

**THE EFFECT OF TRANSCRANIAL MAGNETIC STIMULATION ON DEPRESSION AND  
THE ASSOCIATED OLFACTORY DYSFUNCTION**

by

Hannah Clare Taalman

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## Abstract

**Introduction:** Depression negatively impacts olfactory functioning and as such, olfactory dysfunction has been found in individuals with depression. Expansions of this research have demonstrated an improvement in olfactory functioning after successful pharmaceutical and psychotherapy treatments for depression. However, it is unknown if intermittent theta burst stimulation (iTBS), a form of transcranial magnetic stimulation (TMS) has a similar effect.

**Objectives:** The current study examined the olfactory functioning and depression severity in depressed individuals before and after iTBS, comparing them to non-depressed controls. We hypothesized that depressed individuals would have significantly poorer olfactory functioning compared to controls before treatment, but little to no difference between after successful treatment. We also predicted that depression severity and olfactory dysfunction were negatively correlated.

**Methods:** We recruited 20 depressed individuals receiving iTBS and 9 non-depressed controls. The olfactory function of depressed patients was tested before and after treatment using Sniffin' Sticks Extended Test (examining olfactory threshold, discrimination, and identification). Depression severity was also evaluated. Controls were tested in the same manner with a 5-6 week waiting period in lieu of iTBS.

**Results:** Both the comparison of olfaction before and after treatment in depressed patients and with controls found no significant differences. An effect of age ( $p < 0.05$ ) and baseline depression severity ( $p < 0.05$ ) were found in the depressed group, with younger and less severely depressed individuals having significantly better olfactory functioning than their counterparts both before and after treatment. There were a number of significant correlations between depression severity and olfactory discrimination, identification, and total olfaction score at both time points.

**Discussion:** While no significant difference was found between the depressed and control groups or within the depressed group, the impact of depression severity provided support for the assumption of a reciprocal relationship. The significant difference between younger and older depressed participants

highlights the limitation of age present in the study that may have contributed to the lack of significant differences. Overall, the relationship between depression and olfaction has the potential to be an important part of early diagnosis, examination of treatment progression, and on quality of life of depressed individuals.

## **Co-Authorship**

Dr. Roumen V. Milev of the Department of Psychiatry at Queen's University contributed to the design and execution of the study, as well as the preparation of this document.

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## **List of Abbreviations**

MDD – Major Depression

MDE – Major Depressive Episode

GAD – Generalized Anxiety Disorder

BD - Bipolar Disorder

BD I – Bipolar Disorder I

BD II – Bipolar Disorder II

TRD – Treatment- Resistant Depression

ECT – Electroconvulsive Therapy

TMS – Transcranial Magnetic Stimulation

rTMS – repetitive Transcranial Magnetic Stimulation

iTBS – Intermittent Theta Burst Stimulation

ADM – Antidepressant Medication

MAOI – Monoamine Oxidase Inhibitors

TCA – Tricyclic Antidepressants

SSRI – Selective-serotonin Reuptake Inhibitors

SNRI – Selective-Norepinephrine Reuptake Inhibitors

DRI – Dopamine Reuptake Inhibitors

IPT – Interpersonal therapy

CBT – Cognitive Behavioural Therapy

CT – Cognitive Therapy

BDNF – Brain Derived Neurotrophic Factor

UPSIT – University of Pennsylvania Smell Identification Test

MADRS – Montgomery-Aspberg Depression Rating Scale

CGI – Clinical Global Impressions Scale

HAD – Hospital Anxiety and Depression Scale

HAD-D – Hospital Anxiety and Depression Scale – Depression Measure

HAD-A – Hospital Anxiety and Depression Scale – Anxiety Measure

SHPS – Snaith-Hamilton Pleasure Scale

BDI – Beck Depression Inventory

ANOVA – Analysis of Variance

RM ANOVA – Repeated Measures Analysis of Variance

# Chapter 1: Introduction

## 1.1 General Overview

As knowledge and understanding of mental disorders increases, researchers have begun to examine the impact of such disorders on areas other than mood. One such area where research interest has increased is in olfactory functioning and the impact of mental disorders on olfactory functioning. Olfactory dysfunction has been investigated in psychiatric disorders such as psychoses and schizophrenia (Atanasova et al., 2008; Kopala, Good, & Honer, 1994), anorexia nervosa (Atanasova et al., 2008; Kopala, Good, Goldner, & Birmingham, 1995), and panic disorder (Atanasova et al., 2008; Kopala & Good, 1996). As a result, researchers have begun to examine olfactory functioning in other mental disorders, such as mood disorders and seasonal affective disorder (Atanasova et al., 2008; Gross-Isseroff et al., 1994; Lombion-Pouthier, Vandel, Nezelof, Haffen, & Millot, 2006; Pause, Miranda, Goder, Aldenhoff, & Ferstl, 2001; Postolache et al., 1999, 2002). Depression in particular has been a disorder of interest with regards to olfaction and olfactory dysfunction in this disease state. A reciprocal relationship between olfactory functioning and depression has been proposed based on the findings of previous studies. However, there is a great deal of variation in the results generated from such research, reducing the clarity as to how and what aspect of olfactory functioning is associated with or impacted by depression.

A potential solution to the uncertainty towards the nature of the relationship between olfaction and depression is to examine how successful treatment of depression impacts olfactory functioning when, and if, there is a baseline dysfunction. A handful of studies have examined the effect of antidepressant medications or psychotherapy on olfactory dysfunction associated with depression (Clepce, Gossler, Reich, Kornhuber, & Thuerlauf, 2010; Croy et al., 2014; Gross-Isseroff et al., 1994; Pause et al., 2001). As of yet, no studies have examined if intermittent theta burst stimulation (iTBS), an expansion of the repetitive transcranial magnetic stimulation protocol (rTMS), has similar effects to antidepressants or

psychotherapy. While there have been studies that examined the effect of rTMS on olfaction in primary olfactory disorders (Henkin, Potolicchio, & Levy, 2011), depression has not been an area of interest as of yet. As such, this is one area in the literature that could be expanded upon.

The purpose of this thesis is to examine the relationship between olfaction and depression while also addressing the lack of research regarding the role iTBS has. This thesis conforms to the Queen's University School of Graduate Studies and Research guidelines under "General Forms of Thesis". The proceeding chapter reviews the background, along with major findings and limitations present in the literature, outlines the goals, and brief methodology of the current thesis. The following chapter then outlines the methodology for this study in greater detail. The remaining two chapters examine the results of the current study and discuss the relevant findings with a focus on study limitations and future research.

## **Chapter 2: Literature Review**

### **2.1 Introduction**

This chapter will review the current knowledge on mood disorders, olfactory functioning, and the relationship between the two. The major disorder of interest in this chapter and the available literature is major depressive disorder (MDD); however, bipolar disorder (BD) will also be addressed with regards to olfaction. The major pathways and regions involved in olfaction will be examined in order to better elucidate the connection to depression. As well, limitations of the current research will be addressed and evaluated to provide further insight and propose alterations to future research and clinical implications.

### **2.2 Psychiatric and Mood Disorders**

Mental disorders have been attributed to approximately 15% of the burden of disease in the global population (Atanasova et al., 2008; Prince et al., 2007). Mood disorders are characterized by disturbance of emotions, behavioural patterns, emotions, cognition, and perception (WHO, 2010). The mood change associated with these psychiatric disorders is generally accompanied by some change in the level of activity, such as cognitive or physical activity (American Psychiatric Association, 2013; WHO, 2010). These psychiatric disorders also greatly impact an individual's quality of life, wellbeing, social skills, and relationships (Atanasova et al., 2010). The remainder of this section will define and describe depressive disorders and bipolar disorder.

#### **2.2.1 Major Depressive Disorder**

Depressive disorders include major depressive disorder (MDD; American Psychiatric Association, 2013) and persistent depressive disorder (dysthymia). For the purpose of this study, the literature review will focus on MDD. MDD is characterized by a major depressive episode (MDE) of low mood, decreased activity associated with reduced energy and fatigue, and loss of capacity for interest and enjoyment (anhedonia; Liu et al., 2012; WHO, 2010). Similar to other mental health disorders, it is

assumed in MDD that processing and perception of emotion and emotional stimuli is altered such that individuals with MDD display a reduced anticipation of positive experiences and an increased anticipation of negative experiences (Macleod, Byrne, & Holloway, 1996; Pause et al., 2001).

#### *2.2.1.1 MDD Comorbidity*

A number of disorders, both mental and physical health related, are linked to MDD (Rush et al., 2005). Of these disorders, Generalized Anxiety Disorder (GAD) is consistently comorbid with depression, though less common in the population than depressed with a lifetime prevalence of 8.7 % compared to 11.3% for MDD (Pearson, Jaz, & Ali, 2013). Despite the prevalence being lower, in those that met criteria for GAD 52.6% also met criteria for depression. Similar to what was observed in depression, the rate of GAD has been found to be higher among women (3.2%) than men (2.0%). However, unlike MDD, the rate remained relatively steady across most age groups ranging from 2.4% to 3.0% until the aged 65 and older cohort (Pearson et al., 2013). The occurrence of both MDD and GAD and the symptoms associated with both can often be worse than in disorders that occur alone (Moscati, Flint, & Kendler, 2016). For example, research focusing on patients diagnosed with MDD and comorbid GAD have found poorer social functioning compared to those with MDD alone (Moscati et al., 2016; Zimmerman & Chelminski, 2003). These comorbidities often complicate the presentation and diagnosis of depression and can also impact the treatment planning (Rush et al., 2005). This impact on treatment is commonly associated with poorer outcomes (Zimmerman & Chelminski, 2003). Overall, the presence of GAD in MDD is a key and important characteristic to understanding the progression and experience of MDD.

#### *2.2.1.2 MDD Prevalence and Age*

MDD is one of the most prevalent and disabling mental disorders, affecting 8 to 12% of the population at least once in their lifetime (Croy et al., 2014; WHO, 2010). According to an epidemiological study conducted in 2012, the lifetime prevalence of an MDE in Canada was 11.3% and

past-year episode prevalence was 4.7% in that same sample (Patten et al., 2015). As well, a study released by Statistics Canada found a lifetime prevalence of 11.3% for MDE with an overall prevalence of 12.6% for mood disorders (Pearson et al., 2013). The prevalence of depression changes distribution when examining different age groups. MDD is highest amongst individuals aged 15 to 24 (8.2%; Pearson et al., 2013) and lowest amongst those 65 years and older (1.7%; Pearson et al., 2013). These results are consistent with an earlier epidemiological report of annual prevalence of 5% in those aged 15 - 25 and 1.9% in those aged 65 and older (Patten et al., 2006). In both cases, the rate of incidence decreased as age increased.

### *2.2.1.3 MDD and Gender*

A common report by epidemiological studies examining mood disorders is a difference in the prevalence of depression between males and females. The rate of prevalence has consistently been found to be approximately 1.5 – 2.5 times higher in women than men (Jacobi et al., 2005), with most reporting a general 2:1 ratio (Harkness et al., 2010; Hirschfeld & Cross, 1982; Kessler, 2003; Whiteman, Ruggiano, & Thomlison, 2016). There has been variation between studies with regards to the exact number, with some reporting a 12-month-diagnosis as high as 14% in women compared to 7.5% in men (Jacobi et al., 2005), while others report around 5.8% in women compared to 3.6% in men (Pearson et al., 2013). When examining each group by age, across all age groups the prevalence remained higher in females (Pearson et al., 2013).

A number of hypotheses have been presented that aim to explain why such a difference may occur. A review of the literature conducted by Weissman and Klerman (1977) suggested four possible conclusions for such a difference. First, they suggest that this difference in depression rate is real and not an artifact of a sex-difference in the rate of help-seeking behaviour. Second, while women do not appear to experience stressful life events or consider certain life events to be more stressful than men, women may report significantly greater intensities of symptoms. This conclusion suggests that women may be more willing to admit to symptoms or express symptoms more consistently than men (Hirschfeld &

Cross, 1982; Weissman & Klerman, 1977). Third, the biological and psychological changes associated with the perimenstrual and postpartum periods represent factors that increase the risk of depression during such time (Hirschfeld & Cross, 1982; Weissman & Klerman, 1977). However, the possible endocrinological explanation behind such risk do not support the occurrence of a distinct, separate “involutional” depression in women who are postmenopausal (Weissman & Klerman, 1977). Fourth and finally, social-role expectations and conflicts along with personality factors are likely causes for women’s predisposition to depression.

While some conclusions proposed by Weissman and Klerman (1977) have failed to find significant discrepancies, such as prevalence due to endocrinological changes in the perimenstrual and pregnancy periods (Kessler, 2003), and were proposed some time ago, others continue to be examined in the research community. As a result, recent research has consistently demonstrated that the main component crucial to understanding the prevalence difference in women may be social risk factors, such as life stressors (Whiteman et al., 2016). Life stressors may play a large role given that women have a greater likelihood of experiencing depression as a result of life stressors and these stressors increase in frequency and severity with the aging process (Harkness et al., 2010; Kessler, 2003; Whiteman et al., 2016). The focus on life stressor frequency and severity in women has helped to gain a better understanding of the gender difference in depression and how life stressors impact the lifetime course of depression (Harkness et al., 2010).

### **2.2.2 Bipolar Disorder**

Bipolar disorder (BD) is separated from depressive disorders and placed between depressive disorder and schizophrenia spectrum and other psychotic disorders as a bridge between these two diagnostic classes (American Psychiatric Association, 2013). Within BD, there is further delineation into a number of disorders, such as bipolar I disorder (BD I) and bipolar II disorder (BD II) – the most severe subtypes of the disorders. Diagnosis of BD I requires at least one lifetime manic episode, and may have been preceded and/or followed by a hypomanic or major depressive episode (MDE). For diagnosis of BD

I, a manic episode must be present but hypomanic or major depressive episodes are not required for diagnosis (American Psychiatric Association, 2013). Manic episodes are characterized by a distinct period of abnormally and persistently irritable, elevated or expansive mood, and an abnormal and persistent increase in activity such as: increased talking, grandiosity, psychomotor agitation, decreased need for sleep, distractibility, and/or rapid thought (American Psychiatric Association, 2013; Cuellar, Johnson, & Winters, 2005; Hirschfeld & Cross, 1982). Manic symptoms must have lasted at least a week, be present for most of the day, nearly every day, and be severe enough to cause significant impairment in social or occupational functioning (American Psychiatric Association, 2013). Hypomanic episodes have similar presentation to manic episodes, but are not severe enough to cause significant impairment and symptoms must last at least 4 consecutive days, most of the day, nearly every day (American Psychiatric Association, 2013). MDEs present with the same criteria and symptoms as in MDD and must also be present during the same 2-week period. BD II diagnosis requires at least one hypomanic and one major depressive episode (American Psychiatric Association, 2013; Datto, Pottorf, Feeley, LaPorte, & Liss, 2016). There has been increasing evidence that BD II is at least as prevalent as BD I and has similar impact on quality of life, mortality, comorbidity, and substantial disability (American Psychiatric Association, 2013; Datto et al., 2016). Within both BD I and BD II, the depressive episodes generally exceed the manic or hypomanic episodes in terms of duration and frequency. Given the similarity between the two disorders, the two subtypes can only be distinguished by a careful examination of the individual's psychiatric history in order to elucidate if there is a history of manic or hypomanic episodes (Datto et al., 2016). It is important to note, and is helpful in establishing diagnosis, the duration and frequency of depressive episodes and the chronicity of the illness are typically greater in BD II (Datto et al., 2016).

In diagnosis, BD can be distinguished from MDD in that the individual experiences a manic or hypomanic episode that involve elevated, irritable and/or expansive mood (Hirschfeld & Cross, 1982; WHO, 2010). There are a number of distinctions that set BD and MDD apart. First, BD can be contrasted

from MDD based on prevalence of this disorder. Unlike MDD, which has a lifetime prevalence of 11.3% and 12-month prevalence of 4.7%, the lifetime prevalence of BD is 2.6% and the 12-month prevalence is 1.5% (Pearson et al., 2013). In further contrast to MDD, the prevalence of BD is approximately equal in men and women (Hirschfeld & Cross, 1982). Recent studies focusing on the comparison of BD and MDD has also found a younger age of onset, increased frequency of episodes, and greater mood variability in the short-term in BD (Cuellar et al., 2005). Despite the differences between the two, there is some risk in misdiagnosis of subtype BD II and MDD. The difficulty in diagnosing hypomania correctly means that patients with BD II are at risk of misdiagnosis with MDD due to sharing the same depressive symptoms and as such hypomania occurs in 12% of individuals initially diagnosed with MDD (American Psychiatric Association, 2013; Datto et al., 2016). As a result, misdiagnosis of BD as MDD may lead to inappropriate treatment until hypomanic episodes are identified.

Overall, the understanding and treatment of mood disorders requires correct delineation between BD and MDD through in depth examination of psychiatric history, with the goal of identifying manic or hypomanic episodes in particular. A misdiagnosis can impact the individual's experience of the mental disorder and the use of an incorrect treatment can cause further negative symptoms that place greater burden on the individual and reduction in their quality of life.

### **2.3 Treatment of Depression**

As technologies advance and the understanding of the human body, brain, and chemistry is furthered, the treatment of depression has been an interest to many fields outside of just psychology and psychiatry. Despite an increase in the available treatment options, treatment choice and the success of said treatment depend on a number of factors unique to the individual and the disorder frequency and severity. Treatment success is also mediated by the age of the individual. Older MDD patients are more likely to adhere and be compliant with treatment regimes, particularly in antidepressant medications, compared to younger patients (Sirey et al., 2001). Age is one of many barriers to successful treatment and these barriers greatly impact the treatment of depression.

A particularly important barrier to the treatment of depression is the lack of or delay of help-seeking behaviour in individuals with depression due to psychological barriers (Sirey et al., 2001). Individuals with mild MDD often minimize the need for treatment and this can result in a delay of treatment until the depression increases in severity or an avoidance in treatment overall (Kessler et al., 2003; Sirey et al., 2001). As well, stigma has a large role in treatment seeking behavior and treatment adherence. Many individuals fear the stigma associated with depression and this stigma decreases the likelihood that an individual will seek treatment for depression or will significantly delay the help-seeking behaviour (Sirey et al., 2001). As a result, there is a strong association between perceived stigma and noncompliance such that even when an individual is in need of treatment, they often fear that others will be critical and rejecting (Sirey et al., 2001). Adherence to antidepressant medication, in particular, can be predicted by perception of illness severity and level of perceived stigma before the onset of such therapies (Sirey et al., 2001). Overall, these psychological barriers play a very large role in the individual experience of depression, particularly in how they approach and respond to treatment.

