Longitudinal neuropsychological outcomes of Deep Brain Stimulation for Treatment Resistant Depression: A retrospective review.

by

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Abstract

The purpose of this study was to review the neuropsychological outcomes of bed nucleus of the stria terminalis (BNST) deep brain stimulation (DBS) for treatment resistant depression (TRD). In addition, this study would report the mood outcomes of the treatment. Previous research endeavours have explored the safety and efficacy of available treatment methods for TRD as well as the clinical outcomes. Studies have observed antidepressant effects in patients treated with DBS for TRD. However, limited research exists regarding neuropsychological outcomes. In this study a brief history of the patient was provided. A battery of neuropsychological assessments were administered to one patient by a trained psychologist at baseline and at 6, 9 and 12 month's post-DBS in order to assess cognitive functioning. Neuropsychological testing covered the cognitive domains of attention, memory, executive functions, language, mental processing speed, verbal fluency and visuospatial/construction abilities. The results of these assessments were compared to available normative data and retrospectively reviewed. No adverse cognitive effects were observed following surgery, onset and maintenance of DBS when test results from baseline were compared to results at the 12 month interval. Areas of cognition that were impaired or below average at baseline improved at follow-up. However, attention and visuospatial/construction abilities, did not improve to normative levels at 12 months. Though no statistical analysis were conducted these results lend support for the cognitive safety of DBS of the bed nucleus of the stria terminalis for TRD.

Key Terms: Treatment resistant depression, deep brain stimulation, bed nucleus of the stria terminalis, neuropsychological functioning, mood outcomes, neuropsychological outcomes, cognitive domains, attention, visuospatial/construction abilities, memory, verbal fluency, executive functions.

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Chapter 1

Introduction

1.1 Overview

Deep Brain Stimulation (DBS) for treatment resistant depression (TRD) is an innovative procedure that is still in its experimental stages with continuous clinical trials investigating efficacy (Anderson et al., 2012; Blumberger et al., 2013). Moreover, this procedure is particularly novel in South Africa with only one known patient treated at this time with DBS of the bed nucleus of the stria terminalis (BNST) for specific TRD. Recent research has shown that patients with TRD display neuropsychological impairments in specific cognitive domains and that this outcome of the disorder is pertinent when considering overall treatment plans for patients with TRD (Baune et al., 2012; Beblo, Sinnamon, & Baune, 2011). Many international studies have focused on mood related outcomes for various disorders post-DBS but have neglected to focus on neuropsychological outcomes related to the DBS procedure (Eggers, 2014; Gabriels, Cosyns, Nuttin, Demeulemeester, & Gybels, 2003; Jimenez et al., 2005; Merkl et al., 2013).

Therefore, it is proposed that providing a detailed retrospective case review focusing on neuropsychological performance pre-and-post DBS will contribute to the body of knowledge on DBS for TRD. The aim of this research is to retrospectively review the pre-and-post neuropsychological outcomes of the DBS procedure for a patient with TRD. In addition to this, the mood-related outcomes will also be presented.

1.2 Research Question

Does the Deep Brain Stimulation (DBS) surgical procedure for Treatment Resistant Depression (TRD) contribute to clinical changes in longitudinal neuropsychological outcomes?

1.3 Research Aim

Deep Brain Stimulation (DBS) for Treatment Resistant Depression (TRD) is a novel neurosurgical intervention in South Africa. This retrospective case review focuses on

the only known patient treated with DBS for specific alleviation of symptoms associated with TRD. This surgical technique is characterized by the non-destructive, chronic stimulation of specific areas of the brain by means of implanted electrodes (Anderson et al., 2012). Due to the novelty of this technique many international studies have investigated mood related outcomes. This study will review and discuss the neuropsychological outcomes of DBS at the pre-and-post phases of the procedure. In addition, the mood-related outcomes of the procedure will be presented.

1.4 Chapter Synopsis

The following chapter (Chapter 2) places this study within the growing field of DBS research. The history of neurosurgery as well as previous studies documenting the DBS procedure and its mood and neuropsychological outcomes provide the theoretical basis of this study. Additionally, an overview of TRD, its sequelae and treatment options is provided. The method utilised in this study is presented in Chapter 3 which outlines the details of the review process such as participant information and selection criteria, psychometric instruments, research design and ethical considerations. The results of the study are presented and explained in Chapter 4. The data is tabulated and discussed by means of a comparison to normative data. Chapter 5 provides a discussion of the findings where the relevance of the results are discussed in the context of theory and literature presented in Chapter 2. A conclusion is provided at the end of Chapter 5.

Chapter 2

Literature Review

This chapter presents the contextual background pertaining to Deep Brain Stimulation (DBS) and Treatment Resistant Depression (TRD) and outlines the theoretical framework of the current study.

2.1 Defining and refining the term "Psychosurgery"

"Psychosurgery" is a controversial term coined by Egas Moniz in 1937 (Heeramun-Aubeeluck & Lu, 2013). Psychosurgery was described by the World Health Organization (WHO) in 1976 as a surgical procedure wherein nerve pathways were selected for surgical removal or destruction for the purpose of affecting behaviour (Heeramun-Aubeeluck & Lu, 2013). This definition is no longer applicable as it does not include the novel techniques that have emerged within the last decade. The term psychosurgery has been replaced by the term "Neurosurgery for Mental Disorders (NMD)". The Royal College of Psychiatrists (RCP) includes stereotactic techniques to their definition of NMD (Heeramun-Aubeeluck & Lu, 2013).

2.1.1 The History of Psychosurgery

According to a historical account of psychosurgery provided by Heeramun-Aubeeluck and Lu (2013) one of the first known surgical interventions for psychiatric diseases was completed using a bilateral cortical excision for the treatment of demented and aggressive patients. A rise in more precise surgical techniques followed between 1943 and 1954 with major breakthroughs in the early 1960's. Techniques emerged such as stereotactic anterior cingulotomy and subcaudate tractotomy and were combined and termed limbic leucotomy. Additionally, other reported techniques such as thalamotomy and amygdalotomy emerged (Heeramun-Aubeeluck & Lu, 2013). The limbic leucotomy procedure was known to have the best outcomes. Lesional surgeries were conducted until the mid-1990s and are still utilised at certain institutions, however, today most institutions have moved towards reversible and adjustable technologies (Hurwitz et al., 2012).

