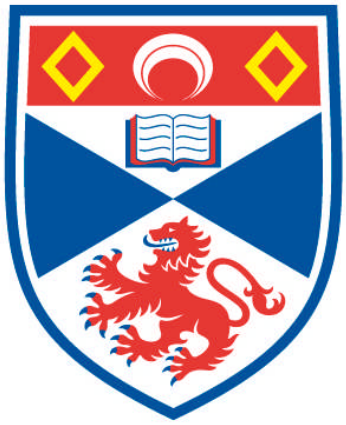
EMOTION RECOGNITION IN CHRONIC TREATMENT-RESISTANT DEPRESSION: BEFORE AND AFTER NEUROSURGICAL TREATMENT

Frazer Alexander Lockhart Grant

A Thesis Submitted for the Degree of MPhil
at the
University of St Andrews



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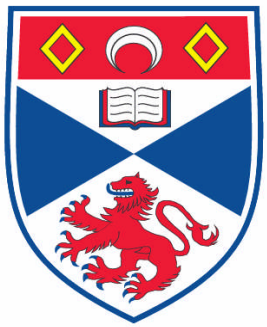

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I was admitted as a research student in August, 2010 and as a candidate for the degree of MPhil in Behavioural and Neural Sciences in August, 2010; the higher study for which this is a record was carried out in the University of St Andrews between 2010 and 2013.

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Abstract:

The neuroanatomical structures underlying Major Depressive Disorder (MDD) are not fully understood. Invasive treatment options now exist that target the brain structures associated with MDD.

In part one of this study, the effects of MDD on emotion processing are being measured and discussed. Emotion processing was examined in patients with chronic, treatment resistant depression (n = 15) and a healthy control group (n = 38). Emotion processing abilities were impaired in the MDD group, especially those of disgust recognition.

In part two, seven of the fifteen MDD patients that had received an Anterior Cingulotomy (ACING) and eight of the fifteen MDD patients that had received a Vagus Nerve Stimulation (VNS) as an intervention for chronic, treatment resistant depression were presented with the same series of emotional processing tasks given in part one. Their post surgical performance was compared with their pre surgical performance. After surgery, the ACING group showed decreased emotion processing abilities and the VNS group showed improvements.

Findings suggest that emotional functions assumed to be associated with certain neural structures that are adversely affected in patients with MDD may be responsible for some of the clinical features of MDD.

1 Introduction

Major Depressive Disorder (MDD) is ranked by the World Health Organisation (WHO) as the number one leading cause of disability (WHO, 2001). It is estimated that MDD affects at least 10% of the world's population (McKenna, 2005). In the United States alone, the economic cost to individuals, society, and the health system due to MDD was $150 billion in 1996 (Hirschfeld, 1998). Every year, depressed individuals report on average 35 days in which they are unable to work or carry out normal activities (Rush, 2007). These facts stress the importance of further research and understanding of MDD with the aim of developing effective treatment strategies.

MDD is considered a neuropsychological syndrome that arises from disordered processing in neural networks that modulate normal emotional behaviour (Mayberg, 2005; Mayberg, 1997; Nemeroff 2002; Nestler, 2002). The aetiology of this abnormal processing is not completely agreed upon, but converging findings concur that irregular synthesis, secretion, and concentrations of fundamental neurotransmitters, hormones, and growth factors can trigger atrophy to specific neural structures. Neuroanatomical volume reductions, abnormal metabolic activity, and differences in neuron size and concentration in the depressed brain have been observed in neuroimaging studies as well as in post-mortem anatomical investigations[1]. These neural abnormalities alter the cognitive and emotional abilities of those affected with MDD, and are associated with the signs and symptoms of the disorder[2]. Below average performance is common on emotional and cognitive tasks administered to MDD patients. It has been hypothesized that impaired emotional processing may be the leading cause of social dysfunction among depressed patients (Surguladze, 2004).

Although current antidepressant medication and psychotherapy are viable treatment options for some patients with MDD, only 50% to 60% respond to any one medication and only 35% of patients become symptom free (Kupfer, 2003). Relapse of depressive symptoms is the norm in the

[1] see section 1.2.3
[2] see section 1.4

majority of depressed patients (Warden, 2007). Approximately 20% of those who have depression are resistant to medications and psychotherapy and are termed 'treatment resistant' patients (Malone, 2010). Due to the disabling symptoms, chronic nature, high relapse rates, wide prevalence, and societal costs associated with MDD, it is vital to further explore the neurophysiology, neuropsychology, and novel treatment options of the condition.

Invasive treatment options exist that target the brain structures associated with MDD. The two invasive treatment options focused on in this thesis are Vagus Nerve Stimulation and Anterior Cingulotomy[3]. After these neurosurgical interventions are performed on a patient with MDD, metabolic activity has been observed to revert back to that expected in a healthy brain. In certain cases, emotional and cognitive deficits subside[4]. Research has recently begun to identify the effects of these invasive procedures measured by scores on emotion processing tasks. These tests of emotional recognition are administered both before surgery takes place, to establish a baseline, and after surgical intervention to measure effects on performance.

With the aim to identify affected neural areas that contribute to symptoms of MDD, an established structure–function relationship was used as a behavioral marker to infer the possible involvement of specific neural substrates (Sprengelmeyer et al., 2011). Specifically, recent meta-analyses show agreement from large bodies of research that link certain brain areas with the processing of specific emotions[5]. By observing if certain emotion processing tasks are impaired among individuals with MDD, inferences can be drawn to which brain structures are functionally impaired as well.

In Part One of the study, the ability of a group with MDD to identify emotional information was determined. Deficits in functional recognition of particular emotions can suggest specific abnormal brain structures. With this information, hypotheses can be made to which structures are being affected by MDD and may play a role in the major symptoms of the disorder.

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[3] see section 1.3.3.2 and section 1.3.3.3
[4] see section 1.3
[5] see section 1.4.3

In Part Two, scores from emotional tests[6] administered before and after Vagus Nerve Stimulation and Anterior Cingulotomy are compared. Statistical analysis is performed on patient's performance before and after therapeutic surgery to determine if emotion processing abilities have been altered due to treatment—or not. As many facets of the surgeries are in fact permanent, it is important to discover what effects these neurological procedures have on a patient's cognitive abilities (Ridout, 2007).

The theoretical part of this thesis describes the aetiology, clinical symptoms, epidemiology, historical approaches, contemporary approaches, neuroanatomical approaches, neurosurgical treatment options, and neuropsychology of Major Depressive Disorder. Building on this corpus of data, two topics are investigated in a behavioural study: the effect of MDD on emotion recognition and the side effects of invasive neurosurgery on emotion processing. The outcomes of these investigations will highlight the efficacy of new invasive treatment options for MDD, as well as the general effect that MDD has on a patient's ability to process emotional information.

1.1 Major Depressive Disorder

1.1.1 Aetiology

Depression can occur idiopathically (Krishnan, 2009) with no obvious external cause. However, certain life events, medications, and health conditions are closely linked with the prevalence of MDD. Divorce and childhood abuse are among the environmental risk factors most associated with depression (Palosaari, 1996; Kendler, 2004). Particular endocrine abnormalities such as hypothyroidism and hypercortisolism are also associated with depression. Cancers such as pancreatic adenocarcinoma and breast tumours are tied to depression as well. Furthermore, certain medications such as isotretinoin, used to treat acne, as well as interferon-α, used to treat hepatitis C, have been shown to significantly increase the risk of developing MDD (Evans, 2005). High instances of depression are also

[6] see section 2.2.2

found in neurological illnesses that cause cell death in brain areas associated with emotional functioning[7] (Sheline, 2003). These illnesses include Huntington's disease, post-stroke syndromes, Alzheimer's disease, epilepsy, and Parkinson's disease.

Although no one single "depression gene" has been isolated that could help to definitively diagnose depression, many studies have explored genetic polymorphisms involved in monoaminergic transmission (Levinson, 2006). For example, if one acquires two short alleles for the serotonin transporter gene they are more vulnerable to develop depression after experiencing stressful life events (Caspi, 2003). It seems that individuals possess a genetic 'stress threshold' which determines how one reacts to stress and whether this reaction can lead to the development of depression[8].

1.1.2 Clinical Description

1.1.2.1 Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) Definition

The DSM-IV defines MDD as a disorder characterised by sad mood or the loss of pleasure in day-to-day activities. In addition, four of the following criteria must be met as well: sleeping too much or too little; psychomotor retardation or agitation; poor appetite and weight loss, or increased appetite and weight gain; loss of energy; feelings of worthlessness; difficulty concentrating, thinking, or making decisions; and recurrent thoughts of death or suicide. These symptoms must be present for at least two weeks every day for most of the day. Finally, these symptoms cannot be due to normal bereavement.

1.1.2.2 Clinical Presentation of the Disorder

1.1.2.2.1 Overview

MDD is a multifaceted disorder that disrupts mood, cognition, sensorimotor, and homeostatic/drive functions (including those that control sleep, appetite, and libido) (Mayberg, 2009). Clinical complaints common

[7] see section 1.2.3
[8] see section 1.2.2.2.2

among MDD patients include impaired concentration, memory, and attention (Delgado, 2009). Patients with depression express difficulty in experiencing pleasure, have both slowed thought processes and movement, psychological pain (an awareness of negative changes in the self, accompanied by negative feelings), dysphoric mood, suicidal ideation, and predisposition to ruminating about past events (Giacobbe, 2009; Orbach *et al.,* 2003). The symptoms of depression are debilitating—depressed individuals report a mean of 35 days a year when they were totally unable to work or carry out normal activities (Rush, 2007).

Depressive episodes can last anywhere from weeks to years and should not be thought of as isolated events. After reaching remission from depressive symptoms, two thirds of individuals are expected to experience a relapse of depressive symptoms at least once within their lifetime (Solomon, 2000). On average, four episodes of depression are experienced (Judd, 1997). In a study performed by Solomon *et al.* (2000) it was observed that with every episode, one's risk for experiencing a relapse episode increased by 16%.

In addition to experiencing harmful day-to-day symptoms, patients with MDD have higher mortality rates associated with comorbid conditions. For example, a 2.3 fold increase in mortality occurs in MDD patients with type 2 diabetes, an eightfold increase is seen in congestive heart failure patients, and a 2.6 fold increase in mortality is seen in individuals with coronary heart disease (Katon, 2005; Barth, 2004). It has been noticed that patients with MDD have lower bone density and increased risk for cardiovascular problems (Cizza, 2011).

Increased rates of suicide are absolutely related with MDD. Based on a meta-analysis performed by Botswick *et al.* (2000), in outpatients with less severe depression, suicide rates are around 2.2%. However, in individuals with severe depression who have been hospitalized for previous attempted suicide, suicide rates are as high as 8.6% (Bostwick, 2000).

Although depression is diagnosed in a symptom-based manner dependent upon clinical presentation, two depressed individuals may only share one symptom in common. Because of this, a wide variety of clinical presentations exist for the syndrome (Drevets, 2001). Given the differences

in presentation of depressive symptoms, five MDD subgroups have emerged and are discussed below.

1.1.2.2.2 A-Typical Depression

As soon as the first generation of antidepressants were introduced to the market in the 1950s, physicians began to recognize a certain type of depressed patient that responded especially well to Monoamine Oxidase Inhibitors (MAO inhibitors). This subgroup includes 15% to 29% of all people with MDD and is named ‘a-typical depression’ (Thase, 2007). The clinical presentation includes hypersomnia, interpersonal sensitivity, leaden paralysis, increased appetite and/or weight, and phobic anxiety (Thase, 2007).

1.1.2.2.3 Melancholic Depression

Melancholia is the oldest documented form of depression. Individuals with melancholia cannot trace their depression to a reaction towards life stressors. To qualify for this subtype, either anhedonia or lack of mood reactivity must be present as well as three of the following: depression that is not secondary to grief or loss, severe weight loss or loss of appetite, psychomotor agitation or retardation, early morning awakening, guilt that is excessive, and worse mood in the morning (DSM-IV text revision, 2008). The ability to experience pleasure is seemingly lost; this anhedonia is not improved by positive external events (Biro, 1989). Biological markers are present to aid in the diagnosis of melancholia. The most prominent markers are shortened eye movement latency and excessive cortisol secretion (Rush, 1997). Medication is especially effective compared to placebo when treating melancholic patients (Rush, 1998).

1.1.2.2.4 Psychotic Depression

Delusions as well as hallucinations that match one's mood are symptoms of psychotic depression. 18% of MDD patients could be diagnosed as psychotic, and usually represent only those individuals suffering from

severe depression (Ohayon, 2002). Due to hyperactivity in the Hypothalamic-Pituitary-Adrenal (HPA) axis[9], elevated serum cortisol levels are found in those with psychotic depression (Coryell, 1996). On a cognitive level, impaired verbal memory and executive functioning is observed (Fleming, 2004). Electroconvulsive therapy is especially effective in the treatment of psychotic depression; however, most individuals with treatment-resistant depression show characteristics of psychotic depression (Coryell, 1996).

1.1.2.2.5 Anxious Depression

Anxious depression includes depressive symptoms that are comorbid with an anxiety disorder (Rush, 2007). Patients with anxious depression are usually severely depressed and are at a high risk to have recurrent thoughts about death and suicide. Other clinical symptoms associated with anxious depression are hypochondriasis and persistent residual anxiety even after being treated with antidepressants (Rush, 2007).

1.1.2.2.6 Treatment Resistant Depression (TRD)

In general, the failure to respond to four full trials of antidepressants consisting of the correct dose and duration as well as failure to respond to electroconvulsive therapy classifies a patient as having TRD (Shields, 2008). More specifically, a treatment has failed if no response is detected when a treatment is administered for at least four weeks, except in the case of electroconvulsive therapy (Nahas, 2006). TRD patients represent 10% to 20% of all individuals with MDD (Shields, 2008). In the case of TRD patients, neurosurgery is often their only viable treatment option.

1.1.3 Epidemiology

1.1.3.1 Prevalence

Differences in criteria used to generate diagnoses and methodologies used in prior studies estimate an overall lifetime prevalence rate of MDD

[9] see section 1.2.2.2.3

from 4-20% (Andrade, 2003). The age of onset for depression is usually in the early to mid-twenties (Andrade, 2003). In an international study including almost 38,000 people, it was discovered that rates of depression are also affected by which country one lives in. For example, in Taiwan only 1.5% of the population is depressed, while in Beirut depression rates are reported to be as high as 19% (Weissman, 1996). This could be explained by differences in distance from the equator, and thus the amount of sunlight one receives. Others hypothesize that the reason for differential rates is tied to culture and national customs (Weissman, 1996). However, no matter where an individual with MDD is from geographically, they are always more likely to abuse alcohol and other substances.

Many health related patterns exist pertaining to MDD. For example, MDD occurs about twice as often in women as in men (Kring, 2010). Rates are higher in the unmarried than in the married, with rates especially high in divorced individuals (Andrade, 2003). Socioeconomic factors are also pertinent, as MDD is three times more common among people who are impoverished than in those who are not (Kessler, 2005).

1.1.3.2 In Children and Adolescents

Recently, more and more evidence seemingly indicates that incidence of depression among people under twenty is on the rise. From 1987 to 1996, data were collected from over 900,000 American youths (Zito, 2003). This study detected that in those 10 years, the amount of antidepressants prescribed to individuals under the age of 20 increased tenfold. However, according to Costello *et al.* (2006), increases in medication prescribed at the moment can be explained by better diagnosis by physicians. The willingness to prescribe antidepressant medications may also have increased in recent years, as well as the number of pharmacologic treatment options.

Additionally, suicide rates among the age range of 5-19 have increased from the 1950s to the 1990s (Centre of Disease Control). A British study conducted over 25 years reported similar results (Collishaw, 2004). The study utilized data from emotional health surveys administered in hospitals and observed that in boys, emotional problems increased from 7.8% in 1974

to 13.3% in 1999. In girls, emotional problems increased from 12.8% in 1974 to 20.4% in 1999; overall, emotional problems increased from 10.2% in 1974 to 16.9% in 1999.

1.1.3.3 In the Elderly

MDD affects up to 4% of the elderly population, while minor depression affects another 10% (Palsson, 1997). Although 36% of men and women in nursing homes take antidepressants, it is estimated that 60% of the elderly population with MDD are untreated (Steffens, 2000; American Society of Consultant Pharmacists, 2002). Suicide rates are especially high in the elderly population compared to younger individuals with MDD. For example, in a Finnish study, all suicides that occurred over the span of a year were investigated (Henriksson, 1995). By retrospectively looking through patient files, the study revealed that 91% of suicide victims had at least one Axis I DSM-IV disorder; and in 67% it was a depressive disorder. Furthermore, almost all the elderly female victims had MDD.

Lastly, epidemiologic studies of adults have reported increasing lifetime prevalence rates of depression in those born later in the 20th century; however, other studies blame this on recall bias, as it may be harder and harder to remember earlier life events for the older age groups (Kessler, 1994).

1.2 Theories of Major Depressive Disorder

1.2.1 Historic Approaches

1.2.1.1 Overview

Since the earliest civilisations, explanations of depression have ranged from work of the gods, imbalanced humours, faulty nerves, and recently neurological and genetic explanations. However, from the very beginning, non-biomedical factors such as the loss of a loved one or loss of an

occupation have never been ruled out as causal factors (Conrad, 1995), implying a diathesis – stress model for depression.

1.2.1.2 From Antiquity to the 19th Century

The earliest mention of depression is for the most part religiously oriented. The Old Testament contains references to depression in the Psalms of David (Davison, 2006). Writings pertaining to depression are also seen on preserved portions of Egyptian papyri and in the Indian *Ramayana* and *Mahabharata*.

The Greeks, specifically Hippocrates, were the first to presume that all bodily processes, health, and disease (including melancholia) were independent of supernatural phenomena (Conrad, 1995). It was thought that an excess of black bile in the brain caused melancholia, which literally translates to ‘black bile’ in Greek. Hippocrates described his depressed patients' symptoms as including "aversion to food, despondency, sleeplessness, irritability and restlessness" (Davison, 2006). Treatment included alterations in one's diet, as well as physical exercise routines.

