THE EFFECTS OF ELECTROCONVULSIVE THERAPY
OR REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION
ON OLFATORY SENSITIVITY AND IDENTIFICATION
IN INDIVIDUALS WITH DEPRESSION

by

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Abstract

Background: Previous research has found links between olfactory deficits and depression. Olfactory ability is restored with successful treatment with antidepressant medication. Electroconvulsive therapy (ECT) and repetitive transcranial magnetic stimulation (rTMS) are two effective treatments for depression. It is not known whether these somatic treatments may, similarly to pharmacotherapy, restore olfactory sensitivity and identification ability in individuals with depression.

Objectives: The objective of the present study was to determine whether treatment with ECT or rTMS is associated with improvement in olfactory sensitivity or identification in individuals with depression.

Methods: Six patients receiving ECT and three patients receiving rTMS completed the study. Before beginning treatment and 20-30 days after their first treatment, patients were assessed using the Smell Threshold Test (STT), Smell Identification Test (SIT), Hamilton Depression Rating Scale (HDRS), Beck Depression Inventory (BDI), and Snaith-Hamilton Pleasure Scale (SHPS). The control group consisted of nine matched healthy participants.

Results: There was no significant difference between the ECT, rTMS, and control groups for olfactory sensitivity either before or after treatment. At both testing visits, the rTMS group performed significantly worse on olfactory identification compared to control, while the ECT group performed comparably to control. Olfactory identification ability was significantly correlated with HDRS score at baseline but not after treatment. Olfactory performance was not correlated with BDI or SHPS score.

Conclusions: The results of this pilot study suggest that individuals with depression may not have decreased olfactory sensitivity ability compared to healthy controls. However, in those who do exhibit poor olfactory identification, rTMS may be effective in restoring sense of smell. Further research is needed to determine whether olfactory deficits are caused by depressive symptoms, and whether ECT may also restore olfaction in individuals who have olfactory deficits. Determining the links between olfaction and depression may be important for promoting the early diagnosis and treatment of depression, and for improving quality of life and everyday functioning.
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List of Abbreviations

ANOVA: Analysis of variance

APA: American Psychiatric Association

BP: Bipolar disorder

BDI: Beck Depression Inventory

BDNF: Brain-derived neurotrophic factor

CGI-S: Clinical Global Impression Severity Scale

CPAP machine: Continuous positive airway pressure machine

DBS: Deep brain stimulation

DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th edition

ECT: Electroconvulsive therapy

fMRI: Functional magnetic resonance imaging

HDRS: Hamilton Depression Rating Scale

HPA axis: Hypothalamic-pituitary-adrenal axis

HRT: Hormone replacement therapy

HSREB: Health Sciences Research Ethics Board

MDD: Major depressive disorder

MDE: Major depressive episode

MAOI: Monoamine oxidase inhibitor

NGF: Neurotrophic growth factor

NT-3: Neurotrophin-3

OB: Olfactory bulb

OBX: Olfactory bulbectomy

OFC: Orbitofrontal cortex

OSN: Olfactory sensory neuron
PEA: Phenyl ethyl alcohol

rTMS: Repetitive transcranial magnetic stimulation

SAD: Seasonal affective disorder

SD: Standard deviation

SHPS: Snaith-Hamilton Pleasure Scale

SIT: Smell identification test

SNRI: Serotonin-norepinephrine reuptake inhibitor

SSRI: Selective serotonin reuptake inhibitor

STT: Smell threshold test

SGZ: Subgranular zone

SVZ: Subventricular zone

TCA: Tricyclic antidepressant
Chapter 1: Introduction

1.1 General Overview

Olfaction and emotion are functionally and anatomically linked. Individuals with depression are more likely to experience olfactory deficits, though the extent to which olfaction is affected is not clear. Some previous research has found that individuals with depression have decreased olfactory sensitivity (e.g. Pause, Miranda, Goder, Aldenhoff, & Ferstl, 2001; Lombion-Pouthier, Vandel, Nezelof, Haffen, & Millot, 2006) but no deficit in olfactory identification (e.g. Amsterdam, Settle, Doty, Abelman, & Winokur, 1987). However, other studies have found conflicting results (e.g. Gross-Isseroff et al., 1994; Swiecicki et al., 2009), due to differences in study methodology, participant characteristics, and other factors.

Antidepressant treatments that act on the brain regions common to olfaction and emotion may have effects on olfactory ability. Studies have found that successful treatment with antidepressant medication can improve olfactory performance (Gross-Isseroff et al., 1994; Pause et al., 2001). Considering that electroconvulsive therapy (ECT) and repetitive transcranial magnetic stimulation (rTMS) are two effective treatments for depression, it is possible that these somatic treatments may also have an effect on olfaction.

One study (Henkin, Potolicchio, & Levy, 2011) explored the effects of rTMS on olfaction, but focused primarily on olfactory distortions. To our knowledge, no other studies have investigated the effects of ECT or rTMS on olfactory loss. In the present study, we explore whether treatment with these two treatments may restore olfactory sensitivity and identification ability in individuals with depression.

Considering the impact of olfaction on everyday functioning (Hummel & Nordin, 2005), finding a link between ECT, rTMS, and olfactory performance may hold implications for improving quality of
life in patients with depression and olfactory disorders. It may also be used as a potential tool in the early
diagnosis and treatment of depression.

1.2 Thesis Organization

This thesis conforms to the Queen’s University School of Graduate Studies and Research
guideline, “General Forms of Thesis”. The following chapter is a review of the literature on the links
between depression and olfaction. The final chapter details the present study on the effects of ECT and
rTMS on olfaction in individuals with depression.
Chapter 2: A Review of Depression and Olfaction

2.1 Introduction

The purpose of this chapter is to review the current knowledge on affective disorders and olfaction. There exist strong connections between depression and olfaction; the focus of this chapter will be on major depressive disorder, though other conditions such as bipolar disorder and seasonal affective disorder will be mentioned. Ideas for future research will also be proposed, including the potential use of olfactory testing in individuals with depression, which may hold important implications for improving diagnosis, treatment, and quality of life.

2.2 Affective Disorders

Affective disorders are a group of conditions whose major characteristic is an alteration of mood and emotions, such as a depressive or happy mood. These disorders, which include depressive disorders and bipolar disorders, typically have complex causes, including genetic, developmental, and environmental factors. For many individuals, the conditions are lifelong and recurring, and even with successful treatment, there are residual symptoms that often never fully improve. As a result, there can be a huge negative impact on quality of life for people living with affective disorders, with disability in areas such as physical, social, and occupational functioning (Keller & Boland, 1998).

2.2.1 Depressive Disorders

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; American Psychiatric Association [APA], 2013), depressive disorders are characterized by symptoms such as a low or irritable mood, along with somatic and cognitive changes, leading to impaired functioning at school,
work, home, or in social settings. They include such conditions as major depressive disorder (MDD) and persistent depressive disorder (dysthymia).

MDD is characterized by one or more major depressive episodes (MDE), with significant changes in mood/affect and cognition lasting two or more weeks. Specifically, there is a depressed mood or a loss of interest or pleasure. There may also be significant changes in weight or appetite, sleeping patterns, or psychomotor activity/movement; low energy; poor concentration/decisiveness; feelings of worthlessness or guilt; or thoughts of death or suicide (APA, 2013).

In terms of both prevalence and disease burden, MDD is one of the biggest modern public health concerns (Greden, 2001). The lifetime prevalence of MDD in Canada is 11%, with more women experiencing the condition than men (Patten et al., 2006; Pearson, Janz, & Ali, 2013). Though MDD is only responsible for 1% of deaths, it is the leading cause of years lost due to disability (World Health Organization, 2009). There can be significant long-term effects on physical, social, and role functioning (Keller & Boland, 1998), affecting health, social relationships, and work.

The course of MDD can be quite variable, but in most cases, individuals have recurrent MDEs with periods of remission in between. In fact, the majority of patients experience more than one episode in their lifetime (APA, 2010). Notably, with each recurrence, individuals are more likely to have subsequent episodes, and the time to the next recurrence is shorter (Keller & Boland, 1998). Thus, early diagnosis and successful treatment are of the utmost importance for improving quality of life.

Persistent depressive disorder has many of the same diagnostic criteria as MDD. However, persistent depressive disorder is more chronic, with the depressed mood lasting for two or more years (APA, 2013). The lifetime prevalence worldwide is 3.6% of individuals (Bland, 1997). Due to the chronicity of this disorder, there can be severe impairment of everyday functioning, just as in MDD.
2.2.2 Bipolar and Related Disorders

In terms of symptoms, bipolar and related disorders (including bipolar I disorder and bipolar II disorder) can be seen as being partway between depressive disorders and psychotic disorders (APA, 2013). The lifetime prevalence of bipolar disorders in Canada is approximately 2-3% (Patten et al., 2006; Pearson et al., 2013), affecting men and women at relatively equal rates.

Bipolar I disorder is characterized by at least one manic episode, with elevated, expansive, or irritable mood, or increased energy, lasting for one week or more. Specific symptoms may include an overinflated sense of self-esteem, decreased need for sleep, pressured speech, racing thoughts, difficulty concentrating, increased activity or agitation, and risky behaviours (APA, 2013). While most individuals with bipolar I disorder experience an MDE in their lifetime, it is not a diagnostic requirement.

In comparison, bipolar II disorder is characterized by at least one MDE and one hypomanic episode, but no manic episode. A hypomanic episode is similar to a manic episode, but lasting for at least four consecutive days, and with less marked impairment in functioning. However, as with persistent depressive disorder, the illness tends to be chronic, resulting in long-term impairment of functioning.

2.3 Treatments for Depression

Choice of treatment often depends on many factors, including the severity of the condition. Psychotherapy, pharmacotherapy, or a combination of both are the main recommended treatment modalities for MDD (APA, 2010), while other treatments such as electroconvulsive therapy (ECT) or repetitive transcranial magnetic stimulation (rTMS) can also be effective.

Unfortunately, individuals with depression do not always receive adequate treatment for their condition. Forty-four percent of people suffering from MDD do not seek treatment (Kessler, Merikangas, & Wang, 2007), and for those who do seek treatment, few receive appropriate treatment for a sufficient
length of time (Hirschfeld et al., 1997). There are many reasons for inadequate treatment, including failure to recognize symptoms, underestimation of severity, misdiagnosis, and stigma (Hirschfeld et al., 1997; Greden, 2001).

For many patients, antidepressant treatments are relatively effective in the short-term. However, without continuous maintenance treatment, relapses tend to occur. One in four patients who recover will relapse within 12 weeks of recovery (Keller, Shapiro, Lavori, & Wolfe, 1982). The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study showed a relatively low cumulative remission rate of 67% over four levels of pharmacotherapy and psychotherapy, with most patients requiring multiple treatment steps to achieve remission (Gaynes et al., 2009). Recovery rates decline steadily with length of episode, where only 50% of patients recover within six months, and 11.5% of patients remain ill even after five years (Keller et al., 1982).

Cases of depression that do not respond adequately to treatment are termed treatment-resistant depression. Treatment-resistant depression is associated with poor clinical outcomes and impaired long-term functioning (Cusin & Dougherty, 2012). For example, there is an increased risk of mortality, both from suicide and from general medical comorbidities (Lisanby, 2007). Thus, despite a variety of treatment options, mood disorders are often life-long afflictions.

2.3.1 Pharmacological Treatments for Depression

Antidepressant medications are generally effective for both acute treatment and relapse prevention in depression (Greden, 2001), though there is some debate as to effectiveness in the clinical setting (e.g., Moncrieff & Kirsch, 2005; Dimidjian et al., 2006). A meta-analysis by Arroll et al. (2005) found that both tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) are effective for treating depression, compared to placebo. In fact, there is comparable effectiveness for the
various classes of medications, including TCAs, SSRIs, serotonin-norepinephrine reuptake inhibitors (SNRIs), bupropion, and monoamine oxidase inhibitors (MAOIs; APA, 2010).

However, while pharmacotherapy is effective for most individuals with MDD, this is not the case for everyone. Approximately 50% of patients do not respond to first-line antidepressant medications (Gaynes et al., 2009), while 20-30% do not respond to two or more antidepressants (Cusin & Dougherty, 2012). In these cases, alternative treatment options can be explored, including somatic treatments such as ECT or rTMS. Though one review (Rasmussen, 2008) found a 59% response rate for ECT compared to 38% for rTMS, other studies have found that both ECT and rTMS give similar lasting clinical benefits (Dannon, Dolberg, Schreiber, & Grunhaus, 2002; Martin et al., 2002).

2.3.2 Electroconvulsive Therapy (ECT)

ECT involves passing electrical stimulation through the brain to induce seizure activity. Originally developed as a treatment for schizophrenia, ECT is known to be effective for both unipolar and bipolar depression (Lisanby, 2007), and is especially successful for depression that does not respond to pharmacotherapy (Fink, 2000; Lisanby, 2007; APA, 2010). ECT surpasses pharmacotherapy in terms of both the rapidness and the degree of reduction in depressive symptoms (Folkerts et al., 1997). In fact, it has the highest response and remission rates of all antidepressant treatments (UK ECT Review Group, 2003; Pagnin, de Queiroz, Pini, & Cassano, 2004), with up to 90% of patients showing some improvement (APA, 2010) and 75% achieving remission (Husain et al., 2004).

