaratnotai, Mosikanon, Lee, & McIntyre, 2017; Mansur et al., 2018). A derivative of the foregoing observation is that disturbances in cognitive function in individuals with MDEs and persons with metabolic/inflammatory comorbidity may exhibit improvement with multimodal treatment targeting inflammatory-metabolic systems.

1.2.2 Cognition Defined

A domain-based approach provides an opportunity to disambiguate the complex phenomenological features of cognition. Disturbances in concentration, executive function, decision-making, and learning and memory are part of the DSM-5 items that determine whether an individual meets criterion for cognitive dysfunction in MDD (McIntyre et al., 2013). Cognitive constructs have been further classified into typologies that are useful in clinical and research settings. For example, the four sub-domains of cognition (i.e., executive function, learning and memory, attention and concentration, and processing speed) are differentially operationalized in clinical and research practice (Harrison, Lam, Baune, & McIntyre, 2016). These interconnected and dissociable phenomena often share overlapping, yet discrete, neurobiological substrates. Disparate neurobiological systems, including, but not limited to, arousal, mood, impulsivity, reward, anhedonia, energy, fatigue, and suicidality, all contribute to cognitive changes in individuals with MDD and BD (McIntyre et al., 2016; McIntyre, Xiao, et al., 2015).
The current discourse on cognition is limited by the absence of consistent language delineating observable cognitive domains. In this regard, the concepts of “hot” and “cold” cognition are relevant. “Hot” cognition refers to cognitive functions that are emotionally-valenced. In other words, “hot” cognitive processes are influenced by an individual’s emotional state (Roiser & Sahakian, 2013). Examples of “hot” cognition include, but are not limited to, rumination, anticipatory anhedonia, negative attentional bias, and emotionally-linked recall. Conversely, “cold” cognition refers to cognitive processes that are uncoupled from emotional valence (Roiser & Sahakian, 2013). Prominent examples of “cold” cognition include the aforementioned sub-domains of executive function, learning and memory, attention and concentration, and processing speed, which are uncoupled from emotional processing. Despite the foregoing typologies separating “hot” and “cold” cognition into distinct entities, a discrete separation between “hot” and “cold” cognition in neurobiological terms cannot be parsed (McIntyre, Xiao, et al., 2015).

1.2.3 Neurobiology

Specific neurobiological mechanisms subserving cognitive function in depression have not been fully elucidated. Notwithstanding, multiple levels of analysis (e.g., genetic, molecular, cellular, circuit) have been implicated. Herein, the working hypothesis postulates that there is a disturbance in the structure, function, reciprocity, and interconnectivity of brain circuits and networks related to cognitive control and function.

The well-established monoamine abnormalities in MDD and BD likely contribute to impaired cellular signaling and neurocircuit deficits (Stephen M. Stahl, 2010). Peripheral inflammation and systemic activation of proinflammatory cytokines may also play a role in the pathogenesis of cognitive symptoms. For instance, the degree and severity of cognitive dysfunction has been shown to be mediated by the location of inflammation, neurotoxicity, and apoptosis (Bortolato, Carvalho, Soczynska, Perini, & McIntyre, 2015). Consequently, the amplification of inflammatory signals provides a compelling explanation for the emergence of cognitive symptoms in depressed
individuals (Pan, Grovu, et al., 2017; Rosenblat, Cha, Mansur, & McIntyre, 2014; Shariq et al., 2018). The role of inflammation in the pathoetiology of BD is reviewed in chapter 1.3.

The structure, function, and chemical composition of fronto-temporal and fronto-subcortical circuitry have also been implicated in the emergence of cognitive symptoms in MDD and BD (K.-M. Han, De Berardis, Fornaro, & Kim, 2018; Jiao et al., 2011; Pizzagalli, 2011). Nodal structures such as the hippocampus, amygdala, and the anterior cingulate cortex have demonstrated susceptibility to volumetric and functional changes as a consequence of greater illness severity, episode frequency, and duration (MacQueen et al., 2005). Neurochemical changes (e.g. catecholaminergic disturbances) have also been implicated as a mediator of cognitive dysfunction. (S. M. Stahl, Zhang, Damatarca - Journal of clinical ..., & 2003, 2003).

Circuits of the orbitofrontal cortex (OFC), dorsolateral prefrontal cortex (DLPFC), and anterior cingulate cortex (ACC) are particularly relevant in the pathogenesis of cognitive dysfunction in bipolar and unipolar depression. Dorsal cognitive networks, formed by the dorsal ACC working in concert with the hippocampus and the DLPFC, have been implicated in deficits of executive function (Kheirbek, Hen - Neuropsychopharmacology, & 2011, 2011). Ventral affective networks, formed by the perigenual ACC, the amygdala, and the OFC, working in concert with the hippocampus, have also been shown to be important for a variety of cognitive processes such as establishing salience, mediating contextually-appropriate responses, planning, working memory, and executive function (Kheirbek et al., 2011).

It is recognized that individuals with unipolar and bipolar depression exhibit a bilateral reduction in hippocampal volume (Doring et al., 2011; K.-M. Han et al., 2018). The foregoing reduction in hippocampal volume may be a consequence of decreased neuronal and dendritic density, and/or reduced size of neuronal soma (Malykhin, Carter, Seres, & Coupland, 2010). The reduction in hippocampal volume has also been shown to be proportional with the frequency of illness episodes. For example, the findings of one study demonstrated that performance in verbal memory decreased as a function of episode frequency in MDD (Gorwood, Corruble, Falissard, & Goodwin,
In addition, Individuals with MDD exhibit hypoactivity of the PFC, which is associated with increases in activity of the ACC. Abnormalities in the connections between cortical and subcortical structures (i.e. prefrontal cortical regions and ACC) have been hypothesized to lead to poor functional outcomes in MDD (Pizzagalli, 2011; Zeng et al., 2012).

Subtle differences in the pattern of activation have been observed in bipolar depression compared to unipolar depression. In particular, individuals with bipolar depression had stronger functional connectivity patterns between default mode networks, frontoparietal networks and the PFC, ACC, and temporal regions than unipolar depression (Han et al., 2018). Volumetric changes in brain regions such as the amygdala, hippocampus and prefrontal regions are also frequent in individuals with BD. Thinning of the DLPFC, reduced integrity in the anterior corpus callosum and posterior cingulate have also been observed (Han et al., 2018). These observations may be mediated by domain-specific deficits in executive function, attention, learning, memory, and processing speed.

Cognitive impairment in individuals with MDD and BD may also be explained by an increase in neural effort. The n-back test is a validated measure of working memory in which subjects were asked to recall the previous stimuli that were presented. In one study, although performance on the n-back test did not differ significantly between MDD subjects and healthy controls, differences were observed in the activation and deactivation of nodal substrates (Harvey et al., 2005). Specifically, depressed subjects exhibited greater activation of working memory networks relative to healthy controls (Harvey et al., 2005). Similarly, in individuals with BD, performance on the n-back test did not differ significantly compared to healthy controls, however, loss in connectivity in prefrontal networks and abnormal activation in dorsal and ventral networks suggest a compensatory mechanism to overcome decreased activation of primary working memory circuits (Cremaschi et al., 2013). These findings suggest that individuals with MDD and BD require greater neural effort to achieve the same level of cognitive performance as healthy controls.

The neurobiological substrates underlying cognition are both integrated and
segregated which rely on a system of reciprocity between integrated and segregated cognitive structures. For example, anti-correlation, which refers to the selective reciprocal activation and deactivation of various brain regions, is critical for proper cognitive functioning (Hamilton et al., 2011). Dysregulation of the normal reciprocity between nodal structures within default mode networks, therefore, may be involved in substrate disturbances and suboptimal functional outcomes resulting from cognitive impairments and reduced cognitive efficiency observed in MDD and BD (Cha et al., 2014).

Mediators of aberrant neural circuitry, structure, and function can involve imbalances in hormonal regulation (i.e. insulin resistance, glucocorticoid abnormalities), neurotrophin dysregulation [i.e. Brain-Derived Neurotrophic Factor (BDNF)], immunoinflammatory activation, and oxidative stress (Andreatza, 2012; M. Li, Soczynska, & Kennedy, 2011; McAfoose & Baune, 2009; Ryan, Sheu, Critchley, & Gianaros, 2012). There is wide recognition of reciprocal relationships between mood, cognition, and metabolism (McIntyre et al., 2009). For example, evidence linking diabetes mellitus type 2 and insulin resistance with cognitive deficits in mood disorders is well-documented (Baker, Cross, Minoshima - Archives of ..., & 2011, 2011). Moreover, an imbalance in insulin and counterregulatory neurohormonal systems (i.e., glucocorticoids) has been suggested to alter proapoptotic intracellular signaling cascades, resulting in the loss of neuronal and glial cells as well as accelerated neurocognitive decline. In addition, metabolic syndrome and obesity have been consistently shown to negatively impact cognitive functions (Hidese et al., 2018).

In summary, the pathoetiology of cognitive dysfunction in depression involves both structural and functional disturbances in neural circuits as well as disturbances in the connectivity of cognitive networks. Substrates that subserve cognition in MDD and BD are discrete but may overlap functionally with other substrates that contribute to affective, metabolic, and inflammatory processes. Interventional strategies should, therefore, take into consideration these underlying pathophysiological changes subserving cognition in depression.
1.2.4 Implications of Function

In individuals with MDD and BD, symptomatic remission does not always translate into functional recovery. The foregoing disconnect indicates that there are extraneous factors that mediate determinants of functional outcome, which are not adequately measured using standard clinical indicators of illness severity. For example, most of the questionnaires that are used clinically to measure the severity of depressive symptoms [e.g. Hamilton Depression Rating Scale (HAMD), Montgomery-Asberg Rating Scale (MADRS)] tend to underemphasize cognitive symptoms (Buist-Bouwman et al., 2008). In addition, cognitive function can be more indicative of self-reported health outcomes than measures of total depressive symptom severity (McIntyre & Lee, 2016). Therefore, a holistic, domain-based approach that incorporates a dimensional measure of cognition may be superior in predicting functional outcomes. In this regard, cognition should be appropriately dimensionalized and integrated into larger composite measures of depressive symptom severity.

Cognition has been previously established as a principal mediator of health outcomes in MDD and BD (Kessing et al., 2017; McIntyre, Soczynska, et al., 2015). Cognitive disturbances are more commonly observed in individuals with depression compared to the general population. Individuals who are unemployed are more likely to exhibit decreased cognitive performance and greater loss of workplace productivity due to absenteeism and presenteeism (McIntyre & Lee, 2016). In addition, cognitive impairment predicted overall psychosocial function in individuals with MDD and BD (Kuswanto et al., 2016; McIntyre et al., 2013). For example, results from the International Mood Disorders Collaborative Project (IMDCP), a collaborative effort between the University of Toronto and Cleveland Clinic, indicated that cognitive function is a greater determinant of overall workplace function than measures of depression severity among working adults with MDD. Moreover, evidence from a recent meta-analysis showed that reductions in cognitive function are predictive of poorer functional and metabolic outcomes (Mansur et al., 2018). Despite the foregoing evidence, current antidepressant regimens do not primarily target psychosocial impairments and workplace disability in MDD and BD. Therefore, there is a need to target cognitive dysfunction to prospectively improve overall performance in
occupational and functional domains.

1.2.5 Non-pharmacological Interventions

Psychosocial approaches such as cognitive remediation therapy (CRT) appear promising in treating cognitive dysfunction in BD. CRT improves learning and enhances cognitive activation via strategy development, monitoring, and pruning. During CRT, individuals are instructed to complete a computerized task that stimulates neuroplastic processes in the brain. Regardless of changes in performance over time, the task ensures that users have relatively high success rates to elicit sustained motivation (McIntyre & Cha, 2016). The ultimate goal of CRT is to develop useful strategies for overcoming cognitively-challenging tasks with the support of social networks (e.g. therapists and peers). “Far-transfer” is the final step in CRT where improvements in cognition and problem-solving are applied to challenges faced in daily life (Medalia, Revheim, & Herlands, 2009). Preliminary results suggest that adjunctive CRT may improve cognitive outcomes in individuals with BD. In one recent randomized trial, 72 individuals with DSM-IV-defined BD were assigned to undergo either 70 hours of computerized CRT or a dose-matched computer control program (Lewandowski et al., 2017). The authors found a medium to large effect of CRT on processing speed, visual learning memory and composite cognition scores compared to controls; the results are promising to support CRT as an efficacious strategy to improve cognitive domains (Lewandowski et al., 2017).

Manualized psychotherapy approaches such as cognitive behaviour therapy (CBT) are effective in the acute treatment of cognitive symptoms in individuals with depression (Lam et al., 2013; Parikh et al., 2016). In one meta-analysis, CBT was found to have positive overall effect on clinical symptom severity, quality of life, and cognitive and behavioural etiopathogenetic mechanisms (Szentagotai & David, 2010). Similarly, comparison of psychoeducation with CBT yielded identical positive effects on cognitive improvement (Parikh et al., 2012).

Studies have shown that brain stimulation techniques such as repetitive
transcranial magnetic stimulation (rTMS) have procognitive effects in subpopulations with depression (Serafini et al., 2015). For example, brain stimulation therapies have been associated with greater tolerability, smaller propensity for cognitive impairment, and higher rates of remission in treatment-resistant patients. As a result, brain stimulation therapies may be useful in targeting cognitive symptoms associated with treatment-resistant unipolar or bipolar depression (Demirtas-Tatlidede, Vahabzadeh-Hagh, & Pascual-Leone, 2013). Indeed, brain imaging studies in individuals with MDD have shown that rTMS may be a viable procognitive neuromodulatory strategy (Kucerova, Prikryl, & Ustoňal, 2008). Furthermore, short-term high frequency direct-current rTMS has been shown to be efficacious in alleviating cognitive and depressive symptoms in individuals with unipolar and bipolar depression (Kedzior, Gierke, Gellersen, & Berlim, 2016).

Aerobic exercise in combination with resistance training is another potential treatment avenue that is cost-effective and accessible. Aerobic exercise improves cognition, has negligible side effects, and is scalable (i.e., has the potential to be a population-wide health intervention) (Smith et al., 2010). For example, a recent review found that performing aerobic exercise three to four times a week for nine weeks at moderate intensity is effective in alleviating depressive symptoms (Stanton & Reaburn, 2014). Likewise, the SMILE study showed lower depression relapse rates in individuals partaking in an aerobic exercise regimen compared to individuals treated with sertraline, a SSRI (Mohlman, Deckersbach, & Weissman, 2015). Both acute and regular aerobic exercise have been shown to improve cognitive functions such as memory. In fact, acute physical activity has been shown to have a greater impact on short- and long-term memory than chronic physical activity. Moreover, greater improvements in memory have been demonstrated with regular exercise in individuals with mild cognitive impairments compared to individuals without cognitive impairments, suggesting that individuals with cognitive difficulties due to depressive disorders may be more sensitive to the procognitive effects of exercise (Heyn, Abreu, & Ottenbacher, 2004; Smith et al., 2010; Stanton & Reaburn, 2014).