During the Medieval Ages, it was thought that melancholy could be caused by changes in the atmosphere that would influence levels of internal bile. In extreme cases of depression the moon was to blame, leading to the origin of the word "lunacy" or "lunatic." Excess "passion" and the influence of the devil were also easy explanations.

The enlightenment brought one-on-one interpersonal therapy as treatment, utilizing kindness, reason, and humanity (Conrad, 1995). This approach was initially hard to practice, as the location of treatment occurred in isolated lunatic asylums where treatment was anything but humane.

1.2.1.3 Psychoanalysis

In the 1890s, Sigmund Freud fathered psychoanalysis. For Dr. Freud, depression was the product of past, often remote, life events that affected the current life of a patient (Davison, 2006). "Guilt ridden anger," caused by these repressed memories, turned inward to cause depressive symptoms. To treat depression, psychoanalysts have three main objectives: first, to

investigate the patient's mind and find out how he or she thinks; second, to establish a systemized set of theories about the patient's behaviour; and third, to develop a method of treatment for the depression (Moore, 1968). In the year 2000, there were over 35 psychoanalytic training institutes in the United States alone accredited by the American Psychoanalytic Association (aspa.org).

1.2.2 Contemporary Approaches

1.2.2.1 Behaviourism

Just after the introduction of psychoanalysis, a new body of thought emerged with another explanation of depression. The behaviourist school of thought only deals with observable and measureable behaviour (Nemade, 2007). American psychologist John Watson eschewed the idea that behaviour has anything to do with unconscious or repressed memories, stating instead that human behaviour is always learned. Behaviourists reasoned that because depression is learned, it could be unlearned (Nemade, 2007). In the 1970s Peter Lewinsoln introduced a learning theory to explain depression. His theory was composed of two variables: life stressors and lack of personal skills. He stated that in the presence of life stressors people receive less positive reinforcement; positive reinforcement occurs after people do rewarding and pleasurable activities (Nemade, 2007). According to behaviourist thought, when people do not receive positive reinforcement after experiencing pleasurable activities they will not learn to repeat them. Lewinsoln suggested that a depressed individual is one who does not know how to act in order to start receiving positive reinforcement, due to poor personal skills. A specific example of this theory could be observed when a child changes schools and loses old friends. If the child lacks personal skills to replace his or her friends, no new friends will be made and the child will receive less positive reinforcement and will become depressed (Nemade, 2007).

1.2.2.2 Biochemical Theories

Specific alterations in neurotransmitters, hormones, and growth factors are seemingly related with the aetiology of depression. Abnormalities in the most abundant inhibitory and excitatory neurotransmitters, Gamma-Aminobutyric Acid (GABA) and Glutamate respectively, are witnessed in the depressed brain (Hasler, 2007; Drevets, 2008). Serotonin, a neurotransmitter associated with the feeling of happiness, as well as serotonin receptors are seen to be abnormal (Ayd, 1956; Caspi, 2003; Drevets, 2008; Haddjeri, 1998; Lopez, 1998; Neumeister, 2002). Furthermore, increased levels of the stress hormone Cortisol is detrimental to brain function and has been linked to MDD (Drevets 2008; Gold, 2002). Finally, low levels of neurotrophic growth factors are witnessed in depression and cause decreased neurogenesis (Banasr, 2006; Chen, 2006; Musselman, 1993; Oomen, 2007; Schmidt, 2007; Wong and Herbert, 2004).

1.2.2.2.1 Glutamatergic and GABA-ergic Systems

Research performed within the last ten years has shown concentrations of GABA to be abnormally low in both the plasma and cerebrospinal fluid of MDD patients (Hasler, 2007). Cortical concentrations of GABA and glutamate can be measured using magnetic resonance spectroscopic methods. These studies have shown deficits in glutamate and GABA concentrations in the occipital cortex of depressed patients (Drevets, 2008). Abnormally reduced GABA concentrations were discovered to be localized in the dorsomedial anterolateral Prefrontal Cortex (PFC) as well (Hasler, 2007). Interestingly, areas in the frontal cortex have been shown to be volumetrically smaller in MDD patients as well[10]. These studies suggest that a change in the ratio between inhibitory and excitatory neurotransmitters may contribute to the altered brain function seen in depression[11].

1.2.2.2.2 Serotonergic System

Low levels of serotonin were speculatively linked to the development of MDD over 50 years ago—an association that has paved the way for current

[10] see section 1.2.3.2.4
[11] see section 1.2.3.2

and more conclusive studies. The association was first realised in 1956 after the release of Reserpine, a drug used to treat high blood pressure. On top of treating hypertension, the drug also caused depression by lowering brain serotonin levels (Ayd, 1956). Once the association between low serotonin and depression was realised, new medications including tricyclic drugs and monoamine oxidase (MAO) inhibitors were introduced to the market to increase levels of serotonin in order to treat MDD. Selective Serotonin Reuptake Inhibitors (SSRI) are now the most common type of antidepressant medication prescribed. SSRIs increase the amount of extracellular serotonin in the brain by inhibiting neurons' ability to reabsorb serotonin from the synaptic cleft. This effectively increases the amount of free serotonin in the synaptic cleft that can interact with presynaptic receptors, causing an antidepressant response. On top of increasing free levels of serotonin in the brain, it has been shown that SSRIs increase post-synaptic serotonin receptor function as well (Haddjeri, 1998). A down side to SSRIs is the fact that antidepressant effects take weeks to be seen, suggesting that efficacy is based upon downstream modulations in neural structures and networks.

More recent research suggests that more complex associations are present between the serotonergic system and MDD. As opposed to simply depleted levels of serotonin, intracellular cascades triggered by the monoamines (including serotonin) are involved in the onset of MDD (Nutt *et al.,* 2006). Overall, it also seems that reduced serotonin receptor functioning is observed in patients with MDD. At this point it is unclear whether this deficit is due to neurodevelopmental or hereditary factors (Drevets, 2008). It has been hypothesized that the reduction in serotonin receptor binding occurs only after cortisol has been released in dangerously high levels—as serotonin receptor density is under tonic inhibition by glucocorticoid receptor stimulation (Lopez, 1998). This also has been observed in rat depression models, as increased cortisol secretion due to stress has decreased serotonin receptor density (Lopez, 1998).

It seems that one's serotonin receptor sensitivity plays a large role in the development of depressive symptoms; it was observed that by artificially lowering patients' serotonin levels, temporary depressive symptoms were

seen in individuals with less sensitive serotonin receptors (Neumeister, 2002). Altered serotonin transporter function may also contribute to the pathophysiology of depression. If an individual acquires homozygous short alleles for the serotonin transporter protein, one is more vulnerable to develop depression after experiencing stressful life events (Caspi, 2003). This seemingly shows that one has a genetic threshold to stress, determined by which alleles of the serotonin transporter one inherits.

1.2.2.2.3 Glucocorticoid System/HPA Axis

The HPA axis is a set of feedback pathways between the Hypothalamus, Pituitary Gland, and Adrenal Gland that regulate one's reaction to stress. When an individual is exposed to a stressful situation, the hypothalamus secretes Corticotrophin-Releasing Factor (CRF), which causes the anterior pituitary gland to release Adrenocorticotropic Hormone (ACTH). ACTH up-regulates the production and secretion of cortisol from the adrenal gland. Cortisol is a steroid hormone, which allows the body to prepare for and to deal with stress. Overactivity of the HPA axis has been observed in MDD patients. Evidence of an overactive HPA axis can be seen in post mortem studies that show decreased CRF receptor density in the PFC of depressed patients, and that corticotrophic cell size is increased in depressed patients' pituitary glands (Gold, 2002; Drevets 2008). In living patients, severe depression is associated with hypersecretion of cortisol, pituitary and adrenal gland enlargement, and higher-than-average levels of CRF in the cerebrospinal fluid—this last finding suggests that deficits exist in the negative feedback system of the HPA axis, as high levels of cortisol usually inhibit ACTH and CRF synthesis and release (Gold 2002; Drevets, 2008). High levels of cortisol have been shown to cause atrophy of hippocampal neurons, explaining why hippocampus volumes are smaller in depressed patients[12].

1.2.2.2.4 Neurogenesis and MDD

[12] see section 1.2.3.2.2

High levels of stress, as measured by high levels of glucocorticoid hormones such as cortisol, are one of the leading causes of the cessation of adult neurogenesis (Oomen, 2007; Wong and Herbert, 2004). High levels of glucocorticoids, such as cortisol, reduce expression of brain-derived neurotrophic factor and nerve growth factor, both of which increase neurogenesis (Schmidt, 2007). After successful treatment of MDD, serum cortisol and CRF levels normalize and neurogenesis is again noticed in adult hippocampal cells (Musselman, 1993; Chen, 2006; Banasr, 2006). This cessation in neurogenesis may have implications on altered brain functioning observed in MDD[13], as well as reduced hippocampal volumes[14].

1.2.3 Neuroanatomical Approaches to Major Depressive Disorder

1.2.3.1 Overview

Converging studies have discovered decreased volumes in multiple regions of the depressed brain, as described in the following sections. Recent technological advancements, predominantly functional Magnetic Resonance Imaging (fMRI), have allowed researchers to also explore metabolic profiles of brain areas affected by MDD. It has been noticed that some areas are hyperactive compared to the healthy brain, while other areas are hypoactive—specific examples are further discussed in this paper[15]. By observing which areas are affected, it seems that the neural networks that modulate aspects of normal emotional behavior have been implicated in the pathophysiology of MDD (Drevets, 2008). These affected brain areas are now being targeted with invasive treatment options[16], and their respective metabolic profiles can be used as markers to track whether treatment has been effective, using fMRI (Mayberg, 2009). When effective, medication, psychotherapy, Electroconvulsive Therapy, Vagus Nerve Stimulation, ablative surgery, and Deep Brain Stimulation have shown convergent fMRI findings in normalization of frontal brain abnormalities (Mayberg, 2009; Fitzgerald, 2008; Kennedy, 2001; Pardo, 2008; Nobler, 2001).

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[13] see section 1.4
[14] see section 1.2.3.2
[15] see section 1.2.3.2
[16] see section 1.3.3.2

It seems that depression is not caused by dysfunction in one specific brain region, but rather it is thought to be a system wide disorder affecting brain regions involved in emotional control (Mayberg, 1997). More specifically, the "dorsal network" associated with emotional regulation (consisting of the dorsal prefrontal cortex regions) and the "ventral network" involved in emotional experience (consisting of the hippocampus, amygdala, ventral ACC, OFC, and basal ganglia—predominantly the striatum[17]) are disrupted in individuals with depression (Davidson, 2002). Usually changes in the structural architecture of the brain are only observed in adult patients with a longer or more severe clinical history (Pattern, 2006). The ability to observe affected brain structures allows us to further understand the neuropsychology of MDD and to discover potential targets for invasive treatment options[18].

It is important to note that side effects of medications could be a very real confounder in studies looking at volumetric changes in the depressed brain. The studies included in this thesis were not controlled for the use of identical medications among subjects, and some subjects are medicated while others are not. Specific examples of this issue are addressed later in this thesis[19].

1.2.3.2 Neural Structures Implicated

Below, volume and activational abnormalities in the MDD brain are discussed. In general, prefrontal areas show decreased activity on fMRI—in the dorsomedial and dorsolateral prefrontal cortices specifically (Phillips, 2003). Limbic regions, important for the recognition and experience of emotion, are overactive in depressed patients—specifically in areas such as the subgenual cingulate cortex, amygdala, insula, ventrolateral prefrontal cortex, ventral striatum, and the thalamus (Phillips, 2003). These affected neural structures have a direct impact on the functional abilities of the brain in actively depressed patients.

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[17] see section 1.2.3.2.6
[18] see section 1.3
[19] see section 2.4.4.1

1.2.3.2.1 Temporal Lobes

In a meta-analysis, Lorenzetti *et al.* (2009) looked at all relevant articles published after the year 2000 pertaining to structural brain abnormalities in MDD. It was found that in studies looking at total temporal lobe volume, no differences could be determined between MDD patients and healthy controls (Lorenzetti, 2009). However, differences could be seen when certain regions of interest were isolated from within the temporal lobe. For example, Vythilingam *et al.* (2004) found evidence that in MDD patients, the left temporal lobe was smaller compared to the right. Studies looking at particular areas of the temporal lobe such as the Superior Temporal Gyrus (STG) have shown mixed results. Smaller volumes of the STG have been observed by Shah *et al.* (2002). The evidence to date provides no proof for differences in the volume of the temporal lobe due to sex, effects of medication, or family history (Lorenzetti, 2009).

1.2.3.2.2 Hippocampus

The hippocampus is the most studied area affected by MDD. Smaller hippocampal volumes are associated with patients who have had multiple depressive episodes as opposed to those experiencing their first episode (Caetano, 2004). The results of multiple studies converge in their findings and state that volume loss in the hippocampus can be observed due to MDD (Bremner, 2000; Caetano, 2004; Frodl, 2002, 2004, 2006; Lange and Irle, 2004; MacQueen, 2003; Neumeister, 2005; Saylam, 2006; Shah, 2002; Sheline, 2003; Weniger, 2006). Other studies have found no difference between hippocampal volumes in MDD patients compared to healthy controls (Hastings, 2004; Monkul, 2007; Morys, 2003; Posner, 2003; Rusch, 2001; Vythilingam, 2002, 2004). Protocol issues, and differing patient genders and ages used in the studies are likely to blame for these differences.

Interestingly, gender may influence the relationship between hippocampal volume and illness duration (Lorenzetti, 2009). After a female experiences her first depressive episode, it has been observed that hippocampal volumes actually increase, while in males under the same

conditions hippocampus volume decreases (Frodl, 2002). This could suggest that the pathophysiology of MDD may affect the hippocampus in males differently than it does in females. These differences may explain why more females become depressed than males.

Medication effects complicate results as well, not only because certain medications affect hippocampal volume, but also because they affect males and females differently. For example, females that responded to antidepressants have been shown to have larger hippocampal volume compared to female non-responders, while in males this was not the case (Vythilingham, 2004). This may suggest that antidepressants affect males and females differently, or that there are different neurological mechanisms of MDD at work in males and females. Medication-free patients have been shown to have smaller hippocampal volumes than patients on medication (Saylam, 2006).

1.2.3.2.3 Amygdala

The amygdala is no exception to the idea that structural changes are associated with longer MDD duration. It seems that the size of the amygdala is dynamic throughout the course of MDD (Lorenzetti, 2009). Interestingly, patients who are experiencing their first depressive episode show increased amygdala volume (Frodl, 2002, 2003; Lange and Irle, 2004;Weniger, 2006). Studies looking at MDD patients with more severe symptoms, as well as longer illness duration, found that the amygdala is volumetrically smaller (Bremner, 2000; Caetano, 2004; Hastings, 2004; Monkul, 2007). Post mortem studies also show reduced glial cell density in the amygdalas of reported depressed individuals (Bowley, 2002).

Gender also appears to play a role in how MDD affects the amygdala. Smaller amygdala volumes have been reported in females, but not in males (Hastings, 2004). Research thus far has shown no relationship between medication or family history on amygdala volume (Lorenzetti, 2009).

1.2.3.2.4 Frontal Lobes

The main area studied in the frontal lobe pertaining to MDD is the orbital frontal cortex (OFC). In patients with a history of multiple depressive episodes and severe symptoms, decreases in OFC volume have been observed; this volume reduction is not seen in patients with less severe depression (Bremner, 2002; Frodl, 2006; Monkul, 2007; Shah, 2002). OFC lesions are associated with negative emotionality (Salloway, 2001). On the other hand, euphoria, exuberance, and hyperactivity are sometimes seen when the OFC has reduced functioning. Speculatively, this would imply that in the case of MDD, a reduction in volume as opposed to reduced functioning of the OFC could be contributing to clinical symptoms. Post mortem studies show reduced glial cell density in the orbitofrontal cortex (Drevets, 1998). Lacerda *et al.* (2004) noted that reduction in volume was seen in only male participants.

Interestingly, studies of post stroke brain functioning also shed insight into this discussion. It has been observed that after left sided lesions to the frontal cortex (including the basal ganglia[20]) depressive symptoms are common. Right-sided lesions, on the other hand, can produce euphoria or indifference (Salloway, 2001). All investigators do not agree upon these findings.

Differences in brain metabolism have also been observed in the frontal lobes. Reductions in brain activity have been detected in the dorsomedial and dorsolateral prefrontal cortices (Soares, 1997), while increases in brain activity have been noted in ventrolateral prefrontal cortex (Drevets, 1992).

1.2.3.2.5 Anterior Cingulate Cortex

The Anterior Cingulate Cortex (ACC) is activated when emotional regulation is required in situations where behaviour is failing to achieve a desired outcome (Ochsner, 2001). A characteristic symptom of depression is the lack of a "will-to-change," possibly arising from a dysfunctional ACC (Davidson, 2002).

The ACC comprises two distinct regions unique in their neural connectivity and cytoarchitectural features (Yucel, 2008). The Subgenual

[20] Specific area within the basal ganglia not mentioned in article.

Prefrontal Cortex (SGPFC) and subcollosal gyrus form the rostral-ventral subdivision of the ACC, an area thought to be associated with the regulation and assessment of emotional responses (Bush, 2000). This rostral-ventral subdivision has connection to other areas that are affected by MDD, including the amygdala, anterior insula, hypothalamus, nucleus accumbens, and the orbitofrontal cortex (Yucel, 2008). The dorsal part of the ACC, including the paracingulate gyrus, is more involved in cognitively demanding information, bordering the prefrontal and parietal cortices (Yucel, 2003). Both of these subdivisions have their own metabolic profile and are differentially affected in MDD (Ressler, 2007), with hyper-activation of the Subgenual Cingulate Gyrus (SCG) and hypo-activation of the anterior cingulate cortex (Mayberg, 2005).