There can be some adverse effects to ECT; however, they are generally transient or curable. Adverse effects, which may include amnesia, aches, nausea, fatigue, and cognitive impairment (Fink, 2000; Cusin & Dougherty, 2012), typically resolve soon after completing treatments, and can also be minimized depending on the ECT technique used. The high relapse rates after ECT (Fink, 2000) can be
reduced with the administration of maintenance treatments. Overall, ECT can be an effective treatment option for depression.

2.3.3 Repetitive Transcranial Magnetic Stimulation (rTMS)

rTMS involves applying rhythmic, repetitive magnetic stimulation to modulate cortical excitability (Martin et al., 2002; Gross, Nakamura, Pascual-Leone, & Fregni, 2007). The insulated coil placed near the surface of the scalp creates a magnetic field that induces current flow in neural tissue, affecting brain circuitry (O’Reardon et al., 2007).

As a somatic treatment, rTMS has historically had less supporting evidence of antidepressant effectiveness compared to ECT (APA, 2010). Some studies (e.g. Martin et al., 2002) have found no difference between rTMS and sham for reducing depressive symptoms. However, there is an expanding body of evidence for rTMS as an effective treatment for depression. Recent, large multi-site randomized controlled trials have shown the effectiveness of rTMS compared to sham (O’Reardon et al., 2007; George et al., 2010). Nine weeks of rTMS gives a 22.6% rate of remission, making rTMS comparably effective to pharmacotherapy (O’Reardon et al., 2007). Outside of research studies, similar effectiveness has been shown in clinical settings, with patients with treatment-resistant depression showing over 50% response rate and over 25% remission rate (Carpenter et al., 2012; Connolly, Helmer, Cristancho, Cristancho, & O’Reardon, 2012). Furthermore, the benefits appear to last with maintenance treatment, with 62% of patients maintaining response to treatment (Connolly et al., 2012), which is comparable to other treatment options for depression. Another advantage of rTMS is its non-invasive and well-tolerated procedure; adverse effects are generally limited to headaches and facial pain (Cusin & Dougherty, 2012). A meta-analysis by Gross et al. (2007) shows that modern rTMS is more effective than previous studies may have shown, and presently, rTMS is considered a good treatment option for depression.
2.4 Olfaction

Compared to other senses such as sight or hearing, sense of smell generally plays a less prominent and obvious role in everyday functioning for the human species. However, olfaction is one of our oldest senses, and serves as a rich unconscious background to life (Sacks, 1985), adding richness, variety, and complexity.

2.4.1 The Olfactory Pathway

The route of an olfactory signal from our nose to our brain is unique in that it is a short, two-synapse pathway from the periphery to the cortex. Unlike all other sensory modalities, olfactory information is not obligatorily relayed by the thalamus, but can instead travel directly to the olfactory cortex (Pause et al., 2003; Gottfried, 2006). The olfactory cortex includes the piriform cortex, periamygdalar cortex, insula, and entorhinal cortex (Soudry, Lemogne, Malinvaud, Consoli, & Bonfils, 2011). Olfactory information is also further relayed to other regions, such as the orbitofrontal cortex, amygdala, hypothalamus, thalamus, hippocampus, subiculum, and cingulate gyrus (Pollatos, Albrecht, et al., 2007; Soudry et al., 2011; Schablitzky & Pause, 2014)

2.4.2 Brain Regions in Olfaction and Emotion

Odorant molecules in the nasal cavity are detected by olfactory sensory neuron (OSNs) in the olfactory epithelium. The axons of the OSNs form the olfactory nerve, going to the olfactory bulb (OB). As the name suggests, the olfactory bulb plays a key role in olfaction. It does not have a known function in mood and emotion. While the olfactory nerve is the main input for the OB, there is also top-down information from numerous areas including the neocortex, amygdala, and hippocampus (Carmichael, Clugnet, & Price, 1994). Axons from the OB then directly project to the olfactory cortex, mainly the piriform cortex (Zatorre, Jones-Gotman, Evans, & Meyer, 1992), but also the anterior olfactory nucleus,
basal forebrain, olfactory tubercle, amygdala, periamygdaloid cortex, and entorhinal cortex (Carmichael et al., 1994).

Like the OB, the piriform cortex has no role in emotion, but plays an important role in olfaction. As part of the primary olfactory cortex, it receives the majority of the inputs from the OB (Gottfried, 2006). The piriform cortex is involved in odour perception (Zatorre et al., 1992), intensity (Pollatos, Albrecht, et al., 2007), identification, and hedonics (Gottfried, 2006). It also forms links between olfactory stimuli and behavioural, cognitive, and contextual information (Haberly, 2001). After processing the olfactory information, the piriform cortex projects to areas such as the insula, amygdala, entorhinal cortex, orbitofrontal cortex, hypothalamus, and hippocampus (Soudry et al., 2011).

The insula is involved in both olfaction and emotion. It plays a role in odour perception (Zatorre et al., 1992), particularly for valenced odours (Soudry et al., 2011). It also integrates taste and smell to represent flavour (Rolls, Kringelbach, & De Araujo, 2003). In addition, it is activated by negative emotion (Lane, Reiman, Ahern, Schwartz, & Davidson, 1997).

The amygdala also plays a role in both olfaction and emotion. It is involved in odour perception (Soudry et al., 2011) intensity (Anderson et al., 2003; Pollatos, Albrecht, et al., 2007), and the emotional processing of olfactory stimuli (Zald & Pardo, 1997). It is activated by valenced odours (Winston, Gottfried, Kilner, & Dolan, 2005), especially aversive or unpleasant odours (Zald & Pardo, 1997). In terms of emotion, the amygdala detects emotional cues (Soudry et al., 2011). It is activated by both positive and negative emotions, but especially fear and disgust (McNish & Davis, 1997; Costafreda, Brammer, David, & Fu, 2008). It also plays a role in reward, attention, perception, and memory (Ledoux, 2007).
The anterior cingulate cortex is activated by both pleasant and unpleasant odours (Rolls et al., 2003; Soudry et al., 2011), as well as emotions experienced during physical, moral, or social pain (Soudry et al., 2011).

The orbitofrontal cortex (OFC) receives input from the olfactory tubercle, piriform cortex, amygdala, and entorhinal cortex, and sends outputs back to these areas (Gottfried, 2006). As a secondary olfactory region, the OFC helps with odour perception (Zatorre et al., 1992), identification, discrimination, hedonics, and memory (Pollatos, Albrecht, et al., 2007). It is activated in tasks that involve judging the familiarity of an odour (Royet et al., 1999). Like the amygdala and insula, it is especially activated by aversive or unpleasant odours (Zald & Pardo, 1997). In terms of emotion, the OFC helps integrate emotion into cognition (Soudry et al., 2011). In addition, the OFC plays a role in reward and decision-making (Kringelbach, 2005).

The hippocampus plays an indirect role in olfaction, receiving input from the entorhinal cortex (Soudry et al., 2011). It helps with olfactory memory and learning (Kesner, Gilbert, & Barua, 2002), especially longer-term memory for odour recognition (Dudchenko, Wood, & Eichenbaum, 2000). Similarly, it is important for emotion in terms of emotional memories (Phelps, 2004) and adding context to emotional situations (Ledaux, 1995).

2.4.3 Olfactory Functions

There are several different classes of olfactory functions (Naudin et al., 2012; Schablitzky & Pause, 2014). Olfactory sensitivity is a measure for olfactory threshold, or the lowest detectable concentration for a given odorant. Olfactory identification is the ability to perceive and name an odorant. Olfactory discrimination is the ability to differentiate between a set of odorants. There are also various psychological attributes related to olfaction, including hedonics (pleasantness or unpleasantness of an odorant), intensity (perceived strength of an odorant), and familiarity (recognisability of an odorant).
The olfactory functions can be divided into lower- and higher-order processes, depending on which areas of the brain are involved. Olfactory sensitivity is generally thought of as a basic chemosensory process, since it involves the peripheral primary olfactory neurons. Olfactory identification and discrimination, as well as the psychological processes, are considered higher-order processes, involving the neocortex (Martzke, Kopala, & Good, 1997). More specifically, olfactory identification is classified as a semantic memory task (Larsson, Finkel, & Pedersen, 2000; Hedner, Larsson, Arnold, Zucco, & Hummel, 2010), since it requires knowledge of a specific odour.

### 2.4.4 Olfactory Dysfunction

Olfactory disorders are extremely prevalent in the general population. An estimated one in five individuals are affected (Croy, Negoias, Novakova, Landis, & Hummel, 2012), and the actual rate may be even higher due to underdiagnosis and inaccurate self-report (Murphy et al., 2002). Olfactory disorders can be quantitative, such as hyposmia, which is partial olfactory loss, and anosmia, which is complete olfactory loss. Olfactory dysfunction can also be qualitative, such as parosmia, in which smell distortions are experienced, and phantosmia, in which smells are perceived when there is no odorant present.

Olfactory loss is more prevalent with age (Murphy et al., 2002; Doty & Kamath, 2014), with olfactory ability peaking in early adulthood (Doty, Shaman, & Dann, 1984). More than half of individuals over 65 years of age experience major olfactory impairment (Doty, Shaman, & Dann, 1984). Olfactory impairment is more prevalent in men and current smokers compared to women and non-smokers (Doty, Shaman, & Dann, 1984; Murphy et al., 2002).

There are many ways that olfactory dysfunction can occur. The most common causes are infections, inflammation, injury/trauma, and chemical exposure, though many cases are also idiopathic (Wysocki & Gilbert, 1989; Temmel et al., 2002; Blomqvist, Bramerson, Stjarne, & Nordin, 2004; Croy,
Conductive olfactory loss occurs when an obstruction in the nose prevents odorant molecules from reaching the olfactory epithelium, e.g. nasal congestion. This type of olfactory loss can generally be treated with anti-inflammatory therapy or surgery. Conversely, sensorineural olfactory loss, which involves damage to the olfactory epithelium or the neural pathways, is much harder to treat (Lee, Mo, Shim, Ahn, & Kim, 2008).

Olfactory loss can have a huge detriment on quality of life (Miwa et al., 2001; Blomqvist et al., 2004; Hummel & Nordin, 2005; Smeets et al., 2009). Thirty-four percent of individuals with olfactory disorders report dissatisfaction with life, compared to 3% of individuals with normal olfaction (Miwa et al., 2001). Olfactory dysfunction can lead to impairment in daily activities, with the most common complaints being related to food, safety (e.g. detecting the presence of fires or chemicals), personal hygiene, and interpersonal situations (Miwa et al., 2001; Temmel et al., 2002; Blomqvist et al., 2004; Santos, Reiter, DiNardo, & Costanzo, 2004; Croy et al., 2012; Croy, Nordin, & Hummel, 2014). Due to the close links between olfaction and taste, complaints about taste loss commonly turn out to actually be a loss of olfaction (Deems et al., 1991). Thus, olfactory dysfunction can affect appetite and eating behaviours, potentially leading to problems with weight and nutrition (Temmel et al., 2002; Blomqvist et al., 2004).

In addition to the negative consequences that can affect anyone with olfactory loss, there are additional implications for individuals suffering from psychiatric disorders. Hardy et al. (2012) found that, in individuals with bipolar disorder, poorer olfactory sensitivity was linked to poorer employment, social avoidance, and fear. Similarly, Cumming & Matthews (2011) found that poorer olfactory identification was linked to poorer social competence in patients with psychotic disorders. This emphasizes the importance of detecting and treating olfactory disorders, especially in individuals with comorbid psychiatric conditions.
2.5 Links between Depression and Olfaction

Some studies have found no difference in olfactory ability between individuals with depression and healthy controls. In one of the earliest studies on olfaction and depression, Amsterdam et al. (1987) used the Smell Identification Test (SIT) to test 51 patients with depression. Compared to healthy controls matched for age, gender, ethnicity, and smoking status, there was no difference in olfactory identification. Similar studies (Warner, Peabody, & Csernansky, 1990; Kopala, Good, & Honer, 1994) also found no difference between MDD patients and controls for olfactory identification.

Gross-Isseroff et al. (1994) used two odorants, isoamyl acetate and androstenone, to test olfactory sensitivity in 9 MDD patients before and at 3 and 6 weeks after antidepressant medications. There was no difference in olfactory sensitivity between MDD participants and healthy controls at baseline. Interestingly, MDD participants experienced improved sensitivity following treatment, to a level above those of control participants. This suggests that antidepressant medications are capable of enhancing olfactory ability.

Croy, Symmank, et al. (2014) used the Sniffin’ Sticks olfactory test battery to test 27 female MDD patients before and after psychotherapy. Compared to age-matched controls, the MDD group showed no difference in olfactory threshold or identification either before or after therapy. Some patients were already on pharmacotherapy at the beginning of the study, which may have attenuated the effects of depression on olfaction (Schabitzky & Pause, 2014). Also, the patients had high scores on the Beck Depression Inventory (BDI) and Hamilton Depression Rating Scale (HDRS) even after treatment, suggesting that the psychotherapy may not have been effective enough to affect olfaction. A similar study by Negoias et al. (2010) tested 21 individuals with MDD and found no difference in olfactory identification; however, there was significantly poorer olfactory sensitivity compared to matched controls.
Swieciicki et al. (2009) also used Sniffin’ Sticks to compare individuals with unipolar and bipolar depression. There was no difference in olfactory threshold or identification compared to controls, and there were also no olfactory differences between unipolar and bipolar depression. This study also did not control for medication use; some patients were already on antidepressant medications at the beginning of the study. Most other studies in patients with bipolar disorder (Hurwitz, Kopala, Clark, & Jones, 1988; Hardy et al., 2012) using the Smell Threshold Test (STT) and SIT have found similar results as Swieciicki et al. (2009), though Cumming & Matthews (2011) found poorer olfactory identification.