Another facet of the treatment of depression worth noting is the presence of a subset of individuals who do not respond to treatment are termed “treatment-resistant depression” (TRD). TRD is broadly defined as a failure to respond to two or more adequate antidepressant trials during a current episode (Cusin & Dougherty, 2012). Those with TRD often have poor clinical outcomes and experience a further impairment in their functioning and quality of life (Al-Harbi, 2012; Cusin & Dougherty, 2012). A number of treatment methods have been developed and implemented with the purpose of providing relief to those with TRD, such as electroconvulsive therapy (ECT) and deep brain stimulation (DBS; Cusin & Dougherty, 2012). This section will focus on one of the therapies proposed to target TRD, which is Transcranial Magnetic Stimulation (TMS).

### **2.3.1 Pharmacological Treatment**

With the discovery of imipramine in the mid-1950s, pharmacological treatments for depression, specifically antidepressant medications (ADM), have become the current standard for acute treatment

(Derubeis, Siegle, & Hollon, 2008; Wong & Licinio, 2001). The main goal of these treatments is to alleviate the negative effects of depressive symptoms. Given this goal, response has been defined as a noticeable improvement, as measured by 50% reduction of depression rating scales while remission is defined by a near absence of symptoms (Derubeis et al., 2008). Given these definitions and the reliance on the pharmacological agent, even if remission is achieved there remains a high risk of return of symptoms within the same episode (relapse) if the patient reduces or discontinues their medication. For this reason, patients are advised to continue with the treatment even after achieving remission with ADM for at least six months; six months after remission is the period with the greatest vulnerability for relapse (American Psychiatric Association, 2000; Derubeis et al., 2008; Hollon & Thase, 2002).

#### *2.3.1.1 Pharmacological Treatment of MDD*

There are numerous ADMs available for the treatment of MDD. These medications fall under the main classes of: monoamine oxidase inhibitors (MAOIs), tricyclic antidepressant (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin/noradrenaline reuptake inhibitors (SNRIs), and dopamine reuptake inhibitors (DRIs; Derubeis et al., 2008). MAOIs and TCAs constitute the older types of ADMs, while SSRIs, SNRIs, and DRIs are treatments that have been most recently developed. Of these treatments, SSRIs have been the most widely prescribed in recent years with the SNRIs increasing in popularity as well (Derubeis et al., 2008).

These medications have been demonstrated through research in humans and animals to alter the regulatory process in monoamine systems and the associated neurotransmitters, specifically serotonin, noradrenaline, and dopamine. Changes in these neurotransmitters have been implicated in the pathological state and patterns in depressive episodes, such as causing a decrease in amygdala activity, reduction of neurogenesis in the hippocampus, and impacting higher cortical processes (Derubeis et al., 2008; Sheline et al., 2001; Warner-Schmidt & Duman, 2006). ADMs affect the neurotransmitter degradation (MAOIs) or reuptake (TCAs, SSRIs, and SNRIs) throughout the limbic system and other areas involved in mood regulation, appetite, sexual response and interest, and sleep (Derubeis et al., 2008;

Hollon & Thase, 2002). These ADMs do not act purely by blocking neurotransmitter degradation or reuptake, rather there is a cascade of biochemical events that accompany ADM action (Hollon & Thase, 2002). For example, one such event includes regulation of gene transcription, resulting in changes in gene products and subsequent neurophysiological response from systems that control hormones or those that control the branching and pruning of neural network structures (Hollon & Thase, 2002).

### *2.3.1.2 Pharmacological Treatment of BD*

An important aspect of the pharmaceutical treatment of depression is the differentiation between BD and MDD, and how this impacts pharmacological treatment approach. Misdiagnosis of the MDE in BD as MDD and the use of an inappropriate pharmaceutical as treatment can greatly impact the course and cycle of manic and depressive episodes. For example, the use of an antidepressant monotherapy has been associated with an elevation in the rate of switch from a mood episode to a manic episode (Altshuler et al., 2006; Bond, Noronha, Kauer-Sant'Anna, Lam, & Yatham, 2008; Datto et al., 2016; Viktorin et al., 2014).

Given these differences, the pharmacological treatment of BD is often approached by using medications not employed in MDD. The recommended pharmacotherapy for BD is divided to address manic or mixed episodes, depressive episodes, and rapid cycling. For manic or mixed episodes, the medication prescribed is typically a mood stabilizer either with an adjunctive antipsychotic, such as lithium and an antipsychotic or valproate plus an antipsychotic, or in combination with another mood stabilizer (American Psychiatric Association, 2002; Hirschfeld et al., 2000; Hollon & Thase, 2002; McCormick, Murray, & Mcnew, 2015). Lithium has typically been the medication of choice for the treatment of mania associated with BD (Post, Leverich, Altshuler, & Mikalaukas, 1992). When BD patients do not respond to or tolerate lithium, anticonvulsant agents and antipsychotics are often employed as they have been efficacious in treatment of mania despite being developed originally for the treatment of disorders other than BD (Hollon & Thase, 2002). Due to the limitations associated with lithium, these two therapies are employed more frequently as maintenance therapies in BD (American

Psychiatric Association, 2002). There are, however, side effects associated with antipsychotics (such as the development of dyskinesia) and anticonvulsants (which can be toxic) that render these treatments only partially effective (Hollon & Thase, 2002). For the treatment of depressive episodes in BD, lithium or lamotrigine are employed (Hirschfeld et al., 2010). Occasionally, BD patients that do not respond to mood stabilizers or whose symptoms return after a period of successful treatment will have an antidepressant added to their treatment regime (Hollon & Thase, 2002). However, some researchers have found that use of an antidepressant as an adjunctive therapy to mood stabilizers was not associated with an increase in treatment efficacy in BD (Datto et al., 2016; Sachs et al., 2007) and use as a monotherapy increases the risk of switching to mania/hypomania (McCormick et al., 2015).

When examining the efficacy and safety of treating the two major BD subtypes, studies examining these two facets of BD II treatment are relatively less than those examining BD I pharmacological treatment (Datto et al., 2016). As a result, medications that have been found to be efficacious and safe in treatment of depressive episodes in BD I are often used to treat BD II. However, a medication that was successful in treatment of BD I depressive episodes may not be directly applicable in the treatment of depressive episodes in BD II given that there is greater chronicity and frequency in BD II than BD I (Datto et al., 2016). As such, there is an increased need in development of medications that are specified for one of the two subtypes and are separate from those used to treat MDD.

Overall, there remains large limitations in the treatment of BD through the use of pharmacotherapies. As found in MDD, there is a great deal of variability in response to the available medications for BD and many are only partially adequate. This variability is further complicated by noncompliance to treatment regimens and the associated decrease in responsiveness after an episode of noncompliance (Hollon & Thase, 2002). In all, development of more effective pharmacotherapies are needed in order to best address BD and its subtypes.

### *2.3.1.3 Limitations in Pharmacological Treatment*

Some researchers have proposed that by understanding the pathways and mechanisms that underlie antidepressant treatments, the understanding of biological foundations of depression can be substantially advanced (Wong & Licinio, 2001). However, there are many aspects of treatment response and success with ADM that create difficulties in this goal. One such difficulty is seen through examination of ADMs finding that they seem to act more as symptom-suppressors rather than symptom-curers (Derubeis et al., 2008). That is, so long as the ADM treatment is maintained, the symptoms will be suppressed and relapse will be prevented. If the therapy is not maintained, the likelihood of relapse increases and symptoms may occur. The remission with termination of treatment suggest that the causal mechanism of depression is not changed but merely moderated and patients remain at risk of relapse if this moderation is removed (Derubeis et al., 2008). While the symptom-suppression by ADMs does provide some insight into the areas and systems of the brain impacted, the information gained has limitations and aspects missing that underlie the causative mechanism or system that leads to depression. Additionally, the selection of ADM and its success is particular for each patient, with no one drug being effective for the treatment of depression in all individuals. The choice of ADM depends on factors such as: likelihood of a particular side effect, personal and familial treatment history, safety in dose, and expense (Hollon & Thase, 2002). The variability in treatment response to different types of ADMs in combination with the variation in which neurotransmitter each ADM targets further complicates the goal of understanding the biology of depression by examining the action of ADMs. While each ADM has a specific target, the variability of action in a given individual does not allow for a clear picture of the etiology or action of depression when applying this information to the general population of depressed patients. In all, the examination of the pathways and mechanisms of ADMs may further the understanding of depression, yet there is still information missing from this examination.

### **2.3.2 Psychotherapy Treatment**

While ADM is often considered and used as a first-line treatment, there are a number of other treatments that are effective in the treatment of depression. Psychotherapy is a broad group of therapies

that have been examined and implemented in the treatment of depression and these include: interpersonal therapy (IPT), cognitive behavioral therapy (CBT), behavioural activation, and mindfulness-based therapies to name a few (Derubeis et al., 2008). Direct comparison of psychotherapy to pharmacological therapies finds no major differences between these two therapies and their effectiveness, though there is some evidence that the effects of psychotherapy are longer lasting than the effects of pharmacotherapy (Cuijpers, 2017). As well, CBT treatments are particularly favorable when contrasted to pharmacotherapies due to the relative lack of side-effects or complications associated with the treatment regime. In further comparison of pharmacotherapy to psychotherapy, there are consistent findings of significantly more effective outcomes when the two therapies are combined as opposed to either therapy alone (Cuijpers, 2017; Hollon & Thase, 2002).

Additionally, there is little difference in the effect of psychotherapy between BD and MDD individuals and as such the same psychotherapy treatments are suggested to be effective in both BD and MDD (Cuellar et al., 2005). Given the similarity, the psychotherapy/psychosocial treatments addressed and examined here will be applied to both MDD and BD and both disorders will be addressed through the general term “depression” throughout the section.

### *2.3.2.1 Psychotherapy Example: Cognitive Therapy*

CBT is one of the best-known and widely tested groups of psychotherapy treatments for depression (Derubeis et al., 2008). Cognitive therapy (CT) is a type of CBT therapy that has also been examined extensively in the literature and was one of the earliest CBT interventions (Hollon & Thase, 2002). CT was developed in the 1960s by A.T. Beck based on the premise that inaccurate beliefs, maladaptive information processing, and a negative cognitive bias have a causal role in depression (Derubeis et al., 2008). CT was developed with the intention of addressing how an individual interprets events and responds to these events by examining the thoughts, images, and beliefs that accompany and precede the experience of a negative event and the associated upsetting emotions (Derubeis et al., 2008; Hollon & Thase, 2002). The main goal of CT is to correct the maladaptive thinking patterns along with

reduce the experience and beliefs associated with distress and reduce the risk of relapse (Derubeis et al., 2008).

Many studies have demonstrated that CT is indeed effective for the treatment of acute depression and this treatment has enduring effects beyond the termination of treatment, unlike pharmacological therapies (Derubeis et al., 2008; Hollon & Thase, 2002). The enduring effects of CT suggest that while the acute response to CT and ADMs might be due to similar changes in the brain, CT is able to produce changes in mechanisms that ADMs cannot yet make (Derubeis et al., 2008). However, this is not the case in more severe forms of depression. While CT and other CBTs are as effective as pharmacotherapies in acute or less severe depression, the efficacy of this therapy in severe depression has been found by some researchers to be less than that of pharmacotherapies (Elkin et al., 1989; Hollon & Thase, 2002). These results have been contested by some researchers who found that CT did just as well as patients on medication (DeRubeis, Gelfand, Tang, & Simons, 1999; Hollon & Thase, 2002). This difference may be due to variation in patient population, sample size, and therapist's expertise (Hollon & Thase, 2002).

Regardless of the differences found in the literature with regards to the application of CT and CBTs to severe depression, interest in and application of these therapies continues. The indication that CBT treatments may have preventative effects for relapse has drawn many to this therapy style (Hollon & Thase, 2002). While these results are promising and attractive, it is important to note that it is rare for even the most efficacious treatments to have long-lasting benefits and while they offer control for symptoms, they do not fully resolve the underlying causes (Hollon & Thase, 2002). While CT has been shown to act on mechanisms that ADMs do not (Derubeis et al., 2008), this action remains symptom-suppressing rather than curative. Nonetheless, with further exploration and development of CBTs, the treatment of depression and prevention of remission could be further improved.

### **2.3.3 Transcranial Magnetic Stimulation**

Treatment-resistant depression (TRD) is a growing issue in the clinical field as more individuals show unresponsiveness to ADMs. The main alternative for TRD has been electroconvulsive therapy

(ECT); however, the side effects and the induction of a seizure have lead patients to opt for less invasive therapies (Chung, Hoy, & Fitzgerald, 2015). One alternative therapy has been transcranial magnetic stimulation (TMS) and as such, the use and research of TMS in the treatment of depression has increased immensely over the last few decades (Arns, Drinkenburg, Fitzgerald, & Kenemans, 2012; Downar & Daskalakis, 2013).

Introduced in 1985 (Cusin & Dougherty, 2012), TMS involves stimulation of brain regions – typically the dorsolateral prefrontal cortex (DLPFC) - through an intact scalp by producing a magnetic field that passes through the skull and induces electrical activity in the underlying neurons, generating action potentials (Bestmann et al., 2008; Chung et al., 2015). The main form of TMS used is called repetitive TMS (rTMS), also called high frequency rTMS since the stimulus is above 1 Hz. rTMS involves delivering a stimulus at 120% above the patient’s motor threshold at 10 pulses per second for 6 seconds with a 24 second interval period for 37.5 minutes (Becker, Maley, Shultz, & Taylor, 2016). rTMS is thought to stimulate cortical firing and therefore modulate the circuit (Becker et al., 2016; Cusin & Dougherty, 2012). Early on, a number of studies found that stimulation of the DLPFC through rTMS cause normalization in this area and these researchers found a correlation between this normalization and antidepressant medication (Chung et al., 2015). However, examination of the literature shows that early rTMS protocols had less of an antidepressant effect when compared to the more recent protocols, resulting in variability in the literature (Chung et al., 2015; Gross, Nakamura, Pascual-Leone, & Fregni, 2007).

Given this variability, a more effective manner of modifying brain activity through TMS was developed and called intermittent theta–burst stimulation (iTBS). This protocol is similar to rTMS; however, the pulse is applied in 2 second bursts at 50-100 Hz every 10 seconds for a total of 190 seconds over a total treatment time of 15 minutes (Chung et al., 2015). iTBS is applied in either a bilateral or unilateral fashion to the DLPFC - though other areas have been investigated in the application. In a recent study by Plewnia et al., (2014), the efficacy of iTBS in treatment of moderate to severe major depression

was examined, and found a reduction of at least 50% on the Montgomery-Asberg Depression Rating Scale (MADRS) in 56% and a remission in 44% of the active depressed group (n=32; Plewnia et al., 2014). While other studies have found similar findings, these have all been preliminary studies with small population sizes. Larger randomized control trials are needed in order to confirm these results and provide stronger support for the antidepressant effect of iTBS.

Although TMS therapies have less evidence of antidepressant effectiveness when compared to ECT and ADMs (American Psychiatric Association, 2013), rTMS and iTBS are less invasive and painful therapies with minimal side effects and a decreased risk of cognitive impairment or physical distress (Bestmann et al., 2008; Ozekes, Erguzel, Sayar, & Tarhan, 2014). The most common side effects experienced are headaches during and after treatment, and facial pain due to stimulation of the motor cortex and a resulting facial muscle twitch (Cusin & Dougherty, 2012). rTMS and iTBS differ in terms of one negative factor of the therapy, which is time commitment. rTMS sessions are approximately 30 to 60 minutes and take place 5 times a week for 4 to 5 weeks (Cusin & Dougherty, 2012). While iTBS does require 5 sessions a week for approximately 4 to 5 weeks, the sessions are only 15 to 30 minutes. This greatly reduces the length of each visit and the burden on the patient in terms of time management and commitment. The reduction of time commitment is more favorable to patients when given the option of rTMS or ECT. Overall, iTBS and rTMS are viable alternatives to the rather invasive ADMs and ECT in the treatment of depression and TRD.

## **2.4 Olfaction**

From an evolutionary perspective, the olfactory bulb (OB) – the central relay of olfactory information in the brain – is one of the most primitive structures. The OB has given rise to the ancient limbic system, which is responsible for emotional processes and contributes to human survival (Croy et al., 2014; Joseph, 2013; Kohli, Soler, Nguyen, Muus, & Schlosser, 2016). Olfaction and an individual's olfactory functioning is often overlooked and deemed less essential compared to vision, hearing, and touch sensation. However, olfaction and the functioning of the olfactory pathway greatly impacts the way

in which an individual experiences and moves within their environment. For example, olfactory dysfunction has a significant impact on quality of life by altering the way in which an individual experiences their sensory environment, how they taste and experience food, and acts as a warning mechanism in situations of danger. More recent research has also found that olfaction has a role in depression, with olfactory dysfunction occurring in depressed patients. However, there remains a lack of agreement as to what extent olfactory dysfunction occurs and if it is related to the disease state and not another factor.

#### **2.4.1 The Olfactory Pathway and Processes**

Olfactory processes and anatomy can be divided into two specific types of processing: peripheral and central, with each type of processing corresponding with a specific area in the olfactory pathway. At the level of the nasal epithelium is the peripheral processing, which begins with binding of the odorant to a receptor in the nasal epithelium after diffusing through the mucus lining of the epithelium (Patel & Pinto, 2014). This processing encompasses olfactory detection, sensitivity, and acuity, which are measured empirically using measurements of olfactory threshold (Atanasova et al., 2008; Cumming, Matthews, & Park, 2011; Negoias et al., 2010). Changes or deficits in peripheral processing reflect impairments in processing at the level of the nasal epithelium, such as changes in the olfactory receptors (Atanasova et al., 2008).