Psychotropic drugs that were used to treat depressive disorders lacked precision as they allowed neurochemistry to be altered in widespread areas of the brain with some areas being unrelated to depression (Blumberger & Mulsant, 2013). In terms of techniques, Electroconvulsive therapy (ECT), introduced in 1937, targeted the entire brain in an attempt to treat psychiatric illness (Shorter & Healy, 2007). The stigma surrounding ECT as well as the adverse cognitive effects associated with the technique prompted researchers to develop new brain stimulation methods for treating psychiatric illness with similar efficacy as well as decreased adverse effects (Blumberger & Mulsant, 2013). Scientists saw a need for more restrained and less-destructive focal techniques as research suggested that emotions are localized to specific brain regions. The current theoretical perspectives on depression, as a dysfunction of specific brain networks that mediate mood, aligns with the introduction of novel neuromodulatory therapies such as DBS (Schlaepfer & Bewernick, 2014).

2.2 Deep Brain Stimulation

The contemporary form of DBS is said to have been introduced by the neurosurgeon/neurologist team of Benabid, Pollak and colleagues in 1987 through their publication on thalamic DBS in patients with tremor (Hariz, Blomstedt, & Zrinzo, 2010). Deep Brain Stimulation (DBS) is a neuromodulatory technique that was initially established for movement disorders but has recently been utilised for neuropsychiatric disorders. Deep Brain Stimulation (DBS) is a recognized treatment for medication-refractory movement disorders such as Parkinson's disease (PD). More recently the Food and Drug Administration (FDA), a federal agency in the United States of America (USA), granted approval for the use of DBS in treatment-resistant Obsessive Compulsive Disorder (OCD) (Riva-Posse, Holtzheimer, Garlow, & Mayberg, 2013).

The DBS procedure entails the stereotactic implantation of electrodes into particular neuroanatomical structures where the area is continuously stimulated by means of a stimulator device implanted subcutaneously below the clavicle (Anderson et al., 2012). This procedure has a variety of advantages over other existing techniques: it is non-ablative and therefore it is reversible, it targets specific areas rather than broader areas, it has acute and long-term effects and it can be adjusted in order to acquire optimal therapeutic effects (Anderson et al., 2012).

Deep Brain Stimulation (DBS) is compared to ablation in that high-frequency stimulation causes a functional lesion by means of neuronal inhibition. However, mechanisms that mediate DBS effects are more complicated than originally thought with evidence for both excitatory and inhibitory effects on areas neighbouring and apart from the location of stimulation (Riva-Posse et al., 2013). Optogenetic neuromodulation combined with DBS revealed that activation and modulation of afferent fibre tracts are a plausible mechanism of action in DBS. Therefore, modulation instead of inactivation is one postulation put forward to explain antidepressant mechanisms of action (Schlaepfer et al., 2014). The specific mechanism of action through which stimulation exerts its influence is still under investigation. Axonal excitation, depolarization blockade, synaptic release of neurotransmitters, jamming of pathological neuronal firing as well as disruption of abnormal neuronal synchrony are all proposed physiological effects of DBS (Lozano et al., 2008).

Acute side effects post-surgery may include: tension, dizziness, and anxiety. Acute side effects such as these, which are only experienced by some patients, are not predictors of long-term effects (Schlaepfer & Bewernick, 2013). Reported side effects are mainly related to the surgical procedure. These side effects may include: intracranial bleeding or infection of the DBS device. Side effects encountered due to surgery are rare and those related to stimulation are transient or can be corrected by altering stimulation settings. Symptom aggravation may occur due to battery depletion or unattended discontinuation of stimulation. Schlaepfer and Bewernick (2013) argue that all research should include at least a 5 year follow-up to assess continued efficacy and pre-implantation baseline of 3 months to manage symptom fluctuation.

2.3. Major Depressive Disorder and Treatment Resistant Depression

2.3.1 Understanding Major Depressive Disorder

Major Depressive Disorder (MDD) is a common, incapacitating psychiatric disorder with a lifetime prevalence of approximately 16.2%. It is understood as a condition in which extreme sadness or melancholia affects an individual's daily functioning (Williams & Okun, 2013). The chief medical treatments available for MDD include: selective serotonin reuptake inhibitors (SSRI's), selective norepinephrine reuptake inhibitors (SNRI's) as well as second line antidepressant medications including monoamine oxidase inhibitors (MAOI's) and tricyclic antidepressants (TCA's)

(Taghva, Malone, & Rezai, 2013). One third of patients diagnosed with MDD do not respond to medications and roughly 10-20% remain severely debilitated despite medication and psychotherapy (Taghva et al., 2013).

Traditional treatment perspectives conceptualize MDD as a general dysfunction of the brain by focusing on hypothesized monoaminergic synaptic dysfunction. Recently, the correlation of disease symptoms with dysfunctions of particular brain networks which mediate mood and reward responses have led to more complete and appropriate treatments (Berton & Nestler, 2006).

2.3.2 Understanding Treatment Resistant Depression

Treatment Resistant Depression (TRD) refers to the ineffective response, seen as a failure to achieve and sustain a fully remitted state, to two or more antidepressant trials with sufficient dose and duration. It includes the failure to reach and sustain a satisfactory level of functioning and well-being when standard psychopharmacological treatments are administered (McIntyre et al., 2014). It is important to understand that a diagnosis of TRD is preceded by an initial diagnosis of MDD. Deep Brain Stimulation (DBS) is the treatment of choice for TRD once a patient is shown to be unresponsive to conventional psychopharmacological treatments, psychotherapeutic treatments, ECT and/or transcranial magnetic stimulation (rTMS) (Williams & Okun, 2013).

The cause of TRD is still under investigation with various postulations being put forth including: genetic predispositions for TRD, abnormal neurochemistry, medical and psychiatric comorbidity as well as specific psychological features as potential explanations for the development of TRD. In addition, clinical factors such as non-adherence to treatment and poor tolerability to antidepressant medications have been linked with non-responsiveness to treatment and resistance. Studies have also detected comorbid post-traumatic stress disorder and the existence of early life adversity as noteworthy predictors of inadequate treatment response (Oremus et al., 2015). Personality biases are one psychological feature that has been investigated in an attempt to understand TRD. Takahashi et al. (2013) found evidence that corroborated seven other studies which stated that patients with TRD displayed high harm avoidance, low self-directedness and low cooperation. These variables correlated significantly with scores on the Hamilton Depression Rating Scale (HDRS)

in patients with TRD and patients in remission. Furthermore, it was found that patients with TRD displayed low reward dependence. Whether these personality biases are primary or secondary to TRD requires further investigation.