The optimum approach to treating cognitive symptoms in depression should involve managing underlying risk factors (i.e., medical comorbidities, adverse lifestyle
factors, iatrogenic confounds, etc.). Modifying these risk factors before the onset of illness could be crucial in preventing neuroprogressive cognitive deficits observed in individuals with BD. However, despite the availability of the aforementioned non-pharmacological intervention strategies, patient adherence is poor (Jones et al., 2013; Parikh et al., 2012). Novel treatment strategies are needed to address cognitive deficits in individuals with depression.

1.2.6 Pharmacological Interventions

Most evidence on the effect of pharmacological agents on cognition has been conducted in trials looking at unipolar depression. Available evidence indicates that improvements in measures of cognitive function with the use of conventional antidepressants are associated with improvements in depressive symptom severity. However, it remains to be seen whether most conventional antidepressants exert direct and clinically significant effects on cognitive functions in individuals with unipolar or bipolar depression. There is currently a paucity of FDA-approved pharmacological agents and/or interventions that are efficacious, tolerable, and specifically target cognitive dysfunction associated with depression. Several studies have examined the efficacy of various antidepressant agents in improving cognitive function in individuals with MDD and BD. For example, bupropion and escitalopram have been reported to improve some aspects of verbal memory and delayed free recall (Cha, 2016; Soczynska et al., 2014). Similarly, sertraline has been shown to improve psychomotor performance (Constant et al., 2005; Schrijvers et al., 2009).

Duloxetine, a Serotonin and Norepinephrine Reuptake Inhibitor (SNRI), has been demonstrated to have significant procognitive effects compared to placebo (Raskin et al., 2007). In addition to improving general symptoms of depression, duloxetine improved verbal learning and memory. Both duloxetine and the multimodal antidepressant, vortioxetine, have been shown to improve learning, memory, and verbal recall as measured by scores on the Rey Auditory Verbal Learning Test (RAVLT). In addition, individuals on vortioxetine also showed significant improvements in acquisition time and delayed recall. While both duloxetine and vortioxetine improved
measures of depressive symptom severity, vortioxetine demonstrated a larger direct effect on RAVLT recall and acquisition scores compared to duloxetine (McIntyre, Lophaven, & Olsen, 2014). In addition, vortioxetine appears to improve a broader range of cognitive functions (i.e., executive function, learning, memory, processing speed, concentration) than duloxetine, which has only been shown to improve measures of learning and memory (McIntyre et al., 2014). Currently, vortioxetine is the only FDA-approved antidepressant agent that has demonstrated direct and independent procognitive effects in individuals with MDD. The procognitive effect of vortioxetine in individuals with BD has yet be validated.

Psychostimulants have been used to treat depressive symptoms in individuals with MDD, however, available evidence is mixed. Notwithstanding the inconsistent evidence, lisdexamfetamine, has been shown to specifically target and improve deficits in executive function in individuals with MDD, particularly among individuals with milder cognitive symptoms comorbid with executive function deficits (Madhoo et al., 2014). In individuals with BD, while psychostimulants improved depressive symptoms, the effect on cognitive symptoms is not clear (McIntyre et al., 2017).

Ketamine, a dissociative anesthetic that antagonizes N-methyl-D-aspartate (NMDA) glutamatergic receptors, has been demonstrated to have rapid-onset antidepressant effects in individuals with treatment-resistant MDD (Venero, 2015). Available evidence indicates that baseline cognitive function may serve as a predictor of response to ketamine treatment (Lee et al., 2016). Moreover, ketamine has demonstrated strong anti-suicidal effects mediated by improvements in executive function (Lee et al., 2016). Treating cognitive deficits via ketamine are currently under investigation.

Preliminary data suggests that incretins may also improve cognitive function. Incretins are a group of metabolic hormones involved in the regulation of blood glucose levels. Incretins are involved in gastric motility, and act as insulin secretion analogues. Exogenously administered glucagon-like peptide (GLP-1) agonists (e.g. liraglutide) are FDA-approved for the treatment of adults with type II diabetes mellitus. Glucagon-like peptide is synthesized in the nucleus tractus solitarius and has receptors distributed
throughout the brain, with a topographical organization of receptors in cognitive controls regions. Preliminary evidence indicates that liraglutide administered at a dose of 1.8 mg is able to improve depressive and cognitive measures in adults with a depressive mood disorder (Mansur et al., 2017). The foregoing results validate previous findings suggesting neuroprotective and neurotrophic properties for liraglutide.

Metabolic regulators present unique opportunities as treatment targets in depressed subpopulations with elevated metabolic and inflammatory status. For example, intranasal insulin has been shown to be procognitive in individuals with MDD. In particular, the procognitive effects of intranasal insulin is stronger in individuals with a history of diabetes and insulin dysregulation comorbid with MDD. In the brain, insulin inhibits pro-apoptotic pathways and plays critical roles in neuroplasticity, neurogenesis, and neuronal growth and survival. Insulin receptors are found throughout the brain, particularly in regions involved in cognitive and emotional processing (Cha, 2016). Therefore, treatment strategies targeting brain insulin may prove efficacious in treating cognitive symptoms in individuals with depression.

Cognitive deficits are a part of the core domain of depressive psychopathology and a principal mediator of psychosocial and workplace functioning. Obtaining cognitive recovery in individuals with unipolar or bipolar depression is necessary to achieve optimal functional remission. This objective is limited by the current clinical paradigm, which insufficiently addresses the deficits in cognitive function experienced by individuals with MDD and BD, and the lack of mechanism-oriented drug development. A domain-based approach to the assessment and treatment of psychiatric conditions may be more pragmatic and may lead to better therapeutic outcomes for patients. Finally, creating a standard discourse related to cognitive dysfunction in psychiatric disorders and understanding the neurobiological mechanisms underlying cognitive dysfunction will be a critical step towards optimally treating cognitive symptoms across psychiatric conditions.
1.3 Inflammation and Bipolar Disorder

1.3.1 Bipolar Disorder and Inflammatory Comorbidities

It has been suggested that there is an interaction between BD and immune dysfunction. In particular, high rates of inflammatory comorbidities have been observed in individuals with BD (Rosenblat & McIntyre, 2017). Despite replicated evidence indicating a connection between BD and inflammation, the direction of causality remains unclear. Immune dysregulation may be the underlying cause of both BD symptomatology and inflammatory comorbidity. Alternatively, BD may be the causal agent underlying inflammation and vice versa. Due to the interconnectivity of the observed relationships between BD and inflammation, it can be postulated that the relationship in etiology may be interactional, in the sense that BD, immune dysregulation, and inflammatory comorbidities positively feedback into each other perpetuating the cycle of illness and functional impairment.

Disturbances in the immuno-inflammatory system have been implicated in the etiology, pathophysiology, phenomenology, and comorbidity of BD. Both preclinical and clinical studies implicate systemic inflammation with “sickness behaviour”, which is a syndrome of depressed mood, anhedonia, lethargy, and decreased motivation, phenotypically similar to an MDE (Pan, Rosenblat, Swardfager, & McIntyre, 2017). Furthermore, increased rates of medical comorbidity relative to healthy controls have been observed in individuals with BD, suggesting common underlying pathophysiology (Rosenblat & McIntyre, 2017).

Autoimmune disorders provide an observational starting point to understand the role of inflammatory comorbidity in BD. The body’s immune system misidentifies host tissue for pathogenic tissue, and triggers both local and systemic inflammatory responses. Proinflammatory cytokines are released and circulate systematically with some degree of central nervous system (CNS) penetration (Rosenblat & McIntyre, 2017). Epidemiological studies have consistently shown autoimmune disorders are comorbid in individuals with BD. In particular, elevated rates of inflammatory bowel syndrome (IBS), psoriasis, and rheumatoid arthritis (RA) have been observed in BD individuals.
Chronic infections may also trigger elevations in systemic proinflammatory cytokines. It is reasonable to expect chronic infections are comorbid with BD, however there is poor replicability with identified associations. One replicated study did observe increased co-prevalence between chronic *toxoplasma gondii* infections and individuals with BD compared to the general population (Sutterland et al., 2015). In addition, BD individuals with chronic infections such as *toxoplasma gondii*, cytomegalovirus, and herpes simplex virus have been associated with impaired cognitive function (Hamdani et al., 2015; Rosenblat, Brietzke, et al., 2015). The exact association between BD and chronic infections has yet to be elucidated, however, it is reasonable to suggest inflammation plays a critical role in the observed relationship.

Immune dysfunction and inflammation play a key role in the progression of cardiovascular disease (CVD). It has been well established that inflammation is a key component of atherosclerotic plaques. Furthermore, replicated studies have identified BD as an independent risk factor for CVD and vice versa (Sayuri Yamagata, Brietzke, Rosenblat, Kakar, & McIntyre, 2017; Swartz & Fagiolini, 2012). Cardiovascular disease and BD are strongly associated with each other in this bidirectional manner and it is postulated that inflammation plays a mediating role within this observed interaction.

Immune dysfunction and inflammation are also implicated in the progression of metabolic disorders. Metabolic syndrome, characterized by hypertension, dyslipidemia, abnormal cholesterol, and central obesity, is strongly associated with BD (McElroy & Keck, 2014). Chronic metabolic conditions (e.g., diabetes mellitus, obesity, metabolic syndrome) have been associated with chronic low-grade inflammation, the degree of which have been directly correlated with metabolic disease progression (Mansur, Brietzke, & McIntyre, 2015). Similar to observations in CVD, rates of metabolic disorders have been found to be elevated in individuals with BD and vice versa (McIntyre, Konarski, Misener, & Kennedy, 2005; Perugi et al., 2015). One factor mediating inflammation in metabolic disorders is central obesity. Abdominal adipose tissue deposits have been found to be a direct source of chronic low-grade inflammation, which may continually activate the production of proinflammatory cytokines,
chemokines, and adipokines (Mathieu, Lemieux, & Després, 2010). In states of chronic positive energy balance (i.e., greater caloric input than output), hypertrophy of adipocytes promotes macrophage activation, which further promote the release of proinflammatory cytokines (Spalding et al., 2008). Elevated rates of inflammatory comorbidities in individuals with BD strongly suggest an interplay between inflammation, immune dysfunction, and psychiatric illness.

1.3.2 Cytokine Abnormalities in Bipolar Disorder

Cytokines are small protein molecules released by immune cells that act to increase or decrease the body's immune response via signaling and receptor binding. Cytokine levels can be measured peripherally (i.e., via serum cytokine levels) or centrally (i.e., in the cerebral spinal fluid) to indicate the inflammatory status of the body. Cytokine studies in individuals with BD have consistently shown elevated levels of proinflammatory cytokines. Specifically, tumor necrosis factor alpha (TNF-α), interleukin-1 beta (IL-1β), interleukin-4 (IL-4), and interleukin-6 (IL-6) have been found to be elevated in individuals with BD compared to healthy controls (Barbosa, Bauer, Machado-Vieira, & Teixeira, 2014; Brietzke et al., 2009).

It is interesting to note that there is variability in the cytokine and inflammatory profiles between different mood states in BD (i.e., depression, mania, hypomania, euthymia). So far, no study has reliably attributed specific cytokine profiles to specific mood states (Rosenblat & McIntyre, 2017). The heterogeneity of inflammatory profiles observed in different mood states suggests elevated inflammation may represent a subset of individuals with BD. This inflammatory BD subpopulation may be pathophysiologically dissimilar to BD individuals without elevated inflammation, which present opportunities for targeted treatment interventions.

Robust associations have been found between proinflammatory cytokines and depressive episodes. In individuals with both unipolar and bipolar depression, serum levels of C-reactive protein (CRP), TNF-α, IL-1β, IL-6, and soluble receptor of TNF-α type 1 (sTNFR1) are elevated during depressive episodes (Barbosa et al., 2014). Greater
depression severity, irrespective of unipolar or bipolar depression, is also associated with greater elevation of proinflammatory markers (Siwek et al., 2017). In individuals with mania, hypomania, or euthymia, inflammatory markers such as serum TNF-α and sTNFR1 levels are also consistently elevated (Barbosa et al., 2014).
1.4 Tumor Necrosis Factor Alpha

1.4.1 Physiology of TNF-α in the CNS

Tumor necrosis factor alpha is a pleiotropic cytokine that has been increasingly recognized as a central, but not exclusive, mediator of CNS function. Elevated levels of TNF-α, along with IL-1 and IL-6, are amongst the most consistently identified proinflammatory cytokine abnormalities in BD (Rosenblat & McIntyre, 2017). Tumor necrosis factor alpha is a 157 amino acid soluble cytokine synthesized and secreted by cells of the immune system, including, but not limited to, macrophages, lymphocytes, astrocytes, and microglia (Bortolato et al., 2015). Transmembrane TNF-α (tmTNF), a homotrimer of 26 kDa, is the precursor to circulating TNF-α. Tumor necrosis factor alpha converting enzyme (TACE) cleaves the cell surface-bound precursor into soluble TNF-α (sTNF), a homotrimer of 17 kDa (Bortolato et al., 2015). Both sTNF and tmTNF ligands are biologically active and can activate proinflammatory cascades via binding to TNF receptors, TNF receptor 1 (TNFR1) and TNF receptor 2 (TNFR2). Both TNF receptors are membrane glycoproteins that specifically bind TNF-α (Brietzke & Kapczinski, 2008). Receptor-mediated effects of TNF and TNF receptor binding mediates apoptosis and cytokine production, as well as the activation of transcription factors such as Nuclear Factor Kappa B (NF-κB) (Tracey, Klæreskog, Sasso, Salfeld, & Tak, 2008).

The expression of TNF-α is increased in response to injury as well as inflammatory and infectious stimuli. Tumor necrosis factor alpha serves a homeostatic function in both innate and adaptive immunity, and is capable of exerting salutary, as well as detrimental effects on immune function. For example, acute modest elevations of TNF-α concentrations can augment host defense mechanisms, while chronically elevated concentrations can exacerbate allostatic load (Brietzke et al., 2009).

Tumor necrosis factor alpha is an important mediator of cell death, immune function, and host defense mechanisms against infections. Under chronic inflammatory conditions, proinflammatory cytokines (e.g. IL-1, IL-17, IL-2) can induce the production of TNF-α. In turn, TNF-α induces the production of additional cytokines (e.g. IL-1, IL-6,
IL-8) which contribute to the proliferation of immune cells and activation of inflammatory and apoptotic cascades (Tracey et al., 2008; M. Zhou, Wang, Yang, & Wang, 2013). Under proinflammatory conditions, peripheral production of TNF-α by monocytes results in positive feedback in the production and secretion of TNF-α from activated microglia (Bortolato et al., 2015). These activated microglia, in turn, become the primary source of TNF-α in the CNS, which further exacerbate the inflammatory cascade with reciprocal increases in the production of TNF and other proinflammatory cytokines (Bortolato et al., 2015; Kerfoot et al., 2006).