Once information is received at the peripheral level, it is then moved through olfactory neurons located in the neuroepithelium to form nerve bundles that cross the cribriform plate and synapse on the glomeruli of the olfactory bulb (Patel & Pinto, 2014). At the level of the olfactory bulb, a signal transduction occurs and the information is passed to other areas in the central nervous system, such as the piriform cortex, amygdala, and hippocampus (Patel & Pinto, 2014). Of the regions connected to the olfactory bulb, the piriform cortex is the main recipient of inputs and is the largest area in the central olfactory areas (Patel & Pinto, 2014). A number of higher order projections from the olfactory bulb converge on the orbital prefrontal cortex, agranular insula, thalamus, hypothalamus, basal ganglia,

amygdala subnuclei, and the hippocampus (Gottfried, 2006; Patel & Pinto, 2014); many of these areas are included in the limbic system of emotional regulation. Central processing is at the level of the OB and these higher order projections. Central processing includes the cognitive processes associated with olfaction, such as discrimination, memory, identification or the ability to label an odor (Atanasova et al., 2008; Cumming et al., 2011; Lombion-Pouthier et al., 2006; Negoias et al., 2010; Pause et al., 2001; Rupp, Fleischhacker, Kemmler, & Al, 2005; Serby, Larson, & Kalkstein, 1990). Central processing is measured using methods examining olfactory identification, which is the ability to identify and name a target scent, and discrimination, which is the ability to distinguish between two different target scents. Deficits in higher order brain processes occur when there are deficits in central processing, especially in the cortical and limbic processing (Atanasova et al., 2008).

#### **2.4.2 Olfactory Dysfunction**

Olfactory dysfunction and impairments are classified into three broad categories based on the origin of the dysfunction: conductive losses due to obstruction of the nasal passage; sensorineural causes due to damage to the olfactory neuroepithelium, and central processing dysfunction due to damage to the central nervous system or central nervous system disease (Patel & Pinto, 2014). Olfactory dysfunction is further characterized on the basis of perpetual symptoms. The first classification is dysosmia: difficulty identifying odors. Dysosmia is further classified down into anosmia (the inability to detect odors), hyposmia (the reduced ability to detect odors), and hyperosmia (an increased sensitivity to odors; Patel & Pinto, 2014; Whissell-Buechy & Amoore, 1973). Anosmia is likely due to a lack of specific olfactory receptor genes or signaling pathways located downstream from the receptor (Olender, Lancet, & Nebert, 2008; Patel & Pinto, 2014). The second classification is parosmia: the sensation of an odor is perceived as different than the typical odor for that specific substance. And third is phantosmia: perception of an odor when none is present (Patel & Pinto, 2014). Olfactory dysfunction is most common in aging individuals, though there are a number of pathophysiological and traumatic changes that can cause dysfunction. These

include: upper respiratory tract infections, inflammatory disease like rhinitis or sinusitis, trauma like skull fractures, and sinonasal disease (Patel & Pinto, 2014).

## **2.5 Depression and Olfaction**

As research focusing on the brain-wide impact of depression increases, connections have been found between depression and other processes in the brain. In recent years, cognition has been a major area of interest within the field of depression research. However, other processes related to cognition have also been found to be impacted by depression; one such process is that of olfactory functioning. While this connection at first may seem unrelated, olfactory functioning is an important aspect of daily life and the quality thereof (Kohli et al., 2016). Within the literature, there is much discrepancy as to how olfactory functioning is altered in depressed patients with a great deal of mixed results as to what aspects of olfaction are impaired, if any.

### **2.5.1 Olfaction and Depression: The Brain Regions Between the Two**

An understanding of the overlap of brain regions related to depression and olfaction is required to better elucidate the relationship between the two. The major areas involved in olfaction have been primarily linked to the limbic system, a set of brain structures involved in behaviour, emotion, motivation, and long-term memory in addition to olfaction (Swenson, 2006). The connection between olfaction and the limbic system is of a primitive nature. With evolution of the human brain these connections have lessened but projections to the core limbic structures remain (Kohli et al., 2016). The maintenance of such connection has been further confirmed by recent neuroanatomical and imaging studies, demonstrating an overlap of olfactory and limbic neural structures in humans and the connection between emotions and odors (Lahera et al., 2016). As confirmed by such imaging studies, the core limbic structures with which there remains projections are the hypothalamus, amygdala, orbitofrontal cortex, anterior cingulate cortex, and the insular cortex (Atanasova et al., 2008; Kohli et al., 2016; Lane et al., 1997; Zald & Pardo, 2000).

Not only are there projections between these core structures and olfactory cortices, but the anatomical location of the primary and secondary olfactory cortices are close and linked to structures of the limbic system. The primary relay that composes the majority of the primary olfactory cortex is the piriform cortex, which also sends signals to the orbitofrontal cortex (a higher order structure) through the amygdala (Kohli et al., 2016). Next, the secondary olfactory cortex is located in the input section of the hippocampus (Kohli et al., 2016; Soudry, Lemogne, Malinvaud, Consoli, & Bonfils, 2011). Recent studies examining the representation of odor perception show that odor intensity is associated with activity in the piriform cortex and amygdala, and odor memory, discrimination, and identification are associated with the piriform cortex (Atanasova et al., 2008; Zald & Pardo, 1997)).

The olfactory pathway is unique in terms of its ipsilateral nature and overlap with the limbic system (Patel & Pinto, 2014). This overlap with limbic structures and the close connections with the amygdala and hippocampus may explain the ability of odor to impact emotional processing (Gottfried, 2006; Kohli et al., 2016; Patel & Pinto, 2014) and may underlie the relationship between depression and olfaction.

### **2.5.2 Olfactory Dysfunction in MDD and BD**

Previous research examining olfactory dysfunction in psychiatric disorders has found an impact in several psychiatric disorders such as psychoses and schizophrenia (Atanasova et al., 2008; Kopala et al., 1994), anorexia nervosa (Atanasova et al., 2008; Kopala et al., 1995), and panic disorder (Atanasova et al., 2008; Kopala & Good, 1996). The findings of a dysfunction in these disorders has lead researchers to examine olfactory dysfunction in further psychiatric disorders, depression in particular. However, despite the growing interest in this area, there remains inconsistencies with regards to the conclusions of how depression impacts olfaction and the number of studies examining such are limited. While the majority of studies find that there is a significant difference between depressed and controls, no one particular aspect of olfactory functioning was found to be impacted in this disease state (Atanasova et al., 2010; Clepce et al., 2010; Croy et al., 2014; Gross-Isseroff et al., 1994; Lahera et al., 2016; Lombion-

Pouthier et al., 2006; Negoias et al., 2010; Postolache et al., 2002; Zucco & Bollini, 2011). A major obstacle in depression research is the inability to display and accurately measure how the higher cognitive human processes, such as motivation and self-esteem, are altered in this condition when using only an animal model is available (Wong & Licinio, 2001). Given that olfactory functioning integrates higher cognitive processes, the examination of this particular aspect in humans may reduce this obstacle by providing a non-invasive way in which to examine higher cognitive processes in depression.

The aspect of olfactory functioning most commonly found to be impacted and significantly different between depressed and non-depressed controls was olfactory threshold, or olfactory sensitivity as termed in some studies. A number of studies found a significant difference between the olfactory threshold of depressed individuals and non-depressed controls (Croy et al., 2014; Hardy et al., 2012; Pause et al., 2001; Swiecicki et al., 2009); all finding that the threshold was significantly lower in depressed participants than the non-depressed controls. Next, while identification was the most commonly studied aspect of olfactory functioning and examination of this aspect also found significantly lower identification scores in depressed compared to non-depressed controls, fewer studies found a significant difference. With regards to discrimination, one study found a significant difference between depressed and non-depressed controls, with depressed scoring lower compared to non-depressed controls (Croy et al., 2014). The findings of these studies and the differences in such, highlights the division in the literature as to which aspect of olfaction is altered. While the majority of the literature finds that there is a significant change in olfaction in depression, if that change is at the peripheral level (as evidenced by an alteration in threshold) or at the central level (as evidenced by an alteration in discrimination and identification) is not clear. Although some studies examine other aspects of olfaction - such as intensity, hedonics, etc. - only threshold, discrimination, and identification are focused on given their clear roles in and separation into the olfactory processes.

With regards to BD, research on olfactory dysfunction in BD has been neglected until recently. This is due, in part, to earlier findings of relatively intact olfactory functioning in persons with BD compared to other disorders (Amsterdam, Settle, Doty, Abelman, & Winokur, 1987). However, more

recent research has shown that there is indeed an olfactory dysfunction in patients with BD. For example, Hardy et al. (2012) found an increase in odor sensitivity related to depressive symptoms and a decrease in odor sensitivity related to manic symptoms. Similarly, Cumming et al. (2011) examined a sample of BD patients and found a deficit in odor identification. The results of these studies mirror a similar pattern of incongruity within MDD research of conflicting findings as to which aspects of olfaction are altered and which are not. A more recent study conducted by Lahera et al. (2016) found results similar to that of Cumming et al (2011), such that the olfactory identification of BD patients was significantly impaired compared to that of healthy controls using the University of Pennsylvania Smell Identification Test (UPSIT). Additionally, Lahera et al. (2016) examined the social cognitive functioning of participants, finding significant relationships between the olfactory identification score and theory of mind, facial emotion recognition, and general cognition. The findings of this study present further evidence of the link between higher olfactory/central processes – such as olfactory identification and discrimination – and cognitive impairment in a mental disease state.

### **2.5.3 Treatment for Depression and the Impact on Olfaction**

Of the available literature focusing on olfactory functioning in depression, very few studies examined how treatment impacts olfactory functioning in depressed individuals. Only a handful of studies employed an experimental design with an intervention for depression of either ADM (Clepece et al., 2010; Gross-Isseroff et al., 1994), psychotherapy (Croy et al., 2014), or a combination of the two (Pause et al., 2001).

Of those studies that examined the role of treatment, only one study examined the impact of psychotherapy. Croy et al. (2014) examined how the treatment of depression with psychotherapy impacted the olfactory functioning in depressed compared to non-depressed (who did not receive psychotherapy) with use of the Sniffin' Sticks olfactory testing paradigm. At baseline, the researchers found lower odor scores in olfactory threshold, discrimination, and identification. However, only discrimination was significantly lower in depressed compared to non-depressed controls. After

psychotherapy, no significant difference regarding any aspect of olfactory functioning was found; suggesting that successful treatment of depression impacted the olfactory dysfunction.

Within the literature, two studies used ADM in the treatment of depression (Clepce et al., 2010; Gross-Isseroff et al., 1994). Both of these studies found significant changes and improvements in olfaction scores after treatment, though which aspect of olfaction improved was different. Gross-Isseroff et al. (1994) examined threshold scores for two odorants at varying concentrations and found no significant difference between depressed and non-depressed controls at baseline or 3 weeks. However, 6 weeks after treatment initiation, a significant improvement in sensitivity to one target odors was found. Similarly, Clepce et al. (2010) measured identification and found significantly lower identification scores in depressed at baseline compared to non-depressed controls. After treatment with ADM, there was a significant difference within the depressed group but no significant difference between the remitted group and non-depressed controls.

Of the studies employing an intervention, only Pause et al. (2001) examined how a combination of psychotherapy and antidepressant medication impact olfaction in depressed. The researchers found a strongly - though not significantly - reduced threshold in depressed before the initiation of a combination of psychotherapy and antidepressant medication. As well, the olfaction scores strongly correlated with the depression score of the Beck Depression Inventory. After treatment, no significant differences nor any correlations were observed between the depressed and control groups.

Examination of the impact of intervention on olfactory dysfunction is key to understanding the relationship between the two and the etiology of the dysfunction in the olfactory functioning of depressed individuals. Previous research examining the central olfactory processing change in schizophrenia after treatment has lead researchers to believe that antidepressant medication may improve olfactory functioning in patients with depression (Croy et al., 2014; Gross-Isseroff et al., 1994; Naudin et al., 2012; Yuan & Slotnick, 2014). As described by Kohli et al. (2016), these researchers are likely applying the assumption of a reciprocal relationship between olfaction and depression in patients with primary depression. Integration of this assumption and the results of the four studies lead to the belief that the

treatment of depression improves not just the depressive symptomology but the olfactory dysfunction as well. While these studies and the results require further replication and validation, they present a point from which further research and a better understanding of this reciprocal relationship can be developed.

Within the literature examining the impact of treatment on olfactory dysfunction, there remains no studies that have focused on the impact of TMS for depression, neither rTMS nor iTBS, on olfactory functioning in depressed participants. The absence of research on TMS and olfactory functioning means that the relationship between treatment and olfactory functioning in MDD or the subset of TRD, that are often referred to rTMS/iTBS, is missing or reduced within the available literature. Many of the studies focusing on the impact of medication or psychotherapy for depression on olfaction do not include patients with TRD. A study examining TMS and olfactory functioning associated with depression would allow for examination and integration of olfaction in TRD. In all, expansion of the treatment methods other than psychotherapy and ADMs would allow for a better perspective and understanding of the relationship between depression and olfaction.

### *2.5.3.1 Neuroplasticity and Olfaction*

Response to treatment and improvement in depression has been linked and attributed to changes in neuroplasticity - the formation, migration, and proliferation of synaptic connections. The mechanism of action of psychiatric and psychotropic drugs – such as antidepressants and antipsychotics – are likely mediated by neuroplasticity, which impacts the clinical efficacy. The same mechanism of action has been attributed to TMS. Neuroplasticity before and after treatment is measured using a neurotrophin related to neuronal survival, synaptic signaling, and synaptic consolidation called brain-derived neurotrophic factor (BDNF; Brunoni, Lopes, & Fregni, 2008). BDNF is measured through blood serum analysis and has been examined in a number of psychiatric disorders (Brunoni et al., 2008; Furtado et al., 2013). Previous research examining BDNF in MDD have found correlations between the two, with lower BDNF serum levels in MDD patients compared to healthy controls and an increase in BDNF levels after treatment with ADMs (Aydemir, Deveci, & Taneli, 2005; Brunoni et al., 2008; Karege et al., n.d.). In particular,

preclinical evidence examining the reduction of volume in certain brain areas due to suppression of neurogenesis in adult humans has found a reversal in volume loss following the use of ADMs in the hippocampus - an area particularly vulnerable to volume loss in MDD (Czeh & Lucassen, 2007; Furtado et al., 2013; Samuels & Hen, 2011; Ueyama et al., 2011).

With regards to TMS, the majority of the research examining the impact of TMS on BDNF levels has been conducted in animals, with a handful of studies also examining the BDNF levels in humans. In animal models of TMS, rTMS specifically, increases in neuroplasticity were found in areas distant from the site of stimulation (Furtado et al., 2013; Gersner, Kravetz, Feil, Pell, & Zangen, 2011; Speer et al., 2000). Similarly, preliminary findings in humans show that high frequency and low frequency rTMS are able to increase BDNF serum levels (Furtado et al., 2013; Yukimasa et al., 2006; Zanardini et al., 2006). A recent study conducted by Furtado et al., (2013) examined the impact of rTMS on the neuroplasticity in the two areas primarily impacted in depression: the amygdala and hippocampus. The researchers found an increase in left amygdala volume of individuals who were responsive to rTMS when compared to non-responders. With regards to the hippocampus, the researchers found no changes in hippocampal volume before or after rTMS in responders. This suggests that though no change in hippocampal volume was found, rTMS may have a neuroprotective role in preventing further reduction of the hippocampus. The researchers concluded that rTMS may promote the same mechanisms of neuroplasticity as seen with ADM (Furtado et al., 2013).

Given the connection of the amygdala and hippocampus to the olfactory bulb and the overlap of areas between depressed and controls, it is likely that neuroplasticity plays a role in olfactory dysfunction in depression. The olfactory system is a highly plastic system that displays a great deal of plasticity (Kollndorfer et al., 2014) and an impact on the plasticity in the brain is likely to affect many regions connected to the main point of decreased plasticity. As such, recent research examining the olfactory bulb in animal models have found a similar reduction in volume of the OB and decreased neurogenesis after periods of sensory deprivation (Croy et al., 2013; Cummings, Henning, & Brunjes, 1997). These levels

are restored after stimulation. Additionally, researchers have demonstrated that deficits in the olfactory bulb impact the hippocampus and can induce a depressed mood by destroying/removing the olfactory bulb – more commonly called an olfactory bulbectomy. Similar to the effects of TMS and ADM, chronic application of ADMs in olfactory bulbectomized rodents reversed the effects of the bulbectomy and the associated depression (Breuer, Groenink, Oosting, Westenberg, & Olivier, 2007). Given the results of these studies, it is likely that treatment for depression in humans can restore the neurogenesis and increase neuroplasticity in the olfactory bulb, leading to an improvement in olfactory functioning.

## **2.6 Limitations and Future Directions**

### **2.6.1 Limitations in the Literature**

Given the limited number of studies examining the relationship between olfaction and depression, it is no surprise that there are a number of associated limitations. In particular, there are a number of limitations associated with the methodology and results of these studies that may contribute to the variability in the results reported throughout the literature. A recent meta-analysis conducted by Kohli et al., (2016) identified such limitations and suggested that the variations may be due to differences in patient populations, variation in the olfactory measurements used, small sample sizes, and some studies focusing on patients with primary olfactory dysfunction while others focus on patients with depression as the primary diagnosis.

#### *2.6.1.1 Methodology: Olfactory Measure*

One aspect of the literature that may be greatly contributing to the variability in the results is the inconsistency in the methodology employed by researchers and the aspect of olfactory functioning being measured. Few studies examined the three main aspects of olfaction; these being threshold, discrimination, and identification. Of the studies available in the literature, two studies (Croy et al., 2014; Negoias et al., 2010) measured all three aspects of olfaction and were able to compare olfaction at both the central and peripheral level of processing. Between the two studies, both employed Sniffin' Sticks

extended test to examine the main aspects of olfaction but differed in the participant gender, number of times assessing olfactory functioning, and if an intervention for depression was part of the methodology. Despite the differences in methodology, both found a significant difference between depressed patients and non-depressed control at baseline with regards to one aspect of olfaction. Negoias et al. (2010) found a significant difference in the threshold score of depressed patients and non-depressed controls, with depressed having a threshold score lower than controls. Conversely, Croy et al., (2014) demonstrated significant differences between the discrimination ability of depressed patients compared to those of controls at baseline and demonstrated no significant difference upon completion of a depression intervention. Although these studies differ on what area of olfaction and, therefore, what olfactory process was impacted, both provide further support for examining both central and peripheral processing changes in order to better understand and provide a more concrete conclusion as to the relationship between depression and olfaction.

With regards to methodology, the most commonly employed are Sniffin' Sticks and UPSIT, while the remaining studies examined olfactory functioning using a lab-made and project specific olfactory test. Variation within testing procedures likely contributes to the inconsistency in the literature, the lack of continuity in the results, and the variation in what aspect of olfaction is being measured. Should researchers adhere to one or two specific methodologies measuring the three main aspects of olfaction, greater consistency could be introduced in the literature and possibly allow for a better understanding of the olfactory dysfunction in depression.