Knowing that age is associated with olfactory deficits, some studies have investigated the links between age, olfaction, and depression. Scinska et al. (2008) compared olfactory ability in older adults with and without depression. Patients were not on any psychotropic medications, and experimenters were blind to participant group. There was no difference in olfactory threshold or identification between the two groups. Other studies testing olfactory identification in elderly individuals have also found no difference between participants with and without depression (Economou, 2003; Pentzek, Grass-Kapanke, & Ihl, 2007).

Conversely, some studies have found decreased olfactory performance in individuals with depression. An early study tested olfactory performance in nine men with MDD (Serby, Larson, & Kalkstein, 1990). Importantantly, the patients stopped taking medications for at least ten days prior to testing. There was no difference in olfactory sensitivity compared to age-matched controls; however, patients performed more poorly in olfactory identification. Though the sample size was small, this study is commendable for the absence of antidepressant medication use, removing the potential confounding effects of pharmacotherapy. Other similar studies also found that MDD patients had poorer olfactory identification compared to controls for some odorants (Steiner, Lidar-Lifschitz, & Perl, 1993; Clepce, Gossler, Reich, Kornhuber, & Thuerauf, 2010).
Pause et al. (2001) tested 24 MDD patients soon after hospital admission. 18 were tested again following successful treatment with antidepressant medications. Olfactory sensitivity was significantly decreased in MDD before treatment compared to control, but there was no difference between the two groups after treatment. This suggests that pharmacotherapy restored olfactory ability in the patients. Pause et al. (2003) tested 25 MDD inpatients and found a slight but non-significant decrease in olfactory identification compared to healthy controls. However, since only two odorants were used in this study, it could be argued that the task involves olfactory discrimination rather than olfactory identification.

Lombion-Pouthier et al. (2006) used the EZUS test to measure olfactory sensitivity and identification in 49 patients with severe depression. There was a significant difference in olfactory sensitivity between depressed and healthy control participants, but no difference in olfactory identification. Thus, individuals with depression may be able to perform well at suprathreshold concentrations but not at very low concentrations. However, the EZUS test, which uses five odorant concentrations, is an inferior measure of olfactory sensitivity compared to the STT, which uses seventeen concentrations in a reverse-staircase procedure, allowing a very exact threshold to be determined.

Postolache and colleagues tested patients with seasonal affective disorder (SAD) using the STT and SIT. In one study (Postolache et al., 1999), they found no difference in olfactory sensitivity or identification compared to controls, and also no olfactory improvement following light therapy. However, in a more recent study (Postolache et al., 2002), they found that participants with SAD had a higher olfactory sensitivity compared to controls and compared to normative data. The 2002 study was of higher quality in terms of length of follow-up and experimenter blinding.

One study investigated olfaction in individuals who experienced depressive symptoms but did not have a diagnosis of clinical depression or other neuropsychiatric disorder (Pollatos, Albrecht, et al., 2007). They found a significant negative correlation between depressive symptoms and olfactory
sensitivity. This suggests that olfactory ability can be affected by emotion even in seemingly healthy individuals, which might hold implications for early diagnosis of depression.

Recently, Zucco & Bollini (2011) compared olfactory identification in unmedicated patients with mild and severe depression. They found no difference between mild depression and age- and gender-matched controls; however, individuals with severe MDD had poorer olfactory identification. Importantly, the absence of antidepressant medication use in this study eliminates potential confounding effects of pharmacotherapy. Not only do individuals with severe depression experience quantitative olfactory loss, but qualitative olfactory loss may also occur. For example, one study found that rates of parosmia and phantosmia were significantly higher in patients with severe depression, compared to patients with minimal or moderate depression (Croy, Yarina, & Hummel, 2013).

Olfactory ability is highly plastic, and is affected by a combination of factors, including lifestyle, genetics, environment, and experience (Gottfried, 2006; Hedner et al., 2010). The conflicting results in the aforementioned studies are likely due to differences in tests and procedures. There are a variety of methods of conducting and scoring olfactory tests, and of measuring symptoms of depression (e.g. BDI, HDRS, clinical interview). Among studies, there are also differences in the sample sizes, medication use, experimenter blinding, control groups, inclusion criteria (e.g. comorbidities), and length of follow-up period.

Based on the existing literature, it is unclear whether olfaction is affected in depression. In general, the studies seems to suggest that olfactory sensitivity may be decreased, while identification may not be affected. Specifically, there may be poor olfactory sensitivity in MDD (Gross-Isseroff et al., 1994; Pause et al., 2001; Lombion-Pouthier et al., 2006; Negoias et al., 2010), normal olfactory sensitivity in bipolar disorder (Swiecicki et al., 2009; Hardy et al., 2012), and improved olfactory sensitivity in SAD.
(Postolache et al., 2002). There may also be greater olfactory identification deficits in severe MDD compared to mild MDD (Zucco & Bollini, 2011).

Just as patients with MDD are more likely to experience olfactory disorders, individuals with olfactory loss are more likely to experience symptoms of depression (Deems et al., 1991; Satoh et al., 1996; Temmel et al., 2002; Seo, Jeon, Hummel, & Min, 2009; Smeets et al., 2009; Croy et al., 2012). Individuals with smell or taste disorders experience depression at a higher rate compared to the general population (Deems et al., 1991; Blomqvist et al., 2004; Hummel & Nordin, 2005). For example, 60% of individuals with olfactory dysfunction experience depressive symptoms (Faulcon, Portier, Biacabe, & Bonfils, 1999), and an even higher proportion experience mood changes (Temmel et al., 2002). Additionally, Henkin et al. (2011) found that some patients with phantosmia or hyposmia had depression associated with their sensory deficits.

Still, not all studies have found links between depression and olfactory loss. This may be since patients are generally able to cope well with olfactory dysfunction; only a small percentage of individuals encounter significant difficulties (Croy, Nordin, & Hummel, 2014). Seo et al. (2009) found that olfactory sensitivity does not predict depression severity. However, the study was conducted in an elderly population, where the high prevalence of olfactory loss in old age may have masked the impact of depression on olfaction.

Though some studies (e.g. Gudziol, Wolff-Stephan, Aschenbrenner, Joraschky, & Hummel, 2009) claim that olfactory loss causes depression, it is not yet clear in which direction the association runs. Does olfaction lead to depression, does depression cause olfactory loss, or are there other common underlying causes altogether? Poor olfaction could certainly contribute to depression, considering that exposure to odorants increases blood flow to the amygdala, thus engaging emotional processing and
modulation (Zald & Pardo, 1997). Anecdotally, odours have the ability to evoke strong emotional memories.

Depression could likewise contribute to olfactory loss through the neuronal loss in brain structures. The dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis in mood disorders results in elevated cortisol levels, which lead to neuronal damage and decreased neuroplasticity (Campbell & McQueen, 2006). As a result, individuals with MDD experience structural and functional changes in the hippocampus (Soudry et al., 2011), prefrontal cortex (Drevets et al., 1992), amygdala (Kronenberg et al., 2009), anterior cingulate cortex, orbitofrontal cortex, and the basal ganglia, among other brain regions (Campbell & MacQueen, 2006). Since many of these areas are involved in olfaction, the neural changes in depression could affect olfactory ability.

These links between depression and olfaction are not surprising, given that emotion and olfaction are very closely intertwined in the brain, both anatomically and functionally (Atanasova et al., 2008). There are extensive reciprocal axonal connections between olfactory and limbic regions, such as the amygdala, hippocampus, and orbitofrontal cortex (Carmichael et al., 1994; Zald & Pardo, 1997; Savic, 2001). Not only are the primary olfactory cortex and the amygdala both activated by unpleasant odours (Zald & Pardo, 1997), but the two areas are continuous with one another. The direct pathway between the OB and the amygdala means that olfactory signals can directly activate neurons in the amygdala without first going to the primary olfactory cortex (Krusemark, Novak, Gitelman, & Li, 2013). This is important since the OB facilitates and modulates limbic system function (Cain, 1974), including through tonic inhibition of the amygdala, which results in a greater vulnerability to stress (McNish & Davis, 1997).

The olfactory-bulbectomized (OBX) rodent is an animal model of depression. Removal of the olfactory bulb reduces the tonic inhibition of the amygdala (McNish & Davis, 1997), resulting in increased amygdalar excitability (Watanabe, Nakanishi, Shibata, & Ueki, 1982). This leads to increased
vulnerability to stress and anxiety (McNish & Davis, 1997), as well as increased emotions such as sadness and fear (Pause et al., 2001; Ledoux, 2007; Costafreda et al., 2008). There is also neural remodelling in areas such as the neocortex and hippocampus (Harkin, Kelly, & Leonard, 2003), resulting in depressive-like behavioural and neurochemical changes (Song & Leonard, 2005), including weight loss, irritability, and decreased interest in sex (McNish & Davis, 1997). There is also a change in neurotransmitter concentrations in OBX animals, including serotonin and dopamine, both in terms of neurotransmitter synthesis and turnover (Croy, Symmank, et al., 2014). Unlike OBX, chemical ablation of peripheral OSNs to induce anosmia does not result in depressive behaviours (Song & Leonard, 2005). This suggests that interrupted central neuronal connections, not indirect brain changes from olfactory deficits, cause the depressive behavioural symptoms in OBX animals. A similar process may be occurring in MDD in humans, where OB dysfunction may be dis inhibiting the limbic system, increasing sadness to the point of causing or prolonging depressive symptoms (Pause et al., 2001). Indeed, there is a decreased OB volume in MDD, which is correlated to depression (Negoias et al., 2010).

2.5.1 Olfactory Loss and Depression in Humans

Poor performance on olfactory tests in depression could be explained by a deficit in top-down processing. Olfactory identification, in particular, is a higher order process that depends strongly on cognitive ability (Steiner et al., 1993; Clepce et al., 2010). For example, memory, attention, executive functioning, and language ability all affect performance on an olfactory identification task (Schablitzky & Pause, 2014). Since decreased attention and concentration commonly occurs in MDD (Scinska et al., 2008; Croy, Symmank, et al., 2014), it is possible that poorer top-down processing of information could affect olfactory identification ability.

However, since the previous research on depression suggests poor olfactory sensitivity but normal olfactory identification, central processing is unlikely to be the main cause of the olfactory deficits
seen in depression. Instead, early sensory processes in the OB and olfactory cortex, such as detection and encoding, may be affected in depression, rather than higher order cognitive processes (Negoias et al., 2010; Schablitzky & Pause, 2014). Indeed, an event-related potential study found a decrease in the early encoding of olfactory information in MDD (Pause et al., 2003). In other words, olfactory processing is attenuated in depression at an early processing stage; this normalized after successful treatment of depressive symptoms. This suggests that the olfactory deficits in depression are due to a decreased ability to detect odours, rather than dysfunctional cognition.

Similarly, Hedner et al. (2010) found that while olfactory identification and discrimination are linked to executive functioning and memory, olfactory sensitivity is not affected by these cognitive factors. Instead, it is mainly driven by lower-order perceptual functions. Only in severe cases of depression would cognitive impairments be likely to affect early sensory processing, and then to a varying degree (Schablitzky & Pause, 2014). It is also important to note that it is not possible to identify an odour that one cannot detect. For example, the age-related decline in odour identification performance is accounted for by the similar decrease in olfactory sensitivity (Larsson et al., 2007). Thus, proper olfactory identification depends on proper olfactory sensitivity (Schablitzky & Pause, 2014).

**Brain regions involved**

If poor olfaction in depression is due to poor early perceptual processing, it may be due to the functional connection between the olfactory bulbs and the amygdala (Pause et al., 2001), as mentioned earlier. There is hyperactivity in the limbic system in depression (Siegle, Thompson, Carter, Steinhauer, & Thase, 2007), including an increase in the volume of (Van Eijndhoven et al., 2009) and blood flow to the amygdala (Drevets, 1992, 2003), and thus increased emotional processing. It could be argued that there might be a similar increase in olfactory processing. However, due to the dual role of the amygdala
and other regions in both emotion and olfaction, increased emotional processing would likely preoccupy these brain regions and interfere with proper olfactory processing (Pollatos, Albrecht, et al., 2007).

Similarly, functional deviations in olfactory regions would not only affect olfactory processing, but potentially also emotional processing. As mentioned previously, the OB plays a role in inhibiting the limbic system. Even though McCaffrey, Duff, and Solomon (2000) found no evidence of olfactory system damage in major depression, Negoias et al. (2010) found a decreased OB volume in MDD, which was correlated with BDI score. Since OB volume is correlated with olfactory threshold but not suprathreshold measures (e.g. identification and discrimination; Haehner, Rodewald, Gerber, & Hummel, 2008), this could account for the poor sensitivity in depression. Thus, there is a two-way link between olfaction and depression, particularly for peripheral olfactory processes.