Furthermore, cross-talk between activated microglia and other glial cells, chiefly, astrocytes and oligodendrocytes, leads to amplified inflammatory responses that may have detrimental effects on cognitive, neural, and behavioural functions (Najjar, Pearlman, Alper, Najjar, & Devinsky, 2013). Astrocytes, in particular, play a significant role in the reuptake and metabolic conversion of glutamate. Microglia and astrocytes are the main producers of TNF-α in the CNS. When released, it can activate apoptotic pathways (i.e., via activated caspases-3, caspase-8 complexes). Tumor necrosis factor alpha contributes to glutamate excitotoxicity in the CNS by upregulating glutaminase and impairing glutamine reuptake and glutamine synthase. High levels of glutamate increase Ca\(^{2+}\) levels via the activation of Ca\(^{2+}\) permeable NMDA receptors which in turn stimulate enzymes such as proteases (e.g., calpain), phospholipases, and endonucleases, leading to damaged cell structures and apoptosis. Excess calcium also promotes caspase processing and the opening of mitochondrial permeability transition pores, resulting in elevated cytoplasmic levels of cytochrome-c, and oxidative stress, further exacerbating apoptosis and neuronal cell death associated with depressive symptomatology observed in BD (Bortolato et al., 2015).

### 1.4.2 Role of TNF-α in Depression

A growing body of evidence links proinflammatory cytokines, in particular, TNF-α alterations, with depressive symptoms. Endotoxin administration to healthy human subjects is associated with increased serum levels of proinflammatory cytokines (i.e., IL-1, IL-6, TNF-α) with concurrent increase in depressive mood severity and cognitive
impairment (DellaGioia & Hannestad, 2010). Immune challenge in utero has been associated with increased prevalence of depression and schizophrenia during adulthood (Khandaker, Zimbron, Lewis, & Jones, 2013). Furthermore, chronic inflammatory disorders are one of the most prevalent comorbidities of depression (Chapman, Perry, & Strine, 2005). Conversely, depressive mood disorders (i.e., unipolar or bipolar depression) are highly prevalent comorbidities in individuals with chronic inflammatory disorders (Dowlatshahi, Wakkee, Arends, & Nijsten, 2014). This interplay between mood and inflammation suggests a common pathophysiological link. Indeed, in both comorbid populations, elevated levels of serum TNF-α have been reported (El-Tantawy, El-Sayed, Kora, & Amin, 2008). Evidence from meta-analyses indicate higher serum concentrations of TNF-α compared to healthy controls (Dowlati et al., 2010). Elevated levels of TNF receptors (i.e., TNFR1 and TNFR2) have also been observed in individuals with MDD compared to healthy controls (Grassi-Oliveira et al., 2009). In treatment resistant populations (i.e., recurrent depression), TNF expression was elevated at both the mRNA and protein levels (Bobińska, Galecka, Szemraj, Galecki, & Talarowska, 2017).

Converging evidence supports the notion that elevation in TNF-α and other proinflammatory cytokines may be relevant in specific subpopulations with depression. Studies consistently report elevated levels of CRP, IL-6, and TNF-α in depressed individuals with inflammatory and metabolic disturbances [i.e., elevated Body Mass Index (BMI), waist circumference, triglycerides, and low-density cholesterol] (Yoon, Kim, Lee, Kwon, & Kim, 2012). Investigations into single nucleotide polymorphisms (SNPs) in the TNF-α gene are gathering interest. While the A/A genotype of the G-308A TNF-α polymorphism have been associated with greater risks of developing MDD, and the G/G genotype associated with greater risks of developing MDD in the elderly, a complete endophenotypic model of depression based on TNF-α polymorphism is still a nascent development (Cerri et al., 2010). Taken together, these findings suggest proinflammatory dysregulation via elevated TNF-α expression are particularly of relevance in depression.
1.4.3 Clinical Evidence of TNF-ɑ on Cognition

It has been suggested that TNF-ɑ may mediate cognitive dysfunction in individuals with BD. Barbosa et al. (2012) first evaluated inflammatory markers as predictors of cognitive function. The authors measured TNF-ɑ, sTNFR1, and sTNFR2 levels in euthymic BD I individuals (n=25) versus healthy controls (n=25). The primary cognition outcome was executive function assessed by the Frontal Assessment Battery (FAB) and the Mini Mental Status Exam (MMSE). Despite finding a positive association between TNF-ɑ levels and inhibitory control in BD I individuals, the authors did not find any significant associations between assessed inflammatory markers and cognition (Barbosa et al., 2012). The authors concede that the study may be insufficient in sample size and lack adequate power to discern significant associations between cognition and inflammation. Furthermore, the cognition tests used lack sensitivity to cognitive changes associated with mood disorders (Gluhm et al., 2013).

Doganavsargil-Baysal et al. (2013) investigated the relationship between inflammatory markers and cognitive function in euthymic BD I individuals (n=54) compared to healthy controls (n=18). Peripheral levels of TNF-ɑ, sTNFR1, and sTNFR2 were collected. Cognition was measured via the Rey Auditory Verbal Learning Test (RAVLT). Levels of sTNFR1 and sTNFR2 were found to be elevated in individuals with BD I compared to healthy controls, but there was no difference in TNF-ɑ levels between the bipolar and healthy individuals. There was also a significant negative association between TNF-ɑ levels and delayed recalled as measured by the RAVLT (Doganavsargil-Baysal et al., 2013). The study findings are interesting in the sense that it is the first study to show direct association between TNF-ɑ and cognitive dysfunction in individuals with BD.

The largest study to date to investigate the relationship between cognition and inflammatory markers in BD individuals was conducted by Hope et al. (2015). The authors compared cognition scores measured by the Wechsler Abbreviated Scale of Intelligence Scale (WASI) and inflammatory marker data in 111 BD individuals, 121 schizophrenia individuals, and 241 healthy controls. After adjusting for age, sex, psychiatric diagnosis, significant negative associations were found between general
cognitive function and sTNFR1 (Hope et al., 2015). The negative association remained significant after controlling for possible confounder such as education, cigarette smoking, BMI, and medication history, indicating a robust relationship between TNF and cognitive dysfunction.

Hoseth et al. (2016) found similar negative associations between sTNFR1 and cognitive function. The study was conducted in 109 schizophrenia individuals, 117 BD individuals, and 236 healthy controls. The study evaluated cognitive function Wechsler Memory Scale Third Edition (WMS-III). The authors found moderate negative associations between sTNFR1 and performance on verbal learning, memory, and recall (Hoseth et al., 2016). Taken together, current available evidence, with the exception of Barbosa et al. (2012), suggest elevated levels of proinflammatory markers, in particular those associated with TNF-α, are correlated with impaired cognitive functioning in individuals with BD. The impaired cognitive domains include, but are not limited to, memory, executive function, attention, and verbal recall.
1.5 Anti-inflammatory Therapy in BD

1.5.1 Omega-3 Fatty Acids

Omega-3 polyunsaturated fatty acids are naturally-occurring lipids with anti-inflammatory properties. A marine diet high in omega-3 fatty acid content has been shown to decrease inflammatory markers such as CRP, IL-6, and TNF-α (K. Li, Huang, Zheng, Wu, & Li, 2014). Omega-3 fatty acids are well-tolerated anti-inflammatory agents with minimum adverse effects. With regard to anti-depressant effect in BD populations, omega-3 fatty acids have shown preliminary efficacy. While several double-blind placebo-controlled clinical trials demonstrated significant antidepressant effects of omega-3s in BD (Frangou, Lewis, & McCrone, 2006; Stoll et al., 1999), several others reported insignificant antidepressant effects compared to conventional BD pharmacotherapy (Hirashima et al., 2004; Keck et al., 2006). Despite these mixed results, when the studies were pooled together in a recent meta-analysis, a statistically significant moderate antidepressant effect was found for adjunctive omega-3 therapy in depressed BD populations (Rosenblat et al., 2016). The results substantiate the notion that inflammation plays a key pathophysiological role in bipolar depression. Whether adjunctive omega-3 fatty acid therapy in BD individuals is procognitive is currently unknown.

1.5.2 N-Acetylcysteine (NAC)

N-acetylcysteine (NAC) is an antioxidant and anti-inflammatory medication currently approved for the treatment of acetaminophen overdose and to reduce mucus in individuals with cystic fibrosis and chronic obstructive pulmonary disease. N-acetylcysteine works by acting as the prodrug for L-cysteine, which is a precursor to glutathione. Glutathione is a biologic antioxidant that minimizes lipid peroxidation of cellular membranes, reduce oxidative stress; there is also evidence to support glutathione binding to NMDA receptors and modulate the redox state of the NMDA receptor complex (Kerksick & Willoughby, 2005).
Among anti-inflammatory agents, NAC has the strongest evidence supporting its use as an adjunctive antidepressant agent in BD. In a double-blind placebo-controlled clinical trial in 75 BD patients, adjunctive NAC was shown to significantly lower overall depression severity than conventional therapy alone (Berk et al., 2008). Post-hoc analysis of 17 participants from the same BD cohort found that in depressed BD individuals, 80% of the NAC group experienced clinically significant response characterized by a greater than 50% reduction in depression severity compared to only 14% of individuals in the placebo group showing clinically significant antidepressant response (Berk et al., 2008). The antidepressant effects of adjunctive NAC have been replicated in an open-label 8-week clinical trial (Berk et al., 2011). Overall, adjunctive therapy with NAC show promise in treating depression in BD individuals. There may also be procognitive effects of adjunctive NAC therapy due to the modulation of glutamatergic systems. However, these relationships require further study.

1.5.3 Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Non-steroidal anti-inflammatory drugs (NSAIDs) are a class of drugs that inhibits the activity of the cyclooxygenase (COX) enzymes 1 and 2. Adjunctive NSAID therapy in individuals with bipolar depression has been explored in a double-blind placebo-controlled trial by Nery et al. (2008). The authors found that although adjunctive celecoxib therapy decreased depression severity in BD individuals compared to placebo by week 1, at the end of week 6, no significant antidepressant effects were observed between the celecoxib group versus placebo (Nery et al., 2008). In another double-blind placebo-controlled trial with male BD patients, adjunctive aspirin therapy showed no statistically significant difference over placebo at the end of the 6-week experimental period (Saroukhani et al., 2013). Despite the negative results, there is preliminary evidence to suggest NSAIDs may have procognitive effects in animal models. In one study, administration of ibuprofen and celecoxib ameliorated cognitive and motor deficits in a rat model of Parkinson’s disease (Naeem, Ikram, Khan, & Rao, 2017). Taken together, whether adjunctive NSAID therapy is procognitive antidepressant in BD remains unclear.
1.5.4 TNF-α Antagonists

Currently, there are several commercially available TNF-α antagonists. These TNF-α antagonists are indicated for the treatment of chronic inflammatory diseases (e.g., Crohn’s disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and psoriasis). Clinical evidence from individuals with chronic inflammatory diseases demonstrated that biologic TNF-α antagonist administration can reduce depressive symptomatology. Etanercept is a fusion protein of two TNFR2 extracellular domains and the Fc fragment of human immunoglobulin 1 which competitively inhibits the TNF-α receptor (Bortolato et al., 2015). In a randomized, double-blind, placebo-controlled trial in 620 patients with active psoriasis, etanercept administration at 50 mg twice weekly significantly improved depression outcomes measured by the Beck Depression Inventory (BDI) and HAMD compared to placebo controls (Tyring et al., 2006). In another clinical trial involving 389 patients with rheumatoid arthritis over 104 weeks, administration of etanercept with methotrexate significantly improved symptoms of depression and anxiety (as measured by HAMD) compared to the methotrexate-only group (Kekow et al., 2011). Administration of etanercept at 25 mg once weekly in a moderate to severe psoriatic population (n=1310) reduce the percentage of depressed patients from 32% to 16% over 24 weeks (Papp, Poulin, Vieira, Shelton, & Poulin-Costello, 2014). Several studies substantiate the antidepressant effect of etanercept in individuals with plaque psoriasis, psoriatic arthritis, and rheumatoid arthritis (Daudén et al., 2009; Gniadecki et al., 2012; Krishnan et al., 2007).

Adalimumab is a human antibody that bind to TNF-α preventing the bind of TNF-α to its receptors (Bortolato et al., 2015). In a double-blind placebo-controlled 56-week clinical trial, following a 4-week adalimumab induction therapy, patients with moderate to severe Crohn’s disease were randomly assigned adalimumab at 40 mg weekly or placebo. Patients receiving the adalimumab treatment reported lower scores on the Zung Self-Rating Depression Scale (ZDS) than placebo controls (Loftus et al., 2008). A separate randomized double-blind clinical trial in patients with moderate to severe psoriasis showed that the adalimumab group exhibited greater reduction in depression severity as measured by the ZDS concurrent with psoriatic symptom
improvements (Menter et al., 2010). Furthermore, a longitudinal 6-week study of adalimumab administration at 40 mg/kg every other week in patients with ankylosing spondylitis demonstrated significant improvements in depression and anxiety symptom severity measured by the HAMD (Arısoy, Bes, Cifci, Sercan, & Soy, 2013).

1.5.5 Infliximab

Infliximab is a chimeric IgG1k monoclonal antibody with a molecular weight of 150 kDa. Infliximab composes of both murine heavy and light chain variable regions and human heavy and light chain constant regions. Infliximab works by binding competitively with high affinity to both the soluble and transmembrane forms of TNF-α and inhibits binding of TNF-α to its receptors (Maini et al., 1999). Infliximab has a serum half-life of 9.5 days and can be detected in the blood up to 8 weeks after infusion.