#### *2.6.1.2 Methodology: Experimental Design*

Many of the studies examining olfactory functioning in depression measure olfaction only once. Very few studies examine olfactory functioning in depression over time or over the course of treatment. While some researchers have found no significant difference between depressed patients and non-depressed controls, in these studies many of the patients were already receiving treatment -often in the form of ADMs. How olfaction changes over the course of this treatment was not examined. One of the

reasons for the variation and confusion in the literature might be that olfaction is not examined longitudinally with the progression of depressive episodes. Employing a methodology that includes an intervention for depression and measurement of olfaction at baseline and after treatment of depression would allow for a more efficient and well-rounded examination of olfactory functioning in depression and how changes in depression impact changes in olfactory functioning. Measurement at two time points could reduce the need for studies that examine olfaction at only baseline by providing the same information and would provide better insight as to how olfaction changes in conjunction with changes in depression.

#### *2.6.1.3 Methodology: Age of Participants*

In addition to inconsistency in the methodology employed and which aspects of olfaction are measured, participant age and the age range of participants may also have greatly impacted the results. Particularly, results may have been impacted by the inclusion of participants over the age of 60 and the lack of comparison of older participants to younger participants. A consequence and common occurrence associated with aging is a decrease in olfactory functioning, likely resulting in a strong influence on the results of psychophysical tests of olfaction (Doty & Kamath, 2014). In individuals 65 years old, the prevalence rate of olfactory dysfunction is 13.9% with the rate increasing to over 50% in individuals 65-80 years old and 80% in the population over 80 years of age (Attems, Walker, & Jellinger, 2015; Doty & Kamath, 2014; Lafreniere & Mann, 2009; Schubert et al., 2012). The increasing prevalence of olfactory dysfunction in the aging population may impact and interfere with the results of studies examining depression that include those over the age of 60. Inclusion of such individuals increases the potential that the olfactory dysfunction observed may be due to age-related decline in olfaction rather than depression. This would interfere with the examination of the disease-state of depression and introduces a confound that could only be eliminated by further limiting the participant age range and inclusion criteria. To avoid and reduce the potential confound of age, limiting the age range of participants to a maximum age

between 50 or 60 years old would allow for a focus on the influence of depression rather than other age-related influences.

### **2.6.2 Olfactory Dysfunction and Depression in Clinical Practice**

Though the literature presents mixed conclusions as to which aspect of olfaction changes in depressed individuals, the presence of a general alteration to olfactory functioning requires further examination at the clinical level to better understand the individual experience of depression and the associated sensory hedonics. Integrating a measurement of olfactory functioning at the onset of a depressive episode, throughout the treatment for said episode, and beyond could provide further insight into the severity and progression of the individual depressive episodes and the history of depression overall. Based on the findings of those studies that examined olfaction before and after treatment for depression (Clepece et al., 2010; Croy et al., 2014; Gross-Isseroff et al., 1994; Pause et al., 2001), measurement of olfactory functioning could provide insight as to treatment response and remission. In all, further sensory measures would allow a greater and more in-depth picture of the underlying mechanisms of hedonics and the experience of depression.

Although it is a sense that individuals often take for granted and rarely notice when there is a slight change, olfaction has a great impact on the quality of life through involvement in eating, appetite, food quality, enjoyment of one's surroundings, and it is also linked to memory storage and recall (Hummel & Nordin, 2005; Negoias et al., 2010). Studies examining primary olfactory dysfunction has shown the impact loss of smell has on enjoyment of preparation and affective experience of food, particularly with detection and avoidance of spoiled or inedible foods (Croy et al., 2014; Kohli et al., 2016). Application of this research to a population with depression, who also experience a decrease in appetite and enjoyment of food, suggests that these declines may be due in part to a decline in olfactory functioning. In addition to the nutritional deficits, this loss of appetite and anhedonia associated with appetite and eating also plays a role in the reduction of socialization of depressed individuals. Improving the understanding of the relationship between olfaction and depression at the clinical level has the

potential to provide a better understanding of how quality of life is impacted in depression. Identifying these deficits in the clinical practice would allow for adjustment and further focus on providing an enriched sensory and emotional environment – especially regarding food and smells that have positive associations - that could improve the quality of life of depressed in- and out-patients.

## **2.7 Goals and Directions of this Thesis**

The purpose of this thesis is to address a number of the limitations within the literature with the goal of providing more insight as to the relationship between olfaction and depression. As addressed in section 2.6.1.1, many studies focus on only one or two of the main aspects of olfaction. This limited focus often means that either peripheral or central processing is examined, while one of the main aspects of olfaction is not focused upon. To address this, we have employed the Sniffin' Sticks Extended paradigm measuring threshold (which will examine peripheral processing), and discrimination and identification (which will examine central processing). Based on the relationship between the two processing streams and higher cognitive processes, it is likely that threshold scores – given that they reflect the peripheral level of processing – will be no different between the threshold at baseline and after treatment. As well, it is unlikely that there will be a significant difference between depressed and controls with regards to this measure. Those reflecting the central level of processing (discrimination and identification) reflect better the relationship between depression and olfaction in terms of higher cognitive processes and are therefore more likely to be impacted in depression. We will compare the olfactory functioning on the three olfactory measures and compare this to that of non-depressed controls in order to determine if there is a significant difference between the two groups.

Further, as mentioned in section 2.6.1.2, many studies do not examine the impact of treatment on olfactory functioning in depressed participants. In order to address this and provide further insight, we will examine the olfactory functioning in depressed before and after treatment for depression. For this study, we will examine patients receiving a course of iTBS. Given the lack of studies in the literature that examine how iTBS impacts olfactory functioning in depressed and, in the case of some patients, TRD.

iTBS is one of the most efficacious treatments for depression that causes an increase in neuroplasticity in areas distant to the main target area. Given this information in relation to the overlap between depression and olfactory functioning, it is likely that iTBS could affect either the olfactory bulb directly or indirectly by increasing the neuroplasticity and neurogenesis in areas of depression that are linked to olfaction. Although we will not be measuring neuroplasticity directly, the examination of the olfactory functioning before and after iTBS would allow for broader insight into the effects of iTBS on olfaction in depression. Once a broad relationship has been established, future studies could integrate a measure of neuroplasticity in the form of serum level BDNF.

In the examination of olfactory dysfunction in depressed individuals receiving iTBS, we propose a number of objectives and hypotheses as to the outcome of the study. Our primary objective is to determine if there is a significant change in the olfactory functioning in participants with MDD or BD following a scheduled course of iTBS compared to non-depressed controls. From our primary objective, we have three hypotheses. First, we hypothesize that olfactory functioning will be decreased in participants with MDD or BD. Second, we hypothesize that depressed will improve in olfactory functioning after the course of iTBS when compared to baseline. Finally, we hypothesized that there will be a significant difference between the depressed and non-depressed control groups at baseline but little to no difference after iTBS. Our secondary objective is to determine if this improvement is correlated with an improvement in depression scores over the course of treatment. From this secondary objective, we hypothesize that an improvement in olfactory functioning will be correlated with an improvement in depression severity.

## Chapter 3: Methodology

### 3.1 Participants

#### 3.1.1 Overview

The current study was conducted at Providence Care Hospital through the Centre for Neuroscience Studies and Department of Psychiatry of Queen's University, Kingston, Canada. The study was approved by the Queen's University Health Sciences and Affiliated Hospitals Research Ethics Board (HSREB). Participants were informed they would be required to smell different compounds and were given full details about the experimental protocol before commencement. All participants provided written consent before participating in the study. All data was collected and stored at Providence Care Hospital, previously Providence Care - Mental Health Services.

A total of 42 participants, 28 depressed and 14 non-depressed controls, were invited to participate in the study (see figure 1.1 for an outline of participation). All depressed participants who were referred for iTBS at the Mood Disorders Clinic at Providence Care Hospital and had a current DSM-IV diagnosis of major depression (MDD) or bipolar disorder (BD) were approached for participation in the study. Depressed participants must have been between the age of 18 and 65 years old in order to avoid olfactory dysfunction due to age rather than depression. Participants were recruited from May 2016 to June 2017. Twenty in- and out-patients (11 females and 9 males, mean age  $47.25 \pm 11.98$ ) agreed to participate in the study and were measured at baseline. Two participants withdrew from the study and discontinued iTBS before all iTBS treatments had been completed. Therefore 18 were measured post-iTBS.

Healthy, non-depressed subjects were recruited from the community through referral from an associated study and were matched with the depression group for age and sex. Controls were between the age of 22 and 61 in order to best reflect the age of those in the depressed group. 11 participants agreed to participate with 2 withdrawing before the second appointment and 2 were measured at the second appointment but were deemed ineligible due to pregnancy and a recent MDE. The nine control participants

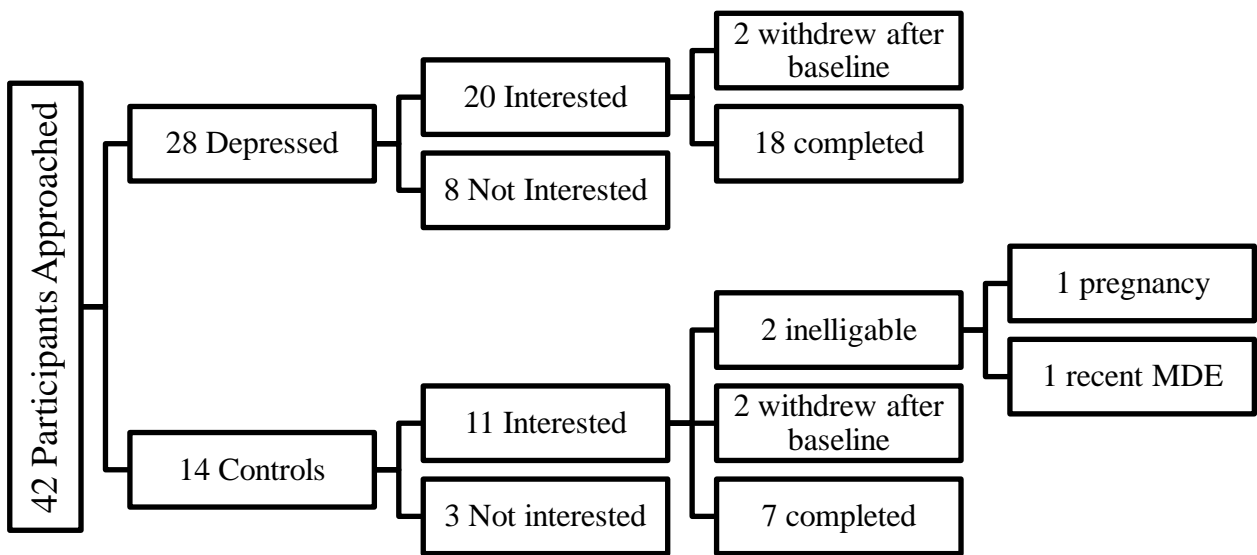
(5 females and 4 males, mean age  $46.76 \pm 12.96$ ) included in analysis had no self-reported history of psychiatric or neurological disorders.

All participants of both the depressed and control groups received small monetary sum as compensation for their time at the second visit. All participants completed a pre-screen questionnaire in order to determine eligibility for participation. The pre-screen covered all inclusion and exclusion criteria listed below.

### **3.1.2 Inclusion and Exclusion Criteria**

All depressed participants must be currently referred to Providence Care Hospital to receive iTBS, have previously been diagnosed with depression (major depressive disorder or bipolar disorder), have not received ECT or TMS ever or in the last 6 months, have no diagnosis of schizophrenia, schizoaffective disorder or other psychotic disorder, and no diagnosis of anosmia or other primary olfactory disorder. Control participants must not have a history of psychiatric or neurological disorders.

Exclusion criteria for all participants included: environmental sensitivities and allergies, current or previous upper respiratory infection(s) or physical trauma affecting sense of smell, no severe nasal or sinus disease, major medical conditions that impact sense of smell (ex. Addison's disease, Parkinson's disease, Huntington's disease, etc.), previous or current history of substance abuse impacting sense of smell, broken nose causing a deviated septum or congenital deviated septum, allergies with nasal symptoms, and trauma or stroke causing possible olfaction impairment. All participants in both groups must meet all criteria and have not stopped or started medication in less than 4 weeks since the first testing visit.



**Figure 1.1: Outline of Participants Approached and Number Completed**

## **3.2 Scales**

A number of scales were used to assess the prevalence and severity of depression, anxiety, and anhedonia in both depressed and control groups.

### **3.2.1 Researcher/Clinician Administered**

The primary scale employed was the Montgomery Asberg-Depression Rating Scale (MADRS; Montgomery & Asberg, 1979), a 10-item questionnaire assessing depression severity in the last two weeks based on the following symptoms: apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts. Each question is scored from 0 to 6, increasing in increments of 2 with 6 being the most severe and 0 an absence of symptoms in the category. MADRS scores of 0 to 6 indicate normal/symptom absent, 7 to 19 indicate mild depression, 20 to 34 indicate moderate depression, and above 34 indicates severe depression. The MADRS is administered by a trained researcher who also scores the symptom severity. The scale was administered to both depressed and control participants.

The Clinical Global Impression Scale – Global Improvement (CGI-I; Busner & Targum, 2007) is a 1-item scale used to assess depression severity prior to and after initiation of a treatment protocol. The severity is rated from 1 to 7, with 1 being not at all ill and 7 being among the most extremely ill subjects. The scale is completed by the attending psychiatrist before and after the iTBS protocol. Control participants were not rated using this scale.

### **3.2.2 Self-Assessments**

A number of self-assessment scales were also employed. The Hospital Anxiety and Depression Scale (HAD; Zigmond & Snaith, 1983) was used to assess both depression and anxiety symptoms in the past week on a scale of 0-3 for each item, with 3 indicating the most severe symptomology. A total of 14-items are included on the scale, divided into 7 measuring depression with questions such as “I still enjoy the things I used to enjoy” or “I feel as if I am slowed down” and 7 measuring anxiety with questions

such as “I feel tense or ‘wound up’” or “I can sit at ease and feel relaxed”. The individual scores for depression and anxiety are calculated with 0-7 representing a normal score, 8-10 being borderline abnormal, and 11-21 being an abnormal score. The scale was administered to both depressed and control participants.

The Snaith-Hamilton Pleasure Scale (SHPS; Snaith et al., 1995), a 14-item questionnaire, was employed to assess anhedonia (the inability to experience pleasure) over the past few days. The questionnaire assesses the ability to experience pleasure/enjoy things such as food, social interaction, sensory experience, and past times/hobbies. Each question is marked on a scale of “strongly disagree”, “disagree”, “agree”, and “strongly agree”, with the first two statements being worth 1 point and the last two worth 0. The scores range from 0 to 14 with scores that are 2 or less are considered “normal” scores while those 3 and above are “abnormal”. The scale was administered to both depressed and control participants.

The Beck Depression Inventory-II (BDI-II; Beck, Steer, & Brown, 1996) was also administered at the first and last iTBS appointment in the TMS clinic by the TMS nurse. The BDI-II is a 21-item self-report scale that measures severity of depression over the past two weeks on a scale of 0 to 3 for each item. Total scores ranging from 0 to 13 indicates minimal depression, 14 to 19 indicates mild depression, 20 to 28 indicates moderate depression, and scores from 29 to 63 indicate severe depression.

### **3.3 Assessment of Olfaction**

Assessment of olfaction was conducted using the Sniffin’ Stick’s Extended Testing Paradigm, also called the “TDI-Test” for Threshold, Discrimination, and Identification (Thomas. Hummel, Kobal, Gudziol, & Mackay-Sim, 2007; Thomas Hummel, Sekinger, Wolf, Pauli, & Kobal, 1997). The Sniffin’ Sticks are large pens filled with a chamber containing liquid odorant or water with an absorbent tip covered by a removable cap. Sniffin’ Stick’s Extended Test consists of three subtests aimed at assessing olfactory sensitivity (threshold), ability to discriminate between target scents (discrimination), and the

ability to identify target smells from a number of options (identification). The results of each of the subtests are added together to create the TDI-score or total as will be denoted for the remainder of this thesis.

Before commencement of the test, participants are instructed to not eat or drink anything other than water in the 15 minutes before testing. The researcher administering the test wears odourless gloves made from cotton in order to avoid contact with skin and the gloves are washed in between participants. Testing occurs in a quiet and well-ventilated room, with air flow controlled in order to reduce the influence of outside scents and the researcher wearing no strong odors or detectable scents. During test, the cap covering the tip is removed and the pen tip presented to the participant 2 cm in front of each nostril. The participant is instructed to breathe in through their nostrils upon the command of “smell”, with the pen being presented for 4 seconds in total. Once the pen has been presented, the cap is replaced and the pen is placed back into the holder. A 30-second interval occurs between presentations of each pen or set of pens and a 3-minute interval occurs between each of the three tests. For both the threshold test and the discrimination test, each pen in the triplet have a single colour (red, blue, or green) and pens are presented in the order of: (1) red, green, blue; (2) blue, red, green; (3) green, blue, red. This cycle is repeated for both tests throughout the whole test. The entire test takes approximately 30 to 40 minutes to complete (Hummel et al., 2007).

### **3.3.1 Olfactory Detection: Threshold**

The threshold test is conducted in a staircase procedure, moving from lowest concentrated dilution to highest in order to determine the dilution step that can be distinguished from non-smelling pens (blanks). In order to do so, participants are blindfolded using a sleeping mask or with their eyes closed if they feel anxious regarding being blindfolded and three pens are presented to the participant. Of the three pens, only one pen has the odorant of n-butanol and the remaining two are odourless water. A total of 16 triplets are include in the threshold test but not all pens will be presented. Pens are presented in a bilateral fashion, 2 cm away from the center of the nostril, and one at a time. The order of presentation

moves from 16 to 14 to 12 or 15 to 13 to 11 and so on – the higher the number on the pen, the lower the concentration of n-butanol in the target pen. Each of the pens are presented only once and after the presentation of the three pens the participant is asked to identify which of the three pens presented they perceive to contain the odorant. For every presentation of the triplet, the participant is required to make a choice as to which pen contains the odorant. Even if the participant is uncertain they must make a choice, this is referred to as a “forced choice”. A certain odorant concentration is identified correctly only if the target pen is identified twice in a row and a triplet is only presented twice if the participant made the correct choice at the first presentation. The initial presentation of the pens occurs in increasing concentration until the correct target pen has been identified twice in a row. Next, the dilution step one higher than the last is presented until a wrong decision is made. After this, the next dilution step lower than the dilution step where the wrong decision was made is presented and the higher dilutions are presented until two correct identifications are made. The two previous steps are repeated until there is a total of 7 reversal points are passed and the smell threshold is calculated by the average of the last 4 reversal points to generate the threshold score (Hummel et al., 2007).