Outside of the OB and the amygdala, other regions of the brain may also play a role. Functional magnetic resonance imaging (fMRI) studies have found that a variety of brain areas are activated during olfactory tasks (Royet et al., 2001). In addition to abnormal amygdalar activity in depression, there is abnormal activation of the orbitofrontal cortex and insula (Drevets, 2001). It has been suggested that hypoactivity of the orbitofrontal cortex in individuals with bipolar disorder provides a link between olfactory sensitivity and mood regulation (Kruger, Frasnelli, Braunig, & Hummel, 2006). Since these regions are involved in both depression and olfaction, this could have implications on smell test performance.

Another question of interest is whether decreased olfaction is a trait or state marker for depression. A state marker is a characteristic that exists during a given episode, but normalizes once the episode is over. In contrast, a trait marker is inherent to the individual, and persists over time, even after successful treatment. This information could hold implications for testing, in that a state marker might be used for diagnosis, while a trait marker might be used to predict future depression or olfactory function.
Interestingly, after a negative emotional experience, healthy subjects experience poorer olfactory sensitivity (Pollatos, Kopietz, et al., 2007), suggesting that a higher olfactory threshold is linked to negative mood as a state marker. Conversely, Postolache et al. (2002), who found an increased olfactory sensitivity in SAD, found that hyperactivity in the orbitofrontal cortex and amygdala persists even in remission, suggesting that olfactory sensitivity is a trait marker. However, abnormal amygdala activity normalizes with antidepressant treatment (Hamilton, Siemer, & Gotlib, 2008). Naudin et al. (2012, 2014) argue that olfactory anhedonia and negative alliesthesia (the increased perception of subjective unpleasantness) are state markers for MDE, since these disappear after treatment of the depressive symptoms. However, others counter that since individuals with MDD have increased hippocampal activation to unpleasant odours even after treatment, their attentional bias for negative stimuli is a trait marker (Croy, Symmank, et al., 2014). It seems that some aspects of olfaction are inherent to individuals with depression, while others are linked to the depressive episode.

2.5.2 Antidepressant Treatments and Olfaction

It is unlikely that antidepressant treatments cause the olfactory impairments seen in depression. Most studies have found that antidepressant medications do not have negative effects on olfactory ability (Ship, Pearson, Cruise, Brant, & Metter, 1996; Rupp et al., 2003), and medication-free depression patients can still show poor olfaction (e.g. Negoias et al., 2010). A case report by Upshaw et al. (2013) found that ECT induced anosmia in two patients; however, this was likely due to the adverse effects of general anaesthesia (Henkin, 1995), and olfactory ability was restored in both cases within a few weeks.

Though antidepressant treatments are not the cause of olfactory dysfunction, they may be a potential solution. In theory, any treatment that acts on the brain regions common to olfaction and emotion could have effects on olfactory ability. Studies have found that antidepressant pharmacotherapy can improve or restore olfactory sensitivity (Gross-Isseroff et al., 1994; Pause et al., 2001) as well as treat...
qualitative olfactory disorders (Landis, Croy, & Haehner, 2012). Similarly, Henkin et al. (2011) found that rTMS restored olfactory acuity and intensity back to normal levels in hyposmic and phantosmic individuals. In fact, rTMS has been proposed as a treatment for phantosmia, since it can reduce sensory distortions (Henkin et al., 2011).

2.5.3 Neuroplasticity

Neuroplasticity is a process that involves changes in neurons and synapses, allowing the brain to adapt to the environment and to experiences. One important aspect of neuroplasticity is neurogenesis, which is the birth and development of new neurons. Historically, it was thought that neurogenesis only occurred during embryonic development, and that the brain did not change much in adulthood. However, Altman (1962) discovered that new neurons also form in adult mammals, primarily in the subventricular zone (SVZ) and subgranular zone (SGZ) of the hippocampus. This section will focus primarily on neuroplasticity in the olfactory system, including OB neurogenesis from the SVZ.

Neuroplasticity in the olfactory system

The olfactory system is rather remarkable for its neural regeneration capabilities. In the olfactory epithelium, progenitor cells have the capacity to proliferate and regenerate OSNs throughout the lifespan (Costanzo, 2005; Marcucci, 2011). The OB receives neuroblasts from the SVZ, but there may also be neural progenitor cells in the OB itself that can generate new neurons, oligodendrocytes, and astrocytes (Pagano et al., 2000; Lotsch et al., 2014).

For new olfactory neuron development from the SVZ, neuroblasts migrate along the rostral migratory stream to the OB. They then integrate into the existing layers of the OB and differentiate into interneurons, mainly granule cells and periglomerular cells (Imayoshi et al., 2008). Approximately 10,000 cells migrate to the OB each day, giving a turnover rate of 3% per month (Whitman & Greer, 2009). This
allows for the olfactory circuitry not only to be maintained, but also to adapt to changes in the environment (Alvarez-Buylla & Garcia-Verdugo, 2002; Imayoshi et al., 2008).

A major challenge in neurogenesis is the integration of newborn neurons into the preexisting network. New OSNs have to send axons to the existing glomerular network in the olfactory bulb. Similarly, adult-born periglomerular cells must form synapses with the constantly changing OSNs, all while integrating into the existing glomerular network. While neuroplasticity is important for forming these new connections, neuron stability is important for promoting functionality (Grubb, Nissant, Murray, & Lledo, 2008).

While most of the neuroblasts migrating to the OB do not survive (Bath & Lee, 2009), the neurons that do survive allow functional synapses to be formed and maintained. Sensory experience in the form of external olfactory stimulation drives new neurons to their appropriate locations, stimulates differentiation into subtypes, and promotes survival and integration once they reach the OB (Rochefort, Gheusi, Vincent, & Lledo, 2002; Alvarez-Buylla & Garcia-Verdugo, 2002; Lledo & Saghatelyan, 2005). Thus, olfactory stimulation by providing novel odorants may allow us to positively modify neuroplasticity in the olfactory system.

Another way of increasing neuroplasticity in the olfactory system is through neurotrophic factors and growth factors. Brain-derived neurotrophic factor (BDNF) promotes such effects as neuron migration, survival, and differentiation; dendritic branching; and long-term potentiation of synapses (Bath & Lee, 2009). The administration of exogenous BDNF into the lateral ventricles of rats results in a substantial increase in neuron proliferation and survival in the OB (Zigova, Pencea, Wiegand, & Luskin, 1998). Little research has explored the role of other neurotrophic factors on SVZ neurogenesis, though there is some evidence for neurotrophic growth factor (NGF) and neurotrophin-3 (NT-3; Bath & Lee, 2009). Outside of
neurotrophic factors, growth factors may also be important for neuroplasticity, though their exact roles remain unclear (Kempermann & Kronenberg, 2003; Bath & Lee, 2009).

Interestingly, it has been argued that OB adult neurogenesis may not be essential for proper olfaction in humans. There is a low level of OB neurogenesis compared to other species (Bergmann et al., 2012), with some studies even finding an apparent absence of neuroblasts migrating to the OB (Wang et al., 2011). Additionally, a decrease in adult OB neurogenesis does not seem to lead to evident sensory deficits, though some cognitive functions may be impaired (Lazarini & Lledo, 2011). Similarly, blocking OB neurogenesis in mice does not affect olfactory discrimination or odor-associated memory (Imayoshi et al., 2008), suggesting that adult-born neurons are not essential for olfaction.

Conversely, another study in mice found that decreased OB neurogenesis affects ability to discriminate between odorants, though olfactory sensitivity and olfactory memory are not affected (Gheusi et al., 2000). Increased survival of newborn neurons are also linked to increased olfactory memory (Rochefort et al., 2002). The differences among studies may be accounted for by factors such as variations in mice, testing conditions, and length of follow-up. Thus, there is some evidence that newborn neurons are important for olfaction, though these studies are mostly correlational. Even if OB neurogenesis plays little or no role in olfaction, neuroplasticity in general is still important. Additionally, neurogenesis in the hippocampus, an area that indirectly plays a role in olfaction (Soudry et al., 2011), may still affect olfaction.

**OB neuroplasticity in depression**

The hypothalamic-pituitary-adrenal axis hyperactivity in MDD results in a heightened stress response (APA, 2013), making neurons more vulnerable to damage and atrophy. Stress-induced release of glucocorticoids and cytokines lead to increased neurodegeneration, atrophy, and neuroinflammation, as
well as decreased neurogenesis (Duman, Nakaawa, & Malberg, 2001; Kubera, Obuchowicz, Goehler, Brzeszcz, & Maes, 2011) in both the hippocampus and the olfactory system. Stress also reduces the expression of neurotrophic factors, including BDNF (Xu et al., 2006).

Furthermore, in MDD, there is the same number of progenitor cells, but fewer mature granule neurons (Boldrini et al., 2013). In other words, cell proliferation occurs at a normal rate, but many cells do not survive or mature into functional neurons, resulting in volumetric loss. This effect is especially pronounced in untreated individuals and in cases of early onset MDD (Boldrini et al., 2013). This corresponds to the findings from Sheline, Gado, and Kraemer (2003) where a longer time spent in untreated depression was associated with a smaller hippocampal volume. The decreased volume of olfactory brain regions in MDD, due to both a decrease in neurogenesis and an increase in neurodegeneration, ultimately affects olfactory ability (Haehner et al., 2008).

**Antidepressant treatments and neuroplasticity**

Fortunately, the reduced neuroplasticity seen in depression may be preventable or reversible with antidepressant treatment. Treatment reduces the aforementioned effects of stress on neurons, decreasing neuroinflammation and neurodegeneration (Kubera et al., 2011). It has been proposed that antidepressant action depends on increasing expression of BDNF and other neurotrophic factors to limit the effects of stress and glucocorticoids on neurons (Duman, Heninger, & Nestler, 1997). Indeed, the administration of chronic antidepressant medication, as well as ECT (Bocchio-Chiavetto et al., 2006), increases BDNF expression, while nonantidepressant psychotropic medications do not (Nibuya, Morinobu, & Duman, 1995). Furthermore, antidepressants have been found to promote dendritic arborisation and neuron maturation (Wang, David, Monckton, Battaglia, & Hen, 2008). The administration of antidepressant medications restores neurogenesis in both the SVZ (Hitoshi et al., 2007) and the hippocampus (Malberg, Eisch, Nestler, & Duman, 2000; Czeh et al., 2001; Sheline et al., 2003; Duman, 2004; Jayatissa, Bisgaard,
Tingstrom, Papp, & Wiborg, 2006; Xu et al., 2006). For example, serotonin plays a role in increasing neurogenesis in both the hippocampus and the SVZ (McEwen & Magarinos, 2001; Banasr, Hery, Printemps, & Daszuta, 2004; Hitoshi et al., 2007). Fluoxetine, an SSRI, increases neuron proliferation, survival, and maturation in the hippocampus (David et al., 2009). However, some studies have found no effect of fluoxetine (Malberg et al., 2000; Santarelli et al., 2003; Kodama, Fujioka, & Duman, 2004) in the SVZ. In fact, antidepressants may have no effect on BDNF in the olfactory bulb or amygdala (Balu et al., 2008).

Neurotrophic factors themselves seem to have antidepressant action. A single infusion of BDNF or NT-3 in rat models of depression gives behavioural improvements comparable to chronic pharmacotherapy administration (Shirayama, Chen, Nakagawa, Russell, & Duman, 2002). Additionally, vascular endothelial growth factor (VEGF) stimulates cell proliferation in both the SVZ and SGZ (Jin et al., 2002). The antidepressant effects of these neurotrophic factors may be due to neurons developing an increased resilience to stress (Shirayama et al., 2002). Unfortunately, most neurogenesis research has been done in the hippocampus; future studies should investigate whether hippocampal research extends to the OB.

The exact mechanism of action of ECT is not yet understood. Neuroplasticity is suggested to play a role, with ECT increasing neurogenesis in a dose-dependent manner (Madsen et al., 2000; Chen, Madsen, Wegener, & Nyengaard, 2009). ECT appears to increase neurotrophic factors like BDNF (Bocchio-Chiavetto et al., 2006) and stimulate cell proliferation in the dentate gyrus of the hippocampus (Perera, 2007) to affect neurons & synapses. However, ECT may not have effects on neurogenesis in the SVZ (Malberg et al., 2000).

It typically requires some time, on the scale of a few weeks, to see clinically significant therapeutic benefits from antidepressant medications (Segman, Shapira, Gorfin, & Lerer, 1995). rTMS
also requires more than two weeks for a detectable improvement in depressive symptoms to appear (O’Reardon et al., 2007). While the effects of antidepressant treatments on the levels of monoamines, such as serotonin or noradrenaline, are rapid (Santarelli et al., 2003), adult neurogenesis takes approximately 4 weeks (Malberg et al., 2000; Esposito et al., 2005; Lepousez, Valley, & Lledo, 2013), since the new cells must not only be created, but also migrate, mature, and form functional connections to existing neuronal networks. This temporal connection suggests the role of neurogenesis in the effects of antidepressant treatments.

Interestingly, ECT can have a more rapid antidepressant response, in a matter of days, where even the first treatment can give a large clinical improvement (Segman et al., 1995). Neurogenesis cannot be responsible for this acute improvement. Madsen et al. (2000) found that neurogenesis peaked in rats 3-5 days after electroconvulsive seizures, and returned to normal by day 7; however, new neurons still require weeks to functionally integrate into the neuronal network. Though antidepressant-induced neurogenesis requires weeks to occur, synaptic changes can occur much faster, in a matter of days (Hajszan, MacLusky, & Leranth, 2005). ECT promotes both the formation of new synaptic connections and the remodelling of existing synapses (Bessa et al., 2009; Chen et al., 2009), as well as changes in glial cells (Kempermann & Kronenberg, 2003). Thus, synaptic changes may account for the rapid effects of ECT.