Accumulated preclinical evidence supports the concept that TNF-α inhibition alleviates depressive behaviour in animal models. Peripheral administration of infliximab at 5 mg/kg weekly to a rat model of depression (i.e., chronic mild stress) reduced depressive and anxiety behaviour compared to saline controls (Karson, Demirtaş, Bayramgürlar, Balci, & Utkan, 2013). In a mouse model of neuroinflammation induced by the administration of TNF-α in the CNS, central administration of anti-TNF antibodies reversed depressive-like and anhedonic behaviour (Kaster, Gadotti, Calixto, Santos, & Rodrigues, 2012). There is also preliminary preclinical evidence to support the administration of TNF inhibitors to reverse cognitive deficits associated with inflammation. In a rat model of neuroinflammation [i.e., chronic lipopolysaccharide (LPS) administration], administration with the TNF synthesis inhibitor 3, 6-dithiothalidomide was able to reverse deficits observed in spatial memory and learning, and reduced microglial activation (Belarbi et al., 2012). In a rat model of neuroinflammation, administration of infliximab peripherally reduced peripheral inflammation via normalized IL-6 and IL-10 levels in serum (Dadsetan et al., 2016). In addition, reduced microglia activation was observed concurrent with normalized hippocampal TNF-α content and improved spatial memory after infliximab administration (Dadsetan et al., 2016).
Several clinical studies support antidepressant effect of infliximab in patients with chronic inflammatory disorders. In one open-label single-dose, 4-week study, 100 patients with Crohn’s disease were infused with infliximab at 5-10 mg/kg. At the end of the 9-month follow-up period, the proportion of depressed individuals decreased from 24% to 16% (Persoons et al., 2005). In a separate pilot placebo-controlled study, 14 patients with Crohn’s disease received saline placebo infusions from baseline to week 2, followed by infliximab infusion at 5 mg/kg from week 2 to endpoint at week 6. There was significant reduction of depressive scores on the Center for Epidemiological Studies Depression scale (CES-D) (Minderhoud, Samsom, & Oldenburg, 2007). In a longitudinal 6-week study in 16 patients with ankylosing spondylitis, infliximab (5 mg/kg) was administered at week 0, 2 and 6. Significant improvements in BDI scores after the first infusion was observed. In addition, patients also reported improved quality of life outcomes (i.e., improved physical and social functioning) (Ertenli et al., 2012).

To date, only one double-blind, placebo-controlled, clinical trial has been conducted to evaluate the antidepressant effect of infliximab in a primary psychiatric population (Raison et al., 2013). In the 12-week trial, 60 individuals with treatment resistant depression (MDD n = 51, BD n=9) were assigned either peripheral intravenous infliximab infusion at 5 mg/kg (n=30) or saline placebo (n=30). Infusions were administered at week 0 (baseline), week 2, and week 6. Treatment with adjunctive infliximab was not associated with significant decrease in depression scores measured by the HAMD. However, in patients with baseline hsCRP concentrations greater than 5 mg/kg, there was a statistically significant antidepressant response to infliximab than placebo (responder 62% versus 33%, effect size 0.41) (Raison et al., 2013). This significant association was also observed on the Clinical Global Impression Severity scale (CGI). Infliximab seem to have exerted the greatest beneficial effects on alleviating anhedonia, psychomotor retardation, depressed mood, and suicidal ideation (Raison et al., 2013). The findings from Raison et al. (2013) are consistent with the idea that baseline inflammation may predict successful antidepressant response to adjunctive infliximab, and more broadly, anti-inflammatory therapy. Whether infliximab improves cognition in individuals with depression is currently unknown. No randomized placebo-controlled trials have evaluated the effect of infliximab on cognition in a primary
psychiatric population. While there are preliminary preclinical evidence supporting the notion that administration of infliximab in animal models of neuroinflammation can reverse inflammation-induced cognitive deficits (Dadsetan et al., 2016; Kim et al., 2016), rigorously controlled studies in humans are warranted.
Chapter 2
Rationale, Aims, and Hypotheses
Rational, Aims, and Hypotheses

2.1 Rationale

Elevated levels of peripheral and central proinflammatory cytokines have been consistently reported in individuals with bipolar depression. Tumor necrosis factor alpha, along with its receptors, sTNFR1 and sTNFR2, are amongst the most consistently identified proinflammatory cytokine abnormalities in bipolar depression. Preliminary evidence suggests that increased inflammation may be associated with a more severe illness presentation and progression. Furthermore, studies in individuals with chronic inflammatory conditions such as rheumatoid arthritis and Crohn’s disease have shown elevated TNF-α expression is correlated with increased depressive symptoms severity (Bortolato et al., 2015). Vice versa, in individuals with depression comorbid with inflammatory disorders, TNF-α expression is elevated (Dowlati et al., 2010).

TNF-α may also mediate cognitive dysfunction in individuals with BD. Studies have shown negative association between TNF-α levels and cognitive function in BD individuals ((Doganavsargil-Baysal et al., 2013). Furthermore, elevated TNF receptor markers (i.e., sTNFR1) have been associated with cognitive dysfunction, in the domains of memory, executive function, attention, and verbal recall. (Hope et al., 2015; Hoseth et al., 2016). Taken together, current available evidence suggests elevated levels of proinflammatory markers, specifically TNF-α, are correlated with impaired cognition in individuals with BD.

In keeping with this view, double-blind, randomized, placebo-controlled studies have documented significant antidepressant effects following adjunctive treatment with the anti-inflammatory agents in individuals with unipolar and bipolar depression. It is reasonable to assume that antagonism of TNF-α, notably in individuals who manifest signs of elevated inflammation, could exert more specific and superior efficacy in mitigating symptoms of bipolar depression.

Several lines of trans-disciplinary evidence indicate that TNF antagonism improves measures of depression. In an animal model of depression, 5 weeks of etanercept, a TNF-α antagonist, demonstrated antidepressant-like effects on the forced
swim test (Krügel, Fischer, Radicke, Sack, & Himmerich, 2013). In clinical trials involving individuals with chronic inflammatory conditions such as psoriasis, rheumatoid arthritis, Crohn’s disease, and ankylosing spondylitis, administration of TNF-α antagonists such as etanercept and adalimumab resulted in a reduction of comorbid depressive symptom severity (Gelfand et al., 2008; Loftus et al., 2008; Tyring et al., 2006).

Amongst currently available TNF-α antagonists, infliximab demonstrated the most robust evidence of antidepressant action in a primary psychiatric population with elevated inflammation. Infliximab is a chimeric monoclonal antibody that binds competitively to the soluble and transmembrane forms of TNF-α and inhibits the binding of TNF-α to its receptors. Treatment with infliximab reduces the access of immune cells into sites of chronic inflammation (e.g., inflamed joints in individuals with rheumatoid arthritis, inflamed intestinal areas in patients with Crohn’s disease) and blocks the recruitment of further proinflammatory mediators to the area.

Similar to results from trials with other TNF-α antagonists, treatment with infliximab in individuals with chronic inflammatory conditions have been shown to improve comorbid depression symptoms. In a 6-week, open-label study, infliximab at 5 mg/kg administered at 0, 2, and 6 weeks was associated with reduced depressive and anxious symptom severity in individuals with ankylosing spondylitis (Ertenli et al., 2012). In a single-dose study of infliximab in individuals with Crohn’s disease, a significantly smaller proportion of subjects met criteria for depression at 4 weeks (16% at baseline vs. 24% at week 4) (Persoons et al., 2005). In patients with advanced cancer, open-label infliximab administration was associated with improvements in fatigue, anxiety, and depression subscores (Tookman, Jones, DeWitte, & Lodge, 2008).

Only one study has been published investigating the effect of adjunctive infliximab in a primary depressed population. Individuals with treatment resistant unipolar and bipolar depression were enrolled in a 12-week, randomized, double-blind, placebo-controlled trial. Infliximab was administered adjunctively at 5 mg/kg at week 0 (baseline), week 2, and week 6, following protocol established and standardized from previous infliximab studies with Crohn’s disease and rheumatoid arthritis. Infliximab
was superior to placebo in mitigating depressive symptom severity in individuals with elevated inflammation at baseline [i.e. as measured by the high sensitivity C-reactive protein (hsCRP) level of ≥ 5 mg/L]. This subgroup of individuals with elevated inflammation also exhibited a significantly higher response rate following treatment with infliximab as compared to placebo (62% and 33%) (Raison et al., 2013). Taken together, the authors conclude that infliximab at 5 mg/kg may offer significant therapeutic benefit for the treatment of depressive symptoms associated with BD in individuals with elevated inflammation.

Cognitive dysfunction is a major factor subserving functional impairment in individuals with BD. Evidence indicates elevated inflammation, and specifically, elevated TNF-α, is associated with cognitive impairment in individuals with bipolar depression. While there is preliminary preclinical evidence in animal models demonstrating the administration of TNF inhibitors such as infliximab can reverse inflammation-induced cognitive deficits (Dadsetan et al., 2016), there is currently no clinical evidence investigating procognitive effect of infliximab in humans. Treatment with the TNF-α antagonist have shown preliminary antidepressant efficacy in a subgroup of depressed individuals with elevated inflammation. Whether infliximab improves cognition in individuals with depression is currently unknown. No randomized placebo-controlled trials have evaluated the effect of infliximab on cognition in a primary psychiatric population. The foregoing evidence strongly support an investigation of the effect of infliximab on cognition in individuals with bipolar depression with elevated inflammation.
2.2 Aims and Hypotheses

Primary Objective

The primary objective is to evaluate the efficacy of adjunctive intravenous infliximab (at 5 mg/kg) on general objective cognition compared to intravenous placebo (saline) controls in individuals with elevated inflammation and DSM-5-defined bipolar I/II depression.

Primary Hypothesis

Compared to intravenous placebo (saline) controls, adjunctive treatment with intravenous infliximab (at 5 mg/kg) will significantly improve general objective cognition in individuals with elevated inflammation and DSM-5-defined bipolar I/II depression as measured by the change between week 0 (baseline), week 2, and week 12 in the composite cognition z-scores defined as the equally weighted sum of the z-scores in the DSST and RAVLT.

Secondary Objective

The secondary objective is to identify any moderating effects influencing the observed outcomes in cognition due to baseline cognitive function and baseline CRP levels.

Secondary Hypothesis

Baseline cognitive dysfunction and/or baseline CRP will moderate the observed response in the composite cognition z-score of individuals treated with infliximab vs. individuals treated with placebo.
Chapter 3
Research Design and Methods
3    Research Design and Methods

3.1  Study Design Overview

The following study is a phase II, 12-week, fixed-dose, multisite, randomized, double-blind, placebo-controlled clinical trial evaluating the efficacy of adjunctive infliximab for the treatment of individuals with bipolar I/II depression.

Patient recruitment was conducted at two sites, the Mood Disorders Psychopharmacology Unit (MDPU), Toronto Western Hospital, University Health Network, Toronto, Ontario, Canada, and the Stanford University School of Medicine, Veterans’ Affairs Hospital, Palo Alto, California, USA. The study was approved by the respective institutional review boards as well as by Health Canada and the FDA.

The study is composed of 10 clinical visits over 12 weeks (Figure 1). Participants were randomized to either the intravenous saline placebo or the intravenous infliximab group. The assignment of participants to either the placebo or the infliximab group was double-blinded to the participants and all research staff. Randomization and group assignment were conducted by staff at the Clinical Research Pharmacy, Toronto Western Hospital, Toronto, Ontario, Canada. Infusion of either saline placebo or infliximab was done at three time points: week 0, week 2, and week 6. Objective and subjective cognition was assessed at week 0, week 2, and week 12.
Figure 1. Study protocol flowchart
3.2 Subject Selection

3.2.1 Inclusion Criteria

Male and female outpatients between the ages of 18 to 65 who met DSM-5-defined criteria for a current MDE as part of BD I/II with elevated inflammation and who are able to provide written informed consent were eligible for inclusion in the study.

Age and sex were confirmed via a standard demographic questionnaire. Eligibility based on DSM-5-defined MDE as part of BD I/II was confirmed via the Mini International Neuropsychiatric Interview (MINI), a minimum Hamilton Depression Rating Scale 17-Item (HAMD-17) score greater than or equal to 20, a minimum MADRS score greater than or equal to 22, and a Young Mania Rating Scale (YMRS) less than 12. In addition, the participant has previously failed a trial of an FDA-approved first-line treatment for the depressive phase of BD during. Treatment failure was adjudicated via self-reported medical history. Female participants of childbearing age must also test negative for pregnancy and must be using adequate birth control throughout the duration of the study and must continue such precautions for six months after receiving last study drug administration. A detailed checklist of all inclusion criteria can be seen in Figure 2.

Participant enrollment is dependent on meeting one of the following inflammatory criteria.

1. Central obesity, based on ethnicity-specific waist circumference (see Table 4) OR a body mass index (BMI) greater than or equal to 30 kg/m², AND one of the following criteria:

   1a. Raised triglycerides ≥ 1.7 mmol/L (150 mg/dL) or have a history of specific serum lipid abnormality

   1b. Reduced HDL-cholesterol as defined as less than 1.03 mmol/L (40 mg/dL) in males and less than 1.29 mmol/L (50 mg/dL) in females
1c. Raised blood pressure (systolic ≥ 130 mm Hg or diastolic ≥ 85 mm Hg or undergoing treatment for previously diagnosed hypertension)

2. Diabetes mellitus as defined by 12-hour fasting plasma glucose ≥ 7.0 mmol/L or Hb-A1C ≥ 6.5%, as per the 2016 CDA recommendations) or previously diagnosed type 1 or type 2 diabetes or are currently undergoing treatment for previously diagnosed diabetes

3. Inflammatory bowel disorder (i.e., ulcerative colitis, Crohn’s disease)

4. Rheumatological disorders (i.e., rheumatoid arthritis, psoriasis)

5. Current smoking, as defined by smoking a minimum of half a pack of cigarettes a day

6. C-Reactive Protein level ≥ 5 mg/L
Table 4. Ethnicity-specific values for waist circumference as a measure of central obesity