### **3.3.2 Olfactory Detection: Discrimination**

Similar to the previous threshold test, participants are blindfolded and presented a set of three pens for a total of 16 triplets. Unlike the threshold test, two of the pens contain the same smell (the non-targets) and only one pen contains a different odorant (the target). The participant is instructed to identify the different smelling pen (target) and must make a decision even if uncertain. Each of the pens are only presented once and the participant is instructed to make a decision after all three of the pens have been presented. The pen number indicated by the participants are noted, with the correct identification of the target pen being worth one point and incorrect identifications having no values. The correct identifications of the target scent are added together to give the discrimination score (Hummel et al., 2007).

### **3.3.3 Olfactory Detection: Identification**

For the assessment of identification, 16 pens are presented to the participant – who in this case is not blindfolded - one after the other. Participants are given cards, one for each pen, that contain 4 options as to which odor the target pen may contain. Target scents range from spices such as clove, peppermint, and cinnamon, to fruit smells such as lemon, apple, and pineapple, and everyday smells such as turpentine, rose, and methanol. After each presentation, participants must choose one of the 4 options as to which the target odor may be. The identification score is calculated based on the total of all of the correct identifications of the target scents (Hummel et al., 2007).

### **3.4 Study Procedure**

Each participant was tested one-on-one with a researcher. The researcher was the same individual each time in order to reduce variation in olfaction and depression measurement. Testing administration was fixed and identical for all participants and the same at both baseline and post treatment/wait period. Prescreen information and determination of eligibility occurred before the first visit, either at the consent to receive iTBS for depressed participants or over the phone for controls. Depressed participants were assessed the day before or same day as their first iTBS appointment and between 7 and 14 days after their 25<sup>th</sup> iTBS or, as a last resort, the same day as their last iTBS appointment. Participants were tested only on the same day as the last iTBS appointment if they were unable to meet due to participant schedule or inability to travel to the hospital outside of iTBS appointments due to distance or transportation issues. Control participants were tested at one time, also denoted as baseline, and a second time 6-7 weeks after their first appointment in order to best match the time period of iTBS in depressed and provide an additional comparative to depressed post-iTBS. For controls, the period between the two visits is denoted as the wait period.

Each of the visits began with collection and confirmation of demographic information, informed consent was collected at the first visit before any other information was gathered. Following collection of demographic information, olfaction was assessed and explained in detail. The assessment of olfaction

began with olfactory threshold and was followed by discrimination and identification. In between each of the olfaction tests, depression severity was assessed to give the participants a break and a chance to return breathing to normal. Overall, the testing occurred in the following order: 1) threshold, 2) HAD, 3) discrimination, 4) SHPS, 5) identification, and 6) MADRS. The CGI was given to and completed by the attending psychiatrist. The BDI was completed by the participant at their first iTBS appointment and at their follow-up appointment with the psychiatrist a week after their last iTBS appointment or on their last iTBS appointment depending on when the participant was being tested. The same procedure was repeated for the second visit.

### **3.5 Statistical Analyses**

All statistical analyses were conducted using SPSS. Olfaction was assessed by total score and broken down into the individual components of threshold, discrimination, and identification. Only 2 of the participants in the study had a diagnosis of BD, and therefore no meaningful analysis could be conducted comparing MDD and BD. Depression scores were assessed by scale total score with the exception of the MADRS which was analyzed by total score and each individual question providing information as to: sadness, sleep, guilt, appetite, suicidality, etc. Depression and olfaction in participants and controls were analyzed separately and together.

## **Chapter 4: Results**

### **4.1 Examination of the Depressed Group**

Examination of the depressed participants was conducted using 20 baseline scores for olfaction and depression measures and 18 post-iTBS olfaction and depression measures due to withdrawal from the study.

#### **4.1.1 Effect of Gender on Depression Severity and Olfaction**

An independent samples t-test comparing the olfactory functioning of depressed women versus depressed men at time one found a significant difference between males and females with regards to threshold scores ( $t_{(18)}=-2.301$ ,  $p=0.034$ ) but not on any other measure of olfaction. For threshold, the mean score for females (mean =6.70, SD = 1.69) was significantly higher than in males (mean=5.36, SD=0.43). This suggests that women have better olfactory acuity at the peripheral (nasal epithelial) level of processing but no difference occurs between males and females regarding higher cognitive processes. Upon completion of iTBS, this difference was no longer present or significant. In order to better understand why there may be a significant difference between males and females at time one but not time two, we compared the means for depression severity as measured by the MADRS, HAD, SHPS, CGI, and BDI at both time one and time two, finding no significant difference between depressed males and females.

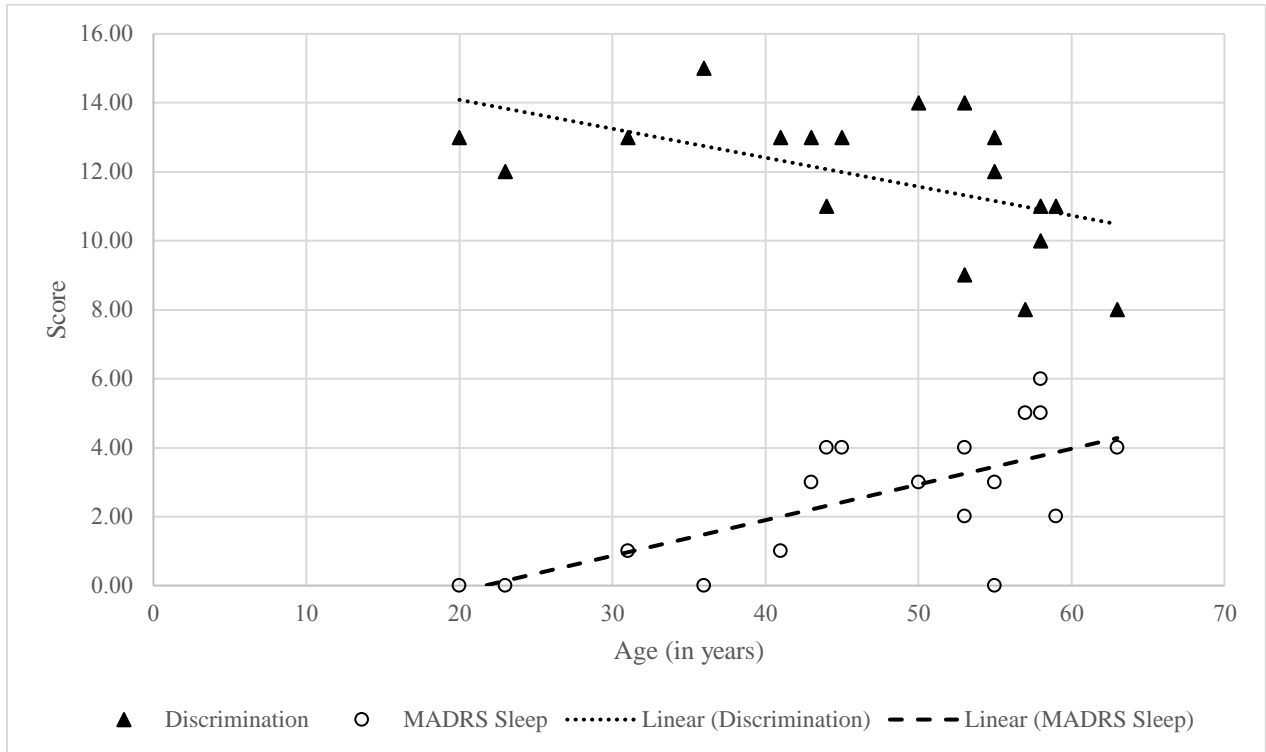
#### **4.1.2 Effect of Age on Depression Severity and Olfaction**

To determine if age and aging were confounding factors or had an impact on the olfactory functioning of depressed participants, we separated the depressed participants into cohorts of those younger than 50 years ( $n=10$ ) and those older than 50 ( $n=10$ ). With regards to baseline (time 1) measurement of olfactory functioning, there was a significant difference in the discrimination scores with the younger cohort performing significantly better on the discrimination task [ $t_{(18)}=-2.923$ ,  $p=0.009$ ;

younger mean = 11.7, SD = 1.06; older mean =10.2, SD=1.23]. Post-iTBS (time 2) scores of olfactory functioning were also significantly different between the older and younger cohorts with regards to both threshold [ $t_{(18)}=-2.342$ ,  $p=0.032$ ; younger mean=6.22, SD=1.71; older mean =4.611, SD=1.16] and discrimination [ $t_{(18)}=-2.919$ ,  $p= 0.01$ ; younger mean = 13.00, SD=1.12; older mean = 10.67, SD=2.12]. In both instances, those in the 50 and older group performed significantly worse on the task than those under the age of 50. To further explain this difference, we again compared the means for depression severity as measured by the MADRS, HAD, SHPS, CGI, and BDI at both time one and time two and found no significant difference in the depression severity at either time in the two cohorts. The correlations between depression and olfaction scores with age were also calculated so as to see if there was a pattern and provide better insight into the findings of a significant difference between the older and younger cohorts. No correlations between age and olfaction scores or depression severity were found at baseline. However, after iTBS there were correlations between discrimination scores ( $r=-0.519$ ,  $p=0.027$ ) and MADRS sleep score ( $r=0.671$ ,  $0.002$ ). Significant correlations between age and post-iTBS treatment support the finding of a significant difference given that as age increases, the discrimination score decreases (see figure 2.1). Given that there were no significant differences between age cohorts with regards to depression measures, the significant correlation between age and MADRS sleep score does not provide significant insight but does show that as age increases, severity of sleep impairment increases as well.

#### **4.1.3 Effect of Depression Severity on Olfaction**

In order to examine the impact of depression severity on olfaction at baseline, we divided the depressed participants into mild/moderate depression ( $n=12$ ; MADRS less than 34) and severe depression ( $n=8$ ; MADRS equal to or greater than 34) based on the total MADRS baseline score. An independent samples t-test was analyzed with the computed depression severity variable as the grouping variable to compare the baseline olfactory functioning between the two groups. There was no significant difference between the two groups with regards to threshold [ $t_{(18)}=1.22$ ,  $p=0.24$ ] and discrimination



**Figure 2.1 Significant correlations between age with discrimination score and age with MADRS sleep in depressed participants.** The correlation analysis displayed a significant correlation between age of depressed participants and discrimination with the linear relationship plotted ( $r=-0.519$ ,  $p=0.027$ ). The linear relationship further supports the reported difference between those under the age of 50 and those over the age of 50 with regards to olfactory discrimination. A significant relationship was also found between age and MADRS sleep score ( $r=0.671$ ,  $0.002$ ), with MADRS sleep severity increasing as age increases.

[ $t_{(18)}=0.53$ ,  $p=0.60$ ]. However, there was a significant difference with regards to identification [ $t_{(18)}=3.92$ ,  $p=0.001$ ] and total olfaction score [ $t_{(18)}=3.01$ ,  $p=0.007$ ]. For both total and identification, the mild/moderately depressed group had significantly higher scores than those who were severely depressed [identification: mild/moderate mean=12.5, SD=1.68; severe mean = 9.38, SD=1.85; total: mild/moderate mean=30.00, SD=3.56; severe mean=25.75, SD=2.18].

Using that same grouping variable of mild/moderate or severe depression at baseline, we examined if there remained a significant difference between these two groups after iTBS with regards to olfaction. An independent samples t-test found that there remained a significant difference between identification [ $t_{(16)}=2.53$ ,  $SD=0.022$ ] and total [ $t_{(16)}=2.61$ ,  $SD=0.019$ ]. When we computed a new variable based on the post-iTBS MADRS score, there were two less participants in the severe group as their MADRS total score decreased post-treatment. Notably, two participants withdrew from the study and therefore were not included in the post-iTBS cohorts but were included in the baseline cohort. An independent samples t-test comparing the post-iTBS olfaction scores in those whose MADRS score was severe ( $n=5$ ) versus mild/moderate ( $n=13$ ) found no significant difference between the two groups with regards to threshold or discrimination but a significant difference with regards to post-iTBS identification score [ $t_{(16)}=2.12$ ,  $p=0.05$ ] and total score [ $t_{(16)}=2.42$ ,  $p=0.028$ ].

#### **4.1.4 Comparison of Baseline and Post-iTBS: Depressed**

A paired samples t-test was conducted to compare baseline versus post-TMS in the depressed group for olfaction and depression scores. Regarding olfaction, there was no significant difference between the scores of depressed at time one versus time two. Only one of the measures, discrimination, was close to significance ( $t_{(17)}=-0.946$ ,  $p=0.069$ ). When comparing the means at both times, in both discrimination (mean<sub>baseline</sub> = 11.06, SD<sub>baseline</sub> = 1.35; mean<sub>post-TMS</sub> = 11.83, SD<sub>post-TMS</sub> = 2.04) and identification (mean<sub>baseline</sub> = 11.28, SD<sub>baseline</sub> = 2.22; mean<sub>post-TMS</sub> = 11.61, SD<sub>post-TMS</sub> = 1.38) the mean score for the olfaction test was higher post-treatment than before. However, for both threshold (mean<sub>baseline</sub> = 6.24, SD<sub>baseline</sub> = 1.45; mean<sub>post-TMS</sub> = 5.42, SD<sub>post-TMS</sub> = 1.64) and total olfaction (mean<sub>baseline</sub> = 28.58,

$SD_{\text{baseline}} = 3.74$ ;  $\text{mean}_{\text{post-TMS}} = 28.31$ ,  $SD_{\text{post-TMS}} = 4.70$ ) score the mean score for the olfaction test was lower post-treatment. This decrease in total score is likely due to the decrease in the threshold score given that both identification and discrimination increase. A paired samples t-test examining the depression severity was also conducted to determine if depression severity differed from baseline to post-treatment. No significant difference was found between the two time points, with the exception of the CGI which was significantly different ( $t_{(15)}=2.183$ ,  $p=0.045$ ) such that participants scored higher (and therefore more severely depressed) at baseline ( $\text{mean}=4.31$ ,  $SD=0.70$ ) than post-treatment ( $\text{mean}=3.75$ ,  $SD=0.93$ ).

#### **4.1.5 Correlations between Depression Scores and Olfaction Measures**

So as to better understand the relationship between olfaction and depression, a correlation analysis was conducted. Each measure of olfaction (threshold, discrimination, and identification) was compared against each depression measure (HAD, SHPS, MADRS, CGI, and BDI) to determine if there was a relationship between the two groups and provide further insight. To gain further insight into depression severity at baseline, the MADRS scale was reported as each individual item (i.e., reported sadness, apparent sadness, inner tension, sleep, appetite, etc.) and compared to each measure of olfaction. There were a number of correlations between the olfaction and depression measures with regards to the measurements at baseline. All negative correlations indicated that as the olfaction score increases, the severity of the depression measure decreases and all positive correlations indicated that as olfaction increases, severity of depression increases as well. A significant correlation was found between threshold score and MADRS measure of Inner tension ( $r=-0.464$ ,  $p=0.039$ ), no other correlations were observed. No significant correlations were found between discrimination scores at baseline and any measures of depression severity. Significant correlations were found between baseline identification and CGI ( $r=-0.586$ ,  $p=0.011$ ), MADRS inner tension ( $r=-0.649$ ,  $p=0.002$ ), MADRS sleep ( $r=-0.595$ ,  $p=0.006$ ), MADRS pessimism ( $r=-0.560$ ,  $p=0.006$ ), MADRS suicidality ( $r=-0.570$ ,  $p=0.009$ ), and MADRS total score ( $r=-0.540$ ,  $p=0.014$ ). For olfaction score total, there were significant correlations with the CGI score

( $r=-0.474$ ,  $p=0.047$ ), MADRS inner tension ( $r=-0.668$ ,  $p=-0.001$ ), MADRS sleep, ( $r=-0.479$ ,  $p=0.033$ ), MADRS pessimism ( $r=-0.554$ ,  $p=0.011$ ), and MADRS suicidality ( $r=-0.471$ ,  $p=0.036$ ).

After iTBS, several correlations remained and others that were not correlated at baseline were after treatment. First, after treatment there were no significant correlations between threshold scores and any depression scales. Unlike at baseline, significant correlations were found between discrimination and the measures of MADRS reported sadness ( $r=-0.544$ ,  $p=0.020$ ), MADRS sleep ( $r=-0.656$ ,  $p=0.003$ ), and MADRS total ( $r=-0.515$ ,  $p=0.029$ ). There remained a correlation between identification and MADRS suicidality ( $r=-0.519$ ,  $p=0.027$ ) and MADRS total ( $r=-0.611$ ,  $p=0.007$ ); however, unlike baseline, there were significant correlations between identification and MADRS apparent sadness ( $r=-0.492$ ,  $p=0.038$ ) and MADRS reported sadness ( $r=-0.628$ ,  $p=0.005$ ). Correlations remained between olfaction score total and MADRS sleep ( $r=-0.484$ ,  $p=0.042$ ) and MADRS suicidality ( $r=-0.558$ ,  $p=0.016$ ) in addition to MADRS reported sadness ( $r=-0.600$ ,  $p=0.008$ ) and MADRS total ( $r=-0.553$ ,  $p=0.017$ ).

## **4.2 Depressed and Controls Compared**

In order to compare depressed and non-depressed controls, a number of analyses were run. For the purpose of analysis, 20 depressed participants at baseline were compared to 9 non-depressed controls and after treatment (or wait time in the case of the controls) 18 depressed participants were compared to 7 controls. The numbers of participants changed due to withdrawals from the study.

### **4.2.1 Comparison of Baseline and Post Wait Period: Controls**

In order to ensure consistency within the control group, a paired samples t-test was conducted using only the data from the non-depressed controls. Olfaction and depression measures were compared before versus after the wait period. The paired samples t-test found no significant differences between the measures of the controls either on any measures of olfactory threshold [ $t_{(6)} = -0.130$ ,  $p=0.901$ ], discrimination [ $t_{(6)} = -0.603$ ,  $p=0.569$ ], identification [ $t_{(6)} = 1.114$ ,  $p=0.308$ ], total [ $t_{(6)} = 0.174$ ,  $p=0.867$ ] nor depression measures of HAD depression [ $t_{(6)}=1.00$ ,  $p=0.356$ ] and anxiety [ $t_{(6)}=0.157$ ,  $p=0.881$ ], SHPS

[ $t_{(6)}=1.549$ ,  $p=0.172$ ], MADRS [ $t_{(6)}=1.00$ ,  $p=0.356$ ]. Mean scores for each of the measures are outlined in table 2.1.