Patients who have experienced three or more depressive episodes have been found to have smaller subcallosal gyrus volumes, while patients with three or fewer episodes have similar subcallosal gyrus volumes to healthy controls (Yucel, 2008). This again follows the idea that MDD symptoms take time to affect brain structures. It is of particular interest that the subcallosal gyrus forms part of the negative-feedback system of the HPA axis (Diorio, 1993) [21]. Post mortem studies show reduced glial cell density in the ACC (Drevets, 1997). No differences were determined in SGPFC or paracingulate gyrus volumes between depressed patients and healthy controls (Yucel, 2008). When the ACC is looked at as one structure it has been found that the left ACC is smaller in MDD patients (Caetano, 2006).

1.2.3.2.6 Basal Ganglia

The basal ganglia is one of the least studied brain areas associated with MDD, with only three articles meeting criteria for a 2009 meta-analysis performed by Lorenzetti *et al.* Certain studies have found that basal ganglia volume decreases in MDD patients compared to healthy controls (Shah, 2002). Among the specific areas involved in the basal ganglia (striatum, globus pallidus, substantia nigra and subthalamic nucleus), it seems that the striatum is the most reduced in volume. Other studies looking at the basal

[21] See section 1.2.2.2.3

ganglia have found no difference in volumes between individuals with and without MDD (Bremner, 2000). Research thus far has not looked into effects related to gender or medication effects (Lorenzetti, 2009).

1.3 Neurosurgery for Mental Disorders (NMD)

1.3.1 Overview

Although current antidepressant medication and psychotherapy are viable treatment options for some patients with MDD, only 50% to 60% of individuals respond to any one medication and only 35% become symptom free (Kupfer, 2003). Relapse of depressive symptoms is the norm in the majority of depressed patients (Warden, 2007). Approximately 20% of those who have depression are resistant to medications and psychotherapy (Malone, 2010). Many antidepressants have undesired side effects—impotence and other sexual problems, headache, and nausea, to name a brief few. It has been observed that the regular administration of psychotherapy is only effective in treating certain subtypes of depression (Frank, 2002). It is because of findings such as these that neurosurgery to treat mental disorders has been considered an experimental treatment option. In some cases, the neurosurgeries discussed below are giving treatment resistant patients a new, depression-free outlook on life.

1.3.2 The Early Days of NMD (1930-1950s)

In 1935, Antonio Caetano de Abreu Freire Egas Moniz won the Nobel Prize for discovering the therapeutic value of the leucotomy in certain psychoses (Nobelprize.org). The procedure disrupted connections to and from the prefrontal cortex, initially performed by drilling holes in a patient's head and injecting an alcoholic solution. Walter Freeman and James Watts, a neuro-psychiatrist and neurosurgeon respectively, developed a new method in 1945 called the trans-orbital lobotomy. Incidence rates of the lobotomy soon decreased as unwanted side effects were observed—including personality changes. 40,000 lobotomies were performed in the

USA, 17,000 in the UK, and 9,300 in Scandinavia (Tranoy, 2005). The quality of published research during this time was very poor, and in some instances data were not collected at all. Understandably, public concern developed in countries where side effects could be observed.

1.3.3 The Renaissance of NMD

1.3.3.1 Overview

In 1977, a US presidential commission was drafted to respond to public concern pertaining to psychosurgery and addressed adverse side effects. The report concluded that psychosurgery should be continued, but more stringent patient consent, surgeon competency, and data monitoring pre and post surgery outcomes should be pursued (Dhew Publication No. (OS) 77-0001, 1977).

NMD is experiencing a renaissance because of the data from MRI and post-mortem studies indicating specific affected brain areas that serve as targets for intervention. The theory behind today's neurosurgical techniques is based upon targeting the dysfunctional emotional and cognitive brain areas discussed above. Very localized lesions are created to minimize side effects. Specific brain areas can be located very precisely using imaging techniques, and in certain procedures no brain tissue needs to be destroyed. Many procedures are reversible, such as Deep Brain Stimulation and Vagus Nerve Stimulation, and many can be modulated even after surgery via external devices (Jamie, 2007).

In the following sections pertaining to surgical treatments of depression, the quality of the research is taken into account to better judge how trustworthy certain studies are. To do this the Eigenfactor (EF) and Article Influence (AI) Scores are used, both of which scale the total impact of a journal. Each test has a possible 100 as a maximum score (http://www.eigenfactor.org).

1.3.3.2 Vagus Nerve Stimulation

Vagus Nerve Stimulation (VNS) was initially used to treat medication resistant epilepsy. In fact, over 17,000 individuals worldwide have had a

VNS implanted to help treat their epilepsy (Elger, 2000). Interestingly, it was observed that not only were these patients having fewer seizures, but also their general mood improved independently of having fewer seizures (Harden, 2000). These findings began an exploration using VNS to treat TRD. On July 15th, 2005 VNS was approved by the US Food and Drug Administration (FDA) for "adjunctive long-term treatment of chronic or recurrent depression for patients 18 years of age or older who are experiencing a major depressive episode and have not had an adequate response to 4 or more adequate antidepressant treatments" (Nahas, 2006).

The known neuroanatomy of the vagus nerve played a large part in the argument of using VNS to treat TRD. The vagus nerve controls the cardiovascular, respiratory, and gastrointestinal systems (Nahas, 2006). 80% of the vagus nerve fibers are afferent and carry information to the brain (Foley, 1937). The vagus nerve enters the brain in the midbrain at the Nucleus Tractus Solitaris (NTS) (Nahas, 2006). From here, fibres create a classic reflex arc and either connect to the reticular activating system or reach the parabrachial nucleus and its connections to other brain areas—the raphe nucleus, thalamus, paralimbic, limbic and cortical regions including the anterior insula and cingulate cortex (Bachman, 1977; Nahas, 2006). Many of these brain areas are involved in the neuroanatomy of depression; of specific note are the cingulate cortex, limbic areas including the amygdala and hippocampus, and the raphe nucleus (where serotonin is synthesized).

An imaging study using Positron Emission Tomography (PET) also played a role in justifying the use of VNS to treat TRD—the study showed increased cerebral blood flow to the rostral and dorsal-central medulla, right postcentral gyrus, hypothalami, thalami, insular cortices, and in cerebellar hemispheres after VNS surgery (Henry, 1998). Blood flow was decreased in hippocampus, amygdala, and posterior cingulate gyri following VNS surgery (Henry, 1998). These areas overlap with the neuroanatomy of MDD. Another study shows similar results, indicating that cerebral blood flow is increased in the dorsolateral prefrontal cortex after VNS in TRD patients (Kosel, 2010).

It is important to note that during VNS it is due to both orthodromic and antidromic stimulation of the Vagus Nerve that leads to aforementioned changes in neural blood flow (Henry, 1998). Orthodromic activation occurs at afferent axonal terminals in the brainstem, while antidromic activation occurs through efferent axons that project from the brainstem to the peripheral autonomic ganglia. It is impossible to determine which medullary nuclei generated the blood flow increases observed during VNS due to limitations of spatial resolution of the PET scanner (Henry, 1998).

To perform a VNS, a neurosurgeon implants a pacemaker-like generator in the anterior chest wall (Nahas, 2006). Leads coming off the pacemaker are wrapped around the cervical portion of the left vagus nerve (Nahas, 2006). The intensity, duration, pulse width, and duty cycle of electricity delivered to the nerve can be varied using an external device. After three months of active VNS it has been observed that the major metabolites of dopamine and serotonin are increased in cerebral spinal fluid (Ben-Menachem, 1995).

Previous studies have shown success in VNS procedures. Patients were considered responders if their depressive symptoms decreased by 50% as measured by the HRSD-17[22] questionnaire; patients were in remission if they scored a seven or less on the HRSD-17 (Eljamel, 2008). In a study published by Nahas *et al.* 2005 in the *Journal of Clinical Psychiatry* (EF: 95, AI: 91) consisting of 60 patients, 30.5% showed a clinical response after only 8 weeks post VNS surgery. At the 12-month mark post-surgery, remission rates increased to 44.1%, and at 24 months post-surgery remission rates were 42.4% (Nahas, 2005). Quality of life self-assessment tests showed that quality of life improved by 47% 12 months post-surgery and 56% 24 months post-surgery (Nahas, 2005). Another study published in the *British Journal of Psychiatry* (EF: 95, AI: 95) including 11 patients showed a 55% clinical response rate and a 27% remission rate post one year of surgery (Corcoran, 2006). It is interesting to note that like antidepressants, there is a lag between initiation of treatment and clinical improvement in symptoms. Whether these time lags are the same between the two different

[22] Hamilton Rating Scale for Depression is a multiple choice questionnaire that rates the severity of a patients depression

treatments is difficult to measure based on the limited number of VNS studies relating to MDD, as well as the fact that remission rates are measured at set intervals. If remission rates were continuously monitored for, a more precise remission time frame could be determined and could be compared to the treatment delay expected of antidepressant therapy.

Side effects are associated with VNS; however they are usually less severe than those associated with the anterior cingulotomy and capsulotomy as no brain matter is destroyed. 1.1% of individuals with a VNS device installed experience hoarseness and temporary vocal cord paralysis if the laryngeal nerve is damaged during surgery (Nahas, 2006). During surgery, 0.1% of patients showed a flatlined electrocardiogram, but were resuscitated with no long-term consequences (Nahas, 2006).

1.3.3.3 Anterior Cingulotomy (ACING)

The anterior cingulotomy is another treatment option for those who have TRD. Although the procedure has been practiced in the United States and Great Britain for many years, an exact lesion location and lesion volume are still not agreed upon and will vary in accordance with an individual's unique anatomy. Procedures using standard stereotactic neurosurgical procedures (Steele, 2008) also differ between centres.

The surgical technique is as follows. MRI is used to determine the lesion site to 1mm accuracy. These coordinates are located in the patient's brain to a 1mm accuracy using a stereotactic frame. The bilateral targets are points 1mm above the roof of the lateral ventricle, 7mm lateral to the midline, and 20mm posterior to the tip of the frontal horn (Steele, 2008). A skin flap is cut and a bur hole created. Through the hole an exposed electrode is inserted into the correct coordinate and heated to 70°C for 90 seconds, repeated twice. The procedure is performed bilaterally.

The lesion affects the cingulum bundle and the cingulate cortex. The cingulum bundle has extensive connections to other regions in the cingulate gyrus, the hippocampus, prefrontal cortex, and the amygdala—all areas where deficits are seen in MDD patients (Steele, 2008; Shields, 2008). The positive effects of the surgery are often seen months after surgery, hinting

that downstream effects, such as rewiring of white matter tracts, are to blame for clinical effectiveness (Shields, 2008).

Lesion volume and location on the cingulate are important variables. It has been observed that more anterior lesions are more effective than posterior lesions, and interestingly that smaller lesions prove to be more effective than larger lesions (Steele, 2008). This is interesting because many centres, such as Massachusetts General Hospital, routinely perform a second cingulotomy if the first is unsuccessful at acquiring remission. It seems that it is in fact the location of the surgery that is more important; more specifically, the more rostral the lesion the more effective it seems to be (Steele, 2008).

In the few studies conducted so far, very positive results have been achieved. In a study conducted at Ninewells Hospital in Dundee, Scotland, eight patients were given an anterior cingulotomy. Patients were considered responders if their depressive symptoms decreased by 50% as measured by the HRSD-17 questionnaire; patients were in remission if they scored a seven or less on the HRSD-17 (Eljamel, 2008). After 12 months post surgery, 25% responded to surgery with less depressive symptoms and 37.5% reached remission (Steele, 2008). Steele et al. 2008 published their findings in *Biological Psychiatry* (EF: 99, AI: 98).

Significant improvements were observed on the Paired Associated Learning and Spatial Learning Memory tasks 12 months after surgery. This shows a greater planning ability, possibly due to alleviation of depressive symptoms. A Harvard Medical School study consisted of 17 anterior cingulotomy patients. At a long term follow up, 41.2 % were classified as responders, 35.3% were partial responders, and 23.5% did not respond (Shields, 2008). Shields et al. 2008 published their findings in *Biological Psychiatry* (EF: 99, AI: 98). In a third study of five patients published in *Neurosurgical Focus* (EF: 85, AI: 95), after 12 months, 60% of patients were responders, and 20% achieved remission (Eljamel, 2008). In all patients who undergo a cingulotomy, hypermetabolism in the subgenual cingulate cortex and prefrontal cortex can predict surgical response (Dougherty, 2003).

Although there are clear clinical benefits related to anterior cingulotomies, side effects do exist. Headache, nausea, dizziness, incontinence, involuntary limb movements, trouble pronouncing words, and facial swelling can occur (Eljamel, 2008; Shields, 2008). Serious side effects have included the development of epilepsy in one patient and serious mental incapacitation in another (Eljamel, 2008; Shields, 2008).

1.3.3.4 Anterior Capsulotomy

The anterior capsulotomy is another example of a stereotactic brain surgery used to treat TRD. The procedure was first used in 1949 by Dr. Talairach and his colleagues to treat chronic pain (Eljamel, 2009). During the procedure, the most anterior portion of the anterior limb of the internal capsule lateral to the head of the caudate nucleus was lesioned. The removed area connects the frontal and anterior cingulate cortex with the thalamus, hippocampus, and amygdala (Eljamel, 2008).

Preparation of the patient and planning of the procedure are exactly the same as the steps used in an Anterior Cingulotomy; MR images are taken to find lesion coordinates and a stereotactic frame is used to precisely locate the mentioned coordinates (Eljamel, 2008). During the operation, an exposed electrode is heated to 70°C twice on both the left and right side, meaning that the lesion is twice as big compared to the anterior cingulotomy. Positive results are often seen months after surgery in the same manner observed in the anterior cingulotomy.

One study conducted in Ninewells Hospital included 20 bilateral anterior capsulotomy patients. 12 months post-surgery, 25% of patients were responders and 10% were in remission. Long-term remission rates were 40%. Despite good remission rates after surgery, side effects are associated with anterior capsulotomy. These include headache, nausea, dizziness, incontinence, involuntary limb movements, trouble pronouncing words, and facial swelling (Eljamel, 2008; Shields, 2008). In one patient, intracerebral haemorrhage occurred during surgery and led to permanent hemiparesis (Eljamel, 2008). Shields et al. 2008 published their findings in *Biological*

Psychiatry (EF: 99, AI: 98), Eljamel published in *Neurosurgical Focus* (EF: 85, AI: 95).

1.3.3.5 Deep Brain Stimulation

1.3.3.5.1 Overview

Deep Brain Stimulation (DBS) has been introduced over the last decade and represents the most recent class of invasive procedures used to treat TRD MDD patients. The surgery is stereotactic and non-ablative, therefore removal of the implanted electrodes is almost completely reversible. Researchers also have the ability to vary stimulation sites and parameters in any individual patient to maximize clinical outcome (Malone, 2010). An abundance of research is underway utilizing DBS technology to study treatment options not only for TRD, but also refractory Obsessive-Compulsive Disorder (OCD) and Tourette syndrome. In fact, recently the use of DBS has been approved by the FDA to treat OCD.

During the surgery, MR images are taken and the patient's head is fixed to a stereotactic frame. Using the desired coordinates, the target brain area is located. Electrodes are inserted through burr holes. The electrodes are connected to a pulse generator inserted under the shoulder blade (Mayberg, 2005). One week after surgery, the electrodes are turned on using the lowest possible voltage. Every week after their surgery the patients must return to have voltage levels adjusted, usually being turned up gradually for the first six months (Mayberg, 2005).

Many brain areas have been targeted for implantation of a DBS device due to their involvement in emotional and cortical brain areas affected by MDD. Brain areas already targeted are the subgenual cingulate gyrus, the ventral striatum/ventral caudate, and the nucleus accumbens. It seems that the efficacy of DBS to treat refractory MDD depends on the brain area targeted[23] Side effects are usually minimal, with infection at the electrode implantation site being the most common, followed by skin erosion over the battery pack inserted under the shoulder blade. Paresthesias, anxiety, mood

[23] see sections 1.3.3.5.2-1.3.3.5.3

changes, and autonomic effects are also observed but all are reversible with adjustment of the stimulation parameters (Malone, 2010).

Below studies investigating the effect of DBS on specific brain structures are discussed.

1.3.3.5.2 Subgenual Cingulate Gyrus

The Subgenual Cingulate Gyrus (SCG) is the brain area most targeted by DBS. Mayberg and colleagues at Emory University in Atlanta, Georgia performed the first study looking into the efficacy of DBS in the SCG published in *Neuron* (EF: 100, AI: 99). Six patients took part in the study, and after six months, four patients showed an antidepressant response measured by a 50% decrease in the Hamilton Rating Scale for Depression (Mayberg, 2005). Two of the six patients reached remission status after 6 months as well. Using MRI technology, it was observed that hyper-activation of the SCG and hypo-activation of the anterior cingulate cortex typical of the depressed brain were both normalized after 4 months of DBS treatment (Mayberg, 2005).

Lozano *et al.* 2008 also had promising results in another study comprising of 20 subjects who underwent DBS in their SCG published in *Biological Psychiatry* (EF: 99, AI: 98). After on month, 35% were responders and 10% were in remission. Six months after surgery, 60% were responders and 35% were in remission, these benefits were maintained at one year (Lozano, 2008). A follow up study on the same patient group by Kennedy *et al.* 2011 showed that the average response rates at 1, 2, and 3 years after DBS implantation were 62.5%, 46.2%, and 75%, respectively.

Holtzheimer et al 2012 performed DBS on the SCG of 10 MDD patients and published results in *The Archives of General Psychiatry* (EF: 99 AI: 99). The group found remission in 18% after 24 weeks, 36% after one year and 58% after two years. Important to note is that none of the patients who experienced remission had a relapse of symptoms.