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Waist Circumference as a Measure of Central Obesity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian</td>
<td>Male ≥ 94 cm</td>
</tr>
<tr>
<td></td>
<td>Female ≥ 80 cm</td>
</tr>
<tr>
<td>Black</td>
<td>Male ≥ 94 cm</td>
</tr>
<tr>
<td></td>
<td>Female ≥ 80 cm</td>
</tr>
<tr>
<td>South Asian</td>
<td>Male ≥ 90 cm</td>
</tr>
<tr>
<td></td>
<td>Female ≥ 80 cm</td>
</tr>
<tr>
<td>Chinese</td>
<td>Male ≥ 90 cm</td>
</tr>
<tr>
<td></td>
<td>Female ≥ 80 cm</td>
</tr>
<tr>
<td>Japanese</td>
<td>Male ≥ 85 cm</td>
</tr>
<tr>
<td></td>
<td>Female ≥ 90 cm</td>
</tr>
<tr>
<td>Inclusion Criteria</td>
<td>Criterion met?</td>
</tr>
<tr>
<td>--------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>1 Age 18-65</td>
<td>Yes/No</td>
</tr>
<tr>
<td>2 DSM-5 criteria for a current major depressive episode as part of bipolar I/II disorder</td>
<td>Yes/No</td>
</tr>
<tr>
<td>3 HAMD-17 total score ≥ 20</td>
<td>Yes/No</td>
</tr>
<tr>
<td>4 YMRS total score &lt;12</td>
<td>Yes/No</td>
</tr>
<tr>
<td>5 Previous failed trial (i.e., inefficacy) of quetiapine and one other CANMAT BD guideline/FDA-approved first-line treatment for the depressive phase of BD during the index and/or during a prior episode</td>
<td>Yes/No</td>
</tr>
<tr>
<td>6 Inflammation criteria met</td>
<td>Yes/No</td>
</tr>
<tr>
<td>6i Central obesity based on ethnicity-specific waist circumference or BMI ≥30 kg/m2 AND</td>
<td>Yes/No</td>
</tr>
<tr>
<td>Raised triglycerides: ≥1.7 mmol/L (40 mg/dL) in males; ≥1.29 mmol/L (50 mg/dL) in females or specific treatment for lipid abnormality</td>
<td>Yes/No</td>
</tr>
<tr>
<td>Reduced HDL-cholesterol: &lt;1.03 mmol/L (40 mg/dL) in males, &lt;1.29 mmol/L (50 mg/dL) in females or specific treatment for this lipid abnormality</td>
<td>Yes/No</td>
</tr>
<tr>
<td>Raised blood pressure: systolic ≥130 mmHg or diastolic ≥85 mmHg or treatment of previously diagnosed hypertension</td>
<td>Yes/No</td>
</tr>
<tr>
<td>8i Diabetes: 8-hour fasting plasma glucose ≥7.0 mmol/L or HbA1c ≥8.5% (as per 2013 CDA diagnostic criteria) or previously diagnosed type 1 or 2 diabetes (current prescription medication for diabetes acceptable as diagnosis), excluding child onset of diabetes.</td>
<td>Yes/No</td>
</tr>
<tr>
<td>8iii Inflammatory bowel disorder (Ulcerative Colitis, Crohn's disease)</td>
<td>Yes/No</td>
</tr>
<tr>
<td>8iv Rheumatological disorders (rheumatoid arthritis), psoriasis</td>
<td>Yes/No</td>
</tr>
<tr>
<td>6v Smoking cigarettes (daily - minimum of half pack)</td>
<td>Yes/No</td>
</tr>
<tr>
<td>6vi C-reactive protein level of ≥ 5 mg/L</td>
<td>Yes/No</td>
</tr>
<tr>
<td>7 If received conventional treatment for bipolar depression, minimum of 4 weeks prior to randomization</td>
<td>Yes/No</td>
</tr>
<tr>
<td>8 Negative pregnancy test</td>
<td>Yes/No</td>
</tr>
<tr>
<td>9 Agreement to use adequate birth control measures (e.g., abstinence, oral contraceptives, IUD, barrier method with spermicide, or surgical sterilization) throughout study and to continue prophylactic measures for 6 months after last infusion.</td>
<td>Yes/No</td>
</tr>
<tr>
<td>10 Agreement to abstain from live viral or live bacterial vaccination during the trial and 3 months after the trial.</td>
<td>Yes/No</td>
</tr>
</tbody>
</table>

Figure 2. Inclusion criteria checklist
3.2.2 Exclusion Criteria

Exclusion criteria of the study include the presence of concurrent psychiatric disorder that requires primary medical attention, history of schizophrenia or active psychotic symptoms, active substance abuse and dependence within six month of study enrollment, or have high risk of suicide according to clinical judgement.

Due to the strong immunosuppressant nature of the intervention drug, participants also meet exclusion criteria if they have a clinically significant unstable medical illness, a history of tuberculosis (confirmed by chest radiography or a positive tuberculin skin test), severe infections such as sepsis, abscesses, and opportunistic infections, viral hepatitis B, hepatitis C infection, documented or suspected human immunodeficiency virus (HIV) infection, any unstable autoimmune disorder, active fungal infection, a history of recurrent viral or bacterial infections, or received within three months prior to screening any live viral or bacterial vaccinations.

In addition, participants also meet exclusion criteria if they have a history of Clostridium difficile infection within the past four months, have a history of lymphoproliferative disease, a history of cancer, unstable cardiovascular, endocrinological, hematological, hepatic, renal or neurological disease determined by physical examination and laboratory testing, a concomitant diagnosis or history of congestive heart failure, concomitant treatment with non-steroidal and steroidal anti-inflammatory medications or other biologics, or have current or past exposure to anti-TNF biologics, a previous immediate hypersensitivity response to an immunoglobulin product, known allergies, hypersensitivity, or intolerance to infliximab, and known allergy to murine proteins or other chimeric proteins. A detailed exclusion criteria checklist is provided in Figure 3.
### Exclusion Criteria

<table>
<thead>
<tr>
<th></th>
<th>Exclusion Criteria</th>
<th>Criterion met?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Another concurrent psychiatric disorder that requires <strong>primary clinical attention</strong></td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>History of schizophrenia</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>Active psychotic symptoms</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>Substance abuse and/or dependence within 6 months</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>ECT in the past 6 months</td>
<td>Yes</td>
</tr>
<tr>
<td>6</td>
<td>Actively suicidal or evaluated as being a suicide risk (HAM-D-17 suicide item ≥3 or MADRS suicide item ≥ 4, or according to clinical judgment using the C-SSRS)</td>
<td>Yes</td>
</tr>
<tr>
<td>7</td>
<td>Clinically significant unstable medical illness including cardiovascular, endocrinological, haematological, hepatic, renal or neurological disease determined by physical examination and laboratory testing</td>
<td>Yes</td>
</tr>
<tr>
<td>8</td>
<td>Any autoimmune disorder</td>
<td>Yes</td>
</tr>
<tr>
<td>9</td>
<td>History of tuberculosis, active tuberculosis (confirmed by chest radiography and skin test) and/or a high risk of tuberculosis exposure</td>
<td>Yes</td>
</tr>
<tr>
<td>10</td>
<td>Viral hepatitis (HepB or C) confirmed by laboratory testing</td>
<td>Yes</td>
</tr>
<tr>
<td>11</td>
<td>Human immunodeficiency virus (HIV) confirmed by laboratory testing</td>
<td>Yes</td>
</tr>
<tr>
<td>12</td>
<td>Active fungal infection</td>
<td>Yes</td>
</tr>
<tr>
<td>13</td>
<td>History of recurrent viral or bacterial infections</td>
<td>Yes</td>
</tr>
<tr>
<td>14</td>
<td>History of cancer, excluding basal cell or squamous cell carcinoma of the skin (fully excised with no recurrence)</td>
<td>Yes</td>
</tr>
<tr>
<td>15</td>
<td>Concomitant treatment with non-steroidal and steroidal anti-inflammatory medications or other biologics</td>
<td>Yes</td>
</tr>
<tr>
<td>16</td>
<td>Current or past exposure to anti-TNF biologics</td>
<td>Yes</td>
</tr>
<tr>
<td>17</td>
<td>Females who are pregnant or breastfeeding</td>
<td>Yes</td>
</tr>
<tr>
<td>18</td>
<td>Severe infections such as sepsis, abscesses and opportunistic infections</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Received or expected to receive any live viral or live bacterial vaccination within 3 months before the trial, during the trial and 3 months after the trial.</td>
<td>Yes</td>
</tr>
<tr>
<td>19</td>
<td>Contracted <strong>C. difficile</strong> infection within the past 4 months</td>
<td>Yes</td>
</tr>
<tr>
<td>20</td>
<td>History of lymphoproliferative disease</td>
<td>Yes</td>
</tr>
<tr>
<td>21</td>
<td>Concomitant diagnosis or any history of congestive heart failure</td>
<td>Yes</td>
</tr>
<tr>
<td>22</td>
<td>Known allergies, hypersensitivity, or intolerance to infliximab or its exipients</td>
<td>Yes</td>
</tr>
<tr>
<td>23</td>
<td>Previous immediate hypersensitivity response (including anaphylaxis) to an immunoglobulin product (plasma-derived or recombinant, e.g., monoclonal antibody)</td>
<td>Yes</td>
</tr>
<tr>
<td>24</td>
<td>Current use or past use of any investigational drug within 30 days prior to screening, or within 5 half-lives of the investigational agent</td>
<td>Yes</td>
</tr>
<tr>
<td>25</td>
<td>Known allergies to murine proteins or other chimeric proteins</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Figure 3. Exclusion criteria checklist
3.2.3 Prohibited Medications

The following medications are prohibited during the study:

- Non-steroidal and steroidal anti-inflammatory medications
- Anakinra
- Abatacept
- Other biologics
3.3 Investigational Product, Treatment, and Dosing

Infliximab was prescribed adjuncitively to a conventional mood stabilizer or atypical antipsychotic agent. Eligible participants have received conventional treatment for bipolar depression for a minimum of four weeks prior to randomization to infliximab or placebo. The choice and dosing of mood stabilizing agents remained unchanged throughout the trial.

Participants were randomized to receive intravenous infliximab (5 mg/kg) or placebo (saline solution) at baseline, week 2 and 6 under clinical observation. Placebo was matched to infliximab in colour and consistency. The dosing schedule are identical to a previously published RCT with infliximab in MDD (Raison et al., 2013).

Infliximab is supplied as a sterile white lyophilized powder for intravenous infusion. Each vial contains 100 mg infliximab, 500 mg sucrose, 0.5 mg polysorbate 80, 2.2 mg monobasic sodium phosphate, monohydrate and 6.1 mg dibasic sodium phosphate dehydrate. No preservatives are present. Infliximab lyophilized concentrate for IV injection is supplied in individually-boxed single-use vials of 100 mg dosage strength.

The lyophilized product was refrigerated at 2°C to 8°C (36°F to 46°F). Reconstitution and dilution of infliximab took place in controlled, aseptic conditions. The infusion solution was administered within 3 hours of reconstitution and dilution. If the diluted infliximab is not used within 3 hours of preparation, the infusion solution may be stored for no longer than 24 hours at 2°C to 8°C.

Single intravenous infusion of infliximab results in a linear increase between the maximum serum concentration and dose of administration (3–20 mg/kg). Infliximab is primarily distributed in the vascular compartment. Its volume of distribution at steady state is independent of dose. Single dose infusion of 3–10 mg/kg indicates that the median terminal half-life is 8.0–9.5 days. Repeated infusions of infliximab at 2 and 6 weeks post-baseline result in predictable concentration-time profiles following each
treatment. No systemic accumulation occurs at 4- or 8-week intervals with 3–10 mg/kg dosing. At 8 weeks, mean serum concentrations of infliximab range from 0.5 to 6.0 mcg/mL (Tracey et al., 2008).
3.4 Ethics

Study procedures and ethics were approved by the Research Ethics Board at the University Health Network and at the respective institutional ethics board at the Stanford University School of Medicine. The study was registered on Clinicaltrials.gov (NCT02363738).

A written and signed informed consent form is obtained from potential study subjects. A member of the research team then explained the study in full detail in understandable common terms. Once the subject has had some time to consider the study, and if the prospective participant understands all the procedures and risks involved, and inquiries have been satisfied, the study participant and the research staff will confirm the subject’s voluntary and informed participation in the study. A copy of the signed informed consent form was also given to the subject for reference.

All subjects were informed of the right to withdrawal. Informed consent can be revoked by the participant at any time during study protocol.

All subjects were eligible to receive financial compensation for participation in the study. Subjects were reimbursed up to $50.00 per visit for travel- and food-related expenses.
3.5 Cognition Assessments

General objective cognition was assessed using the Rey Auditory Verbal Learning Test (RAVLT) and the Digit Symbol Substitution Test (DSST). Subjective cognition was assessed using the Perceived Deficits Questionnaire (PDQ). Cognitive assessments were conducted at baseline (week 0), week 2, and week 12. Practice cognitive assessments were conducted during the screening visit before baseline to reduce practice effects.

3.5.1 The Rey Auditory Verbal Learning Test

The RAVLT is a validated neuropsychological tool used to assess cognitive function in the domains of learning and memory, and attention and concentration (Lezak, Howieson, Loring, & Fischer, 2004). The RAVLT have been shown to be an effective and sensitive tool to identify and diagnose cognitive impairments (Ferreira Correia & Campagna Osorio, 2014). The RAVLT is also efficient and versatile in detecting change in cognitive performance over time in depressed populations (McIntyre et al., 2014).

The RAVLT was conducted at 8:00 am on weeks 0, 2, and 12 prior to any other laboratory or psychiatric assessments to control for spatial and temporal effects on cognition. Each iteration of the RAVLT consists of two word lists (list A and B), each consisting of 15 words. Each week the word list differs from the previous week. A total of 6 different words lists was used over the 3 timepoints. Administration of the RAVLT at each timepoint is standardized; full procedure is outline below. For complete word list used, see table 5.

At 8:00 am, the assessor begins trial I of the RAVLT by saying to the participant:

“I am going to read a list of words. Listen carefully, for when I stop you are to tell me as many words as you can remember. It doesn’t matter in what order you repeat them. There are so many words that won’t remember them all the first time. Just try to remember as many as you can.”
Word list A was then read to the participant at the rate of 1 word per second.

Word list A consisting of 15 common words was read to the participant. and the participant was asked to recall the list of words. The response from the participant was recorded verbatim. When the participant indicates no other words can be recalled, the assessor proceeds to trial II.

The assessor begins trial II by saying to the participant:

“Now we are going to try it again. I am going to read the same list of words to you, and once again when I stop I’d like you to tell me as many words as you can remember, including words you said the first time.”

The same procedure for trial I was followed and responses were recorded.

The assessor begins trial III by saying to the participant:

“I’m going to read the list one more time. As before, when I stop I’d like you to tell me as many words as you can remember, including words you already told me.”

The same procedure as the previous trials was followed and the responses were recorded.

On completion of trial III, the assessor says to the participant:

“Now I’m going to read a second list of words. This time, again, you are to tell me as many words of this second list as you can remember. Again, the order in which you say the words does not matter. Just try to tell me as many as you can.”

Word list B consisting of 15 different common words from list A was then read to the participant. Responses were recorded verbatim. After no other words can be recalled, the assessor proceeds to trial IV.

The assessor begins trial IV by saying to the participant:

“Now I want you to tell me as many words from the first list as you can remember. Again, the order in which you say the words does not matter. Just try to tell
me as many words from the first list as you can.”

The assessor does not read list A again, and the participant is asked to recall the word list. Responses were then recorded verbatim. After completion of trial IV, the assessor does not tell the participant that word list A will be tested again in trial V. At this time, the participant was usually asked to complete the DSST.

The assessor begins trial V 20-30 minutes after completion of trial IV by saying to the participant:

“Earlier I asked you to repeat two lists of words. What I’d like you to do now, is to tell me as many words from the first list as you can remember, the list I read 3 times. The order in which you say the words does not matter. Just try to tell me as many words as you can.”