2.3.2.1 Controversy around Treatment Resistant Depression

Studies have argued that a more accurate diagnosis of TRD may be possible once a standard definition is agreed upon (Malhi, Parker, Crawford, Wilhelm, & Mitchell, 2005). There are three core classification systems for TRD. The first classification system is the 5-stage classification where stages progress depending on the amount of failed adequate trials with stage 5 proposing bi-temporal ECT. The second classification system is the National Institute for Clinical Excellence (NICE) guidelines that provides a short algorithm. The third classification system is the multi-level structured Massachusetts General Hospital (MGH) criteria (Fornano & Giosue, 2010). Another controversy surrounding TRD diagnosis is the idea that undiagnosed bipolar disorder (BD) may be a risk factor for TRD. It is reported that patients who are diagnosed with BD are two to three times more likely to present in the depressive phase than in a manic phase. It is argued that BD-I remains undiagnosed in 35% to 45% of patients with a depressive disorder. Fornano, Giosue, Sharma, Khan, and Smith (2005) found that in 61 patients diagnosed with treatment resistant "unipolar" depression, majority of the patients met the diagnostic criteria for BD (bipolar 2). Correa et al. (2010) systematically reviewed literature pertaining to this controversy and found that moderate evidence substantiates the idea that the TRD population reveal high rates of unrecognized BD. In addition, antidepressants have been poorly tolerated and somewhat ineffective in patients with BD. The authors demonstrate there has been no unequivocal evidence to support the idea that patients with depression who relapse and show treatment resistance despite antidepressant treatment are likely to have BD.

2.3.3 Cognitive Sequelae of Major Depressive Disorder

Cognitive impairment has become a recognizable characteristic of MDD. The phenomenon of 'pseudo-dementia' pertains to MDD and is understood as the reversible cognitive impairment that occurs in MDD which requires antidepressant treatment without cognitive side effects (Grubert et al., 2011). Research has found neuropsychological deficits in the cognitive domains of executive functioning,

attention, attentional set shifting, memory, visuospatial/construction processing and psychomotor functions in MDD. Impairment in executive functioning is the most consistent finding across various studies (Baune et al., 2010).

One hypothesis that is utilised to explain the cognitive impairment experienced by depressed patients is the idea that depression is linked with heightened negative cognitions and rumination (Papazacharias & Nardini, 2012). The focus on negative automatic thoughts may engage neuronal resources that are usually allocated to the processing of cognitive information resulting in poorer performance during depressive episodes. A relationship between depression and difficulty with eradicating negative, irrelevant stimuli from working memory has been demonstrated (Papazacharias & Nardini, 2012). Furthermore, Holmes and Pizzagalli (2008) found that depressed patients exhibited a hyper-activation in neuronal areas involved in the processing of emotion when compared to healthy controls. This occurred after a preliminary error on a demanding neuropsychological test. This finding was linked with a failure to engage the dorsolateral prefrontal cortex and poorer performance on the test (Holmes & Pizzagalli, 2008). The activation of limbic areas during essential processing of emotional information may result in cortical inefficiency and cognitive impairment through inhibitory connections between the amygdala to the prefrontal cortex (Papazacharias & Nardini, 2012).

Evidence suggests that patients with current depression display poorer cognitive performance in all domains when compared to healthy controls. Patients with previous depression exhibit enduring cognitive deficits in immediate memory and attention when compared to healthy controls. In addition, patients with current depression have lower total scores on neuropsychological assessments when compared with previously depressed patients (Baune, Czira, Smith, Mitchell, & Sinnamon, 2012). The authors go on to state there is also evidence that suggests that patients with recurrent episodes of depression tend to suffer further cognitive decline with each consecutive episode. Furthermore, decreased cognitive function is observed in patients with MDD long after remission is achieved (Baune et al., 2012). Corroborating the above findings is a meta-analytic study conducted by Snyder (2013) who synthesized 113 previous studies that compared individuals with MDD to healthy controls on at least one neuropsychological measure of executive functioning. Studies consistently

demonstrated that MDD is associated with impaired performance on measures of executive function with more severe depressive symptoms associated with greater executive functioning impairment.

Lin et al. (2014) suggest that depressed patients are able to recover select neuropsychological functions in remission. The theory of multiple models of depression was utilised by Lin et al. (2014), who compared neuropsychological performance between three depressive subtypes: melancholic, atypical and undifferentiated depression. Supporting the above findings, the chief finding of the study demonstrated that in the course of a depressive episode, all three subtypes showcased extensive cognitive deficits (with the exception of attention). The subtypes differed in terms of severity in the domains of processing speed and verbal fluency. A secondary finding highlighted that in a remitted state, patients were able to recover visuospatial memory and verbal working memory comparable to healthy controls.

These findings are linked with single-photon emission computer tomography (SPECT) results that indicated that melancholic depressives displayed decreased activity in the right frontal lobes, compared to atypical depressives. Hypo-activity in the frontal lobes is linked to decreased levels of chief excitatory neurotransmitters and glutamate, which may result in cognitive deficits. In other domains, subtypes still displayed various cognitive deficits despite being in a remitted state (Lin et al., 2014). Hammar and Ardal (2009) echoed these findings by arguing that the cognitive deficits associated with MDD occur in the acute phase of the illness and residual impairment may persist even with the reduction of symptoms and once a state of remission is achieved.

In addition to this Herrera-Guzman et al. (2010) corroborated the secondary finding of Lin et al. (2014) by concluding in their study of 37 depressed patients treated with SSRI's, that the cognitive functioning of patients with MDD may be improved over time beyond remission and that antidepressant treatment may enhance memory. Additionally, Biringer et al. (2005) researched executive functioning in MDD patients upon recovery. This study, which found an improvement in executive functioning, concluded that neuropsychological impairment associated with long-term depressive symptomology is reversible in recurrent unipolar depression.

Thus, it can be surmised that cognitive impairment that is evident in MDD may persist in spite of remission when individuals are diagnosed with TRD and that these

impairments need to be considered when planning treatment. It is also important to note that studies have suggested that this residual impairment can be reversible when treated.