Indeed, it has been suggested that the decrease in brain volume in depression is not necessarily due to a decrease in cell number, but a decrease in cell volume and neuropil number (McEwen & Magarinos, 2001; Campbell & McQueen, 2006). Decreased efficacy of excitatory synapses may also play a role in depressive symptoms (Chen et al., 2009). Antidepressants can reverse the effects of stress on synaptic structure, and restore neuronal plasticity (Sairanen, O’Leary, Knuuttila, & Castren, 2007). For
example, fluoxetine in rats rapidly increased hippocampal synapse density by 68.8% in a mere five days, even though there was no change in hippocampal volume (Hajszan et al., 2005).

Blocking neurogenesis affects some of the antidepressant effects of medications, such as novelty-suppressed feeding, learned helplessness, and anhedonia, but not other effects, such as the open field test or forced swim test (Santarelli et al., 2003; Wang et al., 2008; Bessa et al., 2009; David et al., 2009). This suggests a variety of actions that are dependent and independent of neurogenesis. Thus, though neurogenesis may augment antidepressant response, neuroplasticity is a more general and comprehensive hypothesis for depression (Kempermann & Kronenberg, 2003; Henn & Vollmayr, 2004). In other words, depression involves impairments in neuroplasticity and neuronal resilience (Chen et al., 2009).

### 2.6 Summary and Future Directions

Both depression and olfactory loss can have a huge impact on quality of life. The brain regions responsible for emotion, and those responsible for olfaction, are functionally and anatomically interconnected. Neuroplasticity likely plays an important role in recovery from both depression and olfactory dysfunction.

Unlike eyeglasses for vision, or hearing aids for hearing, there is no simple way of compensating for poor sense of smell (Croy, Negoias, Novakova, Landis, & Hummel, 2012). However, once the root cause of the olfactory dysfunction is treated, OSNs are likely to regenerate eventually. There is some evidence that certain substances, such as zinc, theophylline, magnesium, and fluoride, may restore olfaction (Henkin, 1994), but they may not be effective for every case.

If there are few successful treatment options for olfactory loss, it could be argued that there is little use in diagnosis. However, many individuals with olfactory loss develop coping skills, such as asking for support (e.g., asking someone to check potentially spoiled food) and positive thinking (e.g.,
will no longer smell bad odours; Blomqvist et al., 2004). Individuals can also be trained to place less importance on olfaction (Croy et al., 2011) and focus on non-olfactory aspects of food, such as colour or texture, to increase enjoyment and appetite. Patients should also be strongly advised to take precautionary safety measures, such as the installation and maintenance of smoke and natural gas detectors. Clinicians may be able to offer patient counseling and monitor for related conditions – including depression – and thus improve well-being (Miwa et al., 2001). Indeed, there is evidence that cognitive behavioural therapy can be used to prevent or treat the depressive symptoms associated with olfactory loss (Smeets et al., 2009), and support groups can further reduce feelings of isolation and vulnerability. Such measures may not cure the olfactory disorder, but can vastly improve quality of life of individuals living with olfactory disorders.

2.6.1 Olfaction in Diagnosis, Treatment, and Prevention

Various patterns of olfactory deficits have been observed in a variety of medical conditions, including Alzheimer’s disease (Solomon et al., 1998; McCaffrey et al., 2000; Pentzek et al., 2007), anorexia nervosa, alcohol and drug addiction (Lombion-Pouthier et al., 2006), and schizophrenia (Hurwitz et al., 1988; Serby et al., 1990; Kopala et al., 1994; Cumming & Matthews, 2011). Thus, olfactory testing could be employed as a diagnostic tool (Pentzek et al., 2007). For example, Alzheimer’s disease can be difficult to distinguish from depression in the elderly, but since Alzheimer’s disease is associated with poorer olfactory identification compared to depression (Solomon et al., 1998; McCaffrey et al., 2000; Pentzek et al., 2007), olfactory tests could help with the differential diagnosis of these two conditions (Scinska et al., 2008).

Olfactory testing could also be used in the differential diagnosis of affective disorders. For example, a certain pattern of olfactory dysfunction could indicate unipolar depression, while another distinct pattern might indicate bipolar disorder. Indeed, individuals with MDD generally have poor
olfactory sensitivity (Gross-Isseroff et al., 1994; Pause et al., 2001; Lombion-Pouthier et al., 2006; Negoias et al., 2010), while those with bipolar disorder tend to have normal olfactory sensitivity (Swiecicki et al., 2009; Hardy et al., 2012), and those with SAD may have improved olfactory sensitivity (Postolache et al., 2002). Additionally, higher-order olfactory testing, such as olfactory identification, could be used to help determine the severity of depression, since severe MDD shows greater olfactory deficits than mild MDD (Zucco & Bollini, 2011). In the future, a battery of olfactory and cognitive tests could be used for diagnosis of depression type and severity (Hardy et al., 2012; Schablitzky & Pause, 2014).

Olfactory testing could also help in earlier diagnosis of depression. Since even a transient sad mood affects olfaction (Pollatos, Kopietz, et al., 2007), olfactory deficits may precede overt depressive symptoms (Schablitzky & Pause, 2014), potentially allowing the diagnosis of depression before mood symptoms become severe. This is important since early diagnosis and treatment plays a major role in the course and recovery of depression.

In addition to helping with diagnosis, olfaction could potentially be used to treat, or perhaps even prevent, affective disorders. Odours have effects on emotion, memory, social interactions, and cognition. It follows that odours could be used to activate the olfactory system in patients with depression to improve affective symptoms. Certain pleasant odours, such as lavender or camphor (Vernet-Maury, Alaoui-Ismaili, Dittmar, Delhomme, & Chanel, 1999), are especially effective at eliciting positive emotions and improving mood. Odour-enriched environments also have therapeutic benefits in terms of reducing negative bias in automatic preattentive processing (Pause et al., 2003). They also promote the survival of new neurons (Rochefort et al., 2002), likely by increasing the number of new synapses and stabilizing their development (Livneh, Feinstein, Klein, & Mizrahi, 2009). In other words, the presence of a variety of odorants may help retain olfactory neurons in MDD. Furthermore, olfactory training can
improve olfactory sensitivity (Hummel et al., 2009) and olfactory memory (Rochefort et al., 2002), and may thus potentially improve quality of life by restoring sense of smell. It has not yet been explored whether such improvements are long-lasting.

Therapeutic olfactory stimulation could occur not only through exposure to odours, but potentially also through brain stimulation techniques. Yuan & Slotnick (2014) proposed using deep brain stimulation (DBS) to activate the olfactory system in MDD patients. Stimulation in olfactory regions could also increase activity in brain areas that are connected to those regions, including the limbic system for emotions and the neocortex for modulation. Hence, while DBS traditionally stimulates areas such as the cingulate gyrus for antidepressant effects (Lozano et al., 2008), future studies might explore the stimulation of olfactory regions to achieve similar results.

2.6.2 Shortcomings and Gaps in Current Literature

Most of the previous research conducted in the area of olfaction and depression has not been well-designed. Ideally, studies will account for factors that impact olfaction, such as medication, smoking, age, and gender; have a long follow-up period; have experimenters that are blinded to the participants’ diagnosis; use reliable, validated olfactory tests such as the STT and SIT; perform neuroimaging to determine changes in brain structures (e.g. OB, amygdala); measure depression symptoms through clinical interviews with trained psychiatrists, rather than questionnaires (e.g. BDI). Future studies should also attempt to identify the neural substrates responsible for the interactions between olfaction and depression (Pollatos, Albrecht, et al., 2007).

Additionally, most adult neurogenesis studies to date have been conducted in the hippocampus. Further research should be done to investigate the extent to which hippocampal and OB neurogenesis are similar. If there are important differences, as suggested by Brown et al. (2003), subsequent studies should investigate OB neurogenesis in more detail.
Another gap in the depression and olfaction literature is in post-partum depression. Most pregnant women report improved olfactory sensitivity (Doty & Cameron, 2009), so it would be interesting to determine whether olfaction is affected after pregnancy if depressive symptoms are present.

In terms of antidepressant treatment and olfactory ability, most studies to date have only looked at antidepressant medication and psychotherapy. To our knowledge, the effects of somatic therapies such as ECT and rTMS have not yet been explored. The present study will investigate whether ECT and rTMS have effects on olfactory sensitivity and identification.

2.7 Goals of the Thesis

Knowing that depression may decrease olfactory ability, that antidepressant medications can restore olfaction, and that ECT and rTMS are very effective treatments for depression, the goal of this thesis project is to investigate whether these treatments can improve olfaction in patients with depression. Our research question is the following: In individuals with depression, is ECT or rTMS treatment associated with an improvement in olfactory sensitivity or identification? We hypothesize that, at baseline, the ECT and rTMS groups will show poorer olfactory sensitivity and normal olfactory identification compared to the control group; and that ECT or rTMS treatment will be associated with an improvement in smell test scores.
Chapter 3: Effects of Electroconvulsive Therapy (ECT) or Repetitive Transcranial Magnetic Stimulation (rTMS) on Olfaction in Patients with Depression

3.1 Introduction

The contradictory findings about whether olfactory sensitivity and identification are affected in depression remain unsolved. Most studies have found that olfactory sensitivity, but not identification, is decreased in depression. Antidepressant medications have been found to effectively restore olfactory ability in depression. It is not yet known whether somatic therapies, such as ECT or rTMS, have similar effects on olfaction.

The present research was a pilot study that aimed to confirm the existence of olfactory deficits in individuals with depression, and to determine whether there are any effects of ECT or rTMS on olfaction. Olfactory performance and depressive symptoms were measured before and after treatment, and compared among ECT and rTMS patients and healthy controls. Based on the previous research, it was hypothesized that patients with depression would perform more poorly on the smell threshold test compared to controls, and perform similarly to controls on the smell identification test. It was also hypothesized that successful treatment of depressive symptoms by ECT or rTMS, as measured by an improvement in HDRS and BDI score, would restore olfaction to a level comparable to controls.

Considering the impact of olfaction on quality of life and everyday functioning, the findings of this study could hold important implications for the diagnosis and treatment of depression. These will be discussed at the end of the chapter.
3.2 Methods

3.2.1 Participants

Informed written consent was obtained following verbal and written explanation of the study. All materials and protocol were approved by the Queen’s University Health Sciences Research Ethics Board (HSREB). All data were collected at Providence Care Mental Health Services site and/or Queen’s University in Kingston, Ontario, Canada.

For the ECT and rTMS groups, participants aged 18 to 70 years old were recruited from the ECT/TMS clinic at the Providence Care Mental Health Services site. This age range was chosen to avoid the high prevalence of olfactory loss in elderly individuals. All inpatients or outpatients who had been referred for ECT or rTMS treatment and had been diagnosed with major depressive disorder (MDD), bipolar disorder, or persistent depressive disorder (dysthymia) were invited to participate in the study. Current medication regimes were followed throughout the study. Active enrollment in the study extended from June 2013 through March 2015.

Healthy subjects were recruited for a control group; an attempt was made to match them with the depression group for age and sex. Participants for the control group were recruited through advertisements placed in local public libraries and around the Queen’s University main campus. Control participants were between the ages of 35 and 70 years old, in order to best reflect the actual ages of the participants in the patient groups. All had no self-reported history of neurological or psychiatric disorders. Each control subject was offered a small monetary sum as compensation for his or her time.

For all participants, a prescreening questionnaire was administered to ensure eligibility for the study. The study exclusion criteria included: having received ECT or rTMS in the past six months; or a diagnosis of schizophrenia, schizoaffective disorder, or other psychotic disorder. Additionally,
participants were not included in the study if they had any pre-existing conditions that may negatively affect olfaction, including: diagnosis of congenital anosmia or other primary olfactory disorder; environmental hypersensitivities (e.g. multiple chemical sensitivity); severe nasal or sinus disease (e.g. severe rhinitis, sinusitis, nasal polyps); or previous infection, injury, or trauma that resulted in long-term changes to sense of smell.

3.2.2 Materials and Procedure

Each participant was tested individually, on a one-on-one basis with a researcher. The order of test administration was fixed for all participants. Following the prescreening questionnaire and informed consent form, all participants filled out a demographics and health questionnaire. The University of Pennsylvania Smell Threshold Test (STT; Sensonics Inc., Haddon Heights, NJ) and the Smell Identification Test (SIT; Sensonics Inc., Haddon Heights, NJ) were then used to measure olfactory sensitivity and identification, respectively. For the ECT and rTMS groups, depressive symptoms were assessed using the following scales and questionnaires, in order: the Hamilton Depression Scale 17 item (HDRS; Williams, 1988), the Beck Depression Inventory-II (BDI; Dozois, Dobson, & Ahnberg, 1998), the Snaith-Hamilton Pleasure Scale (SHPS; Snaith et al., 1995), and the Clinical Global Impression Severity Scale (CGI-S; Busner & Targum, 2007). The HDRS was researcher-administered and the CGI-S was clinician-rated, while the BDI and SHPS were self-administered by the participant. The depression scales were not used for the control participants.