1.3.3.5.3 Nucleus Accumbens (Ventral Caudate/Ventral Striatum)

In animal studies, electrical stimulation of the nucleus accumbens has led to increased exploratory behaviour and increased food intake; self-stimulation of the nucleus accumbens is also easily taught to rats (van Kuyck, 2007). This comes as no surprise, as the nucleus accumbens is rich in dopaminergic connections and has been dubbed a 'pleasure centre' of the brain. Currently, surgeries are being performed inserting DBS into the nucleus accumbens of humans as well. In 2008, a pilot study was released in *Neuropsychopharmacology* (EF: 97, AI: 95) looking at three patients that underwent a DBS procedure in his or her nucleus accumbens (Schlaepfer, 2008). One of the three patients achieved a 50% reduction in his or her depressive symptoms during weeks 6-23. Bewernick *et al.* 2010 performed DBS on the Nucleus Accumbens of 10 patients with MDD and published their study in *Biological Psychiatry* (EF: 99, AI: 98). It was found that five patients reached 50% reduction of the HDRS-17 after one year. Interestingly, decreased metabolism in the subgenual cingulate and prefrontal regions including the orbital prefrontal cortex was observed in these patients, showing down stream effects of the surgery.

The Ventral Caudate and Ventral Striatum (VC/VS) are also becoming common targets for DBS treatment. In the first study performed in 2009 by Malone and colleagues and published in *Biological Psychiatry* (EF: 99, AI: 98), 15 patients were recruited for the procedure. Electrodes were implanted bilaterally in the VC/VS region to follow the dorsal-ventral trajectory of the anterior limb of the internal capsule (Giacobbe, 2009). After one month of DBS treatment, 3/15 patients reached clinical response criteria. After three months, 8/15 reached clinical response criteria. At a 12-month follow up, 40% of patients had reached remission (Malone, 2009).

1.4 The Neuropsychology of Major Depressive Disorder

1.4.1 Memory

Episodic memory, that is, the ability to remember new events in an autobiographical context is affected in patients with MDD. This type of memory is associated with the hippocampus (Brown, 2001). As previously

discussed, smaller hippocampal volumes are associated with the depressed brain. These smaller hippocampal volumes are possibly caused by cellular atrophy due to elevated levels of cortisol (Cahill, 2003; Hinkelmann, 2009; Gomez, 2009; Egeland, 2005). In a study exploring this hypothesis, dexamethasone was administered to depressed patients. Dexamethasone, being a more potent form of cortisol, activates the negative feedback loop of the HPA axis, signalling less cortisol synthesis and secretion by the adrenal cortex. After two days of dexamethasone administration, it was observed that memory performance was improved. The researchers hypothesized that the improvements in memory could be explained by the experimentally reduced levels of cortisol (Bremner, 2004).

In a related study, researchers administered high levels of hydrocortisone (cortisol) to both patients with MDD and healthy subjects. It was discovered that after hydrocortisone administration, healthy subjects scored lower on declarative memory tasks, as well as general memory retrieval, while depressed patients scored the same as they did previously, again supporting the idea that high levels of glucocorticoid hormones do in fact affect declarative memory (Terfehr, 2010).

Working memory is also affected in MDD. Gruber *et al.* (2011) looked at 18 patients with MDD and 18 healthy controls. It was found that eight out of the 18 patients performed significantly worse than the healthy controls on tasks involving working memory. Studies utilizing imaging technologies have also looked into which brain areas are irregularly active in MDD patients while performing working memory tasks. In a study performed by Matsuo *et al.* (2007), it was observed that the MDD brain was hyperactive in the left dorsolateral cortex and anterior cingulate cortex compared to healthy controls while performing working memory tasks. This result emphasizes the role of the ACC in MDD.

Finally, a bias also exists in MDD patients towards negative memory formation. Depressed patients show an enhanced recall for negative information as compared to positive or neutral material (Murray, 1999).

1.4.2 Executive Functions

MDD has been associated with deficits in many subcomponents of executive function. Psychomotor retardation is one of the diagnostic criteria noted in the DSM[24]. In a study looking at 50 depressed patients, it was observed that processing speed was reduced on attention tasks (Egeland, 2003). Mahurin *et al.* (2006) also suggested that processing speed and visual processing speed was reduced in depressed patients measured by performance on the Trail Making Task, a result that was replicated by Smith *et al.* (2006). Verbal fluency, combining verbal and visual cues, spontaneous cognitive flexibility, initiation ability and complex integration of information for concept formation were all impaired in a study performed by Fossati *et al.* (1999). Hill *et al.* (2004) pointed out that spatial abilities, motor skills, and attention capacity were all found to be impaired in patients with psychotic depression compared to healthy controls as well.

Studies utilizing imaging technologies have also looked into which brain areas are irregularly active in MDD patients while performing executive function tasks. In a study performed by van Tol *et al.* (2011) utilizing MRI technology, performance on the Tower of London test was observed. During this visuospatial planning task, a patient is presented with a starting configuration and a target configuration and is asked to find the minimum number of steps needed to get from one to the other (van Tol, 2011). It was found that MDD patients showed increased dorsolateral prefrontal cortex activation while completing the Tower of London task compared to healthy controls. In another study, it was suggested that when depressed patients were performing another attention task, the Stroop test, in an MRI scanner, their anterior cingulate gyrus and dorsolateral prefrontal cortex were hyperactive compared to healthy controls (Wagner, 2006). Finally, depressed patients are faster to respond to sad words compared to happy words, a very similar finding to the bias present to form negative memories (Drevets, 1998).

1.4.3 Emotion Processing

1.4.3.1 Introduction

[24] see section 1.1.2.1

Many neuroanatomical models exist to explain how the human brain recognizes emotion. These models include single-system, dual system, and multi-system explanations. In a meta-analysis published in 2003, 106 PET and fMRI studies were evaluated to find similarities in the vast body of research that pertains to all these explanations. In this section, the different system models are explored and the results of the neuro-imaging meta-analysis are used to support or refute these models.

1.4.3.2 Current Single System Emotion Recognition Models

The first single system model exploring the neuroanatomy of emotion was proposed by Maclean. Included in his function-structure relationship was the explanation that the limbic system formed a set of neural structures that formed a network to decipher emotion (Maclean, 1993; Murphy, 2003). Another single system explanation specifically pertains to the right hemisphere. In humans, it has been shown that emotions are expressed more intensely on the left side of the face, suggesting that the right side of the brain, responsible for coding the left side of the face, is more active when coding emotions (Sackheim, 1978). In another related study, it has been observed that when the right hemisphere is damaged, impaired emotional recognition of facial expressions is noticed (Mandal, 1992; Murphy, 2003).

When looking at the data from the meta-analysis, a relationship between right and left side lateralization was not observed when the brain deciphers emotion, nor was the posterior or anterior sections of the brain more active. A critical role of the right hemisphere in the encoding of emotion was not determined (Murphy, 2003). Many of the structures in the limbic system were activated across studies including the amygdala and the ACC, supporting MacLean's limbic system theory (Murphy, 2003). However, many non-limbic areas were activated as well.

1.4.3.3 Current Dual System Emotion Recognition Models

Explanations relying on dual systems to explain emotion also exist. Examples of these dual explanations are positive vs. negative emotions, pleasant vs. unpleasant emotions, or calm vs. excited emotions. A number of

Electroencephalography (EEG) studies looking at animals, adults and children converge in their findings that positive and negative emotions rely on distinct neural systems (Murphy, 2003). Davidson *et al.* (1984) argued that the right hemisphere encoded positive emotions and the left hemisphere encoded negative ones. Building on this theory, researchers later hypothesized that the positive emotion coding right hemisphere was responsible for an approach system and the negative emotions with a withdrawal system (Davidson, 1999). More specifically, this approach system is involved in approaching positive stimuli, while the withdrawal system is involved in detecting punishment and inhibiting goal-oriented behaviour (Carver, 2004; Gray, 1981).

The meta-analysis did not find a spatial difference between positive or negative emotions, as neural activity was symmetrical. However, it was observed that the left hemisphere was significantly more active for approach emotions, while no relationship was noticed for withdrawal emotions (Murphy, 2003).

1.4.3.4 Current Multi System Emotion Recognition Models

The final family of explanations of emotion recognition fall into multisystem models. In this group of explanations, emotions are stated to be encoded by specific neural programs called affect programs, a term first coined by Charles Darwin in 1872 (Darwin, 1872; Murphy, 2003). The definition of an affect program is a "specific neural mechanism that stores patterns for and triggers complex emotional responses that are quick, complex and organised" (Murphy, 2003). In 1982, Ekman and Friesen proposed fear, disgust, anger, happiness, sadness, and surprise as affect programs; later Ekman proved that these emotions are represented exactly the same cross-culturally (Ekman, 1982; Ekman 1992).

Certain brain regions seem to be involved with specific emotional recognition experiences. For example, following brain lesions to the amygdala and surrounding areas, impairment in one’s ability to recognize the facial expression of fear have been observed (Adolphs *et al.,* 1994). Similarly, lesions to the gustatory insula and basal ganglia have eliminated

patients' ability to recognize disgust (Calder, 2000). Regions associated with the recognition of happiness, sadness, or surprise have not yet been isolated (Murphy, 2003).

Many interesting similarities exist pertaining to the affect program theory of emotion when looking at the 106 imaging studies included in the meta-analysis. An association between the amygdala and fear was determined; activity in the amygdala was observed in 40% of the studies dealing with the emotion of fear and in 60% of the studies looking at the recognition of the facial expression of fear (Murphy, 2003). These data were pioneered in a study by Sprengelmeyer *et al.* (1999), as it was discovered that bilateral lesions of the amygdala impaired one's ability to process fear. In a second meta-analysis looking at brain activity when dealing with the facial expression of fear, the fusiform gyrus was also activated, as well as the cerebellum, left inferior parietal lobule, left inferior frontal, and right medial frontal gyrus (Fusar-Poli, 2008). Associations between both the insula and globus pallidus were established when observing the emotion of disgust; activity in the insula and globus pallidus was found independently in 70% of the studies dealing with the emotion of disgust (Murphy, 2003). In studies dealing with the recognition of the facial expression of disgust, four out of five studies showed activation in both the insula and globus pallidus (Murphy, 2003). The second meta-analysis also showed activation in the left amygdala, fusiform gyrus, bilateral temporal gyrus, and the left middle frontal and right inferior frontal gyri when the brain was looking at a facial expression of disgust (Fusar-Poli, 2008). Lateral OFC activity was noticed in more studies dealing with anger than in any other emotion (Murphy, 2003). The right cingulate and anterior cingulate gyri, the right parahippocampal gyrus, left cerebellum, bilateral inferior frontal gyrus and the right middle frontal gyrus are also consistently active when looking at facial expressions of anger (Fusar-Poli, 2008). When looking at sad emotional faces, increased activation is seen in the right occipital gyrus, left insula and left thalamus (Fusar-Poli, 2008). Finally, when looking at facial expressions of happiness, increased activation was witnessed in the left amygdala, left insula, left medial frontal gyrus, left putamen, left cerebellum, and middle temporal gyrus (Fusar-Poli, 2008).

It is of great importance that a general role of the Anterior Cingulate and Medial Prefrontal Cortices may have been found in the recognition of emotions. These brain areas were active in a "significant portion" of the 106 imaging studies that were part of the meta-analysis (Murphy, 2003). Other studies support the idea that the frontal cortex (including the ACC) is important in processing general emotional cues (Damasio, 1994; Hornak, 1996; Keane, 2002; Rolls, 1999; Murphy, 2003). Other studies have hypothesized that specific brain regions associated with encoding emotions filter into frontal brain areas such as the ACC (Sprengelmeyer, 2008). This hypothesis is further solidified by the fact that when these frontal brain areas are damaged, impairments are seen in general emotional recognition and experience (Keane, 2002; Murphy, 2003).

1.4.3.5 Emotion Processing in Depressed Individuals

According to the DSM-IV criteria, depression is classified as a mood disorder. It is no surprise that researchers have begun to explore emotion and facial expression processing in the depressed brain. Studies thus far have shown differences in how depressed patients interpret and experience emotions and facial expressions. Depression affects one's emotional experience due to specific brain structure volume reductions and abnormal levels of neural metabolism in a variety of brain areas associated with emotional processing mentioned above.

In one of the most clear-cut studies performed thus far, the recognition of the facial expression of disgust was analysed in depressed patients. 68 patients with severe depression were compared against 50 healthy appropriately matched controls. It was detected that the control group was significantly better at recognizing the facial expression of disgust compared to the MDD subjects (Douglas, 2010). It was also determined that MDD patients were more likely to interpret neutral faces as sad and less likely to interpret neutral faces as happy (Douglas, 2010). In another study it was found that depressed patients had a negative emotional bias when interpreting emotion (Morris, 2009). Depressed individuals react faster to sad faces than any other emotion (Drevets, 1998). General emotional

processing deficits in MDD patients have been observed in a number of studies (Feinberg, 1986; Mikhailova, 1996; Persad, 1993).

Ritchey *et al.* (2011) suggested that depressed patients show an enhanced response to negative versus positive emotional stimuli. In the same study, it was also detected that depressed individuals showed lower levels of discrimination between emotional and neutral stimuli. Selection bias towards negative emotional cues such as the facial expression of sadness, and a bias away from positive emotional cues such as happy faces were also mentioned by Lappanen *et al.* (2006). In the same article it was observed that individuals with major depressive disorder show increased neural activity in response to sad faces and decreased neural activity in response to happy faces. Other neuroimaging findings show that increased amygdala activity is detected in MDD patients when recognizing the facial expression of sadness (Drevets, 2001).

A person's ability to deal with society, their environment, and to think rationally was defined as ones 'Emotional Intelligence' by Salovey and Mayer *et al.* (1990). Personality questionnaires such as the TCI-R[25] and SSEIT[26] have been used to study ones emotional intelligence. In one such study, the TCI-R and SSEIT were administered to 54 inpatients with MDD and 54 healthy matched controls (Hansenne, 2009). Lower total Emotional Intelligence scores were seen in the MDD group as compared with controls. In the same study TCI-R and SSEIT were again administered to patients within the MDD group upon reaching remission from their symptoms. These results showed that Emotional Intelligence scores were the same in the MDD patients and controls. This shows that performance on emotional tasks can improve when a MDD patient has been treated and their symptoms subside.

1.4.3.6 Emotion Processing in Depressed Individuals After Neurosurgical Procedures

[25] The Schutte Self Report Emotional Intelligence Test (SSEIT) is a 33 item self-report measure of emotional intelligence

[26] The Revised Temperament and Character Inventory (TCI-R) is an measure for personality traits including Novelty Seeking, Harm Avoidance, Reward Dependence and Persistence

Studies of emotional processing after neurosurgery in TRD patients are rare, and almost all literature that exists on the topic has been written within the last ten years. These studies are important and more are emerging as it has been hypothesized that impaired emotional processing may be the leading cause of social dysfunction among depressed patients (Surguladze, 2004).

One study included five patients that had received both an anterior cingulotomy and anterior capsulotomy and four patients that only underwent an anterior cingulotomy (Ridout, 2007). At the time of testing, four of the nine patients had reached remission and were considered non-depressed, neurosurgically treated patients known as responders. Two control groups were also included in the study for comparison: one group of 17 individuals currently experiencing a depressive episode and 22 healthy individuals. The stimuli presented to the participants were 28 video clips showing emotional facial expressions, body language, and emotional voices. Executive functions were also tested using the Stroop task, the Hayling sentence completion task, and the F-A-S verbal fluency task. After analysing the data, differences were detected among the groups. NMD patients showed inhibited emotional recognition compared to healthy controls. These differences could be explained due to the fact that without a functioning ACC, emotion recognition is impeded due to deficits in attention (Ridout, 2007). The non-responders produced fewer words on the verbal fluency task, made more errors on the sentence completion task, and made more errors on the Stroop task than did the responders or healthy controls. This possibly shows that the responders showed measureable improvements not only in their mood but also in emotional recognition. Patients from the depressed control group produced more words on the sentence completion task and fewer errors on the Stroop task than did the non-responders. This may suggest that the neurosurgery was in fact detrimental to emotional processing due to deficits in attention. The ACING procedure itself has been seen to lead to impaired attention processing (Ridout, 2007; Cohen, 1999). Patients, who received an anterior cingulotomy alone, without the anterior capsulotomy, identified 5% more emotional cues than did patients who underwent both surgeries (Ridout, 2007).

In another study, only one patient was included who underwent an anterior cingulotomy (Wang, 2002). This patient showed specific deficits in the recognition of fear and disgust; however, this patient also had damage to the amygdala, and this could have affected the findings (Ridout, 2007; Wang, 2002). Nonetheless, volume changes are expected in the amygdala of the MDD brain regardless. In a study looking at patients with lesions to the anterior cingulate cortex, patients' ability to recognize primary emotions was jeopardized (Hornak, 2003). This data supports other studies that state the role of the ACC in successful emotional recognition (Blair, 1999; Killgore, 2004).

1.5 Research Questions

This thesis is structured as a two-part analysis. Part One explores the effect of MDD on emotional processing capabilities. To do this, tasks assessing emotional processing[27] were administered to a group of patients with MDD and to a control group with no history of MDD[28]. With the scores from these tests, independent group T tests were used to address the following questions:

- Does MDD have an effect on emotional processing capabilities?
- If MDD does have an effect on emotional processing capabilities, is emotional processing ability generally decreased/increased, or is performance affected in regards to a specific emotion?
- If MDD does have an effect on emotional processing capabilities, are the same emotions consistently affected across different tests?
- Are the results/outcomes consistent with other studies?
- What can this tell us about possible neural structures associated with MDD?