The assessor records the response from the participant verbatim. After no more words can be recalled, the RAVLT is concluded. The responses were checked against the word lists, the number of correct words recalled for each trial is recorded.
Table 5. RAVLT word list

<table>
<thead>
<tr>
<th>RAVLT Week 0 Word List A</th>
<th>RAVLT Week 0 Word List B</th>
<th>RAVLT Week 2 Word List A</th>
<th>RAVLT Week 2 Word List B</th>
<th>RAVLT Week 12 Word List A</th>
<th>RAVLT Week 12 Word List B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drum</td>
<td>Desk</td>
<td>Book</td>
<td>Bowl</td>
<td>Street</td>
<td>Baby</td>
</tr>
<tr>
<td>Curtain</td>
<td>Ranger</td>
<td>Flower</td>
<td>Dawn</td>
<td>Grass</td>
<td>Ocean</td>
</tr>
<tr>
<td>Bell</td>
<td>Bird</td>
<td>Train</td>
<td>Judge</td>
<td>Door</td>
<td>Castle</td>
</tr>
<tr>
<td>Coffee</td>
<td>Shoe</td>
<td>Rug</td>
<td>Grant</td>
<td>Arm</td>
<td>Lip</td>
</tr>
<tr>
<td>School</td>
<td>Stove</td>
<td>Meadow</td>
<td>Insect</td>
<td>Star</td>
<td>Bar</td>
</tr>
<tr>
<td>Parent</td>
<td>Mountain</td>
<td>Harp</td>
<td>Plane</td>
<td>Wife</td>
<td>Dress</td>
</tr>
<tr>
<td>Moon</td>
<td>Glasses</td>
<td>Salt</td>
<td>County</td>
<td>Window</td>
<td>Steam</td>
</tr>
<tr>
<td>Garden</td>
<td>Towel</td>
<td>Finger</td>
<td>Pool</td>
<td>City</td>
<td>Coin</td>
</tr>
<tr>
<td>Hat</td>
<td>Cloud</td>
<td>Apple</td>
<td>Seed</td>
<td>Student</td>
<td>Rock</td>
</tr>
<tr>
<td>Farmer</td>
<td>Boat</td>
<td>Chimney</td>
<td>Sheep</td>
<td>Cottage</td>
<td>Police</td>
</tr>
<tr>
<td>Nose</td>
<td>Lamb</td>
<td>Button</td>
<td>Meal</td>
<td>Lake</td>
<td>Building</td>
</tr>
<tr>
<td>Turkey</td>
<td>Gun</td>
<td>Log</td>
<td>Boat</td>
<td>Pipe</td>
<td>Friend</td>
</tr>
<tr>
<td>Colour</td>
<td>Pencil</td>
<td>Key</td>
<td>Bottle</td>
<td>Skin</td>
<td>Storm</td>
</tr>
<tr>
<td>House</td>
<td>Church</td>
<td>Rattle</td>
<td>Peach</td>
<td>Fire</td>
<td>Village</td>
</tr>
<tr>
<td>River</td>
<td>Fish</td>
<td>Gold</td>
<td>Chair</td>
<td>Clock</td>
<td>Cell</td>
</tr>
</tbody>
</table>
3.5.2 The Digit Symbol Substitution Test

The DSST is a pencil-and-paper cognitive test that requires the participant to copy symbols that are matched to corresponding numbers. It is often referred to as a symbol coding test and is extracted from the Wechsler Adult Intelligence Scale. The DSST is one of the most commonly used tests in psychiatry due to its brevity and high discriminant validity. The DSST is sensitive to cognitive deficits in a wide range of clinical populations (e.g., MDD, schizophrenia, Alzheimer’s disease, traumatic brain injury). In addition, the DSST is sensitive to change over time and is one of the most widely used cognitive assessment tools in clinical pharmacology trials (Jaeger & Zaragoza Domingo, 2016).

The domains of processing speed, attention and concentration, executive function, and learning and memory are assessed by the DSST. Optimum performance on the DSST requires intact function of motor speed, attention, and visuoperceptual processing relating to processing speed and concentration. Performance on the DSST is also affected by associative learning since pairings of symbol and number have to be rapidly learned following the initial trials to improve symbol pairing later on. Therefore, the DSST requires a degree of learning, planning and strategizing as part of working memory and executive function (Jaeger & Zaragoza Domingo, 2016). Indeed, performance on the DSST has been correlated with the principle cognitive domains of processing speed, attention, working memory, executive function, and learning in patients with schizophrenia and MDD (Burton et al., 2013; R. S. C. Lee, Hermens, Porter, & Redoblado-Hodge, 2012). The standard protocol evaluating cognitive dysfunction in a primary depressed population was developed from 2 previous double-blind placebo-controlled clinical trials investigating vortioxetine (Mahableshwarkar, Zajecka, Jacobson, Chen, & Keefe, 2016; McIntyre et al., 2014). The DSST combined with RAVLT are effective and valid indicators of change in cognitive function in populations with depression. The protocol for DSST is as follows.

The assessor begins the DSST by providing the coding page to the participant. The participant was made aware of the symbols corresponding with the numerical digits
at the top of the page. The participant was told that the goal of the test is to substitute as many digits for symbols as quickly and as accurately as possible. The participant was then asked to practice the digit symbol substitution for the first 7 digits until the black line. If any errors were observed, the assessor must quickly correct the error and point the participant to the correct response by referencing the coding guide at the top of the page. Once no errors have been made on the practice run, the participant was given 90 seconds to complete as many digit symbol substitutions as possible. Once the 90 second interval have been reached, the assessor will say “stop” to conclude the test. The total number of correct symbols substituted was recorded. For a sample of the DSST, see figure 4.
**Digit Symbol Substitution Test (DSST)**

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>6</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>7</td>
<td></td>
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<td></td>
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<td>8</td>
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<td></td>
<td></td>
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<tr>
<td>9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

**Thank you. Please sign and date.**

Patient's Signature: ____________________  Date: ____________________

---

Figure 4. The digit symbol substitution test
3.5.3 The Perceived Deficits Questionnaire

The Perceived Deficits Questionnaire (PDQ) 20-item is a neuropsychiatric test developed to provide a self-report measure of cognitive impairment. The PDQ assesses self-reported attention, retrospective memory, prospective memory, and planning and organization (Sullivan, Edgley, & Dehoux, 1990). Although the PDQ is an efficient and validated measure of subjective cognition, there is no correlation between self-rated and objective measures of cognitive performance (Strober, Binder, Nikelshpur, Chiaravalloti, & DeLuca, 2016).

The PDQ was administered after the administration of the RAVLT and DSST during weeks 0, 2, and 12. The participant was asked to rate a series of 20 questions describing cognitive impairments from a scale of 0 to 4 where the higher the score indicate the greater frequency of experiencing that particular cognitive deficit. The scoring of the PDQ is done by summing the scores of the 20 items. The total PDQ is within the range of 0 to 80, with higher the score corresponding to higher levels of self-rated cognitive impairment. For a full list of the 20 items of the PDQ, see appendix.
3.6 Additional Visit Details

3.6.1 Screening

All screening procedures were performed within 28 days prior to baseline (week 0) visit unless approved by the principal investigator. All interested participants were screened for eligibility.

The following information is collected as part of the screening procedures:

- Demographic and social characteristics including age, sex, race, ethnicity, marital status, employment status, education level
- Physical activity history measured by the International Physical Activity Questionnaire (IPAQ)
- Current and past medications
- Medical history obtained via subject interviews and physician assessment
- Diagnosis of BD I/II was confirmed from the Structured Clinical Interview for DSM Disorders (SCID)
- Comorbid psychiatric disorders were assessed with the MINI International neuropsychiatric Interview (MINI) to exclude subjects who code for current psychotic symptoms and active substance abuse and dependence
- Depression severity was assessed via the Montgomery-Asberg Depression Rating Scale (MADRS) and Hamilton Depression Rating Scale (HAMD-17)
- Symptoms of mania and hypomania was assessed using the Young Mania Rating Scale (YMRS)
- Suicidality was assessed using the Columbia Suicide Severity Rating Scale (CSSRS)
- Clinician-rated depressive symptom severity was assessed by the Clinical Global Impression Severity Scale (CGI-S)
- Anthropometric measures such as blood pressure, pulse, weight, and height
- Laboratory testing include: tuberculosis skin test and chest x-ray if indicated, human immunodeficiency virus test, hepatitis B test, hepatitis C test, hematology including hemoglobin, hematocrit, total and differential white blood cell count, and platelet count, serum biochemistry tests include blood urea nitrogen,
creatinine, sodium, potassium, calcium, alkaline phosphatase, total protein, albumin, AST, ALT, total bilirubin, lipid panel, insulin, glucose, CRP, hCG pregnancy test, and urine drug test

3.6.2 Baseline and Endpoint Evaluation

The baseline visit is on day 0 (week 0) of the study. The endpoint visit is on day 84 (week 12) of the study.

The following assessments were conducted:

- Depression severity was assessed via MADRS and HAMD-17
- Symptoms of mania and hypomania was assessed YMRS
- Suicidality was assessed using CSSRS
- Clinician-rated depressive symptom severity was assessed by CGI-S and the Clinical Global Impression Improvement Scale (CGI-I)
- Anthropometric measures such as blood pressure, pulse, and weight
- Quality of life was assessed using Short Form-36 (SF-36), Sheehan Disability Scale (SDS) and Endicott Workplace Productivity Scale (EWPS)
- History of childhood adversity was assessed once using the Childhood Trauma Questionnaire (CTQ) at baseline
- Anhedonia was assessed using the Snaith Hamilton Pleasure Scale (SHAPS)
- Cognition was assessed using the DSST, RAVLT, and PDQ-20
- Diet was assessed using the Brief Diet Questionnaire (BDQ)
- Adverse events and changes to medication were recorded
- Laboratory testing including hemoglobin, hematocrit, total and differential white blood cell count, and platelet count, blood urea nitrogen, creatinine, sodium, potassium, calcium, alkaline phosphatase, total protein, albumin, AST, ALT, total bilirubin, lipid panel, insulin, glucose, and CRP was conducted
3.6.3 Follow-up Visits

Follow-up visit protocol was followed for week 1, 2, 3, 4, 5, 6, 8, and 10. To allow for flexibility with participant scheduling, the follow-up visit can be rescheduled within 2 days of the originally scheduled day and the overall treatment and scheduling protocol was maintained.

The following assessments were completed during follow up:

- Depression severity was assessed via MADRS only
- Symptoms of mania and hypomania was assessed YMRS
- Suicidality was assessed using CSSRS
- Clinician-rated depressive symptom severity was assessed by CGI-S and the Clinical Global Impression Improvement Scale (CGI-I)
- Anthropometric measures such as blood pressure, pulse, and weight
- Quality of life was assessed using SF-36 at week 4, SDS at all visits
- History of childhood adversity was assessed once using the Childhood Trauma Questionnaire (CTQ) at baseline
- Anhedonia was assessed using the Snaith Hamilton Pleasure Scale (SHAPS) at week 6
- Cognition was assessed using the DSST, RAVLT, and PDQ-20 at week 2 to observe for short term changes in cognition
- Diet was assessed using the BDQ
- Adverse events and changes to medication were recorded
- Laboratory testing including hemoglobin, hematocrit, total and differential white blood cell count, and platelet count, blood urea nitrogen, creatinine, sodium, potassium, calcium, alkaline phosphatase, total protein, albumin, AST, ALT, total bilirubin, and lipid panel was conducted at week 2 and 6
3.7 Statistical Analysis

Efficacy analysis was based on the modified intent-to-treat set [i.e., the full analysis set (FAS)], defined as all participants who took at least one dose of study medication and who had at least one valid post-baseline assessment of the primary cognition variable.

The primary outcome of interest was the change in composite cognition z-score from baseline to week 12. The composite cognition z-score is defined as the equally weighted sum of the standardized z-scores of the DSST and RAVLT, allowing the assessment of a broad range of cognitive domains including executive function, learning and memory, attention and concentration, and processing speed. The DSST score was the number of symbols correctly substituted within a 90 second interval (by taking the total number of symbols and subtracting the number of incorrect symbols coded). The RAVLT acquisition score was the average number of words correctly recalled over the first three learning trials, and the RAVLT recall score was the number of words correctly recalled after the 30 minute delay. To obtain the composite cognition z-score, the z-scores of the DSST was assigned a weight of 0.5 and z-scores of RAVLT acquisition and RAVLT recall were each assigned a weight of 0.25.

Exploratory analyses were conducted to evaluate the moderating effects of baseline CRP and cognitive dysfunction. Baseline serum CRP was collected during screening. Following the protocol from Raison et al. (2013), participants with a CRP value greater than or equal to 5 mg/L were categorized as elevated and those with a CRP less than 5 mg/L were categorized as non-elevated. The CRP status was inputted as the moderating variable in the subsequent moderational analysis. Cognitive dysfunction was determined by comparing baseline participant DSST performance against age and gender matched population norms. Those scoring 1 standard deviation or more below the norm were categorized as having baseline cognitive dysfunction. The baseline cognition status was then inputted into the model for moderational analysis.

All statistical analyses were performed using the package for social sciences (SPSS) software (IBM SPSS Version 21). To evaluate between-group differences in
baseline demographic variables, the Mann-Whitney U test was used for ordinal and continuous data and the Chi Square test was used for categorical data. All tests were two-tailed with an alpha value of 0.05.

The primary efficacy analysis was conducted via generalized estimating equation (GEE) models to determine between-group and within-group effects. The GEE considers the dependency of observations by specifying a working correlational structure. The GEE first initiates a naive linear regression analysis assuming observations within subjects are independent. Residuals were then calculated from the naive linear regression model and a working correlation matrix is estimated. The regression coefficients are then refit and corrected for the correlation to determine within- and between-group interactions. The GEE inherently handles missing data using the “all available pairs” method, which assumes all data is missing-at-random and all non-missing pairs of data were used in estimating working correlation parameters. Due to the long form coding of the data within SPSS, the GEE reduces missing data by only losing observations that the participant is missing.

Since the composite cognition z-scores followed a normal distribution after tests for normality using the Kolmogorov-Smirnov and the Shapiro-Wilk tests, a linear GEE model was selected. An autoregressive covariance structure that best fit the data was followed. The independent variables were treatment group (i.e., infliximab vs. placebo), time (week as a categorical variable), and the group × time interaction. Moderators were also analyzed (e.g., treatment × time × CRP status, treatment × time × baseline cognition status) in separate models. Statistical significance was determined at p<0.05.
Chapter 4
Results
4 Results

4.1 Participant Recruitment

A total of 240 individuals expressed interest to participate in the study across both sites [MDPU (n=224), Stanford (n=16)]. Among the 240 individuals that showed initial interest, 143 met at least 1 inflammatory criterion. After assessment for eligibility, 95 individuals completed a full screening visit. Out of the remaining 143 individuals, another 83 individuals were either ineligible or declined to participate.

In total, 60 individuals were randomized to either placebo (n=31) or infliximab (n=29) across both sites [MDPU (n=55), Stanford (n=5)]. Among the placebo group, 5 participants withdrew from the study (2 due to adverse events, 2 due to lack of efficacy, and 1 was lost to follow-up). Among the infliximab group, 8 participants withdrew from the study (5 due to adverse events, 1 due to lack of efficacy, and 2 were lost to follow-up).