All tests and questionnaires were repeated at the second testing visit, which was planned for approximately 20-30 days after the first testing visit. This length of time was chosen because antidepressant-stimulated neurogenesis requires approximately four weeks to occur (Malberg et al., 2000; Esposito et al., 2005; Lepousez et al., 2013). Individual treatment schedules depended on each patient’s needs, but ECT patients generally received three treatment sessions per week, while rTMS patients
generally received five sessions per week. Overall, patients received three to five weeks of ECT or rTMS treatment between the first and second testing visits. The actual interval between visits for each participant varied depending on factors such as treatment schedules, convenience, and availability.

**Smell threshold test (STT):**

The STT is a standardized measure of olfactory sensitivity, or the ability to detect odours. It consists of 16 serial dilutions of half-decimal log step concentrations (v/v) of phenyl ethyl alcohol (PEA) in an odourless mineral oil solvent. PEA is a pure odorant; it stimulates the olfactory nerve (cranial nerve I) without stimulating the trigeminal nerve (cranial nerve V). When measuring olfactory ability, it is important to stimulate only the olfactory nerve, since the trigeminal nerve innervates facial areas, including the nose, but is separate from sense of smell (Toller, 1999).

In each STT trial, participants are presented with a puff of air from each of two bottles, one after the other. One of the two bottles is a blank, containing solvent alone, while the other bottle contains a given concentration of PEA. Participants sniff in their own natural way, as it has been found that natural sniffing tends to optimize olfactory perception (Laing, 1983). A birhinal (involving both nostrils) testing procedure was used. They are then asked to decide which of the two puffs of air, the first or the second, has a stronger odour. If participants cannot detect any difference, they are asked to give their best guess. Feedback is not given on any trial.

The test uses a modified single staircase procedure, with concentrations varying from -12.0 log to -2.0 log vol/vol PEA. The testing begins at -6.0 log concentration and proceeds by increasing in full log steps until five consecutive trials at a given concentration are correctly answered. Testing then moves up or down in half-log steps of concentration, depending on subsequent performance on pairs of trials at each concentration. This procedure is continued until seven reversals are achieved; the geometrical mean of the
final four reversals is considered the olfactory threshold. The STT is scored on a negative log scale, with a more negative score indicating a lower olfactory threshold and therefore better olfactory sensitivity. A negative difference between the two testing visits indicates an improvement in score. The STT has a high test-retest reliability of 0.88 (Doty, 2009).

**Smell identification test (SIT):**

The SIT is a standardized measure of ability to identify odours. It consists of four booklets with ten questions each. Each question consists of a scratch-and-sniff odorant patch, accompanied by four nouns (e.g. lemon, motor oil, turpentine, skunk) in a multiple-choice format. Participants scratch the microencapsulated patch with the provided pencil, sniff the released odorants, and choose which of the four options is best suited to the odorant. Participants are asked to give their best guess if they cannot decide on the name of the odour. Thus, the SIT is a forced-choice, recognition-format test of olfactory identification ability. Rather than the standard at-home self-administration for which the SIT was designed, participants in the present study completed the test under researcher supervision in order to ensure comprehension, concentration, and completion of the task. Examiners were blind to the correct response, and feedback was not given on any trial. A birhinal testing procedure was used. The SIT is scored out of 40 marks, with each question worth one mark. A higher score indicates better olfactory identification ability. The SIT has a high test-retest reliability of 0.918 (Doty et al., 1984).

### 3.2.3 Statistical Methods

The primary outcome measure was the change in STT score between the first and second testing visits. The secondary outcome measure was the change in SIT score between the first and second testing visits. Statistical analysis of data was performed using IBM SPSS Statistics for Macintosh, Version 22.0. The effect of ECT and rTMS treatment on outcome measures was analyzed by comparing groups (ECT,
rTMS, control) across the two visits using repeated measures analysis of variance (ANOVA) with a significance level of 0.05. Independent samples t-test and paired samples t-test were used to explore significant differences. Pearson bivariate correlation coefficient was used to determine whether various factors are associated with olfactory test scores. Hedges’ $g$ was used to report the effect size (magnitude of the difference).

3.3 Results

3.3.1 Participant Characteristics

In total, thirty-four individuals (20 ECT patients, 5 rTMS patients, 9 healthy individuals) were approached for participation in the study (Figure 1). Nine patients with depression (six ECT participants, three rTMS participants) and nine healthy control participants completed both visits of the study. The overall study completion rate was 53% (30% for ECT patients, 60% for rTMS patients, 100% for healthy controls).

In addition, four participants in the ECT group and one participant in the rTMS group began the study but withdrew after the first visit. Reasons for non-completion included: decreased interest, logistical challenges (e.g. coming from out of town), migraine, or discontinuing treatment. For visit one, there was no significant difference between completers and non-completers for SIT score ($t [20] = -0.665, p = 0.169$), STT score ($t [20] = -0.009, p = 0.543$), HDRS ($t [11] = 0.676, p = 0.502$), BDI ($t [11] = 1.789, p = 0.124$), or SHPS ($t [11] = 1.706, p = 0.125$). Thus, visit one data for non-completers were included in the data analysis.

The demographic features of the three groups are summarized in Table 1. Out of the completed participants, 10 (55.6%) were female and 8 (44.4%) were male. A Fisher’s Exact Test revealed a
Figure 1: Participants and reasons for discontinuation

- 34 participants approached
  - 20 ECT participants approached
    - 5 ineligible
    - 5 not interested
    - 4 discontinued study
    - 6 completed study
  - 5 rTMS participants approached
    - 1 not interested
    - 1 discontinued study
    - 3 completed study
  - 9 control participants approached
    - 9 completed study
- 1 catatonic symptoms and developmental delay
- 1 broken nose resulting in long-term change in olfaction
- 1 schizoaffective disorder
- 1 severity of depressive symptoms
- 1 ECT in the past six months
- 3 discontinued treatment
- 1 not interested
Table 1: Demographic characteristics of the sample

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>Control (N=9)</th>
<th>ECT (N=6)</th>
<th>rTMS (N=3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Mean ± SD, in years</td>
<td>55.4 ± 12.8</td>
<td>52.2 ± 7.1</td>
<td>65 ± 6.38</td>
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<tr>
<td>Gender</td>
<td>Male</td>
<td>4 (44%)</td>
<td>1 (17%)</td>
<td>3 (100%)</td>
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<tr>
<td></td>
<td>Female</td>
<td>5 (56%)</td>
<td>5 (83%)</td>
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<tr>
<td>Number of treatments</td>
<td>Mean ± SD</td>
<td>n/a</td>
<td>1 ± 1.054</td>
<td>0.75 ± 0.957</td>
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<td>before first visit</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Occupation</td>
<td>Full-time employed</td>
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<td>1 (17%)</td>
<td>0 (0%)</td>
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<td>Part-time employed</td>
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<td>1 (17%)</td>
<td>0 (0%)</td>
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<td></td>
<td>Unemployed/volunteer</td>
<td>1 (11%)</td>
<td>1 (17%)</td>
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<td></td>
<td>Homemaker</td>
<td>2 (22%)</td>
<td>1 (17%)</td>
<td>0 (0%)</td>
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<td></td>
<td>Retired</td>
<td>3 (33%)</td>
<td>1 (17%)</td>
<td>3 (100%)</td>
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<td></td>
<td>Disability</td>
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<td>1 (17%)</td>
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<td>1 (17%)</td>
<td>0 (0%)</td>
</tr>
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<td>1 (33%)</td>
</tr>
<tr>
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<td>Some university/college</td>
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<td>1 (17%)</td>
</tr>
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<td>University/college</td>
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<td>4 (67%)</td>
<td>2 (67%)</td>
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<td>Some postgraduate</td>
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<td>0 (0%)</td>
<td>0 (0%)</td>
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<td></td>
<td>Postgraduate</td>
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<td>0 (0%)</td>
<td>0 (0%)</td>
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<td>Ethnic background</td>
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<td>6 (100%)</td>
<td>3 (100%)</td>
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<td></td>
<td>East Asian (Chinese)</td>
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<td>0 (0%)</td>
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<tr>
<td>Other diagnoses</td>
<td>Bipolar disorder</td>
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<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td>Anxiety disorder</td>
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<td>4 (67%)</td>
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<td>Asperger syndrome</td>
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<td>0 (0%)</td>
<td>1 (33%)</td>
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<td>Self-reported olfactory impairment</td>
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<td>1 (17%)</td>
<td>1 (33%)</td>
</tr>
<tr>
<td></td>
<td>Anosmia</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (33%)</td>
</tr>
<tr>
<td></td>
<td>Phantosmia</td>
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<td>0 (0%)</td>
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</tr>
<tr>
<td>Alcohol consumption</td>
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<td>Once a month or less</td>
<td>2-4 times a month</td>
<td>2-3 times a week</td>
</tr>
<tr>
<td>-----------------------------</td>
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<td>-----------------</td>
</tr>
<tr>
<td></td>
<td>2 (22%)</td>
<td>1 (11%)</td>
<td>3 (33%)</td>
<td>2 (22%)</td>
</tr>
<tr>
<td></td>
<td>1 (17%)</td>
<td>3 (50%)</td>
<td>2 (33%)</td>
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<td></td>
<td>1 (33%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (33%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Smoking history</th>
<th>Smoker (current, ever)</th>
<th>Never smoker</th>
</tr>
</thead>
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<td>0 (0%), 5 (56%)</td>
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<td></td>
<td>2 (33%), 3 (50%)</td>
<td>3 (50%)</td>
</tr>
<tr>
<td></td>
<td>1 (33%), 3 (100%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

ECT: Electroconvulsive therapy; rTMS: repetitive transcranial magnetic stimulation; SD: standard deviation; n/a: not applicable. Percentages may not add up to 100% due to rounding.
significant gender difference between the ECT and rTMS groups (p = 0.0476), where 16.7% (n=1) of ECT participants were male, compared to 100% (n=3) of rTMS participants. The control group had a gender balance of 4 (44.4%) males and 5 (55.6%) females.

For the participants who completed both visits, the mean (± SD) age in the ECT group was 49.5 ± 6.47 years, ranging from 40-59 years old; 63 ± 6.08 years in the rTMS group, ranging from 56-67 years old; and 55.4 ± 12.8 years in the control group, ranging from 34-69 years old. There was no significant difference among the groups in terms of age (F[2, 20] = 2.485, p = 0.109).

There was no significant difference among the three groups for education level (F[2, 20] = 2.119, p = 0.146), occupational status (F[2, 20] = 1.198, p = 0.323), comorbid medical conditions (F[2, 20] = 0.066, p = 0.936), exposure to toxic chemicals (F[2, 20] = 1.216, p = 0.317), allergies (F[2, 20] = 1.406, p = 0.268), congestion during testing visit (F[2, 20] = 0.040, p = 0.961), pre-existing smell or taste problems (F[2, 20] = 1.216, p = 0.317), or current (F[2, 20] = 1.594, p = 0.228) or ever (F[2, 20] = 2.228, p = 0.134) smoking status. There was a significant difference for presence of comorbid psychiatric conditions (F[2, 20] = 12.605, p = 0.000) and for past problems involving alcohol use (F[2, 20] = 8.261, p = 0.002), and a trend toward significance for medication status (F[2, 20] = 3.043, p = 0.070). However, there was no correlation with SIT score at visit 1 for presence of comorbid psychiatric conditions (p = 0.770) or medication status (p = 0.590). There was a trend toward significance for a negative correlation between past problems involving alcohol use and SIT score at visit 1 (p = 0.070).

All patients in the ECT and rTMS groups were taking at least one antidepressant medication during the duration of the study, while none of the control participants were on psychotropic medication. Five of the depression participants (n=4 for ECT, n=1 for rTMS) started ECT or rTMS treatment before enrolling in the study, with a mean (± SD) of 1 ± 1.054 treatment sessions before visit one for the ECT.
participants, and 0.75 ± 0.957 for the rTMS participants. There was no significant difference in the number of previously completed ECT/rTMS sessions between the ECT and rTMS groups (p = 0.689).

As long as symptoms were rated as mild or very mild, participants were not excluded or rescheduled due to upper respiratory infection, allergy with nasal symptoms, nasal congestion, or other conditions that could affect olfactory ability. Three participants (one participant from each group) showed such mild symptoms at the first testing visit, and two control participants and three ECT participants at the second testing visit. One other control participant mentioned severe allergy with nasal symptoms before their second visit and was rescheduled until their symptoms had mostly improved.

### 3.3.2 ECT and rTMS Effects on STT

Mean (± SD) STT score at visit one was -3.458 ± 0.813 for the ECT group, -3.344 ± 0.09 for the rTMS group, and -3.833 ± 0.354 for the control group. Mean (± SD) STT score at visit two was -4.292 ± 0.785 for the ECT group, -3.625 ± 1.195 for the rTMS group, and -3.611 ± 1.265 for the control group. There was no significant difference in mean STT score among the three groups, nor was there an improvement in STT score between the two visits for any of the three groups (Figure 2). Repeated measures ANOVA (day × group) revealed no significant difference in mean STT score within subjects main effect of day ($F[1, 19] = 0.183$, $p = 0.674$), or within subjects day × group ($F[2, 19] = 0.328$, $p = 0.725$).