Part two explores the side effects of ACING and VNS to treat depression, as measured by scores on emotional processing tasks. To achieve this, two groups are analyzed: one that underwent an ACING and

[27] see section 2.2.2
[28] see section 2.2.1

one that underwent a VNS. Tasks assessing emotional processing were administered to each group before and one year after surgery. Side effects were compared and measured by scores before and after surgery. With the scores from these tests, independent group T tests were performed and significant increases/decreases in ability to recognize emotion were expressed as changes from baseline. The following questions were explored:

- Did the invasive treatment option (ACING/VNS) affect patient's emotional processing capabilities?
- If the invasive treatment option (ACING/VNS) affected patient's emotional processing capabilities, is the emotional processing ability generally decreased/increased or is performance affected in regards to a specific emotion?
- If the invasive treatment option (ACING/VNS) affected patients' emotional processing capabilities, are the same emotions consistently affected across different tests?
- Can this information help us determine which neural structures are affected by ACING and VNS?
- What can this tell us about possible neural structures associated with MDD?

2 Study

2.1 Introduction

All testing was conducted in accordance with the Declaration of Helsinki — 2008, and required ethical approvals were obtained from the relevant NHS research ethics committees. Study participants provided written consent.

Sprengelmeyer et al. (2011) used similar participants in their study as are used in this one, in that: " [this study] not only tested participants who were not only taking prescribed antidepressant medication, but who had histories of exposure to a range of psychotropic medications. We therefore

cannot exclude an effect of previous or current medication to either the behavioural or structural findings in the MDD participants. Similarly, although the MDD participants were clinically representative of specialist and psychiatric practice in the UK and presented with a robust primary diagnosis, we did not exclude common co-morbidities such as anxiety and personality disorders" (p.121). The fifteen MDD participants in Part One are the same participants that undergo an Anterior Cingulotomy (n=7) and a Vagus Nerve Stimulation (n=8) in Part Two.

2.2 Methods

2.2.1 Participants

Fifteen clinically referred participants with chronic (>2yr) MDD (5 male, 10 female) were tested. All MDD participants were assessed by an experienced psychiatrist and met criteria for a diagnosis of DSM-IV MDE. Mean age of participants with MDD was 51.2 (SD 8.3) years and their IQ as measured with the NART - National Adult Reading Test (Nelson, 1982) was 120.6 (SD 3.1). On the BDI-II - Beck Depression Inventory (Beck et al., 1996) and the (17 item) $HDRS_{17}$ - Hamilton Depression Rating Scale (Hamilton, 1960) the groups mean scores were 34.9 (SD 8.8) and 22.5 (SD 5.0) respectively. All MDD participants were receiving antidepressant medication. Medication as total dose per day was: Phenelzine (60mg), Sertraline (200mg), Isocarboxazid (10mg), Venlafaxine (75-375mg), Trimipramine (150mg), Amitriptyline (350mg), Citalopram (20mg) and Tranylcypromine (30mg). Additional combination/ augmentation strategies were: Lithium carbonate (600-800mg), Quetiapine (400-750mg), Buproprion (300mg), Mirtazapine (45mg), Valproate Sodium (500mg), L-Tryptophan (2-4 grams) and Chlorpromazine (75mg). Further, a total of 3 participants were taking benzodiazepines, at a Diazepam dose-equivalent of 10-30mg/ day. Two participants were taking hypnotics (Zolpidem and Zopiclone).

2.2.1.1 Anterior Cingulotomy

Seven participants from the MDD group (6 female, 1 male) with a mean age of 50.0 years (SD 3.9 years), and a mean IQ of 120.4 (SD 7.6) underwent Anterior Cingulotomy[29]. Participants of both Anterior Cingulotomy and Vagus Nerve Stimulation groups were tested before surgical treatment and 1 year after.

2.2.1.2 Vagus Nerve Stimulation

The remaining eight participants from the MDD group (4 female, 4 male) with a mean age of 51.8 years (SD 8.9 years), and a mean IQ of 122.9 (SD 3.4) underwent surgical procedures to implant a Cyberonics VNS device[30], which consist of a lithium battery fuelled generator, a lead wire system with electrodes, and an anchor tether to connect leads to the left vagus nerve. Participants of both Anterior Cingulotomy and Vagus Nerve Stimulation groups were tested before surgical treatment and 1 year after.

2.2.1.3 Controls for Emotional Processing Tasks

38 control participants without histories of MDD (14 male, 24 female) were tested. Mean age of the control participants was 50.9 (8.3) years, and their IQ was 121.7 (SD 5.7). Student t-tests showed no significant differences between groups for age ($t=0.10$, $df=51$, $p=.92$) and estimated pre-morbid intelligence ($t=-0.90$, $df=51$, $p=.35$).

2.2.2 Tasks assessing Emotional Processing

2.2.2.1 Ekman 60 Faces Test

Faces are presented one at a time for 5 seconds each, and the participant is asked to decide which of the emotion (happiness, sadness, surprise, disgust, anger, and fear) best describes the facial expression shown. The

[29] see section 1.3.3.3
[30] see section 1.3.3.2

names of these six emotions are visible on the computer screen throughout the test. The order in which the emotion names are shown on the screen is randomized each time the test is given. Full details of the procedure can be found in the manual accompanying the FEEST (Young et al., 2002).

The Ekman 60 Faces test contains photographs of the faces of 10 people from the Ekman and Friesen series (Ekman and Friesen, 1976). Ten pictures are used to test for each of six emotions (happiness, surprise, fear, sadness, disgust, and anger) making the test contains 60 total pictures. The pictures are presented in random order. The maximum score is 10 for each of the 6 emotion categories.

2.2.2.2 Emotion Hexagon

The faces are presented one at a time for 5 seconds each, and the participant is asked to decide which of the emotion names (happiness, sadness, surprise, disgust, anger, and fear) best describes the facial expression shown. The names of these six emotions are visible on the computer screen throughout the test. The order in which the emotion names are shown on the screen are randomized each time the test is given.

The Emotion Hexagon test uses photographic-quality morphed images of an individual's face from the Ekman and Friesen series, which were prepared by blending different emotional facial expressions. The test set consists in 30 stimuli, comprising 5 morphed images for each of 6 emotions: happiness – surprise, surprise – fear, fear – sadness, sadness – disgust, disgust – anger, and anger – happiness, in proportions 90/10 (e.g., 90% fear + 10% surprise), 70/30 (70% fear + 30% surprise), 50/50 (50% fear + 50% surprise), 30/70 (30% fear + 70% surprise), and 10/90 (10% fear + 70% surprise). The test contains 30 practice trials, followed by 5 test blocks. In each test block 30 images are presented in random order. For the purposes of scoring, the responses to the 50/50 morphed images (which are not usually identified as a particular emotion) and to the practice block trials are excluded, leaving a maximum score of 20 for each of the emotion. Data for this test is only included for Part One.

2.2.2.3 Calder Emotional Numbers

Recognition of vocally presented emotions was also assessed using the Emotional Numbers Test. 10 strings of numbers were spoken by an actor with a happy, fearful, sad, disgusted, or angry vocal intonation. This gives a total of 50 stimuli with a possible maximum of 10 for each of the five emotions. Stimuli were presented in pseudo-random order. The participants had to decide which of the 5 emotion labels best described the vocal intonation.

2.2.2.4 Morgenstern Test

The Morgenstern test assesses one's ability to recognize and identify specific emotions associated with a voice sample (Sprengelmeyer et al., 1996). Meaningless words were used to create a set of 10 different nonsense "sentences", each spoken by an actor with a happy, surprised, fearful, sad, disgusted, or angry vocal intonation. This gives a total of 60 stimuli with a maximum score of 10 for each of the six emotions. Stimuli were presented in pseudo-random order. As in the facial expression tasks, participants had to decide which of the 6 basic emotion labels best described the vocal intonation.

2.2.2.5 Emotional Gestures

2.2.2.5.1 Full/Point Light Movies

Finally, we examined one's ability to recognize emotions expressed by body language. Ten actors (5 male, 5 female) were asked to produce movements expressing 5 basic emotions: happiness, fear, sadness, disgust, or anger. These movements were recorded under two viewing conditions, a full light condition, in which the whole body of the acting person was visible, and a point light conditions. In the latter condition, 13 reflective stripes were attached to the major joints and the forehead of the actor. When presented, only the reflective strips are visible as moving patches against a black background (Atkinson et al., 2004). For each condition, there were 50 short video clips with a length between 4.5 and 9 seconds and with 10 clips for each emotion. The clips were arranged in a fixed pseudo-random order

and shown to the participant's one after the other. After each presentation, the participants had to decide which of the emotion names (happiness, fear, sadness, disgust, or anger) best described the emotion expressed by the actor. The five emotion words were shown at the bottom of the screen. Responses were made verbally and noted by the examiner.

2.3 Results

2.3.1 Part One: Comparison of Controls vs. non-NMD treated MDD

2.3.1.1 Tasks assessing Emotional Processing

2.3.1.1.1 Ekman 60 Faces Test

For the Ekman 60 tests a repeated measures ANOVA was performed with emotion (happiness, surprise, fear, sadness, disgust, and anger) as a within-subject factor, and group (MDD vs. control participants) as a between-subjects factor. The findings suggested a significant effect of emotion ($F_{(5,255)}$= 27.16, P<.001). No significant group effect was seen ($F_{(1,51)}$=2.99, p=.09), but there was a significant emotion x group interaction ($F_{(5,255)}$=3.17, p<.01). To explore the interaction, independent t-tests were performed which showed no significant differences for happiness (t=-1.30, p=.19), surprise (t=-1.33, p=.19), fear (t=1.84, p=.07), sadness (t=.06, p=.96), and anger (t=.55, p=.59). The only exception was the recognition of disgust (t=3.31, p=.002), which was impaired in MDD as compared to controls. The degree of freedom for all t-tests performed was 51. Results are given in Figure 1.1 and Table 1.1.

Figure 1.1

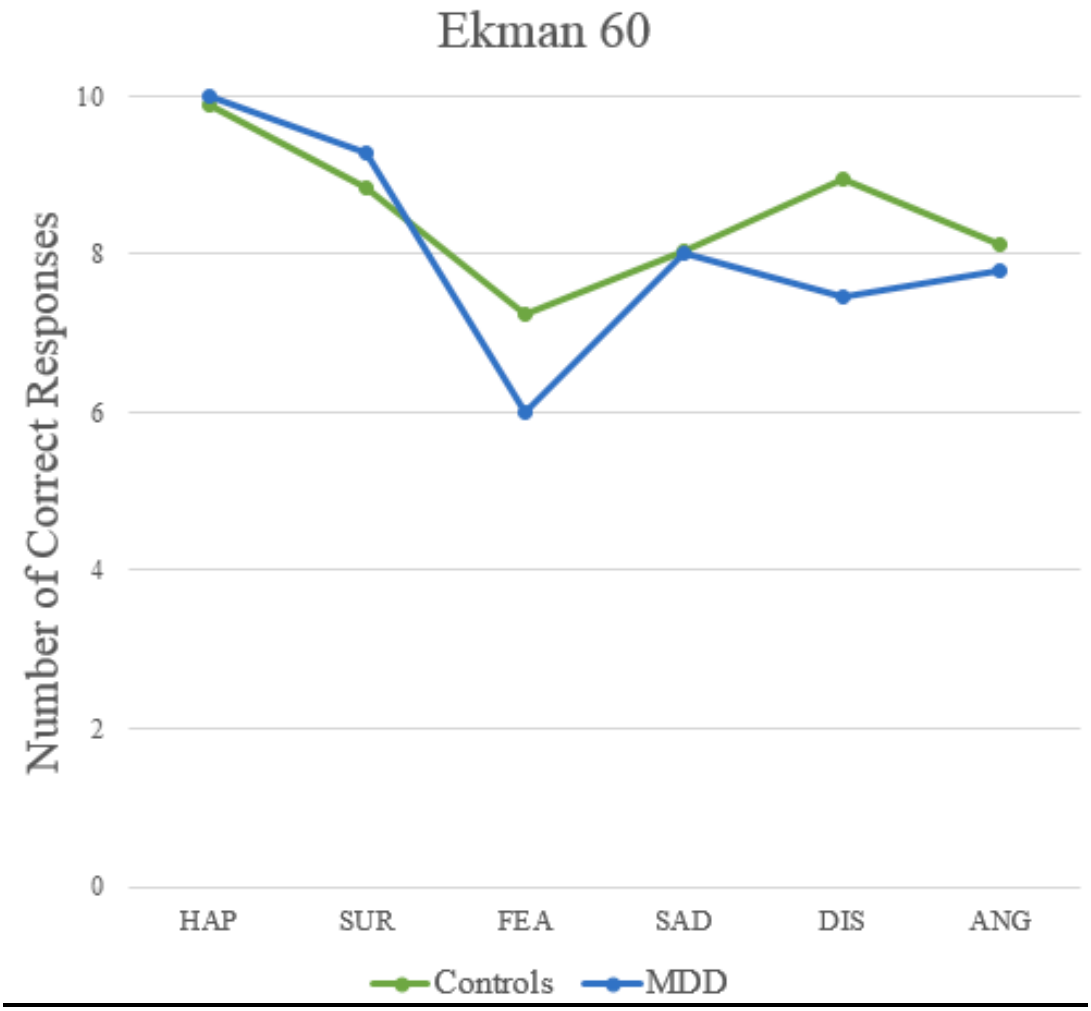

Table 1.1

Ekman 60	Controls		MDD	
	Mean	Std. Deviation	Mean	Std. Deviation
HAP	9.89	0.31	10.00	0.00
SUR	8.84	1.13	9.27	0.80
FEA	7.24	2.05	6.00	2.56
SAD	8.03	1.57	8.00	1.41
DIS	8.95	1.25	7.47	1.92
ANG	8.11	1.77	7.80	1.97

2.3.1.1.2 Emotion Hexagon

For the Emotion Hexagon test we performed a repeated measures ANOVA with emotion (happiness, surprise, fear, sadness, disgust, and anger) as a within-subject factor, and group (MDD vs. control participants) as a between-subjects factor. The findings suggested a significant effect of emotion ($F_{(5,255)}$= 10.60, p<.001), a significant group effect ($F_{(1,51)}$=5.35, p<.05), as well as a trend towards a significant emotion x group interaction ($F_{(5,255)}$=2.17, p=.06). To explore the interaction, independent t-tests were performed which showed no significant differences for happiness (t= -.30, p=.77), surprise (t=-.01, p=.99), fear (t= .585, p=.56), and sadness (t= 1.94, p=.06). Recognition of disgust (t= 2.16, p=.04) and anger (t= 2.55, p=.01) were impaired in MDD as compared to controls. The degree of freedom for all t-tests performed was 51. Results are given in Figure 1.2 and Table 1.2.

Figure 1.2

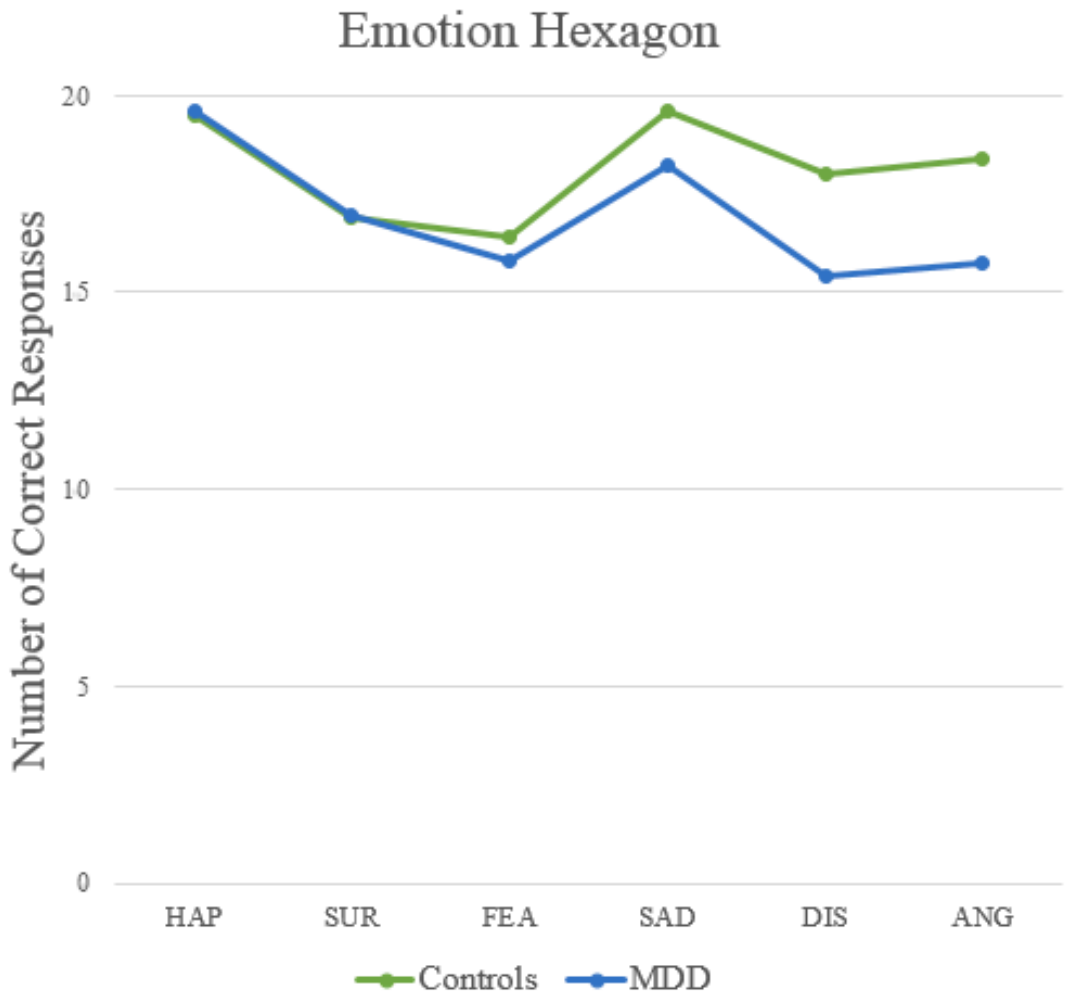

Table 1.2

Emotion Hexagon	Controls		MDD	
	Mean	Std. Deviation	Mean	Std. Deviation
HAP	19.50	1.03	19.60	1.30
SUR	16.92	2.89	16.93	3.54
FEA	16.39	3.09	15.80	3.91
SAD	19.58	0.95	18.20	4.18
DIS	18.00	2.48	15.40	6.38
ANG	18.37	1.95	15.73	5.65

2.3.1.1.3 Calder Emotional Numbers

For the Calder Emotional Numbers test a repeated measures ANOVA was performed with emotion (happiness, surprise, fear, sadness, disgust, and anger) as a within-subject factor, and group (MDD vs. control participants) as a between-subjects factor. The analysis gave a significant effect of emotion ($F_{(4,204)}$= 4.78, p<.01), a significant group effect ($F_{(1,51)}$=9.30, p<.01), but no significant emotion x group interaction ($F_{(4,204)}$=1.98, p=.10). To explore the interaction, independent t-tests were performed which showed no significant differences for happiness (t= 1.38, p=.17), fear (t= .53, p=.60), and sadness (t= .77, p=.45). Recognition of disgust (t= 2.58, p=.01) and anger (t= 3.10, p=.003) were impaired in MDD as compared to controls. The degree of freedom for all t-tests performed was 51. Results are given in Figure 1.3 and Table 1.3.