2.3.3.1 Neuropsychological Sequelae and General Functioning

Major Depressive Disorder (MDD) may have detrimental and enduring cognitive deficits which Baune et al (2010) suggests may, in part, be related to general functioning. In relation to this, Quality of Life (QoL) is being researched in patient's undergoing DBS as the amelioration of other clinical measures such as QoL and anxiety have been linked with antidepressant results (Schlaepfer, Bewernick, Kayser, Hurlemann, & Coenan, 2014). In addition, it was found that in PD a change in motor symptoms was not necessarily linked with an improvement in QoL (Daniels et al., 2011). Quality of Life (QoL) assessments measure features that extend beyond symptom improvement such as the ability to socialize and manage everyday activities (Schlaepfer et al., 2014). Treatment for MDD has been found to improve QoL acutely but QoL remains low compared to healthy controls even when symptoms are in remission (Ishak et al., 2011). Limited studies have looked at QoL in TRD patients and the link between QoL and response status in DBS for TRD patients is unclear.

Furthermore, a correlation has been shown to exist between cognitive performance and general functioning (physical and mental health, QoL, activities of daily living and employment status) in individuals with current and previous MDD. This notion was investigated by Baune et al. (2010) who found that patients with current depression showcased poorer cognitive performance in all domains when compared to healthy controls. Patients with previous depression showed enduring cognitive deficits in immediate memory and attention when compared to healthy controls. Patients with current depression had lower total scores when compared with previously depressed patients. Furthermore, cognitive performance was not related to physical or mental quality of life or activities of daily living (Baune et al., 2010). Thus, patients with MDD may suffer harmful and long-lasting cognitive deficits which may affect their overall general functioning.

2.3.4 Treatment options for Treatment Resistant Depression

Once an individual diagnosed with MDD has failed to respond to antidepressant treatment there are various other treatment options which are considered. The first option involves altering medication. This can be accomplished by combining two of the same antidepressant medications, combining the original antidepressant medication with another of a different class or augmenting antidepressants with other pharmacological substances such as lithium (Perez-Wehbe, Perestelo-Perez, Bethencourt-Perez, Cuellar-Pompa, & Penate-Castro, 2014).

Somatic treatments such as rTMS have shown to provide notable benefits in short-term treatment studies. However, rTMS evidences low response and remission rates and does not boast a large number of systematic follow-up studies which prevent it from being considered the first choice of treatment once antidepressants have failed. Vagus Nerve Stimulation (VNS) has shown promise yet efficacy studies are still lacking. Altogether, the somatic treatments of DBS, rTMS and VNS have all shown promise, however, the optimal stimulation areas and parameters require further investigation (Perez-Wehbe et al., 2014).

The cognitive behavioural analysis system of psychotherapy (CBASP) is a psychotherapy model created specifically for individuals who are chronically depressed. The model was developed according to contemporary learning theories with its chief goal being to facilitate the connection of the patient to the environment. This is done so that others may exert a positive influence on the patient. It is also done to promote stimulus learning and response learning to allow the patient to acquire adaptive coping skills in order to decrease interpersonal avoidance and enhance positive reinforcements. Sayegh et al. (2012) studied the efficacy of CBASP in a group context for the treatment of TRD. Patients displayed marked reductions in symptoms of depression and emotion-orientated coping when compared to their pre-treatment symptoms. In addition, patients showed an increase in social adjustment and interpersonal self-efficacy. However, it was found that self-reported interpersonal difficulties did not decrease to normative levels, in spite of observable improvements once treatment was terminated.

Deep Brain Stimulation (DBS) studies have advocated its use with patients who are suffering from TRD. Other somatic methods for treating TRD have been explored above. ECT has demonstrated efficacy, however, memory impairments as well as a relatively high relapse rate has accompanied this form of treatment. The efficacy of ablative techniques which are more invasive such as anterior cingulotomy, anterior capulotomy, subcaudate tractotomy as well as limbic leuctomy have not been firmly established (Serra-Blasco et al., 2015). Thus, researchers have proceeded with investigating the DBS procedure, the optimal target sites and stimulation parameters as well as understanding the mood and neuropsychological outcomes associated with the procedure.

2.4. Deep Brain Stimulation for Treatment Resistant Depression

2.4.1 Target Sites and Stimulation Parameters

Target selection has been guided by means of tractography of older ablative methods and via neuroimaging studies. Neuroimaging studies pinpoint neuroanatomical structures within presumably dysfunctional neural circuits which modulate MDD through connections to the limbic, cortical and subcortical regions (Berlim, McGirr, Van Den Eynde, Fleck, & Giacobbe, 2014). A network model of depression has been developed utilising electrophysiological imaging (Morishita, Fayad, Higuchi, Nestor, & Foote, 2014). This model suggests that a dysfunction of limbic-cortical connections may result in depression. Pathological changes in dorsal regions which include the dorsolateral prefrontal cortex, inferior parietal cortex as well as striatum were associated with the cognitive symptoms of depression (apathy, anhedonia, problems with attention and concentration). Pathological changes in ventral areas such as the insula, subgenual cingulate, brain stem and hypothalamic-pituitary-adrenal axis were associated with somatic symptoms (sleep and appetite disturbance, endocrine deregulation) (Morishita et al., 2014).

Based on the network model, different DBS targets have been identified: the subgenual cingulate gyrus (SCG), the anterior limb of the capsula interna (ALIC), the nucleus accumbens (NAcc), the ventral striatum (VS), the subcallosal cingulate (SCC) (Williams & Okun, 2013), the medial forebrain bundle (MFB) (Coenen et al., 2011), the inferior thalamic peduncle (ITP) (Jimenez et al., 2005) and lateral habenula (LH)

(Sartorius et al., 2010). With the utilisation of larger samples, significant results of the short-term (Lozano et al., 2008; Lozano et al., 2012) and longer-term (Holtzheimer et al., 2012) effects of DBS to the SCC have been found. These results have subsequently been confirmed by Puigdemont et al. (2012). Other studies (Bewernick et al., 2010, Bewernick et al., 2012, Malone et al., 2009, Schlaepfer et al., 2008) have also found promising results with stimulation sites corresponding to the ventral part of the striatum, including the ventral caudate (VC) and NAcc. The SCG, ALIC and NAcc are identified as major targets for stimulation.

The SCG is a brain region that is involved in mood-regulation and self-generated sadness (Merkl et al., 2013). According to functional imaging studies the subgenual cingulate white matter (SCGwm) demonstrates increased activity which is associated with depression (Merkl et al., 2013). Modulation of pathological activity and modifications of brain metabolism in this area is linked to antidepressant effects in patients undergoing chronic DBS (Martin-Blanco et al., 2015; McNeely, Mayberg, Lozano, & Kennedy, 2008). Stimulation of the ALIC has been utilised in treating OCD as well as PD. Antidepressant effects have been observed in OCD patients when the ALIC and the VS were stimulated leading to this being a target site in treating TRD (Schlaepfer & Bewernick, 2014).