### 3.3.3 ECT and rTMS Effects on SIT

Mean (± SD) SIT score at visit one was 33 ± 6.305 for the ECT group, 19.5 ± 7.594 for the rTMS group, and 33.556 ± 2.603 for the control group. Mean (± SD) SIT score at visit two was 32 ± 4.427 for the ECT group, 24 ± 7.55 for the rTMS group, and 33.222 ± 3.032 for the control group. There was a significant difference in mean SIT score among the three groups (Figure 3). Repeated measures ANOVA
Figure 2: Smell threshold test (STT) score at visit one and two for control, ECT, and rTMS groups

Solid lines represent scores for each participant; dotted lines represent mean score for each group. A more negative score indicates better olfactory sensitivity.
Figure 3: Smell identification test (SIT) score at visit one and two for control, ECT, and rTMS groups

Solid lines represent scores for each participant; dotted lines represent mean score for each group. A higher score indicates better olfactory identification.
(day × group) revealed no significant within subjects main effect of day ($F[1, 15] = 1.284, p = 0.275$), but a significant within subjects day × group interaction ($F[2, 15] = 5.594, p = 0.015$). Paired samples t-test for SIT scores revealed a trend toward significance between visits ($t[2] = -3.671, p = 0.067$). There was no significant change in mean SIT score for the control group between the two visits ($t[8] = 0.555, p = 0.594$), suggesting that any change in score between visits was not due to time or practice effects.

At visit one, there was a significant difference among groups ($F[2, 19] = 10.849, p = 0.001$) for SIT score. Independent samples t-test revealed a significant difference at baseline between the rTMS and control groups ($t[11] = 5.146, p = 0.000$) (Hedges’ g = -2.877) and between the rTMS and ECT groups ($t[11] = -3.363, p = 0.006$) (Hedges’ g = -1.880), but no difference between the ECT and control groups ($t[16] = -0.244, p = 0.810$).

At visit two, there was a significant difference among groups ($F[2, 15] = 5.149, p = 0.02$) for SIT score. Independent samples t-tests revealed a trend toward significance between the rTMS and ECT groups ($t[7] = -2.056, p = 0.079$) (Hedges’ g = 1.292), and a significant difference between the rTMS and control groups ($t[10] = -3.194, p = 0.010$) (Hedges’ g = 1.965), but no difference between the ECT and control groups ($t[13] = -0.638, p = 0.534$).

### 3.3.4 ECT and rTMS Effects on Depression

At visit one, the ECT group had a mean (± SD) score of 23 ± 7.649, 36.556 ± 10.187, and 6.444 ± 3.127 for the HDRS, BDI, and SHPS respectively, while the rTMS group had 10.5 ± 5, 27.25 ± 23.472, and 6 ± 5.354 respectively (Figures 4-6). At visit two, the ECT group had a mean (± SD) score of 8.333 ± 5.574, 16.75 ± 13.356, and 2.667 ± 4.676 for the HDRS, BDI, and SHPS respectively, while the rTMS group had 9 ± 4, 11.333 ± 3.055, and 2.333 ± 1.528 respectively. CGI-S scores were not analyzed due to incomplete data.
Figure 4: Hamilton Depression Rating Scale (HDRS) score at visit one and two for ECT and rTMS groups

Solid lines represent scores for each participant; dotted lines represent mean score for each group.
Figure 5: Beck Depression Inventory (BDI) score at visit one and two for ECT and rTMS groups

Solid lines represent scores for each participant; dotted lines represent mean score for each group.
Figure 6: Snaith-Hamilton Pleasure Scale (SHPS) scores at visit one and two for ECT and rTMS groups

Solid lines represent scores for each participant; dotted lines represent mean score for each group.
All ECT and rTMS participants had been diagnosed with depression by a psychiatrist. However, at the first testing visit, 4 (67%) ECT participants had an HDRS score of 17 or higher (moderate or severe depression; Zimmerman, Martinez, Young, Chelminski, & Dalrymple, 2013), while none of the rTMS participants did. For the BDI, 5 (83%) of ECT and 1 (33%) of rTMS participants had a BDI score of 17 or higher (depression cut-off score; Veerman, Dowrick, Ayuso-Mateos, Dunn, & Barendregt, 2009).

There was a significant difference in mean HDRS score between the two clinical groups (ECT and rTMS). Repeated measures ANOVA (day × group) revealed a significant within subjects main effect of day ($F[1, 7] = 5.092$, $p = 0.059$) and within subjects day × group interaction ($F[1, 7] = 6.120$, $p = 0.043$). Paired samples t-test revealed a significant difference between visits ($t[8] = 2.552$, $p = 0.034$). Independent samples t-test revealed a significant difference between the rTMS and ECT groups at visit one ($t[11] = -2.961$, $p = 0.013$) but not at visit 2 ($t[7] = 0.182$, $p = 0.861$). There was a significant correlation between HDRS score and SIT score at visit 1 ($p = 0.008$) but not at visit 2 ($p=0.946$).

Repeated measures ANOVA (day × group) for BDI score revealed a significant within subjects main effect of day ($F[1, 7] = 12.892$, $p = 0.009$) and trend toward significance for within subjects day × group interaction ($F[1, 7] = 3.613$, $p = 0.099$). Paired samples t-test revealed a significant difference between visits ($t[8] = 3.890$, $p = 0.005$). Independent samples t-test revealed no significant difference between the rTMS and ECT groups at visit one ($t[11] = -1.031$, $p = 0.325$) or visit 2 ($t[7] = -0.672$, $p = 0.523$). There was no significant correlation between BDI score and SIT score at visit 1 ($p = 0.228$) or at visit 2 ($p=0.853$).

Similarly, repeated measures ANOVA (day × group) for SHPS score revealed no significant within subjects main effect of day ($F[1, 7] = 1.357$, $p = 0.282$) or within subjects day × group interaction ($F[1, 7] = 0.013$, $p = 0.913$).
Two participants from the rTMS group failed to respond to treatment, as defined by a lack of decrease in HDRS scores. Of the one rTMS participant who responded to treatment, there was a reduction of 4 points in HDRS score, representing a 44.4% mean reduction in HDRS score between the two visits. In the ECT group (n=6), there was a mean (± SD) reduction of -14.5 ± 9.9 points, representing a 63.5% mean reduction between the two visits. Repeated measures ANOVA (day × responder) for SIT score reduction revealed no significant within subjects main effect of day ($F[1, 7] = 1.969$, $p = 0.203$) and a trend toward significance for within subjects day × responder interaction ($F[1, 7] = 4.813$, $p = 0.064$).

3.4 Discussion

The aim of this pilot study was to investigate the effects of ECT and rTMS on olfactory sensitivity (as measured by the STT) and identification (as measured by the SIT) in depression. Contrary to our hypothesis, there was no difference in STT score among the three groups at either visit. However, the rTMS group had a worse SIT score at baseline compared to the ECT and control groups, as well as at the second visit compared to the control group. SIT score was significantly correlated with HDRS score at baseline, but not after treatment. There was no correlation between SIT score and any of the other depression questionnaires. Our study found no effects of depression on olfactory sensitivity, and a worsening effect of depression on olfactory identification; rTMS treatment improved olfactory identification ability.

3.4.1 Olfactory Scores and Depression

The lack of difference in STT score among the three groups supports the findings of several previous studies, which found no change in olfactory sensitivity in depression patients compared to healthy controls (Serby et al., 1990; Gross-Isseroff et al., 1994; Postolache et al., 1999; Scinska et al., 2008; Swiecicki et al., 2009; Croy, Symmank, et al., 2014). However, other studies have found decreased
olfactory sensitivity in depression (Pause et al., 2001; Lombion-Pouthier et al., 2006; Negoias et al., 2010). The present study contributes to the evidence that there is no deficit in olfactory threshold in individuals with depression.

The lower SIT score in the rTMS group is consistent with some previous studies that found poorer identification in depression (Serby et al., 1990; Steiner et al., 1993; Clepce et al., 2010; Zucco & Bollini, 2011). However, most previous studies found no difference in olfactory identification compared to control (Amsterdam et al., 1987; Warner et al., 1990; Kopala et al., 1994; Solomon et al., 1998; Postolache et al., 1999; McCaffrey et al., 2000; Pause et al., 2003; Lombion-Pouthier et al., 2006; Pentzek et al., 2007; Scinska et al., 2008; Swiecicki et al., 2009; Negoias et al., 2010). The present SIT results may be confounded by the sex difference between the rTMS and ECT groups. There is evidence that males have poorer olfactory identification compared to females (Doty, Shaman, et al., 1984; Wysocki & Gilbert, 1989; Ship et al., 1996; Murphy et al., 2002). In the present study, all three rTMS participants were male, while only one of the six (16.7%) ECT participants was male. Thus, the sex difference could account for the difference in olfactory identification performance between the two groups.

The improvement in SIT score in the rTMS group between the two visits may be the result of neurochemical changes in the brain. Naudin et al. (2014) propose that the restoration of olfactory ability following antidepressant pharmacotherapy is due to the medication normalizing activity in regions like the amygdala and orbitofrontal cortex, as well as stimulating neurogenesis in the OB. It is likely that there are similar mechanisms in somatic therapies such as rTMS and ECT. However, this study did not directly measure brain activity or neuroplasticity.

The fact that olfactory identification, but not sensitivity, was impaired in some depressive participants suggests that higher-order, but not lower-order, olfactory areas are affected. In other words, higher-order processing regions such as the piriform cortex, prefrontal cortex, entorhinal cortex,
orbitofrontal cortex, and amygdala (Haberly, 2001; Pollatos, Albrecht, et al., 2007) may be dysfunctional, while olfactory detection areas such as the olfactory epithelium and OB (Haehner et al., 2008) may not be affected. Olfactory identification involves various cognitive processes, including executive functioning, memory, attention, verbal ability, and recall of contextual information (Schablitzky & Pause, 2014).

Though the ECT group had a worse HDRS score at baseline compared to the rTMS group, the rTMS group had a worse SIT score. This does not support a previous finding that severe depression is linked to poor olfactory identification (Zucco & Bollini, 2011). It is possible that the depressive symptoms in our patients were not severe enough to affect olfactory ability; some of our participants did not meet the criteria for depression as measured by the HDRS or BDI. Other than the HDRS at visit one, there was no significant correlation between scores on the SIT and any of the measures of depression. This is contrary to previous studies, which found a negative correlation between olfactory performance and BDI scores (Pause et al., 2001), but not HDRS scores (Gross-Isseroff et al., 1994).

### 3.4.2 Participant Factors

The participants for the two patient groups in this study were recruited from the ECT and TMS clinics at Providence Care Mental Health Site. Notably, patients whose depressive symptoms were considered too severe by the ECT and TMS nurses were not referred for the study. This may have resulted in selection bias, in that the patients had depression that was severe enough to require ECT or rTMS treatment, but not so severe that they were incapable of participating in a research study.

Another potential source of selection bias in the present study involves how participants were placed in groups. Whether a subject with depression was placed in the ECT or rTMS group depended on the treatment recommended by the psychiatrist based on various factors, including symptom severity. Ideally, participants would be randomly assigned to the two treatment groups; however, this was not feasible in our pilot study.
There was also a difference in recruitment methods for the control group and patient group. The control group was recruited by poster advertisements, while the ECT and rTMS groups were recruited in-person. Even though all participants were told they could withdraw from the study at any time, there may have been a difference in subject motivation levels. For example, compared to the two patient groups, where six declined participation in the study and five more dropped out, all of the control subjects that we met with completed both visits. This suggests a difference among the three groups in terms of the level of interest in the study, and may have reflected in their performance on the olfactory tests.

Sex

As mentioned previously, research on sex differences in olfaction has generally found better identification in women compared to men (Doty, Shaman, et al., 1984; Wysocki & Gilbert, 1989; Ship et al., 1996; Murphy et al., 2002). There is also evidence of better sensitivity (Wysocki & Gilbert, 1989; Doty & Cameron, 2009) in women for many odorants, though other studies have found no sex differences for sensitivity (Larsson et al., 2000; Postolache et al., 2002) or identification (Larsson et al., 2000). If differences do exist, they may be due to better verbal ability, psychosocial environment, or hormones in women (Larsson et al., 2000). However, hormones may not be a major factor, since the sex differences in olfactory ability are detectable even before puberty (Doty, Shaman, et al., 1984).

Furthermore, women’s performance on olfactory tests may depend on their menstrual cycle and menopausal status (Doty, Snyder, Huggins, & Lowry, 1981; Doty & Cameron, 2009), though there is no difference between women who are and are not on oral contraceptives (Doty et al., 1981). However, estrogen protects against olfactory loss, and postmenopausal women undergoing hormone replacement therapy (HRT) perform better on the SIT than those not on HRT (Deems et al., 1991). One control participant in the present study mentioned being on HRT. However, we did not adjust for menstrual or
menopausal effects. Thus, depending on the timing of each testing visit, female participants’ performance may have been higher or lower than expected.

Age

In this study, there were no statistically significant age differences, but overall, the ECT group had the lowest mean age and the rTMS group had the highest. Age, which is a well-established factor in olfactory ability, accounts for up to 20% of individual variability (Venstrom & Amoore, 1968). It is uncommon for individuals over the age of 65 to have unimpaired olfactory functioning (Doty, Shaman et al., 1984; Stevens & Cain, 1987). Olfactory threshold deteriorates logarithmically with age, at a rate of -0.046 log steps per year (Venstrom & Amoore, 1968; Stevens & Cain, 1987; Larsson et al., 2000). Olfactory identification also decreases significantly with age (Stevens & Cain, 1987; Yousem, Geckle, Bilker, & Doty, 1998; Larsson et al., 2000; Murphy et al., 2002). The degree of age-related decline can be non-uniform, depending on subject, odorant, gender, and measure used (Wysocki & Gilbert, 1989; Ship et al., 1996).