#### **4.2.2 Frequencies and Percentages of Demographic Information**

To better understand the two groups, we examined the frequencies of the demographic information (see table 1.1 for full frequency table). Comparison of the two groups found that both were close in mean age and range, with depressed having a mean age in years of  $47.25 \pm 11.98$  and a range of 20-63 years and controls with a mean age in years of  $46.78 \pm 12.96$  and range of 22-61 years. The frequency of males and females within the two groups were also relatively equal with 11 (55%) female and 9 (45%) male depressed participants and 5 (55.6%) female and 4 (44.4%) male non-depressed controls. The education of the participants was similar, with the lowest education completed being secondary school in depressed and some college/technical training in controls. The ethnicity of the participants was also similar with 18 (90%) Caucasian and 2 (10%) other depressed compared to 8 (88.9%) Caucasian and 1 (11.1%) other non-depressed controls. An independent samples t-test further confirmed the similarity between the groups, with no significant difference between the two with regards to age [ $t_{(27)}=0.096$ ,  $p=0.924$ ], gender [ $t_{(27)}=-0.027$ ,  $p=0.979$ ], education [ $t_{(27)}=-0.953$ ,  $p=0.349$ ], and ethnicity [ $t_{(27)}=-0.088$ ,  $p=0.931$ ]. Examination of the frequency of alcohol consumption, number of drinks on a typical day, alcohol interference, current smokers, and past smokers found no significant difference between the two with the exception of alcohol consumption in which controls drank more frequently compared to depressed [ $t_{(27)}=-2.185$ ,  $p=0.038$ ]. Despite the difference in frequency, the number of drinks consumed on a typical day of drinking [ $t_{(27)}=0.551$ ,  $p=0.586$ ] and if alcohol has impacted work, school, or personal life [ $t_{(27)}=0.664$ ,  $p=0.512$ ] were not significantly different between the two groups. Although there were no control participants that smoked (0%) and three depressed participants that currently smoke (15%), this difference was not significant. Table 1.1 outlines the frequencies and percentages of key demographic measures collected at baseline and confirmed again at during the second testing visit for both the depressed and non-depressed controls.

**Table 1.1 Demographic Frequencies and Percentages.** The percentages and frequencies of key demographic questions collected at baseline for both depressed participants and non-depressed controls.

<b>Variable</b>		<b>Depressed (n=20)</b>	<b>Non- Depressed Control (n=9)</b>	
<b>Age</b>	Mean $\pm$ SD, in years	47.25 $\pm$ 11.98	46.78 $\pm$ 12.96	
	Range	20 - 63	22-61	
<b>Gender</b>	Female	11 (55%)	5 (55.6%)	
	Male	9 (45%)	4 (44.4%)	
<b>Occupation</b>	Employed	Full Time	5 (25%)	5 (55.6%)
		Part Time	-	2 (22.2%)
	Student	Full Time	1 (5%)	-
		Part Time	-	1 (11.1%)
	Unemployed	Disability	7 (35%)	-
		Retired	2 (10%)	1 (11.1%)
		Homemaker	1 (5%)	-
Other	4 (20%)	-		
<b>Education</b>	Secondary School	Educated	4 (20%)	0 (0%)
		Some	1 (5%)	1 (11.1%)
	College/Technical School	Educated	6 (30%)	2 (22.2%)
		Some	1 (5%)	1 (11.1%)
	University	Educated	2 (10%)	2 (22.2%)
		Some	1 (5%)	-
Post-graduate Degree	Educated	5 (25%)	3 (33.3%)	
	Some	-	-	
<b>Ethnic Background</b>	White/Caucasian	18 (90%)	8 (88.9%)	
	Other	2 (10%)	1 (11.1%)	
<b>Comorbidity</b>	None	6 (30%)	8 (88.9%)	
	Anxiety	11 (55%)	-	
	ADD/ADHD	1 (5%)	1 (11.1%)	
	Anxiety and ADD	1 (5%)	-	
	Anxiety and Bulimia	1 (5%)	-	
	Anxiety and PTSD	1 (5%)	-	
<b>Other Medical Diagnosis</b>		9 (45%)	3 (33.3%)	
<b>Diabetes</b>		1 (5%)	-	
<b>Alcohol Frequency</b>	Never	4 (20%)	-	
	Once a month or less	9 (45%)	3 (33.3%)	
	2 to 4 times a month	5 (25%)	3 (33.3%)	
	2 to 3 times a week	1 (5%)	2 (22.2%)	
	4 or more times a week	1 (5%)	1 (11.1%)	
<b>Alcohol Drink Number</b>	None	4 (20%)	-	
	One to Two	12 (60%)	8 (88.9%)	
	Three to Four	4 (20%)	1 (11.1%)	
<b>Alcohol Interference</b>		3 (15%)	-	
<b>Current Smoker</b>		3 (15%)	-	
<b>Past Smoker</b>		7 (35%)	1 (11.1%)	

There were some incongruities with regards to the demographics. As to be expected, the frequencies and independent samples t-test found significant differences between the means of the two groups regarding other psychological comorbidities, the percentage of individuals with anxiety or anxiety and other comorbidity (this was 0% in the case of controls) and the occurrence of another general medical condition. In the case of all of these demographic measures, there was a higher frequency in depressed. With regards to occupation, a higher percentage of depressed participants were unemployed (70%) compared to controls (11.1%). Comparison of the means through the t-test further supported this difference [ $t_{(27)}=2.89$ ,  $p=0.007$ ]. A frequency analysis of the olfactory classification was conducted based on the baseline and post-iTBS/wait period total olfaction scores. The baseline olfactory classification of depressed participants ( $n=20$ ) found 20% of participants with a normal sense of smell (normosmia) and 80% with an impairment in sense of smell (hyposmia). After iTBS, 27.8% of depressed participants ( $n=18$ ) had a normal sense of smell and 72.2% an impairment in smell. With regards to controls, at baseline 66.7% of controls ( $n=9$ ) has a normal sense of smell and 33% an impairment in smell. After the waiting period, 42.9% of controls ( $n=7$ ) has a normal sense of smell and 57.1% had some impairment.

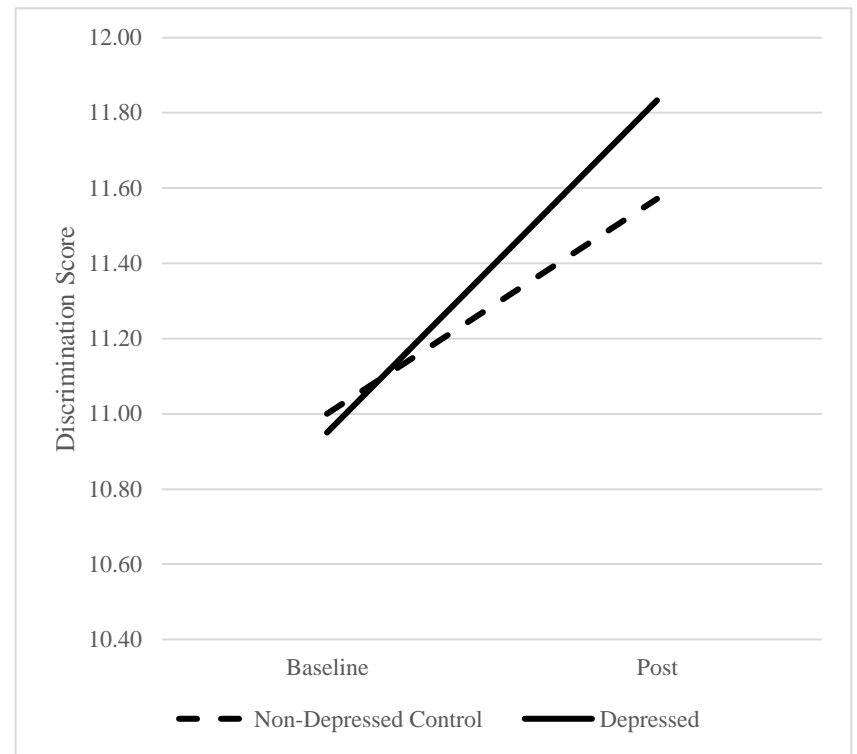
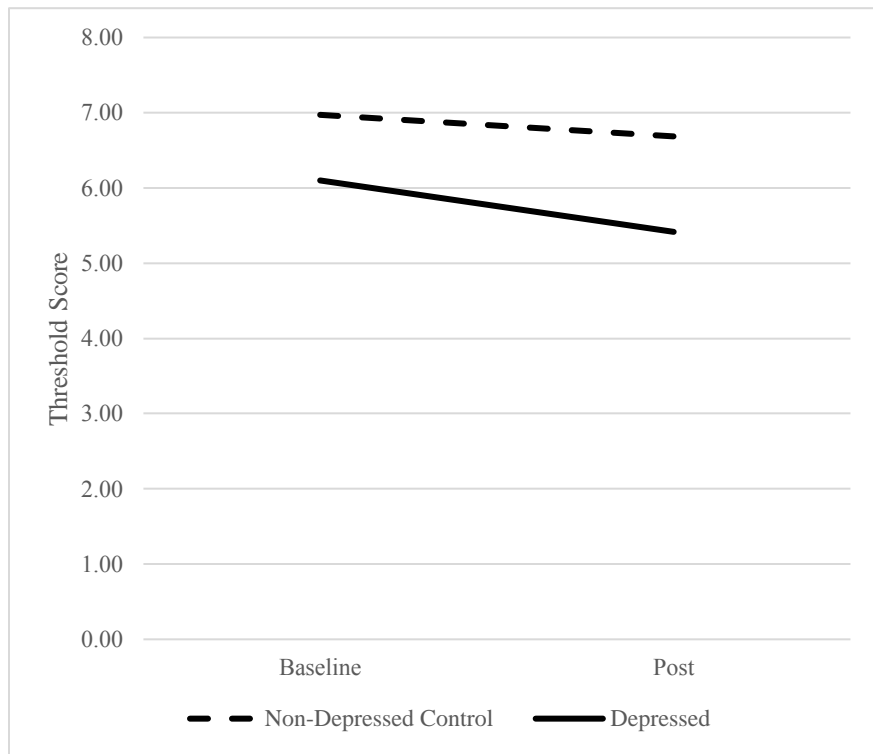
#### **4.2.3 Depressed versus Control at Baseline and Post-Treatment/Wait Period**

Next, we examined the olfaction scores at baseline and post-treatment (or wait time in the case of the controls) using an independent samples t-test and a one-way analysis of variance (ANOVA) for validation. Both the independent samples t-test and the ANOVA found no significant difference between the olfaction scores of the depressed and the non-depressed controls at either baseline or post-treatment. With regards to identification at baseline, the difference was close [ $F_{(1,27)}=4.081$ ,  $t_{(27)}=-2.02$ ,  $p=0.053$ ] but not significantly different between depressed and controls. Table 2.1 outlines the means for each group at baseline and after iTBS or the wait period, as well as the results of the ANOVA and independent t-test.

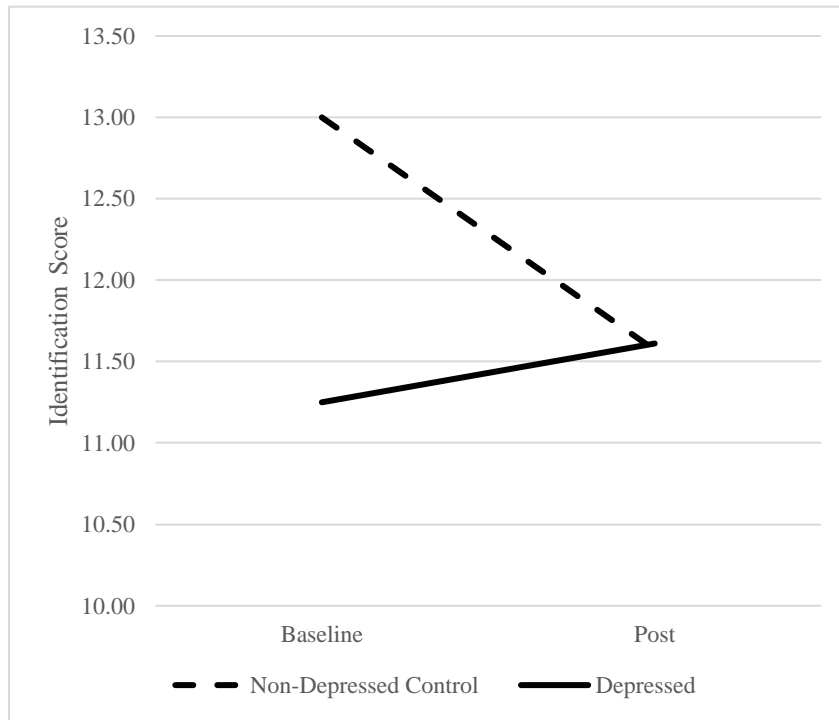
The two groups were further compared using a repeated measures (RM) mixed model ANOVA for each measure of olfactory functioning. The RM ANOVA for threshold found no significant effect of

**Table 2.1 Olfaction and Depression Scores Means and Comparisons for Depressed and Controls.** Mean scores for depressed and controls for the olfactory measures and depression measures at baseline and after iTBS of the wait period. The two groups were compared using an independent t-test and ANOVA finding no significant difference with regards to the olfactory methods neither before nor after iTBS or the wait period. All measures for depression were significantly different between the two groups at both baseline and after treatment/wait period ( $p < 0.05$ ).

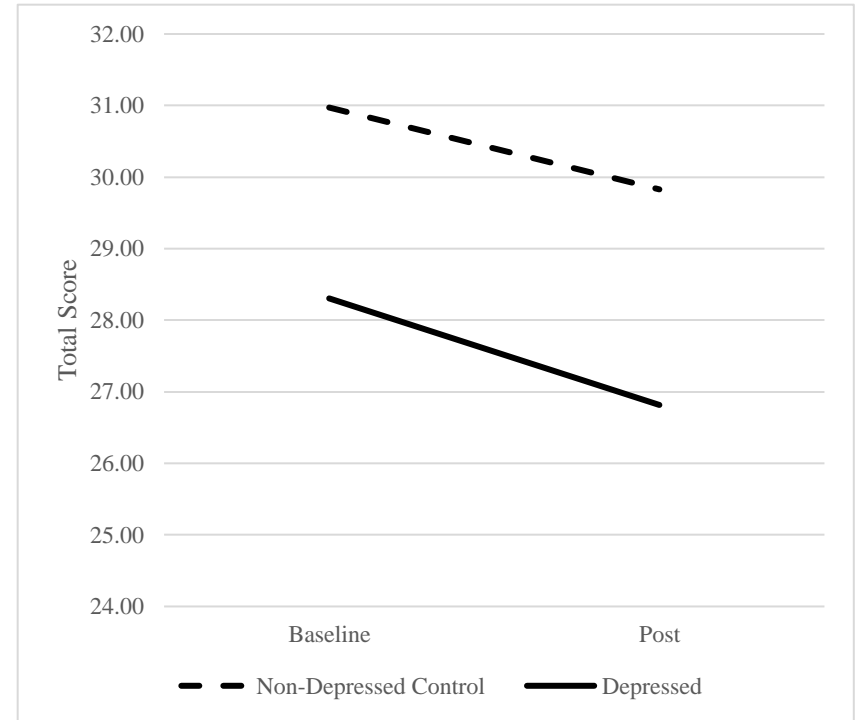
Measure	Time	Depressed (n=20)		Non-Depressed Control (n=9)		Depressed vs Control			
		Mean	SD	Mean	SD	F	t	p	
Olfaction	Threshold	Before	6.1	1.44	6.97	1.85	1.911	-1.382	0.178
		After	5.42	1.64	6.69	1.58	3.074	-1.753	0.093
	Discrimination	Before	10.95	1.36	11	1.58	0.008	-0.087	0.931
		After	11.83	2.04	11.57	1.81	0.088	0.297	0.76
	Identification	Before	11.25	2.31	13	1.73	4.081	-2.02	0.053
		After	11.61	1.38	11.57	2.76	0.002	0.048	0.962
	Total	Before	28.3	3.7	30.97	3.76	3.2	-1.789	0.085
		After	28.31	4.7	29.83	3.68	0.589	-0.768	0.451
Depression	HAD - Depression	Before	12	4.84	1.67	3.32	33.51	5.79	0
		After	11.5	3.76	0.43	0.79	58.18	7.628	0
	HAD - Anxiety	Before	11.45	3.14	2.44	2.13	60.9	7.8	0
		After	10.17	4.05	1.86	1.95	26.56	5.15	0
	MADRS Total	Before	29.35	7.02	1.33	0.04	130.17	11.41	0
		After	27.94	8.48	0	0	74.02	8.6	0
	SHPS	Before	6.15	3.72	0.22	0.44	22.297	4.72	0
		After	5.11	4.14	0	0	10.38	3.22	0.004
	BDI	Before	29.19	12.81	-	-	-	-	-
		After	27.94	8.48	-	-	-	-	-
	CGI	Before	4.22	0.73	-	-	-	-	-
		After	3.75	0.93	-	-	-	-	-



**Figure 3.1 Olfaction Threshold and Discrimination Scores Across Baseline and Post-iTBS/Wait Period for Depressed and Controls. A.** Mean olfactory threshold scores of depressed and non-depressed controls plotted at baseline and post-iTBS/wait period. No significant differences were found between the two groups at either baseline or post-iTBS/wait period and no significant difference was found within each group when comparing baseline to post-iTBS/wait period threshold scores. **B.** Mean olfactory discrimination scores of depressed and non-depressed controls plotted at baseline and post-iTBS/wait period. No significant differences were found between the two groups at either baseline or post-iTBS/wait period and no significant difference was found within each group when comparing baseline to post-iTBS/wait period discrimination scores.