Deep Brain Stimulation (DBS) was utilised by Robert Heath to treat schizophrenia as well as pain and epilepsy. He observed that patients stimulated in the septal area (which is close to the NAcc) experienced feelings of joy and euphoria (Hariz et al., 2010). The NAcc is a reward pathway that has been speculated to be partly dysfunctional in depression. The NAcc is understood as being involved in motivation and acts as a motivation gateway between systems involved in emotion and motor control. Deep Brain Stimulation (DBS) to the NAcc is shown to have acute anti-anhedonic and longer-term antidepressant effects due to stimulation increasing monoaminergic neurotransmitters to the prefrontal cortex (Millet et al., 2014).

With regard to stimulation parameters for TRD, the optimal electrical stimulation parameters are unknown and still subject to trial and error selection. The selection of stimulation parameters is guided by adapting DBS parameters used for movement disorders (Ramasubbu, Anderson, Haffenden, Chavda, & Kiss, 2013). The standard parameters utilised for chronic stimulation with the SCG are 130Hz, 90-microsecond

pulse width and 6-8mA (Riva-Posse et al., 2013). Ramasubbu et al. (2013) investigated the relationship between stimulus parameters in the SCC and the clinical effects of changing parameters. This study found that "shorter pulse widths with higher amplitude stimulation and longer pulse widths with lower amplitude stimulation" could generate comparable benefit (Ramasubbu et al., 2013, p. 330). The study concluded that further research needs to be done in order to establish optimal stimulation parameters.

2.4.2 Deep Brain Stimulation to the Bed Nucleus of the Stria Terminalis

It has been postulated that neurogenic mechanisms (mechanisms controlled by the nervous system) play a role in the pathophysiology of a variety of disorders including psychiatric and cardiovascular disorders (Crestani et al., 2013). In predisposed individuals, persistent life stressors are related to maladaptive reactions that present as psychopathological conditions such as MDD (Conrad, Louderback, Gessner, & Winder, 2011). The bed nucleus of the stria terminalis (BNST) is a heterogeneous limbic forebrain structure which plays a role in regulating autonomic, neuroendocrine and behavioural responses. The BNST is also assumed to play an integral role in relaying information from limbic forebrain structures to hypothalamic and brainstem nuclei and plays an important role in the regulation of hypothalamus-pituitary-adrenal (HPA) responses to stress. It also receives projections from the hippocampus and the medial prefrontal cortex (MPFC) (Crestani et al., 2013).

The BNST forms a continuum with amygdaloid structures. Therefore, it is viewed as a sub-region of the extended amygdala (which includes the shell of the NAcc) that has been associated with the integration of stress and reward responses (Beck, 2008). A hypersensitive amygdala is associated with both a genetic polymorphism and a pattern of negative cognitive biases and dysfunctional beliefs which constitute risk factors for the development of depression. The combination of a hyperactive amygdala and hypoactive prefrontal regions is associated with diminished cognitive appraisal and the occurrence of depression (Beck, 2008).

It is proposed that limbic processing of emotional information in conjunction with HPA axis stress responses are integrated at the individual BNST neuron (Crestani et al., 2013). The BNST has been linked with longer-duration and sustained increases in

anxiety-like behaviour (Conrad et al., 2011). It is hypothesized that the BNST may be involved in modulating coping mechanisms during uncontrollable stress situations and is thus considered a potential target site for DBS (Schulz & Canbeyli, 2000).

Deep Brain Stimulation (DBS) of the BNST has mainly been carried out on patient's suffering with treatment-resistant OCD in order to further the understanding of electrode placements as well as further investigation into mood outcomes (Nuttin et al., 2013; Islam, Franzini, Messina, Scarone, & Gambini, 2015). Islam et al. (2015) looked at eight patients who underwent DBS for treatment-refractory OCD. Four patients underwent DBS of the BNST and four patients underwent DBS of the NAcc. Patients who received BNST stimulation showed significant improvement in OCD symptom. These patients exhibited a significant decrease in compulsive behaviours. These findings may be linked to the anxiolytic effects of BNST stimulation. The study found that patients who underwent DBS of the BNST experienced better outcomes than NAcc patients as they showcased remarkable improvement in symptoms (50% reduction in OCD symptoms) that occurred between 6 and 12 months post-DBS. Whereas the NAcc patients showcased improvements between 12 and 22 months post-DBS. It is also interesting to note that Patient 4 in the study, who underwent BNST stimulation, showed a significant improvements in mood symptoms. (Islam et al., 2015).

2.4.3 Inclusion and Exclusion Criteria Guidelines for Deep Brain Stimulation for Treatment Resistant Depression

Deep Brain Stimulation (DBS) has notable risks that are associated with the surgery such as intra-cerebral bleeding and wound infection. According to Schlaepfer and Bewernick (2013) efficacy evidence for DBS is also lacking. Therefore, when DBS research is performed it requires strict and ethical guidelines. Inclusion and exclusion criteria that are based on the severity, chronicity, disability, and treatment-resistance are proposed by Schlaepfer and Bewernick (2013). Inclusion criteria include: the diagnosis of MDD, and HDRS score of >20, a GAF score of <45, at least four episodes of major depression or a chronic episode of >2 years and 5 years after the first episode of depression.

As mentioned in the definition of TRD the patient would have to meet adequate trials of antidepressant medication from at least three different classes, adequate trials of augmented primary antidepressants with at least two different combination treatments such as lithium and anticonvulsants, an adequate trial of ECT and an adequate trial of individual psychotherapy. The patient must also be able to provide written informed consent and must be drug-free or on a stable drug regime six weeks before study entry and 6 months during follow-up.

In terms of exclusion criteria, Schlaepfer and Bewernick (2014) suggest that patients should not have a history of current or past non-affective psychotic disorders and any current clinically significant neurological disorders or medical illness affecting brain functioning, other than motor tics or Gilles de la Tourette syndrome. The patient should not possess any clinically significant abnormality on pre-operative magnetic resonance imaging (MRI). The patient should not display any surgical contra-indications to undergoing the surgery and should not display any current or unstable remitted substance abuse. Pregnant or woman of childbearing age not using effective contraception should also be excluded from the surgery. Finally, patients with severe personality disorders should not be considered for this surgery.