Studies in older populations may mask the effects of depression on olfaction, since, with the olfactory decline that occurs with age, these individuals would likely have an already poor performance. Indeed, when olfactory performance was measured in older adults (aged 53-79 years old), there was no difference in either sensitivity or identification between individuals with and without depression (Scinska et al., 2008). In the present study, where the mean (± SD) age was 55.7 ± 10.4 years old, there was similarly no difference in olfactory sensitivity. Participants also performed more poorly than expected from the normative data (Doty, 2008, 2009).

With age, there is a decline in the number, morphology, survival, and regeneration of neurons in the olfactory epithelium (Loo, Yougentob, Kent, & Schwob, 1996). In fact, there is a decreased volume
in the OB and olfactory tract with increasing age (Yousem et al., 1998). This neural loss is due to factors such as changes in nasal airflow, nasal disease, environmental insults, viral infections, decreased mucosal enzymes, ossification of the cribriform plate, loss of selectivity in olfactory receptor cells, changes in neurotransmitters, and expression of aberrant proteins (Doty & Kamath, 2014). With aging, neurofibrillary tangles can also arise in olfactory brain regions, including the anterior olfactory nucleus (Price, Davis, Morris, & White, 1991). Thus, participant age could greatly affect olfactory ability.

**Diagnosis**

The subjects also differed in terms of their diagnosis. Olfactory performance may vary based on diagnosis, including the type of depression (e.g. MDD, BP, SAD), subtype (e.g. melancholic; Clepce et al., 2010), acuity (e.g. acute episode, remission), episode (e.g. first, recurrent), symptom severity, as well as the diagnostic criteria that were used (e.g. 4th. or 5th. edition of the *Diagnostic and Statistical Manual of Mental Disorders*). Some of the patients in the present study were diagnosed with bipolar disorder, but were grouped together with the MDD patients. Similarly, the present study grouped together individuals with mild, moderate, and severe depression. It is possible that stronger effects would have been seen if our ECT and rTMS groups were comprised entirely of patients with severe MDD.

In addition to the effects of depression itself, hospitalization may reduce neurogenesis (Macklis, 2012), due to more deprived environments where a smaller variety of novel odours are encountered. This could hold implications for this study, since all of the depression patients were hospital inpatients on a depression ward, while all of the control participants were living in the community.

**Medications**

Any antidepressant treatment, including medications and psychotherapy, could also affect performance. Treatments that are started before a study begins may affect study results in terms of
olfaction or depressive symptoms at both visits. In the present study, several participants (4 ECT and 1 rTMS) had started ECT or rTMS treatment before beginning the study. Additionally, all patients in the ECT and rTMS groups were already on at least one antidepressant medication at the beginning of the study. Since antidepressant medications can improve olfactory ability (Gross-Isseroff et al., 1994), this may have restored our patients’ olfactory thresholds to the level of healthy controls. This could account for the absence of difference in olfactory sensitivity between the depressed and control groups.

Four participants (1 control, 1 ECT, 2 rTMS) mentioned past use of nasal decongestant spray. The use of such medications can result in a decrease in sense of smell, though it can also improve olfaction in some individuals by reducing inflammation in the nasal passages (Henkin, 1994). In our study, the olfactory scores of these four individuals were overall slightly better than the mean scores of their respective groups.

**Medical conditions**

Two participants in this study had thyroid conditions. One control participant had hypothyroidism, and one ECT participant had Graves’ disease, which is associated with hyperthyroid symptoms. Thyroid conditions have been found to affect sense of smell, with hypothyroidism being associated with poor olfaction (McConnell, Menendez, Smith, Henkin, & Rivlin, 1975; Mackay-Sim & Beard, 1987) and hyperthyroidism being associated with improved olfaction (Johanson, 1980). However, these effects are reversed by treatment with thyroid hormones (Mackay-Sim & Beard, 1987). Both participants were taking thyroxine, and indeed, the scores of the two participants were similar to the mean scores of their respective groups.

At least two ECT/rTMS participants in the present study used continuous positive airway pressure (CPAP) machines. Sleep apnea is correlated with poorer olfactory threshold and identification
scores, as well as smaller OB volume, since the hypoxia and sleep deprivation can both lead to neuron loss (Salihoglu et al., 2013).

**Lifestyle factors**

In this study, there was no significant difference among the three groups in alcohol use per month. However, the rTMS group had a significantly higher proportion of patients who had experienced past problems involving alcohol use. Regular alcohol use is associated with poor olfactory function (Rupp et al., 2003). Further investigation needs to be done to determine the effects of previous alcohol abuse on olfaction.

Smoking status could also be a potential factor, though there was no significant difference in smoking status among the three groups in this study. Current smokers generally have olfactory impairments (Doty, Shaman, & Dann, 1984; Doty, Shaman, et al., 1984; Murphy et al., 2002), with a dose-response curve between hyposmia and the number of cigarettes smoked per day (Vennemann, Hummel, & Berger, 2008). There is also a smaller OB volume in smokers compared to non-smokers (Schriever, Reither, Gerber, Iannilli, & Hummel, 2013). Conversely, there is no difference in olfaction between former smokers and never smokers (Murphy et al., 2002).

**3.4.3 Olfactory Factors**

Performance on olfactory testing can depend on an odorant’s valence. Negative stimuli produce a higher level of arousal in individuals with MDD, compared to controls (Pause et al., 2001). Similarly, individuals with depression are better at identifying unpleasant odours than pleasant ones (Atanasova et al., 2010). This may be related to the negative bias associated with depression, which affects a variety of processes, including memory, attention, and executive function (Atanasova et al., 2010; Naudin et al., 2012). As a result of this negative bias, negative stimuli are more salient and elicit a higher arousal than
pleasant ones. In fact, the increased perception of unpleasant odours, termed negative alliesthesia, can render certain foods less appetizing, resulting in a decreased appetite, which is a common symptom of depression (Naudin et al., 2012, 2014). The present study used phenyl ethyl alcohol, which is considered to be a pleasant, emotionally positive, rose-like odour (Pause et al., 2003). Thus, patients may have been less aroused in this experiment compared to control participants, and a low level of arousal could negatively affect test performance. Similarly, it is likely that previous studies obtained contradictory results partly due to differences in the hedonic valences of the odorants used.

Every participant in the present study, including those in the healthy control group, scored more poorly on the STT and SIT than expected from the normative data (Doty, 2008, 2009). The low test scores may be due to various factors such as small sample sizes, cohort effect, or selective recruitment. It is also possible that some sets of smell tests used in this study were no longer valid. The validity of the STT and SIT tests is guaranteed for only six months (Doty, 2008), and for some of our participants, the new order of tests had not arrived in time for testing. This could explain the poor test scores of our participants, as well as the small effect sizes that were seen. However, most of the subjects were tested using valid test materials, so test expiration should not have had a major effect on final results.

The conditions under which olfaction and depression are measured could also affect the results of a study like the present one. Participants in the control and patient groups completed the study under different testing conditions. Control participants completed the study in a private campus library room, while participants from the patient groups completed the study in a hospital interview room or personal patient room. Due to differences in the environment, such as air quality or temperature (Doty, 2009), it is possible that the testing conditions could have influenced test performance.

Depressive symptoms improve approximately three weeks after starting antidepressant medications, yet olfactory improvements do not improve for another three weeks after that (Gross-Isseroff
et al., 1994). Therefore, whether researchers see an improvement in olfaction may depend on how long they follow their subjects after treatment. The present study followed participants for a mean (± SD) 36.158 ± 13.623 days on average. This follow-up period might be criticized as too short for a study that may involve neuroplasticity. However, four- to six-week periods are commonly employed in depression studies due to practicality (Folkerts et al., 1997).

### 3.4.4 Strengths and Limitations of the Study

This study has a number of strengths. It is the first study to compare the effects of ECT and rTMS on olfactory ability in patients with depression. Though previous studies have investigated the effects of antidepressant medication and psychotherapy on olfaction in individuals with depression, no research has been conducted for somatic therapies such as ECT and rTMS. Our findings provide preliminary evidence that, in patients who experience decreased olfactory identification, rTMS may result in improvement in SIT scores.

Another strength of this study lies in the measures used. Due to their validity and reliability, the STT and SIT are among the best methods of olfactory testing. The STT, which uses seventeen concentrations in a reverse-staircase procedure, allows a very precise olfactory threshold to be determined compared to other tests, such as the EZUS (5 concentrations; Lombion-Pouthier et al., 2006) or the Sniffin’ Sticks (12 concentrations; Hummel et al., 1997). Similarly, the SIT consists of 40 multiple forced choice questions, compared to the EZUS (16 questions; Lombion-Pouthier et al., 2006) or the Sniffin’ Sticks (16 questions; Hummel et al., 1997). The test-retest reliability for the STT and SIT is 0.88 (Doty, 2009) and 0.918 (Doty et al., 1984) respectively, which is higher than the test-retest reliability of the Sniffin’ Sticks (0.61 for threshold and 0.73 for identification; Hummel et al., 1997).

Furthermore, this study used a number of depression scales, which helped ensure that depressive symptoms were appropriately assessed. The HDRS, BDI, and SHPS are validated measures of depressive
symptoms. This combination of scales also balances the advantages and disadvantages associated with researcher-administered and self-administered depression scales, including self-report and demand characteristics.

The main limitation of this pilot study is the small sample size. We encountered significant difficulties in participant recruitment, despite having recruited for 22 months. Patients with severe symptoms of depression often did not wish to participate in the study, or else did not complete the second visit of the study, resulting in potential selection bias. Subsequent studies should involve a greater number of participants, for improved statistical power to detect olfactory effects of ECT and rTMS in depression. The challenges of recruiting and retaining participants could be overcome through various methods, including recruiting from multiple ECT and rTMS clinics, offering greater incentive for participation, or making the testing visits shorter or easier.

There are certain limitations associated with olfactory testing. Most tests use pure odorants to limit activation to the olfactory nerve. However, the smells encountered in everyday life generally involve complex mixed odours. Thus, performance on clinical olfactory tests may not reflect true olfactory performance in the outside world. There are also potential habituation effects (Yuan & Slotnick, 2014), where an individual gets used to the odorant over the course of testing. The present study did not explicitly schedule in breaks to prevent or reduce habituation, though subjects were welcome to take breaks as desired. Additionally, this study used birhinal olfactory testing, where stimuli were presented to both nostrils. Such a testing procedure may not be able to detect monorhinal deficits, which may be masked by normal performance on the contralateral side (Postolache et al., 1999).

Another inherent problem with olfactory testing is that it can be very repetitive and require a high level of concentration and motivation. This is not ideal for individuals with depression, some of whom may not be able to concentrate for long periods of time (Marine & Boriana, 2014). Some of the patients in
the present study mentioned poor concentration abilities. In order to determine a direct link between olfaction and depression, participants could undergo a cognitive test battery as well as control tests in other sensory modalities, in order to control for cognitive or motivational deficits (Schablitzky & Pause, 2014).

3.4.5 Directions for Future Research

This study has identified a number of ways to improve future studies in this topic. For example, future studies should incorporate age- and gender-balanced groups in order to determine the true effects of antidepressant treatment on olfactory ability in depression. Additionally, it is not clear why the ECT and rTMS patients’ scores on the depression scales did not reflect their clinical diagnosis of severe depression. It is possible that stronger effects would have been seen if our patient groups comprised wholly of individuals with severe MDD. Future studies should also aim to recruit patients who either are not on medication, or can stop taking medication for several weeks prior to the study.

In terms of study procedure, it is recommended that future studies employ a second rater for conducting and scoring interviews. Moreover, to further reduce bias, the testing visits should be conducted and evaluated by a rater who is blind to participant group. In retrospect, control participants in the present study should have also completed the depression questionnaires, similar to depressed participants. This would allow us to confirm the absence of depressive symptoms in our healthy control group, rather than relying solely on self-reported lack of diagnosis.

In the present study, olfactory identification was affected in depression, but not olfactory sensitivity. This suggests that it is higher order regions of the brain, such as the amygdala and prefrontal cortex, and not lower order regions, such as the OB, that are affected in depression. Neuroimaging and other measures of brain changes could be used to confirm which brain regions are involved in olfaction and depression. Considering that olfactory identification is heavily dependent on cognitive ability (Steiner
et al., 1993; Clepece et al., 2010), future research could also include a cognitive test battery. Since the brain regions involved in olfactory identification are also responsible for functions such as olfactory memory and hedonics, further studies should determine whether these higher-order olfactory processes are also affected. Future research should also investigate whether there are long-term effects of ECT and rTMS on olfaction, as well as effects on quality of life.

3.5 Conclusions

The results of this pilot study suggest that individuals with depression may not have decreased olfactory ability compared to healthy controls. However, among those who do have poor olfactory identification, rTMS may be effective in restoring sense of smell. Further research is needed to determine whether the present results are truly due to the presence of depressive symptoms, and whether ECT may also restore sense of smell in individuals with olfactory deficits. Links between olfaction and depression may be important for promoting the early diagnosis and treatment of depression, as well as for improving quality of life and everyday functioning. This study has identified a number of ways to improve future studies.
References


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