Figure 1.3

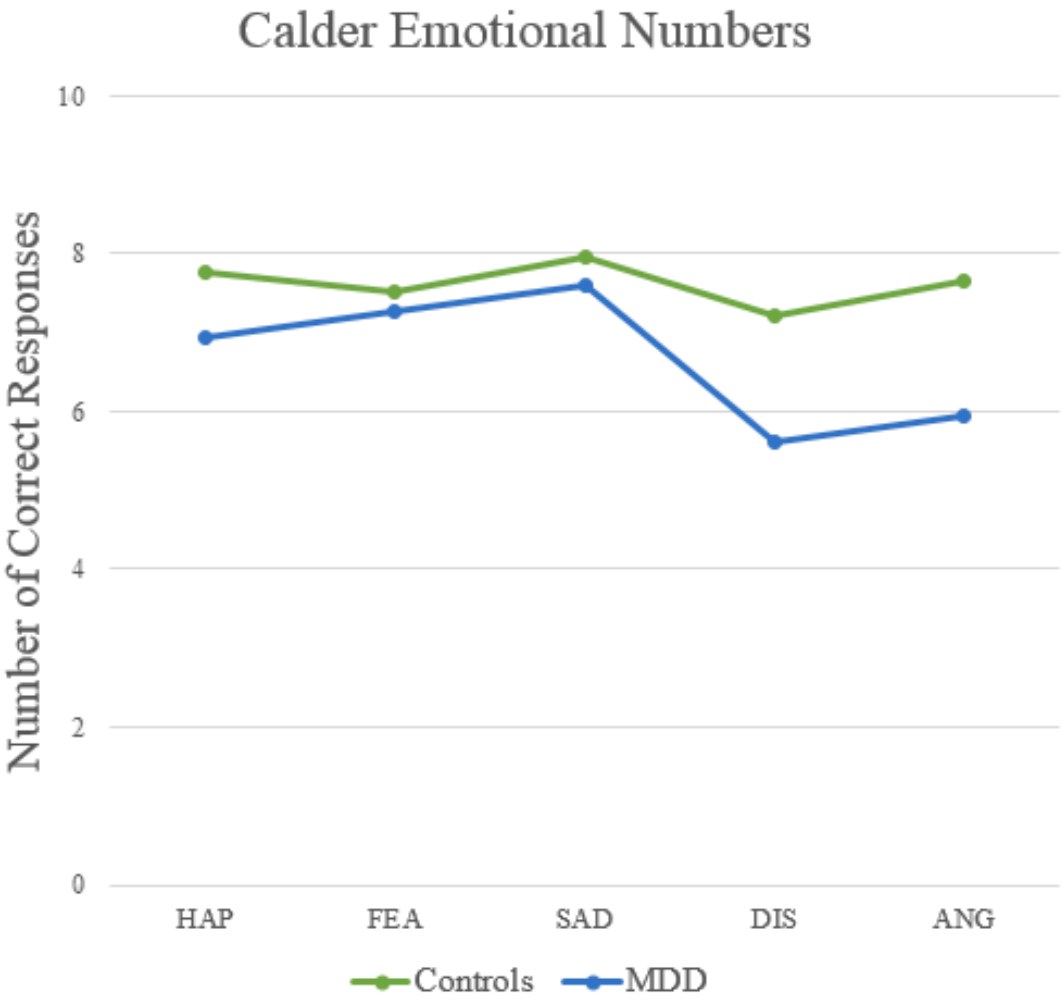

Table 1.3

Calder Emotional Numbers	Controls		MDD	
	Mean	Std. Deviation	Mean	Std. Deviation
HAP	7.76	2.12	6.93	1.49
FEA	7.50	1.41	7.27	1.53
SAD	7.95	1.45	7.60	1.55
DIS	7.21	1.65	5.60	2.85
ANG	7.66	1.76	5.93	1.98

2.3.1.1.4 Morgenstern Test

For the Morgenstern test a repeated measures ANOVA was performed with emotion (happiness, surprise, fear, sadness, disgust, and anger) as a within-subject factor, and group (MDD vs. control participants) as a between-subjects factor. We found a significant effect of emotion ($F_{(5,255)}$= 69.29, p<.001), a significant group effect ($F_{(1,51)}$=61.60, p=.21), and a significant emotion x group interaction ($F_{(5,255)}$=6.28, p<.001). To explore the interaction, independent t-tests were performed which showed no significant differences for surprise (t=-1.62, p=.11), fear (t= 1.81, p=.08), sadness (t= -1.74, p=.09), disgust (t=.9, p=.34) and anger (t= -.60, p=.55). Recognition of happiness (t=3.85, p<.001) was impaired in MDD as compared to controls. The degree of freedom for all t-tests performed was 51. Results are given in Figure 1.4 and Table 1.4.

Figure 1.4

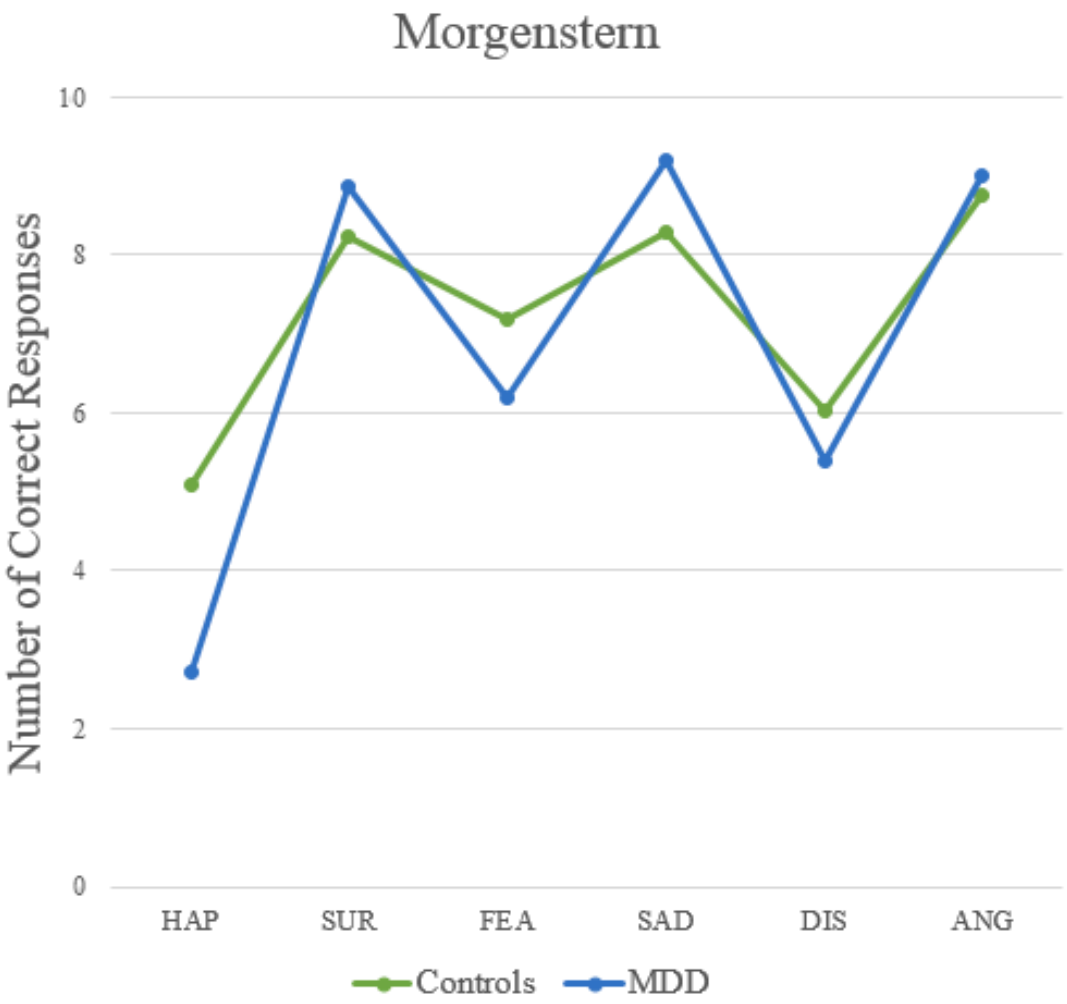

Table 1.4

Morgenstern	Controls		MDD	
	Mean	Std. Deviation	Mean	Std. Deviation
HAP	5.08	2.02	2.73	1.94
SUR	8.24	1.34	8.87	1.06
FEA	7.18	1.77	6.20	1.82
SAD	8.29	1.86	9.20	1.27
DIS	6.03	1.95	5.40	2.53
ANG	8.76	1.32	9.00	1.20

2.3.1.1.5 Emotional Gestures: Full Light Movies

For the Full Light Movies test a repeated measures ANOVA was performed with emotion (happiness, surprise, fear, sadness, disgust, and anger) as a within-subject factor, and group (MDD vs. control participants) as a between-subjects factor. The analysis gave a significant effect of emotion ($F_{(4,204)}$= 12.18, p<.001), a significant group effect ($F_{(1,51)}$=17.62, p<.001), but no significant emotion x group interaction ($F_{(4,204)}$=1.39, p=.24). To explore the interaction, independent t-tests were performed which showed no significant differences for happiness (t= 1.96, p=.06) and anger (t= 1.16, p=.25). Recognition of fear (t= 4.50, p<.001), sadness (t= 2.20, p=.033), and disgust (t= 2.50, p=.016) were impaired in MDD as compared to controls. The degree of freedom for all t-tests performed was 51. Results are given in Figure 1.5 and Table 1.5.

Figure 1.5

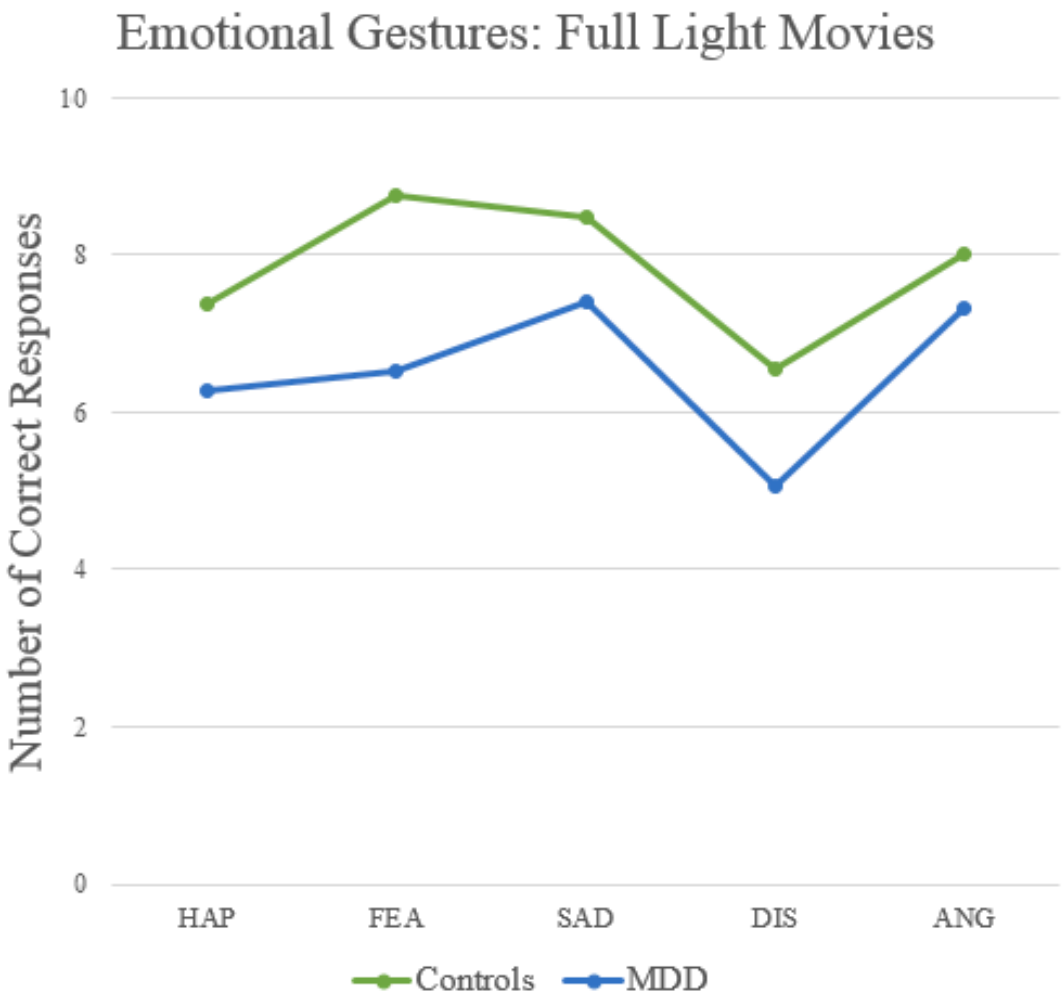

Table 1.5

Full Light Movies	Controls		MDD	
	Mean	Std. Deviation	Mean	Std. Deviation
HAP	7.37	1.72	6.27	2.15
FEA	8.76	1.34	6.53	2.20
SAD	8.47	1.54	7.40	1.77
DIS	6.55	1.67	5.07	2.55
ANG	8.00	1.58	7.33	2.53

2.3.1.1.6 Emotional Gestures: Point Light Movies

For the Point Light Movies test we performed a repeated measures ANOVA with emotion (happiness, surprise, fear, sadness, disgust, and anger) as a within-subject factor, and group (MDD vs. control participants) as a between-subjects factor. The analysis gave a significant effect of emotion ($F_{(4,204)}$= 16.91, p<.001), a significant group effect ($F_{(1,51)}$=16.43, p<.001), but no significant emotion x group interaction ($F_{(4,204)}$=0.94, p=.44). To explore the interaction, independent t-tests were performed which showed no significant differences for sadness (t= 1.96, p=.06) and anger (t= 1.92, p=.06). Recognition of happiness (t= 3.50, p<.001), fear (t= 2.46, p=.02), disgust (t= 2.92, p=.005) were impaired in MDD as compared to controls. The degree of freedom for all t-tests performed was 51. Results are given in Figure 1.6 and Table 1.6.