2.5. Mood and Neuropsychological Outcomes after Deep Brain Stimulation

2.5.1 Mood Outcomes

A slow response pattern in DBS for TRD has been identified with most effects occurring weeks to month's post-DBS (Merkl et al., 2013). Acute effects have not been demonstrated to be predictive of long-term effects. Only after a stimulation period of 1 to 6 months have anti-depressant responses been observed. The acute effects post-DBS include a more positive change in mood, increased relaxation, spontaneous engagement in conversation, increased calmness as well as a higher activity level. Long–term anti-depressant effects as well as effects such as increased quality of life and decreased anxiety have been observed for all three major target sites: the SCG, ALIC and NAcc. For example, Morishita et al. (2014) reviewed twenty two clinical research papers which included a total of five different approaches to DBS using various stimulation targets including the three chief targets mentioned above. Taken as a whole, 40-70% of patients in each study were responsive to stimulation.

Responsiveness is uniformly described as a 50% reduction on HDRS scores (Schlaepfer et al., 2014).

Twenty patients who were stimulated at the SCG had response rates (meaning significant clinical improvement of depressive symptoms after the DBS procedure) of 55% at the 1 year period, 45% at the 2 year period, 60% at the 3 year period and 55% at approximately a 6 year period post-DBS (Schlaepfer & Bewernick, 2013). Merkl et al. (2013) assessed the efficacy of DBS in six patients with TRD. These patients received bilateral DBS to the SCG. Acute stimulation was carried out at all four contact sites followed by chronic stimulation with the clinical effect being assessed at 24-36 weeks. The study found that after 24 hours acute stimulation yielded moderate reduction in depression scores (as measured by HDRS), Montgomery-Asberg Rating-Scale(MARS) as well as the Beck Depression Inventory-II (BDI-II). At the 24-36 week marker two patients were remitters and four other patients were non-responders. Merkl et al. (2013) proposed that factors contributing to non-response may include patient selection, microlesional effects as well as inter-individual variability of neuroanatomical structures. The study concluded that stimulation of the SCG has the ability to exert moderate acute and chronic antidepressant effects.

In one of the longest follow-up studies, Kennedy et al. (2010) investigated 20 patients who received stimulation to the SCG and were followed-up on average 3-6 years after the procedure. The study found that the average response rates (understood as a significant reduction in HDRS scores) at 1, 2 and 3 years was 62.5%, 46.2% and 75% respectively. At year 3 more than one third of patients were in remission. Additionally, improvements in social functioning as well as physical health were observed up to the last follow-up visit. Consistent response rates are suggestive of a delayed yet progressive improvement in depressive symptoms which persists over several years (Kennedy et al. 2010).

Schlaepfer, Bewernick, Kayser, Madler, and Coenan (2013) assessed the safety and efficacy of stimulation to the supero-lateral branch of the MFB in seven patients with TRD. The study found that all patients showed markedly similar effects related to increased appetitive motivation. Six of the seven patients attained response criterion with a >50% decrease in the MARS score at day seven post-stimulation onset. Follow-up between 12 and 33 weeks found six patients with continual response and four being

categorized as remitters. The researchers concluded that stimulation to the above-mentioned region resulted in clinically significant reduction of symptoms with antidepressant efficacy being rapid in its onset.

Positive improvements in mood were also demonstrated by Millet et al. (2014), who studied the effects of DBS to two targets: the NAcc and the caudate nucleus. Three of the four patients responded to the DBS and showcased a significant improvement in mood demonstrated by lower scores on the HDRS over a period of 15 months following the procedure. Additionally, patients displayed a better response when the NAcc was stimulated, which corroborates previous findings suggesting that NAcc be retained as a potential target site for patients with TRD. Deep Brain Stimulation (DBS) of the VS was investigated by Malone et al. (2009). Follow-up ensued after a minimum of 6 months and a maximum of 4 years. Findings of the study indicated significant improvements in depressive symptoms with mean HDRS decreasing from 33.1 at baseline to 17.5 at 6 months post-surgery and 14.3 at the last follow-up visit. Remission rates were 20% and 40% at 6 months and last follow-up respectively.

The SCC is a stimulation target that has been proposed for TRD (Williams & Okun, 2013). Berlim et al. (2014) conducted a meta-analyses looking at four studies which focus on stimulation to the SCC for TRD on a total of 66 patients. The study found, at 12 months post- procedure, response and remission rates were 39.9% and 26.3% respectively. This stands in stark contrast with response and remission rates for TRD which mostly employ psychopharmacological treatment which are estimated at 11.6% and 3.6% respectively. Moreover, significant reductions in depression scores were observed in the analysis. Antidepressant effects were viewed within 3 to 6 months following the procedure. Berlim et al. (2014) advocate DBS as a treatment for TRD by stating that the long-term clinical effects are notable considering the 23% relapse rate at 12 months when anti-depressant medications are used. The above findings elaborate on and confirm previous research findings that suggest that DBS to the SCC result in significant anti-depressant effects in short, medium and long term periods.

2.5.1.1 Limitations of previous research

Long-term data on DBS for TRD has only recently been reported and remain limited despite the increased attention being given to the field of DBS (Lozano et al., 2008; Malone et al., 2009; Mayberg et al., 2005; Puigdemont et al, 2011). The average time

of the longitudinal studies range from a minimum of 6 months with Malone et al. (2009) conducting follow-up sessions 4 years post-DBS. These studies have sparked new interest in pertinent antidepressant results despite their limited generalizability due to small sample sizes (n<20) and absence of sham control (Schlaepfer et al., 2014). There is limited data available on sham-controlled DBS in TRD due to small sample sizes which do not allow for a reliable estimation of a sham effect. It is argued that sham effects in the TRD population are unlikely as the probability of placebo responses decreases as treatment resistance increases (Schlaepfer et al., 2014).

A pertinent study conducted by Dougherty et al. (2015) revealed that DBS to the VC/VS was not superior to sham stimulation. The amount of patients responding to sham and active stimulation was similar (20% responded to active stimulation and 14.3% responded to sham stimulation) and the average reduction in MARS was greater in the sham stimulation group (-24.6%) compared to the active stimulation group (-19.6%). This study emphasized the pivotal role design aspects in DBS studies, especially the amount of time utilised to find optimum stimulation parameters and the point when sham conditions are introduced to study protocols are still under review (Schlaepfer et al., 2014). It has also been found that in DBS for PD, expectation and placebo effects explain clinically significant aspects of improvement (Dougherty et al., 2015).