Twenty-five of 29 participants (86.2%) randomized to infliximab and 27/31 participants (87.1%) randomized to placebo received all three infusions. A total of 47 participants (78.9%) completed all 12 weeks; differences in study completion rates between treatment groups were not statistically significant [infliximab: 21/29 (72.4%), placebo: 26/31 (83.9%), p=0.282]. The intent-to-treat sample is 60; the modified intent-to-treat sample is 58. Participant recruitment flowchart is outline in figure 5.
Figure 5. CONSORT flow diagram for randomized controlled trial participant enrollment
4.2 Baseline Demographic Characteristics

There were no significant differences between the infliximab and placebo groups in baseline age ($p=0.523$) and ethnicity ($p=0.415$). Despite both the infliximab and the placebo groups skewing heavily towards the female sex, no statistically significant difference was observed between the groups ($p=0.152$). Additional baseline demographic characteristics were described in table 6.
Table 6. Baseline demographic characteristics of the intent-to-treat population

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Placebo (n=31)</th>
<th>Infliximab (n=29)</th>
<th>Total (N=60)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age in years (mean, SD)</strong></td>
<td>46.5 (10.1)</td>
<td>44.9 (11.6)</td>
<td>45.7 (10.8)</td>
</tr>
<tr>
<td><strong>Sex (n, %)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>5 (16.1)</td>
<td>8 (27.6)</td>
<td>13 (21.7)</td>
</tr>
<tr>
<td>Female</td>
<td>26 (83.9)</td>
<td>21 (72.4)</td>
<td>47 (78.3)</td>
</tr>
<tr>
<td><strong>Ethnicity (n, %)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>25 (80.6)</td>
<td>25 (86.2)</td>
<td>50 (83.3)</td>
</tr>
<tr>
<td>Black</td>
<td>2 (6.5)</td>
<td>0 (0)</td>
<td>2 (3.3)</td>
</tr>
<tr>
<td>Asian</td>
<td>0 (0)</td>
<td>1 (3.4)</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>Native American</td>
<td>1 (3.2)</td>
<td>0 (0)</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (9.7)</td>
<td>3 (10.3)</td>
<td>6 (10.0)</td>
</tr>
<tr>
<td><strong>Marital Status (n, %)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>9 (29.0)</td>
<td>13 (44.8)</td>
<td>22 (36.7)</td>
</tr>
<tr>
<td>Living common-law</td>
<td>4 (12.9)</td>
<td>1 (3.4)</td>
<td>5 (8.3)</td>
</tr>
<tr>
<td>Separated</td>
<td>2 (6.5)</td>
<td>3 (10.3)</td>
<td>5 (8.3)</td>
</tr>
<tr>
<td>Status</td>
<td>Column 1</td>
<td>Column 2</td>
<td>Column 3</td>
</tr>
<tr>
<td>-----------------</td>
<td>----------</td>
<td>----------</td>
<td>----------</td>
</tr>
<tr>
<td>Divorced</td>
<td>5 (16.1)</td>
<td>4 (13.8)</td>
<td>9 (15.0)</td>
</tr>
<tr>
<td>Single</td>
<td>10 (32.3)</td>
<td>8 (27.6)</td>
<td>18 (30.0)</td>
</tr>
<tr>
<td>Widowed</td>
<td>1 (3.2)</td>
<td>0 (0)</td>
<td>1 (1.7)</td>
</tr>
</tbody>
</table>

**Employment Status (n, %)**

<table>
<thead>
<tr>
<th>Status</th>
<th>Column 1</th>
<th>Column 2</th>
<th>Column 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retired</td>
<td>2 (6.5)</td>
<td>1 (3.4)</td>
<td>3 (5.0)</td>
</tr>
<tr>
<td>Paid employment</td>
<td>12 (38.7)</td>
<td>5 (17.2)</td>
<td>17 (28.3)</td>
</tr>
<tr>
<td>Sheltered/welfare</td>
<td>1 (3.2)</td>
<td>0 (0)</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>Unemployment</td>
<td>7 (22.6)</td>
<td>13 (44.8)</td>
<td>20 (33.3)</td>
</tr>
<tr>
<td>Student</td>
<td>2 (6.5)</td>
<td>2 (6.9)</td>
<td>4 (6.7)</td>
</tr>
<tr>
<td>Other</td>
<td>7 (22.6)</td>
<td>8 (27.6)</td>
<td>15 (25.0)</td>
</tr>
</tbody>
</table>

**Education (n, %)**

<table>
<thead>
<tr>
<th>Level</th>
<th>Column 1</th>
<th>Column 2</th>
<th>Column 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>High school</td>
<td>5 (16.1)</td>
<td>6 (20.7)</td>
<td>11 (18.3)</td>
</tr>
<tr>
<td>College or university</td>
<td>24 (77.4)</td>
<td>17 (58.6)</td>
<td>41 (68.3)</td>
</tr>
<tr>
<td>Graduate school</td>
<td>1 (3.2)</td>
<td>5 (17.2)</td>
<td>6 (10.0)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (3.2)</td>
<td>1 (3.4)</td>
<td>2 (3.3)</td>
</tr>
</tbody>
</table>
4.3 Baseline Clinical and Cognition Characteristics

There were no significant differences between the infliximab and placebo groups in terms of baseline clinical characteristics. There was no significant difference between infliximab and placebo in terms of baseline depression and mania severity as measured by MADRS ($p=0.316$) and YMRS ($p=0.327$), respectively. There were also no significant differences between the two groups in terms of BMI ($p=0.964$), CRP ($p=0.095$), and total number of inflammatory criteria met ($p=0.247$). No significant differences were observed in the length of current depressive episode ($p=0.880$), self-reported total number of lifetime depressive episodes ($p=0.165$), and self-reported number of lifetime manic episodes ($p=0.477$). Baseline clinical characteristics of the modified intent-to-treat population are described in table 7. Available current medications records are described in table 8. No significant differences were found between the infliximab and the placebo groups in terms of current medication.

The infliximab and placebo groups did not differ in any measure of baseline cognition. There were no significant differences in raw baseline DSST ($p=0.116$), RAVLT learning ($p=0.172$), RAVLT recall ($p=0.243$), and PDQ scores ($p=0.979$) (table 9).
Table 7. Baseline clinical characteristics of the modified intent-to-treat population

<table>
<thead>
<tr>
<th>Measure</th>
<th>Placebo (n=30)</th>
<th></th>
<th>Infliximab (n=28)</th>
<th></th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Standard deviation</td>
<td>Mean</td>
<td>Standard deviation</td>
<td></td>
</tr>
<tr>
<td>MADRS total score</td>
<td>28.80</td>
<td>7.72</td>
<td>30.76</td>
<td>7.13</td>
<td>0.316</td>
</tr>
<tr>
<td>YMRS total score</td>
<td>4.45</td>
<td>4.19</td>
<td>3.52</td>
<td>3.00</td>
<td>0.327</td>
</tr>
<tr>
<td>CRP level (mg/L)</td>
<td>8.65</td>
<td>10.50</td>
<td>5.17</td>
<td>4.12</td>
<td>0.095</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>34.57</td>
<td>7.95</td>
<td>34.46</td>
<td>9.97</td>
<td>0.964</td>
</tr>
<tr>
<td>Total number of inflammatory criteria met</td>
<td>2.10</td>
<td>1.01</td>
<td>1.79</td>
<td>1.03</td>
<td>0.247</td>
</tr>
<tr>
<td>Length of current depressive episode (months)</td>
<td>11.11</td>
<td>20.16</td>
<td>11.85</td>
<td>15.48</td>
<td>0.880</td>
</tr>
<tr>
<td>Total number of lifetime depressive episodes (self-reported)</td>
<td>34.10</td>
<td>34.48</td>
<td>56.50</td>
<td>73.57</td>
<td>0.165</td>
</tr>
<tr>
<td>Total number of lifetime manic or hypomanic episodes (self-reported)</td>
<td>58.86</td>
<td>173.22</td>
<td>33.04</td>
<td>64.61</td>
<td>0.477</td>
</tr>
</tbody>
</table>
Table 8. Available medication information of participants

<table>
<thead>
<tr>
<th>Medications (n, %)</th>
<th>Placebo (n=27)</th>
<th>Infliximab (n=26)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lithium</td>
<td>5 (18.52)</td>
<td>6 (22.22)</td>
<td>0.907</td>
</tr>
<tr>
<td>Valproate</td>
<td>3 (11.11)</td>
<td>5 (19.23)</td>
<td>0.421</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>5 (18.52)</td>
<td>8 (30.77)</td>
<td>0.701</td>
</tr>
<tr>
<td>OFC</td>
<td>1 (3.70)</td>
<td>0 (0.00)</td>
<td>0.326</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>5 (18.52)</td>
<td>4 (15.38)</td>
<td>0.766</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>7 (25.93)</td>
<td>8 (30.77)</td>
<td>0.706</td>
</tr>
<tr>
<td>Antidepressant</td>
<td>20 (74.07)</td>
<td>13 (50.00)</td>
<td>0.202</td>
</tr>
</tbody>
</table>
Table 9. Baseline cognition of the modified intent-to-treat population

<table>
<thead>
<tr>
<th>Measure</th>
<th>Placebo</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th>Infliximab</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td>p-value</td>
<td>Mean</td>
<td>SD</td>
<td>p-value</td>
<td></td>
</tr>
<tr>
<td>DSST total correct symbols</td>
<td>51.70</td>
<td>12.15</td>
<td>45.86</td>
<td>15.65</td>
<td>0.116</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAVLT learning (number of words)</td>
<td>7.70</td>
<td>1.88</td>
<td>7.01</td>
<td>1.87</td>
<td>0.172</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAVLT delayed recall (number of words)</td>
<td>6.23</td>
<td>3.15</td>
<td>5.29</td>
<td>2.96</td>
<td>0.243</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PDQ total score</td>
<td>46.50</td>
<td>18.16</td>
<td>46.63</td>
<td>19.36</td>
<td>0.979</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
4.4 Primary Efficacy Analysis

Both the infliximab and placebo groups had improved composite cognition z-scores at the end of week 12. Significant time effects were found ($\chi^2=30.237, p<0.001$). Pairwise comparisons showed that the composite cognition z-score is significantly improved at week 12 for both infliximab ($p=0.006$) and placebo ($p<0.001$) compared to week 2 (infliximab $p=0.531$; placebo $p=0.602$). However, there were no significant treatment group ($\chi^2=3.504, p=0.061$) and treatment group $\times$ time interactions ($\chi^2=0.619, p=0.734$) at all timepoints (figure 6). Results remained insignificant after controlling for age, sex, and education.

A separate GEE model was performed for subjective cognition as measured by the PDQ. Despite finding significant time effects ($\chi^2=25.297, p<0.001$), there were no significant treatment group ($\chi^2=0.070, p=0.791$) and treatment group $\times$ time interactions ($\chi^2=2.187, p=0.355$) at all timepoints. Subjective cognition scores were significantly decreased at week 12 for placebo ($p=0.001$), but not for infliximab ($p=0.377$). Negative treatment group $\times$ time interactions indicate no discrimination was found between the two groups at all timepoints (figure 7). Results remain insignificant after controlling for age, sex, and education.
Figure 6. Composite cognition z-scores over time for infliximab vs. placebo

Figure 7. Subjective cognition scores as measured by the Perceived Deficits Questionnaire (PDQ) over time for infliximab vs. placebo
4.5 Additional Moderational Analyses

Separate GEE analyses were conducted to determine whether there are moderational interactions underlying changes in composite cognition z-scores. To determine moderational effects of baseline cognitive dysfunction, participants whose composite cognition scored 1 standard deviation below the norm was categorized into the baseline cognitive deficit group. There was no treatment group × time × baseline cognitive dysfunction interaction ($\chi^2=2.096$, $p=0.351$). Among individuals that had baseline cognitive deficits, those receiving placebo had greater cognition score at week 0 than those receiving infliximab ($p<0.001$). However, at all other timepoints, there was no discrimination in composite cognition z-scores between the infliximab and placebo groups in individuals with and without baseline cognitive dysfunction (figure 9, figure 9).

Due to methodological limitations, the sensitivity of clinical CRP results was poor below 3 mg/L. Therefore, baseline CRP was coded into dichotomous “elevated” or “non-elevated” categorical variables. The dichotomous CRP variable was inputted into a GEE model. There was no treatment group × time × baseline CRP interaction ($\chi^2=3.045$, $p=0.081$). Pairwise comparisons revealed that among individuals with non-elevated baseline CRP, the composite cognition z-score of the placebo group was significantly higher than the infliximab group at week 12 ($p=0.012$). At all other timepoints, there was no discrimination in composite cognition scores between the infliximab and placebo groups with and without elevated baseline CRP (figure 10, figure 11).
Figure 8. Composite cognition z-scores of infliximab- vs. placebo-treated individuals with baseline cognitive dysfunction

Figure 9. Composite cognition z-scores of infliximab- vs. placebo-treated individuals without baseline cognitive dysfunction
Figure 10. Composite cognition z-scores of infliximab- vs. placebo-treated individuals with elevated baseline C-reactive protein (CRP) level

Figure 11. Composite cognition z-scores of infliximab- vs. placebo-treated individuals with non-elevated baseline C-reactive protein (CRP) level
Chapter 5
Discussion
5 Discussion

5.1 Discussion

The results herein indicate that the anti-TNF-α agent infliximab was not more efficacious in treating cognitive symptoms in individuals with bipolar depression compared to placebo. Despite both the infliximab and placebo groups demonstrating significant improvement in cognition as defined by the composite cognition z-score in the primary efficacy analysis, the GEE model did not show a significant separation between the two groups in terms of efficacy. In other words, the infliximab group did not improve cognition more than placebo.

It is interesting to note that within-group effects for both placebo and infliximab were significant at week 12. The composite cognition score was significantly higher compared to both week 2 and week 0, whereas the composite cognition score did not differ between week 0 and week 2 in both groups. Both groups had similar trajectory in the improvement of cognition; the greatest improvement in cognition occurred between week 2 and week 12, and not between week 0 and week 2.

The observed trajectory of late improvement in cognition in both the placebo and infliximab groups most likely did not result from practice effect. All participants were acclimated to the cognitive assessment tasks during screening to eliminate any potential practice effects on the baseline visit. In addition, longitudinal studies have shown that practice effect was more pronounced during early phases of repetitive cognitive testing (Bartels, Wegrzyn, Wiedl, Ackermann, & Ehrenreich, 2010). While both the infliximab and placebo groups improved in cognition from week 0 to week 2, the improvement of 0.06 and 0.04 standard deviation from baseline, respectively, was not statistically significant and negligible compared to the improvement observed between week 2 and week 12. There was also no additional cognition testing in the 10-week period between week 2 and week 12 that could have contributed to additional practice effect.