Figure 1.6

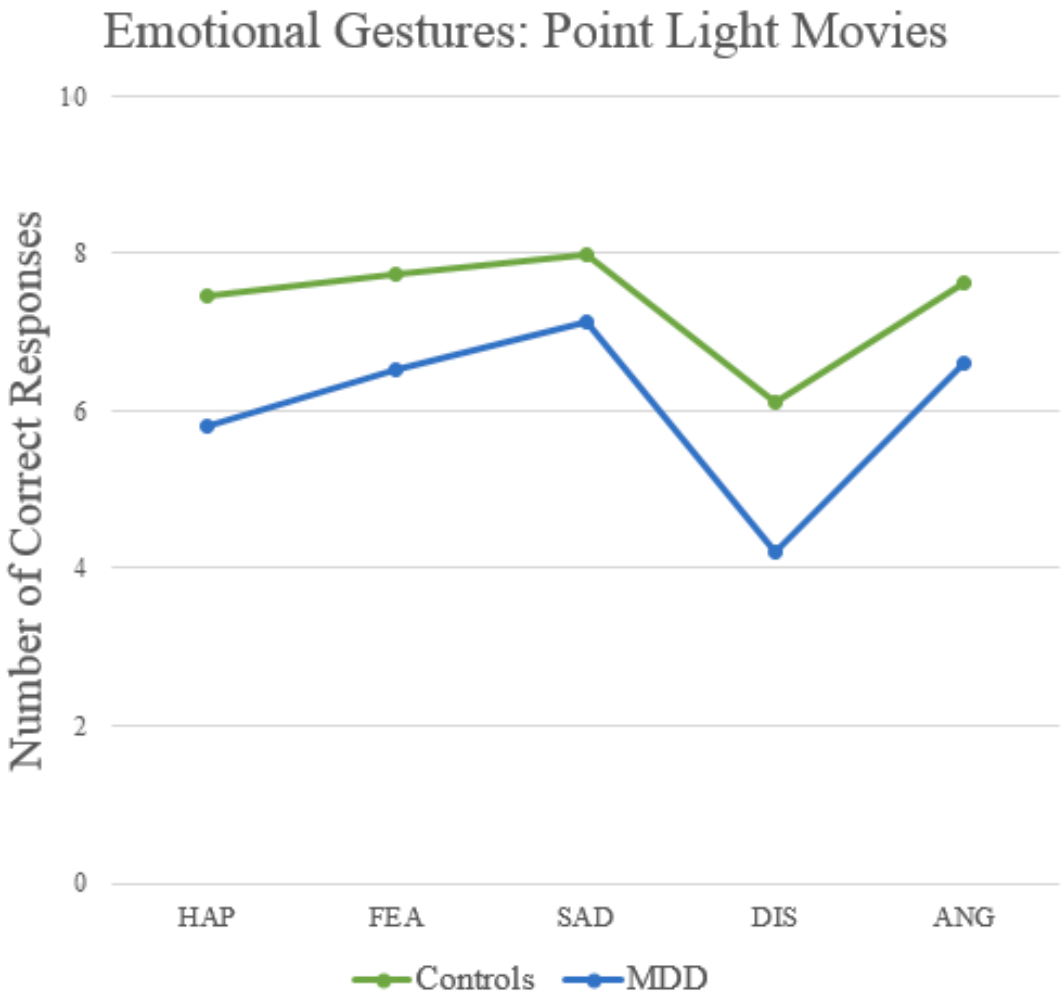

Table 1.6

Point Light Movies	Controls		MDD	
	Mean	Std. Deviation	Mean	Std. Deviation
HAP	7.45	1.50	5.80	1.66
FEA	7.74	1.48	6.53	1.89
SAD	7.97	1.39	7.13	1.46
DIS	6.11	2.00	4.20	2.48
ANG	7.63	1.63	6.60	2.06

2.3.1.2 Part One Summary Table

	Happiness	Surprise	Fear	Sadness	Disgust	Anger	Total Score
Ekman 60					√ *(p=.002)*		
Emotion Hexagon					√ *(p=.036)*	√ *(p=.014)*	√ *(p=.023)*
Calder Emotional Numbers					√ *(p=.013)*	√ *(p=.003)*	√ *(p=.003)*
Morgenstern test	√ *(p=.00033)*						
Full Light			√ *(p=.000039)*	√ *(p=.033)*	√ *(p=.016)*		√ *(p=.00012)*
Point Light	√ *(p=.001)*		√ *(p=.017)*		√ *(p=.005)*		√ *(p=.00017)*

√ = MDD Group made significantly more errors than Control Group

2.3.2 Part Two: Comparison pre- and post-NMD treatment

2.3.2.1 Tasks assessing Emotional Processing

2.3.2.1.1 Ekman 60 Faces Test

For the pre-post comparison of the *Ekman 60 Faces Test* results, a repeated measures ANOVA was performed with pre-and post surgery, as well as emotion (happiness, fear, sadness, disgust, and anger) as within-subject factors, and group (VNS vs. ACING participants) as a between-subjects factor. The analysis gave a significant effect of emotion ($F_{(5,65)}$= 16.22, p<.001), no significant group ($F_{(1,13)}$=0.11, p=.75), and no significant pre-post effect ($F_{(1,65)}$= 0.05, p=.82). There was a significant pre-post x group interaction ($F_{(1,65)}$= 4.98, p<.05), qualified by a significant pre-post x group x by emotion interaction ($F_{(5,65)}$= 2.64, p<.05). The emotion x group ($F_{(5,65)}$= 0.45, p=.81), and the emotion x pre-post surgery interactions ($F_{(5,65)}$= .11, p=.37) were not significant. To explore the significant pre-post x group x by emotion interaction, paired t-tests were performed separately

for each clinical group, comparing the performance before and after surgery for single emotions.

2.3.2.1.1.1 ACING

There was no significant change for all emotions in the ACING group. The paired t-tests gave the following results: happiness (no variance), surprise (t=1.86, p=.11), fear (t=1.20, p=.28), sadness (t=1.00, p=.36), disgust (t=-.28, p=.79), and anger (t=-0.66, p=.54). The degree of freedom for all t-tests performed was 6. See Table 2.1.1 for means and standard deviations. Results are given in Figure 2.1.1 and Table 2.1.1.

Figure 2.1.1

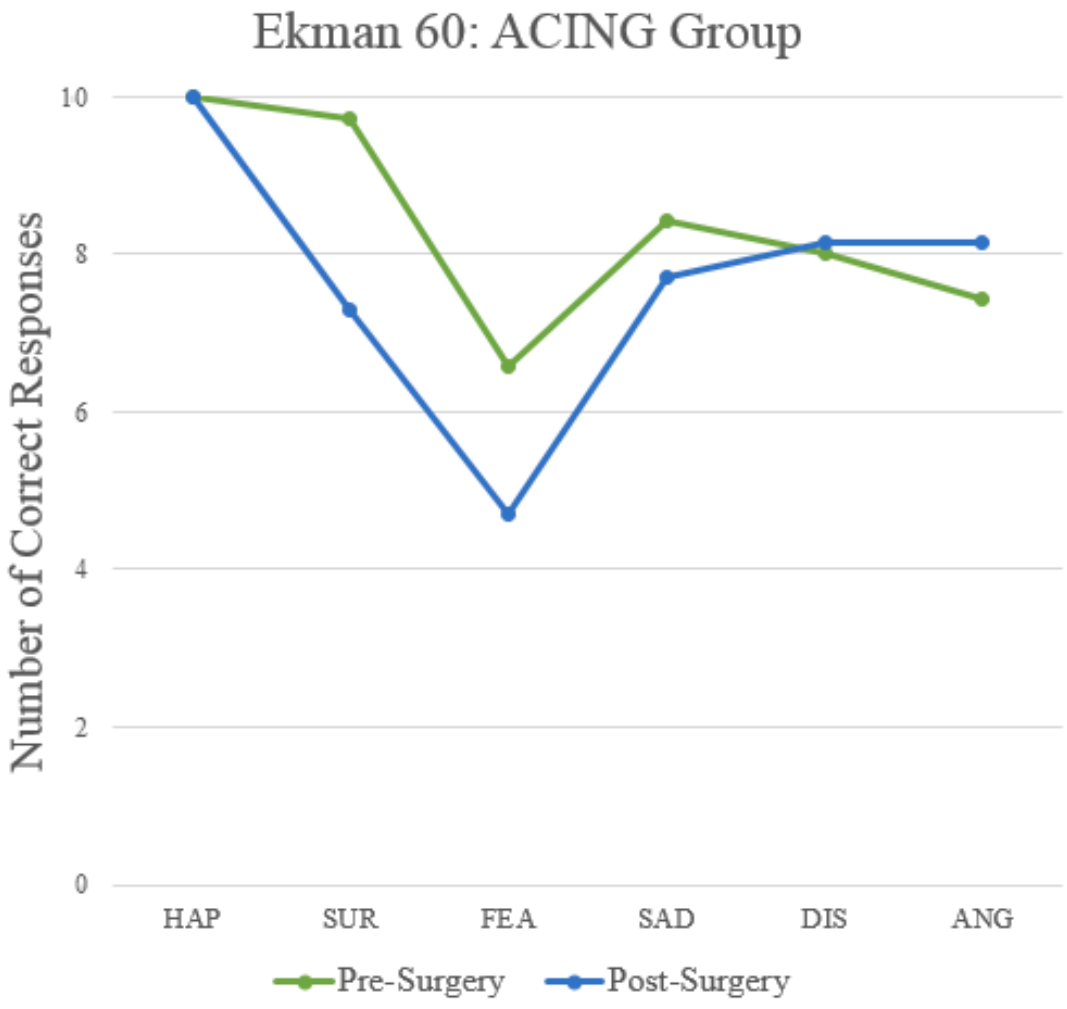

Table 2.1.1

Ekman 60	Pre-Surgery		Post-Surgery	
	Mean	Standard Deviation	Mean	Standard Deviation
HAPPY	10.00	0.00	10.00	0.00
SURPRISE	9.71	0.49	7.29	3.30
FEAR	6.57	3.05	4.71	2.81
SADNESS	8.43	1.13	7.71	1.50
DISGUST	8.00	0.82	8.14	1.77
ANGER	7.43	2.57	8.14	1.57

2.3.2.1.1.2 VNS

The VNS group's disgust recognition improved significantly, and there was a trend towards significance for recognition of fearful faces. Recognition of all other emotions showed no significant changes. The paired t-tests gave the following results: happiness (t=1.0, p=.35), surprise (t=-0.51, p=.63), fear (t=-1.94, p=.09), sadness (t=-1.31, p=.23), disgust (t=-2.76, p=.03), and anger (t=-0.64, p=.54). The degree of freedom for all t-tests performed was 7. Results are given in Figure 2.1.2 and Table 2.1.2.

Figure 2.1.2

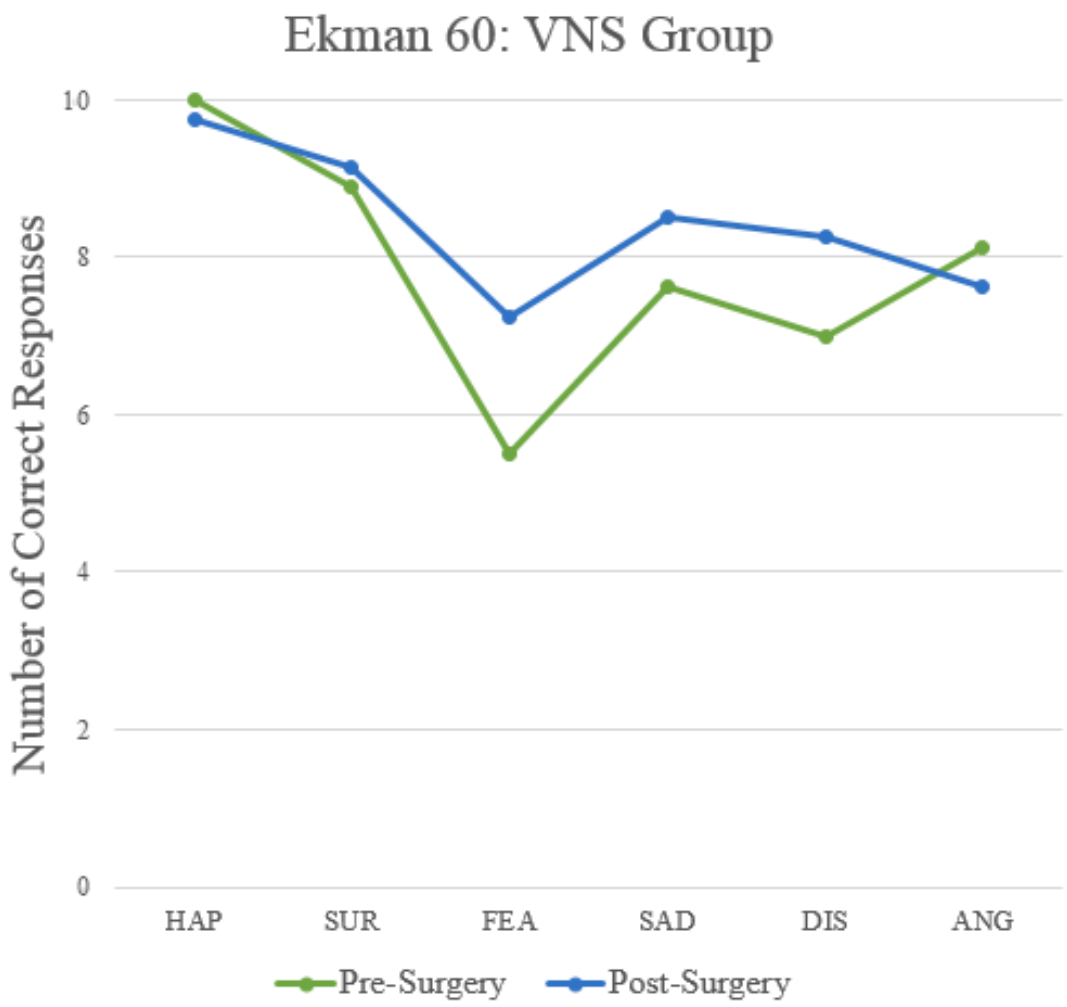

Table 2.1.2

Ekman 60	Pre-Surgery		Post-Surgery	
	Mean	Standard Deviation	Mean	Standard Deviation
HAPPY	10.00	0.00	9.75	0.71
SURPRISE	8.88	0.84	9.13	0.83
FEAR	5.50	2.14	7.25	1.67
SADNESS	7.63	1.60	8.50	0.93
DISGUST	7.00	2.51	8.25	2.05
ANGER	8.13	1.36	7.63	2.07

2.3.2.1.2 Calder Emotional Numbers

For the pre-post comparison of the results from the *Calder Emotional Numbers Test*, a repeated measures ANOVA with pre-and post surgery and emotion (happiness, fear, sadness, disgust, and anger) as within-subject factors, and group (VNS vs. ACING participants) as a between-subjects factor was performed. The analysis gave a significant effect of emotion ($F_{(4,65)}$= 3.54, p<.05), a trend towards significance for the group effect ($F_{(1,13)}$=3.34, p=.09), and no significant pre-post effect ($F_{(1,52)}$= 0.32, p=.58). The pre-post x group interaction ($F_{(1,52)}$= 2.92, p=.11) and the pre-post x group x by emotion interaction ($F_{(4,52)}$= 0.91, p=.47) were not significant. The emotion x group ($F_{(4,52)}$= 0.38, p=.82), and the emotion x pre-post surgery interactions ($F_{(4,52)}$= 0.38, p=.8) were also not significant. See Table 2.3.1 and Table 2.3.2 for mean and standard deviation.

2.3.2.1.2.1 ACING

Table 2.3.1

Calder Emotional Numbers	Pre-Surgery		Post-Surgery	
	Mean	Standard Deviation	Mean	Standard Deviation
HAPPY	6.86	0.90	6.29	2.69
FEAR	6.86	1.77	6.43	1.99
SADNESS	7.43	1.51	7.29	2.56
DISGUST	4.71	3.15	4.86	2.79
ANGER	5.86	2.34	5.29	2.81

2.3.2.1.2.2 VNS

Table 2.3.2

Calder Emotional Numbers	Pre-Surgery		Post-Surgery	
	Mean	Standard Deviation	Mean	Standard Deviation
HAPPY	7.00	1.93	7.75	1.67
FEAR	7.63	1.30	7.75	1.04
SADNESS	7.75	1.67	7.88	0.64
DISGUST	6.38	2.50	6.75	2.12
ANGER	6.00	1.77	7.75	2.12

2.3.2.1.3 Morgenstern Test

For the pre-post comparison of the results from the *Morgenstern Test*, a repeated measures ANOVA with pre-and post surgery and emotion (happiness, surprise, fear, sadness, disgust, and anger) as within-subject factors, and group (VNS vs. ACING participants) as a between-subjects factor was performed. The analysis gave a significant effect of emotion ($F_{(5,60)}$= 48.52, p<.001), no significant group effect ($F_{(1,12)}$=1.40, p=.26), and no significant pre-post effect ($F_{(1,60)}$= 1.91, p=.19). The pre-post x group interaction ($F_{(1,60)}$= 2.43, p=.15) and the pre-post x group x by emotion interaction ($F_{(5,60)}$= 1.57, p=.18) were not significant. The emotion x group ($F_{(5,60)}$= 0.47, p=.80), and the emotion x pre-post surgery interactions ($F_{(5,60)}$= 0.91, p=.48) were also not significant. See Table 2.4.1 and Table 2.4.2 for means and standard deviations.

2.3.2.1.3.1 ACING

Table 2.4.1

Morgenstern	Pre-Surgery		Post-Surgery	
	Mean	Standard Deviation	Mean	Standard Deviation
HAPPY	3.17	2.31	1.00	1.67
SURPRISE	9.00	0.89	7.00	1.67
FEAR	6.67	1.86	6.17	3.25
SADNESS	9.50	1.23	8.67	2.42
DISGUST	4.67	2.25	4.66	1.21
ANGER	9.17	1.17	8.33	1.21

2.3.2.1.3.2 VNS

Table 2.4.2

Morgenstern	Pre-Surgery		Post-Surgery	
	Mean	Standard Deviation	Mean	Standard Deviation
HAPPY	2.50	1.85	3.25	3.15
SURPRISE	9.00	1.07	8.88	1.36
FEAR	6.25	1.50	7.13	1.25
SADNESS	9.25	1.17	9.38	1.77
DISGUST	6.00	2.88	5.63	1.69
ANGER	9.00	1.31	8.13	1.13

2.3.2.1.4 Emotional Gestures

The Emotional Gestures tests include both the Full and Point Light Movies. For the pre-post comparison of the results from the *Emotional Full* and *Point Light Movies*, repeated measures ANOVAs with pre-and post surgery and emotion (happiness, fear, sadness, disgust, and anger) as within-subject factors, and group (VNS vs. ACING participants) as a between-subjects factor was performed.

2.3.2.1.4.1 Full Light Movies

The analysis gave a significant effect of emotion ($F_{(4,52)}$= 4.95, p<.01) and a borderline pre-post effect ($F_{(1,52)}$= 4.57, p=.05). The pre-post x group interaction ($F_{(1,52)}$= 3.04, p=.11), group effect ($F_{(1,13)}$=5.77, p=.26), and the pre-post x group x by emotion interaction ($F_{(4,52)}$= 0.32, p=.86) were not significant. The emotion x group ($F_{(4,52)}$= 1.20, p=.32), and the emotion x pre-post surgery interactions ($F_{(4,52)}$= 0.77, p=.55) were also not significant. See Table 2.5.1 and Table 2.5.2 for means and standard deviations.