These findings in conjunction with small sample sizes and the novelty of the field highlight the need for larger studies that include sham conditions in order to improve the understanding of DBS. This may prove to be problematic as patients with TRD find it difficult to tolerate off-phases which may lead to a worsening of symptoms with enhanced suicidal ideation (Goodman et al., 2010). Therefore, this field of study is not without its limitations, however, the above-mentioned studies consistently demonstrated that positive and pervasive mood outcomes follow DBS when major and minor sites are targeted.

2.5.1.2 Understanding the Cognitive Neuropsychological Model of Major Depressive Disorder

Beck (2008) explained that individuals with MDD possess a negative self-bias, due to dysfunctional attitudes about themselves, that affect information processing and lead

to symptoms of depression. Cognitive models of depression postulate that a negative self-bias is the first distinguishing characteristic of MDD (Beck, 2008). Negative self-bias is described as an emotion-by-depression interaction. Individuals with MDD are hypothesized to have increased negative emotional processing and/or reduced positive emotional processing. This purports that at a secondary level individuals with MDD display a systematic cognitive bias in terms of information processing which leads to selective attention towards negative aspects of experiences and negative interpretations of events.

It is proposed that monoamine antidepressant treatment may be responsible for initial changes in emotional processing which are independent from alterations in mood (Harmer, Goodwin, & Cowen, 2009). This early alteration in emotional bias is attributed to a change in bottom-up processing rather than top-down, strategic processing. Therefore, antidepressant effects may occur as a result of a decrease in the processing of negative stimuli or an increase in processing positive stimuli (Hilimire et al., 2015).

The cognitive vulnerability model states that adverse life events that occur during childhood cultivate negative attitudes and biases about the self which are then incorporated into the individual's cognitive organization as schemas. These schemas are galvanized by later adverse life events which draw upon cognitive vulnerabilities and results in the negative self-bias at the centre of depression (Beevers, 2005).

Self-bias is measured by utilising an emotional self-referential task where participants are requested to indicate whether adjectives describing negative and positive personality traits are self-descriptive. Research shows that both current and remitted patients have automatic attentional biases towards negative self-referential content (Shestyuk & Deldin, 2010; Hilimire et al., 2015). Self-referential emotional processing is shown to activate a network of brain areas such as the MPFC and SCC. Depressed patients displayed hyperactivity in the MPFC and SCC when processing negative self-referential tasks compared to healthy controls (Yoshimura et al., 2014). Furthermore, it is suggested that hyperactivity in the ventral MPFC promotes increased automatic attention to self-referential information in depression. Hyperactivity in the dorsal MPFC exhibits strategic control processes such as the comparison of self-referential information to negative schemas of the self in depression (Lemogne, Delaveau,

Freton, Guionnet, & Fossati, 2012). It can be hypothesized that DBS of the BNST could modulate controlled and automatic processes thereby reducing the processing of negative self-referential information and increase the processing of positive self-referential material through its connections with the MPFC.

In a recent study investigating the above theory Hilimire et al. (2015) studied the longitudinal alterations in emotional self-referential processing and its relationship with chronic DBS to the SCC in TRD patients. The study confirmed that patients underwent behavioural and physiological changes in emotional self-bias which was related to significant clinical improvement (determined by a reduction in HDRS scores). After 1 month patients negative self-bias was decreased as evidenced by reduced negative words being identified as self-descriptive. This alteration was maintained after 6 months. Furthermore, at the 6 month period the percentage of reduction in negative words as being self-descriptive was significantly correlated with the percentage change in depression severity after 6 months post-DBS.

These results corroborate the theory that DBS to the SCC alters negative self-bias at the initial stages of treatment by decreasing automatic processing biases toward negative self-referential content. At a later stage (approximately 6 months post-DBS) findings indicate that stimulation to the SCC modifies negative self-bias by reducing strategic, controlled processing of negative self-referential content. This change is said to relate to the motivational relevance of emotional stimuli. Therefore, at the 6month interval change may reflect a decrease in rumination over negative self-referential content.

2.5.2 Neuropsychological Outcomes

Somatic interventions for TRD such as ECT, VS and rTMS that are ablative in nature and involve brain stimulation, have shown success in treating depression, but have been associated with adverse cognitive effects (McNeely et al., 2008). Since DBS for TRD is a novel procedure, cognitive performance is a vital facet to consider when planning treatments. This notion is emphasized by some patients with PD who display cognitive decline following DBS (Bergfeld, Mantione, Hoogendoorn, & Denys, 2013). In addition, there are conflicting results regarding neuropsychological impairment in patients with OCD and TS, however, this may be due to a lack of differentiation in the

neuropsychological assessments utilised and differential target sites that are stimulated (Grubert et al., 2011).

Jimenez et al. (2005) reported the neuropsychological assessment results in a patient with TRD who received stimulation to the ITP. The study found that abstraction, manual praxis, hemispheric dominance as well as memory showed spontaneous fluctuations with a tendency to present the same abnormalities detected in the preoperative evaluation. Insertion of electrodes during the DBS procedure augmented certain atypical preoperative neuropsychological performances. These included: learning-to-learn abilities on the Wisconsin card sorting test, which decreased from -1.2 (mild abnormality) to -10.8 (severe abnormality) (Jimenez et al., 2005). The authors argue that depression-related cognitive deficit may be improved by DBS as depressive symptom severity decreases.

A study by McNeely et al. (2008) focusing on the neuropsychological outcomes of bilateral SCG DBS on six patients found that no consistent pattern of cognitive decline was displayed following surgery, onset and maintenance of DBS. In addition, several areas of cognition which were found to be below average at baseline measurement improved to an average range at follow-up. Unlike the previous study findings, this study indicated that these changes were not statistically associated with improvements in mood. One patient who received stimulation unilaterally to the right SCG improved in verbal and visual memory, cognitive flexibility and fluency 8 months post-surgery. Moreines et al. (2014) found evidence that both replicated and expanded on the findings of McNeely et al. (2008) that DBS does not cause cognitive impairment and that neuropsychological function remains stable and can improve with stimulation to the subcallosal cingulate white matter (SCCwm) in patients with TRD. The study expanded findings to include the results that no disinhibition or impulsivity was observed when the Cambridge Gambling Task (CGT) was administered but rather patients displayed heightened willingness to engage with the task and more efficient processing of the task. Furthermore, processing speed increased post-DBS (McNeely et al., 2008).