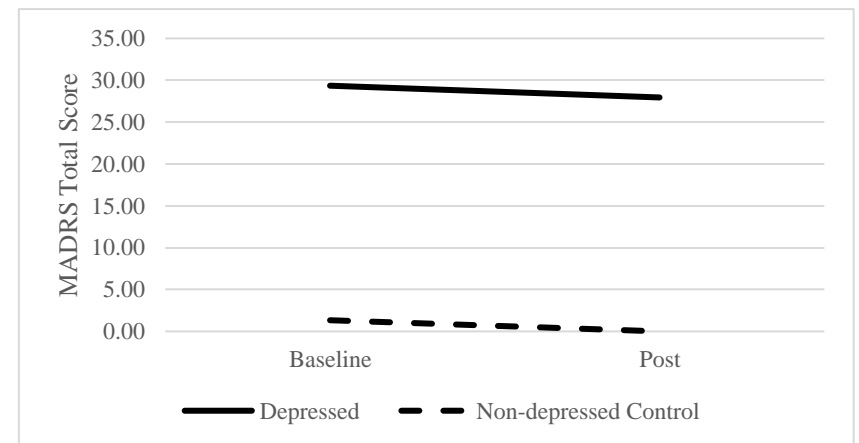
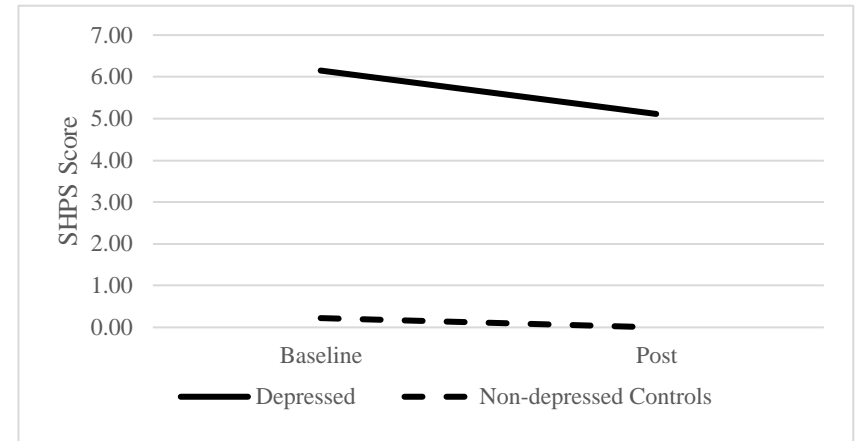
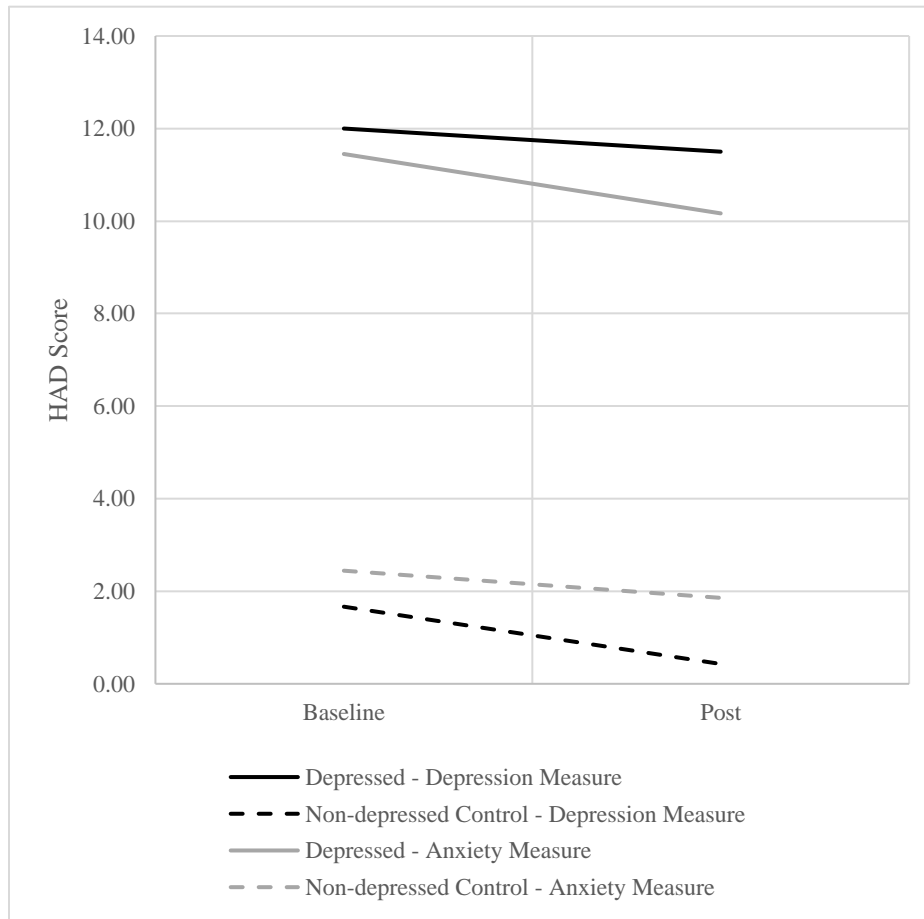


**A**



**B**

**Figure 3.2 Olfaction Identification and Total Scores Across Baseline and Post-iTBS/Wait Period for Depressed and Controls. A.** Mean olfactory identification scores of depressed and non-depressed controls plotted at baseline and post-iTBS/wait period. No significant differences were found between the two groups at either baseline or post-iTBS/wait period and no significant difference was found within each group when comparing baseline to post-iTBS/wait period identification scores. **B.** Mean olfactory total scores of depressed and non-depressed controls plotted at baseline and post-iTBS/wait period. No significant differences were found between the two groups at either baseline or post-iTBS/wait period and no significant difference was found within each group when comparing baseline to post-iTBS/wait period total olfaction scores.



**Figure 3.3 Depression Scores Across Baseline and Post-iTBS/Wait Period for Depressed and Controls.** Mean depression scale scores of depressed and non-depressed controls plotted at baseline and post-iTBS/wait period for the scales completed by both depressed and control participants. Significant differences were found between the two groups on all measures at both time points. **A.** Mean scores for the Hospital Anxiety and Depression (HAD) scale for the depressed and non-depressed control groups for both the anxiety and depression measure of this scale at baseline and post-iTBS. **B.** Mean Scores for the Snaith-Hamilton Pleasure Scale (SHPS) for the depressed and non-depressed control groups for both the anxiety and depression measure of this scale at baseline and post-iTBS. **C.** Mean scores for the Total Montgomery-Asberg Depression Rating Scale (MADRS) for the depressed and non-depressed control groups for both the anxiety and depression measure of this scale at baseline and post-iTBS.

depressed or non-depressed and time ( $F_{(1,23)} = 1.045$ ,  $p=0.317$ ) nor an effect of time alone ( $F_{(1,23)} = 0.711$ ,  $p=0.408$ ) on the olfactory threshold score in either group, further confirming the results of the t-test and one-way ANOVA. The RM ANOVA for discrimination found no significant effect of depressed or non-depressed groups and time ( $F_{(1,23)} = 0.057$ ,  $p=0.814$ ) nor an effect of time alone ( $F_{(1,23)} = 2.430$ ,  $p=0.133$ ) on the olfactory discrimination score in either group. The RM ANOVA for identification found no significant effect of depressed or non-depressed groups and time ( $F_{(1,23)} = 2.614$ ,  $p=0.120$ ) nor an effect of time alone ( $F_{(1,23)} = 0.506$ ,  $p=0.484$ ) on the olfactory identification score in either group. The RM ANOVA for total olfaction score found no significant effect of depressed or non-depressed groups and time ( $F_{(1,23)} = 0.001$ ,  $p=0.970$ ) nor an effect of time alone ( $F_{(1,23)} = 0.084$ ,  $p=0.775$ ) on the olfactory threshold score in either group, further confirming the results of the t-test. Overall, no significant differences were found with regards to olfactory functioning of depressed when compared to controls either before or after treatment, or the wait period in the case of controls.

## **Chapter 5: Discussion**

### **5.1 Evaluation of the Olfactory and Depression Scores**

#### **5.1.1 Evaluation of Primary and Secondary Objectives**

The aim of this study was to examine the effect of iTBS on olfactory functioning in depression. With regards to our primary objective of determining if there was a significant change in olfactory functioning in patients with MDD or BD following a course of iTBS compared to non-depressed controls, we did not find a significant difference or significant change from baseline to post-iTBS. Due to our results being contrary to our primary objective, the three hypotheses proposed in relation to our primary objective were also consequently not supported. The first hypothesis suggested that olfactory functioning would be decreased in patients with MDD or BD. There was no significant difference between depressed and controls at baseline, indicating that depressed participants did not have reduced olfactory functioning in comparison to non-depressed participants.

Similarly, our findings did not support our second hypothesis which proposed that depressed participants would improve from baseline to post-treatment. No significant difference was found within the depressed group regarding any measure of olfaction or depression severity, with the exception of the CGI. While the significant difference between the CGI scores does indicate an improvement, this was the only scale that had significant findings and therefore no conclusion of a significant difference in the depression severity overall can be made. Our main scale of interest was the MADRS and this detected no significant difference in depression score from baseline and post-iTBS. However, the lack of significant difference within the depressed group does provide support to the proposed reciprocal relationship between olfaction and depression. Under the assumption of a reciprocal relationship, a lack of significant change between baseline and post-iTBS with regards to depression severity would mean no significant change in olfactory functioning. This predicted effect was demonstrated in our results, with the lack of change or improvement in depression and olfaction following iTBS lending support to this assumption.

While our results do not provide substantial insight as to the effect of treatment on olfactory dysfunction associated with depression, they do further substantiate the proposed theory of interaction between the two and lend some support to the findings of previous studies.

With respect to the third hypothesis, there was no difference between controls and depressed either at baseline or after iTBS. Although our findings support part of hypothesis three in that we found no difference post-iTBS, this is rendered insignificant by the lack of significant difference between depressed and controls at baseline. As per our findings, there were no significant differences between depressed and controls either before or after treatment/wait period with regards to olfactory functioning. While there were significant differences between the two groups with regards to depression severity (see table 2.1 and figure 3.2 for further detail), no difference between the two groups on any measure of olfaction at either baseline or post-iTBS/wait period. Additionally, no significant effects were found for time or depressed vs control, as evidenced by the findings of the RM ANOVA. In all, we found no significant difference with regards to the olfactory functioning of depressed and non-depressed controls.

Our secondary objective was to determine if olfaction score improvement correlated with an improvement in depression scores after treatment. While there was no improvement in olfaction over the course of treatment, there were a number of significant correlations between olfactory functioning and depression. There were many correlations between olfaction scores and many of the individual MADRS measures, but for the purpose of the discussion we will primarily focus on the significant correlations with the total scores of the scales – with the exception of specific correlations that provide additional insight. At baseline, significant negative correlations were found between identification and CGI, identification and MADRS total, and total olfaction score and CGI. Post-iTBS, significant negative correlations were found between discrimination and MADRS total, identification and MADRS total, and total olfaction score and MADRS total. All of these correlations were negative, meaning that as olfaction score improved, depression severity decreased. At both baseline and post-iTBS, there were significant correlations between the measures of higher olfactory cognitive processes (discrimination and/or identification) and depression. Given that these two olfaction measurements represent the functionality of

processes in the olfactory anatomy that are connected to major brain regions impacted by depression, the higher olfactory scores and lower depression scores suggest higher functionality of both regions and support the theory previously presented in the literature of a reciprocal relationship between olfaction and depression (Kohli et al., 2016). In particular, the significant correlation between MADRS total and identification and discrimination post-iTBS lends further to support of this theory and indicates a stronger negative relationship between depression and olfactory functioning.

The lack of correlations between threshold and depression measures, with the exception of MADRS inner tension at baseline, and the lack of significant difference within the depressed group for threshold score provides further support to our proposed notion that threshold should not be impacted by depression and that no matter the treatment there will be no significant difference after treatment. We expect to only observe a significant difference and significant correlations between depression measures and discrimination and identification given that they reflect the higher cognitive processes. Threshold is representative of the level of the nasal epithelium and nasal receptors, and is indirectly connected to the limbic system and those areas impacted in depression (Patel & Pinto, 2014). This theory is contrary to many of the findings of other studies, which have found a significant difference within depressed and between depressed and controls regarding olfactory sensitivity (threshold). Within the literature, some researchers have found that this is the only significant impairment with regards to olfactory functioning in depressed. Many of these studies compare only threshold and identification, finding that identification is intact and threshold is affected (Lombion-Pouthier et al., 2006). Some studies, such as those conducted by Gross-Isseroff et al. (1994) and Postolache et al. (2002), examined only threshold with no other measure of olfaction for comparison. While depression likely is likely impacting the signaling at the level of and above the nasal epithelium and thereby impacting the olfactory threshold, if there is no significant impact on the higher cognitive olfactory processes then it is unlikely that depression is impacting solely threshold and there must be additional factors - such as individual variation or previous experiences - that are impacting olfactory threshold.

### **5.1.2 Evaluation of the Effect of Age on Olfaction and Depression**

In order to gain a better understanding of olfactory impairment in depressed participants and to further examine the potential limitation of age range presented in the literature, the groups were divided into age cohorts of those 50 and younger (n=10) and those above 50 years old (n=10). The purpose of dividing the depressed group into age cohorts was to determine if there was a significant difference between the two groups, particularly post-iTBS, and to further examine the possibility of age having an impact in olfaction rather than depression. Comparison of the younger cohort and older cohort showed a significant difference between the two at the baseline measurement of olfactory discrimination and at the post-iTBS measurements of olfactory discrimination and threshold. Comparison of the two groups regarding depression severity, however, found no significant difference between the older and younger cohorts. As previously discussed, the threshold difference post-iTBS is likely due to an improvement in the signaling pathway and the higher cognitive processes rather than an impact solely on the level of the nasal epithelium (as measured by threshold).

The finding of a significant difference between younger and older cohorts at both baseline and post-iTBS for discrimination scores and the improvement in the mean discrimination score in the younger cohort after-iTBS suggests that age has an impact on the higher cognitive processes. If there was a significant difference between the two groups in terms of depression severity, it would be unlikely that age would impact olfaction greater than depression. However, this possible impact of age rather than depression is further supported by the lack of significant difference between the two groups for depression severity scores. When relating these findings to the lack of significant difference within the depressed group and between the depressed and control groups, it is evident that age may have impacted the analysis of the depressed group given that it includes both younger and older participants. The significant difference between the younger and older cohorts leads to two possible conclusions. The first being that the lower scores of those above the age of 50 are due to age related decline in cognition and general functioning. It is reasonable that the significant difference in olfactory functioning, particularly

with cognition, is due to the general age related cognitive decline that is globally impacting all cognitive processes, including olfactory functioning. The second possible conclusion is that age has no impact on the observed effect and that an additional factor assessed or measured for must be causing such a difference. There remains the possibility that an aspect of participant demographics or another unmeasured factor may be causing the difference in the two groups regarding olfactory functioning.

### **5.1.3 Evaluation of the Effect of Gender on Depression and Olfaction**

While there was a significant difference between men and women with regards to the baseline measurement of threshold, this difference was not present after iTBS. Though this may suggest that there was some small difference between men and women, the lack of significant difference between the two with regards to discrimination and identification at both baseline and post-iTBS suggests no effect of gender on olfaction. Additionally, while the rate of prevalence of depression is approximately 1.5 – 2.5 times higher in women than men (Jacobi et al., 2005), with most reporting a general 2:1 ratio (Harkness et al., 2010; Hirschfeld & Cross, 1982; Kessler, 2003; Whiteman et al., 2016), there was no significant difference between males and females with regards to depression severity and the inclusion of males and females was relatively even. There was a higher enrollment of females in the study, but only by 10% and therefore our sample was not representative of the reported 2:1 ratio of males to females. Based on the findings of the current study, gender had no significant difference regarding either olfaction scores or depression severity.

### **5.1.4 Evaluation of Depression Severity on Olfaction**

To better understand the relationship between depression severity and olfactory functioning, we divided the participants into mild/moderately depressed and severely depressed based on their baseline total MADRS score. The results of these comparisons showed a significant difference between mild/moderately depressed and severely depressed individuals with regards to olfactory identification and total score (the culmination of the threshold, discrimination, and identification score). This significant

difference remained post-iTBS when comparing the groups based on their severity at baseline and after iTBS. This significant difference between the two demonstrates that as depression severity increases, olfactory functioning decreases. When comparing the number of participants included in the cohort established based on baseline total MADRS score and the number of participants in the cohorts based on post-iTBS total MADRS score, we found little change between the two groups with one participant moving from the severely depressed group to the mild/moderately depressed group. While applicable to identification and overall total olfactory score, this does provide further insight as to the relationship between depression severity and olfaction.

Though there was not a significant difference within the depressed group with regards to depression severity and olfactory functioning after iTBS, the lack of significant difference can be feasibly attributed to the lack of improvement in depression. The inclusion of participants with a long history of depression – particularly those participants in the older age range - that had not been successfully treated suggests that participants may have experienced some resistance to treatment. If this assumption of resistance holds, then depression is indeed impacting olfactory functioning and therefore no improvement in olfaction could occur without an improvement in depression symptoms and severity. Application of this assumption to the current study may provide further rationale for the lack of significant findings and support for the relationship between depression and olfaction. Additionally, if the assumption that individuals in the older age range are experiencing resistance to treatment and impacting the ability to improve in both olfactory functioning and depression severity is indeed correct, the etiology of the observed difference in the age cohorts may be elucidated. As such, it may be that the difference in the age groups was not due to the empirical age or age-related declines in cognitive functioning, but rather due to an increase history of nonresponse to primary and secondary measures for treatment of depression.

## **5.2 Study Limitations**

As with any study, there were limitations present; however, these limitations present a number of possibilities for expansion of the research and future directions. In addition to the limitation of individuals

between the age range of 50 and 65 (for further details see sections 2.6.1.3 and 5.1.2), there are three main limitations to the studies: familiarity with target scents, medication use, and sample size.

### **5.2.1 Familiarity with Target Scents**

The first and most notable limitation was the potential for unfamiliarity with the target scents in the identification task. While the majority of the scents were everyday scents most have experienced, there were some scents – such as anise and turpentine – that participants were unfamiliar with and indicated such when presented with the scent. The unfamiliarity either resulted in a positive choice based on a guess or an incorrect choice in favor of a more familiar and possibly related option. For those that did recognize the scent, the choice was easy and instant. Unfortunately, there was no specific way to control for participant familiarity in the scent without testing for it, given that the experience of smell is subjective, influenced by the environment and lifetime exposure. In addition to differences in lifetime exposure, the population in which the methodology employed was validated is incongruent with the current population. The Sniffin' Sticks Extended Test was validated and employed primarily within the European population, though there have been some studies conducted in North America that have also used this testing method. While there may not be an apparent difference between the two populations, the cultural and geographic differences likely impact the subjective experience and exposure to different types of smells. These differences may rationalize why many of the participants in the current study have not experienced the smell of anise, for example. All of the participants in the study, with the exception of two depressed and one control, were Caucasian individuals meaning that it is unlikely that the variation within the population is due to cultural differences within North America and Canada rather than experience or cultural differences between North America and Europe. Additionally, exclusion of the two scents during preliminary analysis made no significant difference as the unfamiliarity was present in both the depressed and control groups. Further validation of the testing procedure in the North American population or alternative options better fitting the current population may help to eliminate this potential issue.