2.3.2.1.4.1.1 ACING

Table 2.5.1

Full Light Movies	Pre-Surgery		Post-Surgery	
	Mean	Standard Deviation	Mean	Standard Deviation
HAPPY	5.86	1.86	6.29	2.75
FEAR	6.29	2.43	7.00	1.73
SADNESS	7.43	1.27	7.29	2.50
DISGUST	4.29	2.98	3.88	3.44
ANGER	6.00	3.11	6.00	2.71

2.3.2.1.4.1.2 VNS

Table 2.5.2

Full Light Movies	Pre-Surgery		Post-Surgery	
	Mean	Standard Deviation	Mean	Standard Deviation
HAPPY	6.63	2.45	7.50	1.93
FEAR	6.75	2.12	9.00	0.53
SADNESS	7.38	2.20	8.25	0.89
DISGUST	5.75	2.05	7.13	2.85
ANGER	8.50	1.07	8.75	1.83

2.3.2.1.4.2 Point Light Movies

The ANOVA gave a significant effect of emotion ($F_{(4,52)}$= 9.64, p<.001), a significant group effect ($F_{(1,13)}$=13.13, p=.01), and a non-significant pre-post effect ($F_{(1,52)}$= 1.10, p=.31). The pre-post x group interaction ($F_{(1,52)}$= 0.04, p=.87) and the pre-post x group x by emotion interaction ($F_{(4,52)}$= 0.08, p=.99) were not significant. The emotion x group ($F_{(4,52)}$= 1.12, p=.36), and the emotion x pre-post surgery interactions ($F_{(4,52)}$= 0.43, p=.79) were also not significant. See table 2.6.1 and Table 2.6.2 for means and standard deviations.

2.3.2.1.4.2.1 ACING

Table 2.6.1

Point Light Movies	Pre-Surgery		Post-Surgery	
	Mean	Standard Deviation	Mean	Standard Deviation
HAPPY	5.14	1.57	4.86	2.61
FEAR	5.71	1.98	6.43	3.10
SADNESS	6.43	1.72	6.86	2.12
DISGUST	2.71	1.80	2.86	2.27
ANGER	5.29	2.06	5.29	2.63

2.3.2.1.4.2.2 VNS

Table 2.6.2

Point Light Movies	Pre-Surgery		Post-Surgery	
	Mean	Standard Deviation	Mean	Standard Deviation
HAPPY	6.38	1.60	6.38	1.30
FEAR	7.25	1.58	8.00	1.31
SADNESS	7.75	0.89	7.88	1.81
DISGUST	5.50	2.33	6.10	2.42
ANGER	7.75	1.28	7.75	1.28

2.3.2.2 Part Two Summary Table

	Happiness	Surprise	Fear	Sadness	Disgust	Anger
Ekman 60						
ACING						
VNS					+ (p=.03)	
Calder Emotional Numbers						
ACING						
VNS						
Morgenstern test						
ACING						
VNS						
Full Light						
ACING						
VNS						
Point Light						
ACING						
VNS						

+ = Emotion recognition improved significantly one-year post surgery compared to pre surgery

2.4 Discussion

2.4.1 Introduction

The discussion section focuses on MDD as a neuropsychological syndrome where physical neuroanatomical changes modulate cerebral dysfunction. The clinical symptoms of MDD are directly related to disordered processing among complex neural circuits affected by these physical abnormalities (Mayberg, 2009). The aetiology of the dysfunction of abnormal neural substrates is not completely understood, but converging evidence agrees that altered synthesis, secretion and concentrations of fundamental neurotransmitters, hormones, and growth factors can trigger atrophic changes to specific neural structures—for example, hypercortisolemia causes atrophy to hippocampal neurons. It also seems that certain individuals have lower genetic thresholds for stress and thus a higher risk of developing MDD (Caspi, 2003). Namely, the affected structures are the dorsomedial and dorsolateral prefrontal cortices, as well as the limbic regions including the subgenual cingulate cortex, amygdala, insula, ventrolateral prefrontal cortex, ventral striatum, and thalamus (Phillips, 2003). These affected brain structures disrupt neural networks that are crucial for normal emotional processing abilities (Phillips, 2003). Scores on emotional processing tasks have been observed to be lower in patients experiencing depressive episodes (Morris, 2009; Douglas, 2010).

The aim of Part One of the discussion is to examine whether a group of patients with chronic treatment-resistant MDD showed deficits in emotional processing compared to healthy controls, as measured by the results of tasks assessing emotional processing. This will serve as a baseline for whether the MDD group has measureable deficits in emotional processing before surgical intervention. Hypotheses and speculations may also be made to which brain areas are most affected in our patient group based upon their abilities to recognize specific emotions.

Part Two discusses the effects of therapeutic neurosurgical interventions (ACING and VNS) on chronic treatment-resistant MDD by comparing the results of emotional processing tasks administered before and after surgery.

Statistically significant side effects of ACING and VNS procedures will be considered in order to determine the effects of NMD on emotion processing and what neural side effects may be occurring after surgery. The independent group t-tests performed are interpreted as changes from baseline, more specifically improvement after surgery as compared to before.

It is important to note that as the number of t-tests increase, so does the likelihood of type 1 or alpha errors. The study is at risk for experimentwise error, or an increased type 1 error rate. To protect against inflating Type I Error rate in the individual t-tests, we first performed a repeat measure ANOVA analysis.

2.4.2 Part One

The MDD group had decreased ability to recognize at least one emotional expression (e.g., fear, sadness, and anger) in each of the six tests administered (*Ekman 60 Faces Test, Emotion Hexagon, Calder Emotional Numbers, Morgenstern Test, Full Light Movies and Point Light Movies*) as compared to healthy controls. The results show that the control group was better at processing emotions than the MDD group. Overall, the depressed group showed decreased emotion recognition in 12 out of the total 33 emotional expressions presented. Deficits in disgust recognition were most severe and were noticed in five of the six tests administered. Anger, fear and happiness recognition were each noticed to be decreased in two out of the six tests administered. Surprise recognition was affected in one of the six tests administered.

t-test and repeated-measures ANOVA results show recognition of disgust was the most affected by MDD. MDD patients presented a significant decrease compared to controls in their ability to recognize the emotion of disgust on five out of the six tests administered—specifically on the *Ekman 60 Faces Test, Emotion Hexagon, Calder Emotional Numbers, Full Light Movies and Point Light Movies*. Both tasks measuring the ability to identify emotional facial expressions, the Ekman 60 Faces Test and

Emotion Hexagon test, demonstrated decreased disgust recognition. Both tests measuring the ability to identify emotional body language and gestures, the Full Light Movie and Point Light Movie tests, showed decreased disgust recognition as well. One of the two tests measuring the ability to identify emotional voices and sounds, the Morgenstern Test, also presented decreased disgust recognition. The fact that disgust recognition was impaired across tests that measured emotion-processing abilities using emotional faces, voices, and gestures suggests that this deficit impairs disgust recognition across multiple modalities of perception.

Speculatively, deficits of disgust recognition in the MDD group, as compared to healthy controls, suggest possible involvement of certain neural structures in MDD. Previous studies have shown that the temporal and frontal gyri, insula, globus pallidus and amygdala are activated in the recognition of disgust (Murphy, 2003; Fusar-Poli, 2008). More specifically, disgust recognition has been linked to the insular cortex (Calder 2000; Hennenlotter et al., 2004; Kipps et al., 2007; Phillips et al., 1997; Sprengelmeyer et al., 1998; Wicker et al., 2003). This suggests that this structure may be dysfunctional in MDD, a finding consistent with research performed by Sprengelmeyer et al. (2011). In the same study, significant grey matter reductions in the insular cortex were found in the MDD participants. Sprengelmeyer et al. (2010) showed that the ability to recognize the facial expression of disgust was significantly correlated with volumetric reduction in the anterior insula.

The deficit in disgust recognition noted in the MDD group agrees with the findings of Douglas *et al.* (2010). His study used similar methods, as he compared the ability of 68 MDD patients to recognize facial expressions compared to controls. The MDD group was significantly impaired in recognizing the facial expression of disgust. This disgust deficit has been noticed in people with Huntington's disease and unmedicated patients with Parkinson's disease as well (Sprengelmeyer et al., 1996, 2003). This deficit may be explained by the fact that patients who carry the Huntington's disease gene show significantly higher rates of depressive symptoms as

compared to controls (Julien et al., 2007). Furthermore, smaller insular cortex volumes are associated with onset of symptoms in Huntington's disease (Thieben et al., 2002). The deficit in disgust recognition from Part One possibly agrees with other studies in that the insular cortex is affected by MDD and may be associated with major symptoms of the disorder (Sprengelmeyer et al., 2011).

The t-test and one way ANOVA findings of Part One also show that MDD patients had decreased ability in recognizing the emotion of fear. Decreased fear recognition was noticed in both tests measuring the ability to identify emotional body language and gestures, the Full Light Movie and Point Light Movie tests. Speculatively, deficits in fear recognition suggest possible involvement of certain neural structures in MDD. Fear recognition is associated most strongly with the amygdala, as lesions to the amygdala lead to impaired fear recognition (Adolphs et al., 1994). Volumetric grey matter reductions of the amygdala in the MDD brain have been observed (Bremner, 2000; Caetano, 2004; Hastings, 2004; Monkul, 2007; Sprengelmeyer et al. 2011). Post mortem studies also show reduced glial cell density in the amygdalas of reported depressed individuals (Bowley, 2002). This suggests that the MDD group studied in Part One may have experienced pathological changes to their amygdalae that has lead to deficits in fear recognition. Furthermore, one may propose that because of this, the amygdala is affected by MDD and may be associated with major symptoms of the disorder.

A decreased ability in anger recognition was observed in two of the six tasks administered to the MDD group. Specifically, these deficits occurred on a task measuring ability to recognize emotional faces, the Emotion Hexagon test, as well as in a test measuring ability to identify vocally presented emotion, the Calder's Emotional Numbers Test. The ventral striatum, specifically the nucleus accumbens, has been associated with the facial expression of anger, as lesions to this area create anger recognition deficits (Calder et al., 2004). Converging findings from 106 PET and fMRI studies show that lateral OFC activity was noticed in more studies dealing with anger than any other emotion (Murphy, 2003). Amygdala-lesioned

individuals also have deficits in recognizing anger, but less severe than their deficits in fear recognition (Adolphs et al., 1995; Calder et al., 1996; Sullivan and Ruffman, 2004). Therefore, the deficits in fear and anger observed in the MDD group may be at least partially due to abnormal function of the amygdala. Furthermore, abnormalities in both the nucleus accumbens and OFC could explain the deficit in anger recognition observed in the MDD group. This may suggest the nucleus accumbens and OFC are affected by MDD and may be associated with major symptoms of the disorder.

Decreased happiness recognition was observed in two of the six tasks administered: specifically in a task-measuring ability to recognize emotional body language, the Point Light Movie Test, as well as in a test measuring ability to identify vocally presented emotion, the Morgenstern Test. MDD patients showed decreased ability in recognizing the emotion of sadness in one out of the six studies performed. Decreased sadness recognition was observed in a task measuring ability to recognize emotional body language (Full Light Movie Test). Surprise recognition was unaffected for the MDD group across all six tests. Neural structures associated with the recognition of happiness, sadness, or surprise, have not yet been isolated (Murphy, 2003).

Finally, it is important to note that clinically depressed individuals have impaired concentration, memory, and attention (Delgado, 2009). Patients with MDD also have slowed thought process (Giacobbe, 2009). The pattern of results could be due to the fact that depressed patients are less motivated and do not stay on task. What appears to be decreased recognition of a specific emotion across the MDD group may in fact be an artefact of decreased motivation and impaired concentration among these individuals.

2.4.3 Part Two

Upon remission of depressive symptoms, pathological brain activation in the amygdala, ACC, and OFC has been noticed to revert to levels expected in healthy individuals (Stuhrmann, 2011; Mayberg, 2009). The treatment options that are explored in Part Two are the ACING and VNS. Data are not

available as to whether or not the individual patients reached remission after treatment, but we can measure their response to surgery as measured by their performance on emotional processing tasks.

After undergoing a VNS for therapeutic intervention for chronic, treatment-resistant MDD, patients showed improvements in emotion recognition, as compared to their pre-surgical results. The VNS one-year post-surgery scores on the Ekman 60 Faces task showed improvements in disgust recognition, compared to pre-surgery scores. VNS is targeting regions associated with MDD. The vagus nerve has connections to the insular and cingulate cortices, as well as the limbic and paralimbic structures (Bachman, 1977; Nahas, 2006). Increased cerebral blood flow to the insular cortices has been witnessed after VNS surgery (Henry, 1998). Increased blood perfusion to the insular cortex provided by VNS may return insular cortex function back to that of healthy individuals. This would explain the improvements in disgust recognition. However, increased cerebral blood flow also occurs in the rostral and dorsal-central medulla, right postcentral gyrus, hypothalami, thalami, and cerebellar hemispheres after VNS surgery, and decreased cerebral blood flow occurs in the hippocampus, amygdala, and posterior cingulate gyri following VNS surgery (Henry, 1998).

2.4.4 Conclusion

Findings in Part One and Two are consistent with previous research in which impairments in the recognition of emotional facial expressions in the depressed population are studied (Douglas, 2010). This study shows that deficits in emotional voice and gesture processing likewise exist in the MDD population, as compared to healthy controls. Disgust recognition was most severely affected in the MDD group, a finding convergent with previous research (Douglas *et al.,* 2010; Sprengelmeyer et al., 2011) suggesting that the insular cortex is affected by MDD and may be associated with major symptoms of the disorder. Fear and anger recognition were also affected in the MDD group, but not as severely as disgust. Speculatively, these deficits propose that the amygdala, nucleus accumbens, and the OFC are affected by MDD, and may be associated with major symptoms of the

disorder as well. However, it is also possible that an integrated system able to code for all emotions is being affected. Volumetric or metabolic abnormalities to one neural substrate may inhibit a network responsible for mood and emotion regulation (Maclean, 1993; Murphy, 2003; Phillips, 2003).

Patients who underwent VNS for therapeutic intervention of chronic, treatment-resistant MDD showed improvement in emotional processing abilities in regards to disgust after surgical intervention as compared to their abilities before neurosurgery. In fact, disgust recognition that was significantly better recognized one year post VNS surgery was also the emotion that showed significant deficits among the MDD group in Part One. More specifically, disgust recognition on the Ekman 60 was significantly decreased in the MDD group compared to controls, and disgust recognition on the Ekman 60 was significantly improved one-year post VNS surgery. It is of particular interest that disgust recognition improved after VNS, as this was the most affected emotion in the MDD group from Part One. As the insula, OFC, nucleus accumbens and amygdala are responsible for the recognition of disgust, it seems that the function, and therefore possibly the structure, of these areas are restored one year after VNS. Perhaps the increased cerebral blood flow post VNS to brain areas proposed to be involved in the pathogenesis MDD may induce neurogenesis in these areas. This is purely speculative, but as neurogenesis in the hippocampus has been measured after administration of SSRI medications (Banasr, 2006; Schmidt, 2007), it may not be far fetched to think this may be the case.

The ANOVA results show no consistent impact of surgery as measured by improvement in scores on emotional tasks. Specifically, the ANOVA, as shown in the results, suggested no consistent improvement across all tests administered. The t-tests are to be interpreted as a change in baseline in score on emotion processing tasks from before surgery to one-year post surgery. However, the t-tests showed significant improvement on a few tests. This leads us to two speculative hypotheses. Firstly, the possibility that the surgeries were not effective, as consistent improvement was not seen across all tests administered. Secondly, the select t-test results emphasize a

need for further research meant to analyze the equivalency of the emotion tests administered. The latter is worthy of research as the tests used implement 3 very different interpretation of emotion: facial expression (Ekman 60 Faces, Emotion Hexagon), emotional voices (Calder, Morgenstern), and emotional body language (Full and Point Light Movies). While the lack of consistent improvement across all tests administered could suggest the surgeries were not effective, it also raises the query that it may not be possible to measure the efficacy of neurosurgery using 6 emotion processing tasks that require the patient to interpret 3 different representations of an emotion. The possibility exists that the results of the analysis would have been more consistent if tasks assessing only one modality (facial expression, voice, body language) had been utilized.

2.4.4.1 Further Research and Potential Limitations

Potential limitations exist in the study design. It has been shown that pathologic neuroanatomical changes associated with MDD can manifest differently with regards to gender (Frodl, 2002; Hastings, 2004; Lacerda, 2004). Of the 15 MDD patients included there was a 10:5 female to male ratio, which was analyzed in Part One. The VNS group had a 4:4 ratio, and the ACING group had a 6:1 ratio. There is a large gender discrepancy in the ratios, which might influence performance on the tests. Repeating the methods of this study with all male or all female groups may allow for more reliable and reproducible results.

Another limitation is the unique medication history of each patient, which differs substantially within the MDD group. It has been shown that medications can have unique side effects that alter one's emotion-processing abilities (Fu, 2004). Decreased ability to recognize disgust has also been associated with citalopram administration in healthy controls (Harmer, 2004). This is significant as citalopram was being administered to a few of the MDD participants of this study during the time of testing. Furthermore, other serotonergic antidepressants with similar mechanisms of action as citalopram were being administered as well. Deficits in emotion processing noticed in the MDD group may be due to MDD itself, or may be due to the

side effects of medication taken by the MDD group (Harmer, 2004). Medications can also have an effect on volumes of neuroanatomical structures that are important in emotion processing (Vythilingham, 2004). Repeating the methods of this study with a group taking the same medications or preferably (but unrealistically) without medications would eliminate potential confounders.

Potential order effects could also be present in Part Two of the study. Specifically, upon taking the same tests twice (pre and one year post surgery) it is possible that a certain degree of practice may exist. This may lead to artificially increased scores one year post. A fatigue effect may also be present, in that participants may become bored or tired when taking the tests thus creating a decline in performance (Cozby, 2009).

Further study would require information on whether or not the patients that underwent NMD reached remission from their depressive symptoms. If data were available as to whether or not individuals reached remission of clinical symptoms after their respective NMD, it would be possible to examine changes in emotional recognition in order to determine whether these changes may reflect objective markers of treatment outcome in MDD.

Furthermore, studies should include several observations over a longer time span in order to check the validity of the data. For example, after surgical intervention TRD patients should perform behavioral tests two times per year for 10 years.

2.5 References

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