It is possible that the observed effect on cognition was due to separate neurobiological mechanisms. Improved cognitive performance in the placebo group is most likely due to the placebo effect. Literature suggests that the placebo effect involves
perceptual and expectation-based cognitive processes. Furthermore, the placebo effect is enhanced after longitudinal social interactions (Schwarz, Pfister, & Büchel, 2016). The experimental design of the study may have facilitated the placebo effect due to the longitudinal and interactional nature of the 10-visit 12-week design. Results from the GEE analysis of subjective cognition supports the assertion of a strong placebo effect. Indeed, a significant decrease in PDQ scores was observed from week 2 to week 12 in the placebo group, indicating an improvement in subjective perceptions of cognitive competency amongst the placebo individuals. While the PDQ scores decreased significantly in the placebo group, the infliximab group did not experience similar significant reductions in PDQ scores. The trajectory of objective cognitive improvement in the placebo group was concurrent with significant improvements of subjective cognition. Conversely, the observed improvement in objective cognition in the infliximab group may be due to interactions independent of improvement in subjective cognition that has yet to be determined.

We endeavoured to identify subpopulations of adults with bipolar depression who may be more likely to respond to an on-target anti-inflammatory therapy. Additional exploratory analyses did not reveal significant moderational effects due to baseline cognition and CRP status. Among individuals with baseline cognitive dysfunction, the infliximab group demonstrated lower cognition scores at baseline than the placebo. It could be argued that the observed differences in the primary cognition efficacy analysis may be due to differences in baseline cognition among those with cognitive dysfunction. However, this assertion is unlikely due to the non-significant nature of baseline demographic, clinical, and cognition scores between the infliximab and placebo groups. In addition, all collected baseline data points to two very similar groups after the randomization process such that both the infliximab and placebo groups demonstrated similar levels of inflammatory and depression status.

The acute phase reactant, CRP, is one of the most replicated inflammatory markers observed in individuals with bipolar disorder (Dargél, Godin, Kapczinski, Kupfer, & Leboyer, 2015). C-reactive protein was therefore selected as a proxy of inflammation to determine whether subpopulations exist that respond better to infliximab than placebo. Among individuals with CRP levels less than 5 mg/L, indicating
non-elevated baseline inflammation, the composite cognition score of the placebo group was significantly higher than that of the infliximab group at week 12. These results suggest there may exist an elevated placebo response in individuals without elevated baseline inflammation. Raison et al. (2013) demonstrated significantly greater antidepressant response in placebo individuals with baseline CRP less than 5 mg/L. While the study did not include cognition data, Raison’s findings provide some preliminary evidence to suggest elevated placebo response in individuals without baseline CRP elevation. The negative treatment group × time interaction of the primary efficacy analysis may be due to an elevated placebo response at week 12 in individuals with non-elevated baseline CRP.

To our knowledge, our study is the first double-blind, placebo-controlled clinical trial to examine the effects of infliximab on general cognition in individuals with bipolar depression with elevated inflammation. Our results indicate infliximab did not demonstrate significant benefit to cognition compared to placebo. The negative results should be interpreted with caution provided that significant placebo effects may have influenced the outcome of the analysis. Furthermore, given that both infliximab and placebo improved cognition in individuals with recurrent bipolar depression, it can be speculated that there may exist efficacious response to targeted anti-inflammatory therapy with mechanisms yet elucidated.

Taken together, it is unlikely that anti-inflammatory interventions alone can significantly improve cognition in depression. Cognitive dysfunction and related functional impairments continue to be elusive targets in depression treatment and management. An ongoing challenge in CNS therapeutics is that it is not known to what extent is infliximab CNS-penetrant. Whether CNS penetrate is absolutely essential for putative psychiatric drugs remains an unresolved matter. Intuitively, agents that have CNS penetration may be more likely to exert CNS effects. However, there remains the possibility that indirect effects via central and peripheral mechanisms may occur. Although infliximab did not demonstrate superior effects on cognition compared to placebo, extant literature suggests that adjunctive anti-inflammatory therapies are still promising approaches to target cognitive dysfunction in bipolar depression. Continued research of currently available pharmacological agents may provide innovative therapies
for a subpopulation with suboptimal treatment outcomes.
5.2 Limitations

The inferences and interpretations derived from the results of the study have to be considered in the context of several methodological limitations. A limitation is the relatively small sample size (n=60) that may be insufficient to detect small effect sizes. Due to the significant time and energy commitment required by the study and the rigorous nature of the 12-week assessment process, many eligible subjects declined to participate. The exclusive nature of the selection process may have contributed to a particularly motivated population that may not functionally represent the full spectrum of the subpopulation with elevated inflammation and depression.

The recruited population skewed heavily towards the female sex. Approximately 80% of the recruited individuals are female. While most studies report roughly equal gender ratio in the prevalence of BD, replicated findings report increased risks of hypomania, rapid cycling, and mixed episodes in females (Diflorio & Jones, 2010). The recruited sample with the heavy female skew was not representative of reported prevalence rates in females with bipolar disorder. This gender imbalance may represent underlying differences in disease characteristics that could have confounded the therapeutic response.

Furthermore, the recruited participant population is highly heterogeneous in terms of inflammation. Subjects were recruited with diverse inflammatory conditions that may not overlap biochemically and pathophysiologically. Unlike the Raison study, inflammatory status was not solely determined via baseline CRP. A multitude of inflammatory conditions such as autoimmune diseases, metabolic syndrome, diabetes, and rheumatological disorders, in addition to baseline CRP, were all used to meet the inflammatory criterion. As a result, the inflammatory state of the participant population may not necessarily be due to an elevation of TNF-α. While serum TNF-α and soluble TNF receptor levels were collected, due to time constraints of the master’s project, such data was not analyzed. Therefore, it is uncertain whether the recruited population in question exhibited elevated inflammation based on TNF-α dysfunction.

In addition, the participants were allowed to receive complex and mixed
pharmacotherapy during the clinical trial, including, but not limited to, antidepressants, antipsychotics, mood stabilizers, and anticonvulsants. Although the study controlled for anti-inflammatory medications such as NSAIDS and any other biologic anti-inflammatories, there may be confounding effects on cognition due to participants’ concurrent medication regimens. There may also be confounding drug-drug interactions that could affect cognitive performance.

Disproportionate recruitment across study sites could also have biased the sample. The differential recruitment rates could indicate some level of procedural divergence between the sites. What role site location played in cognitive function is unknown. Despite efforts to standardize study procedures, procedural fidelity across sites may be compromised in light of significant recruitment differences.

The selection of cognition tests to proxy general objective cognition may be limited. While the domains of learning and memory, executive function, processing speed, and attention and concentration have been well-characterized by the DSST and RAVLT, general cognition may include other cognitive functions not fully assessed by these tests. For example, while the DSST and RAVLT assess “cold” cognition, emotionally-valenced “hot” cognition was not investigated. Several studies have shown that “hot” cognition also play significant roles in mediating functional outcomes in depression (Roiser & Sahakian, 2013). Furthermore, the performance on cognition tests, especially those reliant on verbal memory, may be dependent upon a participant’s English language fluency. Objective measures of language comprehension and fluency were not assessed.

A final limitation is that additional post hoc testing was not performed to disambiguate the results obtain from the primary efficacy analysis. Significant within group differences (i.e., over time) suggest the existence of underlying therapeutic mechanisms that have not yet been deciphered. Ideally, the moderational effects of depression and mania/hypomania symptomatology, social and occupational function, anhedonia, childhood adversity, diet, and serum inflammatory markers should be investigated to identify subpopulations that may be more susceptible to infliximab or placebo.
5.3 Conclusion

Cognitive dysfunction continues to be an elusive target in the treatment and management of depression. It is estimated that approximately 3.2 million individuals in Canada currently report symptoms of depression and functional impairment (Pearson, Janz, & Ali, 2013). Despite pharmacological advances, available antidepressants insufficiently address cognitive symptoms in individuals with depression. A significant subpopulation of individuals with depression experience immune dysregulation and elevation of proinflammatory cytokines. Although infliximab did not perform superiorly to placebo within the context of our study, extant literature suggests that adjunctive anti-inflammatory therapies continue to provide novel therapeutic targets to treat cognitive dysfunction in depression and may preferentially benefit specific subpopulations. Taken together, the conceptualization, identification, and testing of novel therapeutic agents targeting inflammation in depression are necessary and worthwhile endeavours.
5.4 Future Directions

A logical next step is to identify subpopulations that may benefit from adjunctive infliximab therapy. A wealth of secondary measures has been collected during the clinical trial which could prove useful for further analyses. These measures were outlined in Chapter 3.

The moderating role of baseline depression severity on cognitive performance should be investigated. Raison et al. (2013) was the first double-blind placebo-controlled trial to demonstrate differential antidepressant effects after infliximab infusion. Inflammation, cognition, and depression are interconnected domains in BD treatment and management. Greater depression severity in BD has been linked with decreased cognitive efficacy (Lynham et al., 2018). It is reasonable to suggest that greater baseline depression severity may predispose individuals’ response to anti-inflammatory therapies.

Continuing on the trajectory of investigating potential moderating influences on cognitive performance, serum biomarkers of inflammation should be investigated. First, serum levels of TNF-α and its receptors should be characterized to determine whether these markers are elevated in our population of depressed BD individuals. Comparison of serum TNF-α concentrations over time between the infliximab and placebo groups could determine whether the infliximab therapy was on-target, and if on-target, whether infliximab therapy is efficacious in reducing serum levels of TNF-α. Baseline levels of TNF-α and its related constituents (i.e., sTNFR1, sTNFR2, CRP) can all be inputted into additional GEE models to determine moderational effects on cognition.

To address issues of sample heterogeneity, the effects of inflammatory and psychiatric comorbidity, current and past medication history, childhood adversity, and metabolic and clinical characteristics on cognitive performance within our cohort of recruited BD individuals should be investigated. If there is sufficient power, separate analyses should be conducted to further delineate subpopulations that may differentially respond to infliximab or placebo based on these factors. For example, there is evidence to suggest that childhood abuse and adversity may be correlated with greater
inflammatory activation in adulthood and worsened functional outcomes (Baryshnikov et al., 2017). Metabolic dysfunction such as metabolic syndrome, obesity, and diabetes, have also been correlated with cognitive dysfunction in patients with BD (Bai et al., 2016). These subpopulations present opportunities for novel treatment strategies. The extent infliximab affects cognition in these subpopulations should be investigated.

The effect of infliximab on reducing depressive symptoms in individuals with bipolar depression with a priori elevated inflammation is currently being investigated as part of the efficacy analysis of the clinical trial. The effect of infliximab on anhedonia and functional outcomes is also being investigated to further clarify the therapeutic targets of infliximab. Building upon the results of Raison et al. (2013), delineating subpopulations that may preferentially respond to anti-inflammatory therapies in depression is an important research objective.

Taken together, it is worthwhile to further investigate anti-TNF agents as novel therapies targeting cognitive dysfunction in depression. Preclinical animal studies have shown that administration of various investigational TNF antagonists such as XPro1595 and 3,6′-dithiothalidomide reversed Alzheimer models of cognitive dysfunction in rats and improved hippocampus-dependent synaptic function (Cavanagh et al., 2016; Gabbita et al., 2012). Several TNF-α antagonists are commercially available and are indicated for the treatment of chronic inflammatory diseases. Promising agents include etanercept, a competitive TNF-α receptor inhibitor, and adalimumab, a competitive TNF-α antagonist. Several studies demonstrate preliminary antidepressant effects of both etanercept and adalimumab in populations with chronic inflammatory disorders such as psoriasis and Crohn’s disease (Loftus et al., 2008; Tyring et al., 2006). Clinical evidence of etanercept and adalimumab on cognition is scarce. Several longitudinal studies have demonstrated improvements to quality of life measures after infusion with adalimumab (Arsoy et al., 2013). However, generalizing such findings to clinical populations with depression may be premature. These preliminary results warrant large-scale clinical trials to investigate the effect of anti-TNF agents on cognition in individuals with depression.

Novel anti-inflammatory therapies should be investigated toward the aim of
treating cognitive dysfunction in depression. Several lines of evidence indicate that in addition to TNF-α, IL-6 abnormalities may underlie cognitive dysfunction in depression. Interleukin-6 is a pleiotropic cytokine synthesized and released in response to inflammatory stimuli with both pro- and anti-inflammatory properties (A. J. Zhou et al., 2017). As a proinflammatory cytokine, IL-6 acts as a potent transcriptional stimulus for the production of acute phase reactants such as CRP and other proinflammatory chemokines (Gabay & Kushner, 1999; Naugler & Karin, 2008). The transcriptional effect of IL-6 on CRP mechanistically link IL-6 with proinflammatory mediators such as CRP and TNF-α. Indeed, elevated peripheral IL-6 concentrations have been correlated with depression severity in individuals with MDD (Bob et al., 2010). Preclinical and clinical evidence also suggest that peripheral IL-6 elevation is associated with cognitive dysfunction in individuals with depression (Rosenblat, Brietzke, et al., 2015).

Sirukumab is a human monoclonal antibody that inhibits IL-6 with high affinity. Interventional studies with sirukumab in chronic inflammatory disorders provide preliminary evidence of improved patient-reported health outcomes, including measures of occupational functioning and quality of life (Szepietowski et al., 2013). A separate study reported functional improvement after sirukumab therapy in a patient population with active rheumatoid arthritis (Smolen, Weinblatt, Sheng, Zhuang, & Hsu, 2014). Although improvement in function may not equate with improvement in cognition, these preliminary results indicate that targeted anti-inflammatory therapy may be efficacious in producing favourable results in a population with inflammatory and psychiatric comorbidities.

Taken together, repurposing available anti-inflammatory agents towards the treatment of cognitive dysfunction in depression is a promising avenue of research. Feasible and testable hypotheses can be generated to target cognitive dysfunction in individuals with complex and comorbid disease characteristics that is currently inadequately addressed by available antidepressant therapies.
## Appendices

Appendix 1. The perceived deficits questionnaire 20-Item

<table>
<thead>
<tr>
<th>During the last 7 days, how often did you...?</th>
<th>Never in the past 7 days</th>
<th>Rarely (once or twice)</th>
<th>Sometimes (3-5 times)</th>
<th>Often (about once a day)</th>
<th>Very often (more than once a day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Lose your train of thought when speaking</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2) Have difficulty remembering the names of people, even the ones you’ve met several times</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3) Forget what you came into the room for</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4) Have trouble getting things organized</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5) Have trouble on what people are saying during a conversation</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>6) Forget if you have already done something</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>7) Forget appointments and meetings you have scheduled</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>8) Have difficulty planning what to do in the day</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>9) Have trouble concentrating on what you were reading</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Question</td>
<td>Score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>--------------------------------------------------------------------------</td>
<td>-------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Forget what you did during the past 24 hours</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Forget the date unless you looked it up</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Have trouble getting started, even if you had a lot of things to do</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Find you mind drifting</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Forget what you talked about after a telephone conversation</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Forget to do routine things like lock the door, turn off the stove, or turn on your alarm clock</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>Feel like you mind went totally blank</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>Have trouble remembering numbers even for a few seconds</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>Forget what you did 2 or 3 days ago</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>Forget to take your medication</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>Have trouble making decisions</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Total Score</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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