### 5.2.2 Medication Use

One potential issue and possible contributor to the lack of significant difference is the use of medication in the depressed group. As established by previous studies, ADMs have a positive effect on olfactory dysfunction associated with depression and use of ADMs has shown to improve both depression and olfaction (Clepce et al., 2010; Gross-Isseroff et al., 1994). All of the depressed participants had a history of ADM use and the previous use of medication may have already had a positive or corrective impact on olfactory dysfunction associated with depression. It may be possible that ADMs have already positively impacted olfactory dysfunction associated with depression by alleviating the dysfunction to some extent or entirely. In this case, the lack of significant difference between depressed and controls and the lack of change within the depressed group can be attributed to this aspect of the depressed group.

While this may explain why the results found no significant differences, there remains issues associated with this possible conclusion. Primarily, this undermines the prediction that the relationship between olfactory functioning and depression is a reciprocal one, or a relationship at all (Kohli et al., 2016). If ADMs had already improved the olfactory functioning, according to the theory of a reciprocal relationship the depression symptoms should also have improved. Yet, all of the depressed participants were referred to iTBS due to a previous limited or lack of response to ADMs, indicating that depression symptoms had not improved and no measure of olfactory functioning was obtained before each participant had been prescribed ADM. While there were some who fell within the mild/moderate severity on the MADRS at baseline, the subjective experience of depression was still clinically impairing and none were close to remission or on the lower end of mild. If it were the case that ADMs had improved the olfactory functioning of those in the depressed group, then no significant reciprocal relationship can exist between olfaction and depression severity. Though our results do not fully contradict the notion of a lack of relationship, our findings of significant correlations between depression severity and olfaction measures do provide evidence of a reciprocal relationship. In all, the history of ADMs in the depressed

participants introduce a potential confound that complicates our understanding of the relationship between depression severity and olfactory functioning in a population receiving iTBS.

### **5.2.3 Sample Size**

Similar to the other limitations of the study, the number of the participants included in the study is likely impacting the results of the current study. Sample size in particular is an issue throughout the literature, with many studies having small sample sizes and therefore low power. In previous studies, the sample sizes have primarily been around 20-30 depressed and a similar number for controls (Atanasova et al., 2010; Croy et al., 2014; Gross-Isseroff et al., 1994; Naudin et al., 2012; Warner-Schmidt & Duman, 2006). The current study included a sample size of 20 depressed at baseline and 18 depressed post-iTBS. Both the sample sizes in the current study and the literature may not have enough power to accurately describe and present the relationship between olfaction and depression. The low power likely means that future replications of these studies on a larger scale may not have similar results. However, there remains the possibility that similar, stronger results may be found and the findings may be further substantiated. Overall, the sample size of the current study may mean that the findings are unique to this study and may not be properly replicable in future studies.

## **5.3 Future Research**

Based on the results and limitations of the current study, a number of possible directions for future research are apparent. Below, we outline the possible future directions that will better improve the methodology and limit possible confounds present in the study design.

### **5.3.1 Limitations on Age Range**

Within the available literature examining the relationship between depression and olfactory functioning, there remains a major limitation. As discussed in section 2.6.1.3 and 5.1.2, age of participants may have greatly impacted the olfaction scores of this current study. The inclusion of participants older than 60 and even, as seen in the current study, 50 and over may be introducing the

confound of age-related decline rather than depression-related decline. In order to address and reduce this possible limitation, changing the age range of the participants included in the study seems advisable. Including only participants between the age of 18 to 50 may reduce the possibility of age-related decline in cognition and limit the observed effect to primarily depression. While many studies do limit participation to 65 or 70 (Clepce et al., 2010; Gross-Isseroff et al., 1994; Lahera et al., 2016; Postolache et al., 2002; Swiecicki et al., 2009), it may be more beneficial to include participants in the age range of 50 or 60 and above in studies that are examining olfaction and depression in a senior/elderly population. Examining the olfactory functioning of 50 and above would allow for determination the point at which age impacts olfaction more than depression. These studies may still be compared to populations younger than 50 in order to observe the impact of depression across a wide range of age and determine if the findings of our current study are replicable. However, the lack of clear and conclusive results as to the relationship between depression and olfaction require elimination of as many confounds as possible. The limiting of age range may provide greater insight and further understanding as to how and if depression impacts olfactory functioning and how treatment plays a role in this relationship.

### **5.3.2 Inclusion of a Cognitive Measure**

The conclusions as to the difference between olfactory functioning in the two age cohorts were the possibility that there is an impact on the general cognitive functioning and the possibility that a factor that was not tested for or assessed is causing such a significant difference. These two possibilities both lead to the same solution for further investigation and determining if there is support for one over the other. This solution being the inclusion of a cognitive battery in the testing procedure. Inclusion of a cognitive battery would allow for a better assessment of the impact of age on the olfaction of depressed given that discrimination was the measure that was significantly impacted and that discrimination and identification measures are representative of higher olfactory and cognitive processes (Atanasova et al., 2008; Cumming et al., 2011; Negoias et al., 2010; Patel & Pinto, 2014). Inclusion of a cognitive battery would also be beneficial to a number of other findings and possible confounds associated with the study.

While there was no significant difference within the depressed group before and after treatment, the addition of a measure of cognitive functioning may provide further insight into treatment response and further explain why there was no difference. Previous studies have demonstrated an impact of depression on cognition and with olfaction being a cognitive process, an improvement or lack thereof in cognitive scores of depressed may provide further insight as to if depressed participants are improving after iTBS and further correlate with depression or olfaction scores. Additionally, if a correlation and relationship were to be found between the cognitive measure and the measures of olfactory discrimination and/or identification, greater insight could be gained as to how depression impacts olfactory functioning and how well these olfaction tests measure cognition.

### **5.3.3 Expansion of Olfactory Measurements**

One of the major limitations of the current study was the unfamiliarity with a number of the target scents in the identification test (for further evaluation, see section 5.2.1). A possible way to address this would be to expand the range and number of olfactory measurements employed. In addition to the use of the Sniffin' Sticks Extended Test, it may be advisable to add a measure of olfactory identification that does not add a substantial amount of time to appointments and has been validated to the North American population from which the participants are sampled. One such test could possibly be the University of Pennsylvania Smell Identification Test (UPSIT). This self-administered test uses microencapsulated odorants that are released by scratching the odor-impregnated test books and divided over 40 to 50 questions (Doty, Shaman, & Dann, 1984; Doty, Shaman, Kimmelman, & Dann, 1984). The odor stimuli included in the test have a wide range of qualitative odors, including both pleasant and unpleasant odors, and are comprised of single and multiple component odorants (Doty, Shaman, Kimmelman, et al., 1984). Similar to the Sniffin' Sticks test, each of the odorants have four options and the participant is required to choose one of the four options – a forced choice paradigm. The UPSIT is a highly reliable test that has been validated within the North American population and as such may be a beneficial addition to the current methodology. While the Sniffin' Sticks Extended Test does have benefits in that is a relatively

efficient testing method that involves more than one measurement of olfaction, the addition of the UPSIT to the experimental design with the Sniffin' Sticks test may provide better comparative measures and a way to validate the efficacy of the Sniffin' Sticks Identification task in the North American population. The addition of the UPSIT may also address if there is an issue within the methodology of a lack of unfamiliarity based off of differences in experience or if this was an isolated occurrence. While it would extend the length of the visit slightly, it may provide greater insight that could not be gained without it.

#### **5.3.4 Expansion of Sample Size**

Another major limitation in the literature and in the current study, the sample size of the participants was rather small – often too small to provide enough power. It is evident that a larger sample size must be included in order to confirm or disprove the findings of the current studies and those in the literature. In particular, expansion of the sample size may better explain why there is a discrepancy regarding which aspect of olfaction is impacted in depression, olfactory threshold or higher cognitive olfactory processes. It may be possible that the observed significant differences in olfactory threshold are not due to a direct impact on threshold, but instead either a general difference between the small sample of participants or an impact of depression on processes upstream. Replications or expansions of these studies with larger participant numbers may provide further insight into these observations and clarify the mixed results reported in the literature. Expansion of those included to approximately 50 or above may allow, depending on the study design, for increased power and better ability to examine the relationship between depression and olfaction. A power analysis would be needed to determine the exact number but above 50 in each participant group (depressed and control) would be a favorable addition to further expansions of the current methodology.

#### **5.3.5 Comparison of Olfaction in BD and MDD**

As with the literature examining the olfactory functioning of MDD patients, the conclusions as to if and which aspects of olfaction are altered in BD patients is mixed (Hardy et al., 2012; Lahera et al.,

2016). While the current study was not able to properly compare the olfactory functioning between these two groups due to too small a sample size of BD participants, this represents an area of potential for future research. Comparison of the two disorders in a large sample size may allow for discernment of a significant difference between the two at baseline, if a difference exists, and examination of how treatment impacts the olfactory functioning. Further comparison within the BD group could be conducted to determine if there is a difference in BD participants in manic/hypomanic versus depressive episodes. This comparison may provide greater insight as to how olfaction is impacted in BD and if there is a difference between mood states. Breaking down the BD episodes would allow for comparison of both manic/hypomanic and depressive episodes with MDD to determine if the olfactory functioning of BD participants in depressive episodes is impacted in a similar manner as MDD. Expansion of research into comparison of MDD and BD may provide greater insight into the relationship between depression and olfaction and how related disorders impact this relationship.

### **5.3.6 Comparison of iTBS, ADM, and Treatment Naïve Depressed**

Another limitation of the study was the use and history of use of ADM in depressed participants. Many of the depressed participants who were referred for iTBS and enrolled in the study had a long history in terms of the previous medications used. Since ADMs have been shown to improve olfactory functioning (as explained further in section 5.2.2), the results of the current study are complicated by the potential confound of ADM already positively impacting olfactory functioning. As such, it may be advantageous to examine the impact of iTBS on olfactory functioning in depressed participants who have no history of treatment. This would eliminate the potential confound introduced by ADMs and may also allow for insight as to the variation within individuals as to response to iTBS. Under this expansion of the methodology, participants without a history of treatment for depression would receive iTBS as their initial treatment and olfactory functioning would be examined before, during, and after the scheduled iTBS treatments. The addition of a visit during treatment may provide further insight as to if there is an observable change or improvement during treatment that was not observed post-treatment. As well,

including a follow-up visit approximately 2-4 months after the cessation of treatment may also be advantageous. However, if some participants receive maintenance treatments in addition to the 25 scheduled, the 2-month follow-up time may be varied between participants with some receiving more iTBS sessions than others. While this may be a beneficial expansion of the literature since many of those receiving iTBS have a long treatment history, iTBS is not often seen as a first line treatment and therefore may not be possible or appropriate with the current guidelines to examine this treatment in a treatment naïve population. A potential solution to minimize the impact of ADMs treatment and as a measure to reduce the potential confound of resistance to treatment would be to add a measure of treatment history and determine if there is an olfactory difference in those who have undergone multiple therapies before being referred to iTBS. While the current study did ask for a recent history of medication, it was not possible to analyze this in greater depth due to the limit of information that was gathered.

One aspect of the literature that is lacking is the examination of ADM over the course of the treatment from initiation. Though there have been some studies that have examined the impact of ADM on olfactory dysfunction associated with depression (Clepece et al., 2010; Gross-Isseroff et al., 1994), the number of studies are small and not enough were conducted in the human population to offer reliability and validity to these findings. Replications of these studies using a treatment naïve population with a greater number of measurement time points, similar to as suggested for iTBS, may provide greater insight into the relationship between depression and olfaction and the role that treatment with ADMs has in this relationship. To address the issue of history of ADMs, the potential impact needs to be validated and replicated further with a greater number of time points.

Likewise, there have been no studies that have compared treatment methods to each other in treatment naïve populations. A combination of the proposed alterations to the treatment history of the depressed group may provide a great deal of insight and information that has not yet been examined. In this methodology, the depressed group would be subdivided into the suggested iTBS with no treatment history and ADM with no treatment history, along with an additional group of treatment naïve depressed

participants who will be placed in a wait-list condition and later referred to one of the experimental groups. The treatment naïve group will be employed to ensure that there are no major changes between the time points in the depressed group that are not associated with treatment. A control group should still be used as measure of non-depressed olfactory functioning from a sample that is derived from a similar geographic area as those in the depressed group. There has yet to be any studies that have compared the impact of iTBS, ADMs, and no treatment in olfactory functioning of depressed participants. Three major analyses could be achieved using this methodology. First, the impact of treatment and the potential differences in treatment on olfactory functioning could be analyzed and contrasted with no treatment depressed group and healthy control group. These particular contrasts may provide valuable insight as to if one form of treatment is more efficacious in restoring olfactory functioning. Second, this methodology would also allow for a greater pool of data from depressed participants at baseline that has yet to be achieved within the literature - addressing the issue of limited sample size. Third, application of this methodology would allow for examination of these treatment groups individually over time and against each other at multiple time points. These analyses could improve upon the current methodologies for examining olfactory functioning in depression and address a number of limitations in the research, in particular the lack of multiple time points and small sample sizes.

Moreover, the comparison of iTBS and ADMs as first line treatments may allow for greater awareness of the variation within these populations with regards to treatment response, or often lack thereof. The contrasting of these populations and examination of demographic features may elucidate similarities among ADM non-responders and iTBS responders and vice versa that could greatly contribute to the current clinical practice. While ADMs are often the first treatment used for depression, there are some that benefit more iTBS but must try a number of different options before referral. If a number of unique variants that are associated with iTBS or ADMs can be found, treatment of depression may be more efficient and less stressful for those who are not responding.

The proposed methodology, while seeming to be a viable expansion for future research, may not be possible in the near future given the current guidelines for the referral to iTBS and would require a great deal of resources in order to recruit enough participants in each arm of the depressed group. As such, it may be beneficial to divide the current proposed methodology into a number of different experimental procedures using the same methodology for each experiment. For example, one study may examine the olfactory functioning and impact of iTBS in treatment naïve depressed and contrast this to non-depressed controls. Another study may examine the impact of ADM, either one or more, on olfaction at multiple time points in comparison to treatment naïve and non-depressed. If the same methodology is employed in both studies, the data from these studies could be combined after the fact and compared outside of the parameters of each of the studies. This would eliminate the burden on the researchers in terms of recruitment and time required to test all participants in each of the arms of the depressed group at multiple time points. The completion of one experimental design before the other may also find a number of limitations that could be addressed in the future study and determine if the additional time points have an impact. Regardless of the current resources for this research, the suggested examination of a number of different treatments at multiple time points could vastly improve the understanding of the relationship between depression and olfaction, as well as the role that treatment has on improvement in both.

## **5.4 Conclusions**

Within the confines of the current study two primary objectives were set. Although our results did not support the primary objective, which predicted a significant change in olfactory functioning in patients with MDD or BD following a course of iTBS compared to non-depressed controls, we did find evidence to support our secondary objective of determining if olfactory functioning improves with an improvement in depression severity. Despite the lack of improvement in depression severity in the depressed group, examination of correlations between olfaction measures and depression severity showed that as depression severity increases, olfactory functioning declines. These correlations provide further substantiation of a reciprocal relationship and application of the theory of a reciprocal relationship to our

findings does find support in that neither depression severity nor olfaction improves with iTBS. While significant findings and change would provide more concrete support, they lend further support for future research regarding this topic and the foundation for the possibility of a reciprocal relationship.

It is notable that the limitations apparent in the study, while impactful, may offer an explanation as to why no significant difference was observed and why our primary objective was not met. Primarily, the age of the participants may have introduced confounds associated with age-related cognitive and general decline. The significant difference between the age cohorts regarding olfaction and the lack of significant difference with regards to depression severity indicates the influence of factors not related to depression but related to age instead. Further, the impact and use of ADMs in the depressed population may justify the lack of change in olfactory functioning within the depressed group. The ability of ADMs to improve olfactory functioning and the use of ADMs in the depressed group may have alleviated the dysfunction before commencement of iTBS and thus no change could be expected even with the introduction of another treatment method. What's more, the limited sample size and the lack of familiarity with target scents may also have impacted the current findings by limiting the power of the results and increasing the effect of variation, or lack thereof, within the groups.

Despite the limitations, the potential for future research is vast. The current study offers insight into the major limitations and issues within the literature and highlights the potential for improvement, as addressed in sections 2.6 and 5.2. A number of possible changes may provide a stronger methodology and therefore stronger, more reliable results. The inclusion of one of the suggested changes/additions to future replications of the methodology would be beneficial. However, inclusion of all of the suggested changes/additions should be feasible and ideal to properly examine the olfactory functioning in depressed participants receiving treatment. Integration of these changes and the expansion of the methodology to allow for comparison among multiple treatment methods (see section 5.3.5 for further explanation) would provide larger and more expansive data that would permit deeper investigation of the relationship between depression and olfaction. Expansion of the current methodologies and adherence to a prescribed standard for how to observe olfactory functioning in depression (see section 2.6.1.1 and 2.6.1.2 for further

explanation) may greatly improve our understanding of the impact of depression on a global scale and with regards to sensory processing systems.

Olfactory functioning in depression, although not often seen as a major concern to clinicians, does greatly impact the quality of life and the experience of the sensory environment of the depressed individual. In particular, olfaction significantly impacts the motivation towards and the enjoyment and experience of eating and preparing food (Croy et al., 2014; Kohli et al., 2016); all of which are lost in depressed and cause major nutritional deficits. The loss of nutrition plays a large role in the physical manifestation of depression and acts in tandem with the reduced sleep to impact cognition - concentration and motivation in particular. Though only small, loss of olfaction does contribute the cycle of depression by worsening the experience of symptoms, impacting motivation, and contributing to the cognitive decline. By examining the relationship between depression and olfaction, the underlying neurological mechanisms and reciprocity between the two systems can be elucidated. The results of such studies would provide greater insight into the global and focal impact of depression on cognition and sensation. A better understanding of depression on the sensory experience may open the proverbial door to alternative or adjunctive treatments focused on enrichment and improvement of the sensory environment of the depressed individual as a way to alleviate some of the depression severity and stimulate systems associated with improved mood. However, in order to do so, further replications of the suggested methodology with the proposed improvements and the commitment of clinicians to include an olfactory examination as part of their clinical practice is needed. This is an area of research that has a great deal of potential and could greatly contribute to and expand our current understanding of the experience and manifestation of depression in the human brain.

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