A meta-analytic study conducted by Bergfeld et al. (2013) looked at twenty-six studies which, in total, reported the cognitive performance of 130 psychiatric patients. Twenty-eight of the patients suffered from MDD and the remaining patients suffered from OCD,

Alzheimer's Disease (AD) and Tourette's Syndrome (TS). Cognitive decline was not observed in any of the studies. Importantly, thirteen studies reported cognitive improvement following DBS. Studies looking at patients who underwent the DBS procedure showed improvement in the domains of verbal and visual memory, sustained attention, visual fluency, visual organization and no decline was observed (Bergfeld et al., 2013). The latest findings by Galvez et al. (2015) extensively reviewed the anatomic, electrophysiological, cognitive, and treatment data pertaining to the MFB as a target for DBS. Their review linked the MFB to antidepressant responses as well as motivated behaviour and mood regulation. Patients receiving DBS to the MFB reported high remission rates and improvements in functioning. No adverse physical health or cognitive outcomes were observed in any of the studies reviewed.

Studies have reported improvement in the impaired cognitive domains of memory (Bogod et al., 2014; Moreines et al., 2014) as well as frontal abilities (Holtzheimer & Mayberg, 2011). Serra-Blasco et al. (2015) support the above findings that maintain that cognitive safety is established in DBS of the SCG and moreover that cognitive functioning does not deteriorate with chronic stimulation but rather leads to improved performance when memory in particular is assessed. It is hypothesized that DBS of the SCG improves memory via the "neural jamming effect" (Lozano et al., 2008) which argues that DBS allows for the regulation and correction of abnormal activity in the neural circuitry being stimulated by means of suppressing unplanned neural signalling of the altered neural processes witnessed in depression. This may in turn alter transmission, which may then stabilize information flow within distal neural pathways such as the temporal region and the hippocampal area. Thus, when considering that DBS stimulation may affect distal areas to the target site via white matter tracts it is plausible that memory performance may be improved by indirect stimulation to temporal and hippocampal areas.

A study conducted by Baune et al. (2012) looked at the neuropsychological functioning of 13-25 year olds with a history of MDD. The results of the study showcased that depression in youth correlates with impairments on complex mental activities that require attention, working memory, set-shifting, set-maintenance, cognitive flexibility and complex problem solving. Impairments in planning and visuospatial/construction skills were not observed. In addition, the study found that positive affect correlated with improved attention, working memory, and verbal learning independent of gender

and education (Baune et al., 2012). The link between mood and neuropsychological status is therefore unclear. Some studies purport that antidepressant treatment in itself causes an improvement in cognitive status whereas other studies such as Baune et al. (2012) suggest that an improvement in mood results in an improvement in neuropsychological functioning. Thus far, studies have demonstrated positive mood and neuropsychological outcomes following DBS for TRD.

2.6 Conclusion

After many years of research into DBS for TRD as well as other psychiatric disorders, studies have shown relevant antidepressant effects at various stimulation sites. Extensive research has also supported the link between DBS and improved mood and cognitive functioning. Taken together, available evidence on DBS for TRD that has accumulated until today holds the promise that DBS as an intervention may alleviate the mood-related symptoms of TRD for patients that may have previously had little to no hope due to unresponsiveness to alternative treatments. However, due to the novelty of the field research has remained modest and researchers are cognisant of the fact that further investigation is warranted in order to establish optimal stimulation parameters and target sites.

Chapter 3

Method

The aim of this study was to explore the neuropsychological outcomes of DBS at the pre-and-post phases of the procedure. In addition to this, the mood-related outcomes would be presented. This chapter outlines the rationale for the use of a case study methodology, the design, the participant selection, specific measuring instruments, the data collection and the descriptive data review utilised in this study as well as ethical considerations pertaining to this study.

3.1 Rationale for Case Study Methodology

Yin (2003) explained that a researcher would utilise a case study methodology if the researcher wanted to carry out a meticulous examination of a case and explore its related contextual conditions believing that these conditions are pertinent to the phenomenon under investigation. Case study research focuses on a selected case in order to illustrate a specific issue or phenomenon. This research methodology deals with situations where there are more variables of interest than data points, where multiple sources of information are reviewed and triangulated based on the notion of convergence and confirmation of findings and where prevailing theoretical knowledge is available to guide data collection and data analysis (Baxter & Jack, 2008; Knafl & Breitmayer, 1989).

A case study methodology is utilised when the researcher seeks to contribute to the existing body of knowledge pertaining to a particular phenomenon (Yin, 2003). Conducting case study research allows for the expansion, exploration and generalization of theories, however, the research is generalizable to theoretical propositions and not to populations (Gomm, Hammersley, & Foster, 2000). A retrospective case review for this particular research endeavour would be beneficial in that it has the potential to generate hypotheses that can be tested prospectively in order to apply findings to the population diagnosed with TRD.

The case study approach in neuropsychology has made a significant contribution to understanding the architecture of the human cognition (Shallice, Burgess, & Frith, 1991). A single case study is a methodology wherein a patient's performance is not

referenced to a controlled sample but rather compared intra-individually on one or more measures. This is viewed as one of the key benefits of case study approaches as the researcher is able to administer numerous tests to a patient and inferences do not depend on averaging scores across patients (Shallice et al., 1991)

Various studies have employed a single case study methodology. For example, Jimenez et al. (2005) explored the effect of electrical stimulation on the inferior thalamic peduncle (ITP) in a patient with TRD. The case study research methodology was utilised in this study and this method allowed for the authors to provide in-depth information related to contextual conditions such as the patient's case history, symptoms, and previous treatment attempts as well as surgical procedural information such as stimulation parameters and information related to acute and chronic stimulation. A more recent study conducted by Kosel et al. (2010) looked at mood improvements in a patient suffering with TRD who underwent DBS to the internal globus pallidus (IGP) for tardive dyskinesia. This study reported both mood and movement improvements in one patient by providing a detailed case history as well as information related to the neurosurgical procedure and neuropsychological assessments pre-and-post DBS.

With this in mind, due to the patient being the only known individual at this time to be treated with DBS of the BNST for specific TRD in South Africa, it would be impossible for one to conduct research with a methodology that utilises a large sample and comparison of scores amongst participants. This research endeavour employs the method of comparison, however, results will be compared to normative data and findings will be discussed in relation to existing DBS studies that have explored the neuropsychological outcomes of DBS for TRD.

3.2 Case Study Design

The essence of a case study is that it focuses on a particular case. Due to the fact that this is the only known DBS of the BNST for TRD surgery performed within the South African context at this time, structuring the research as a single case review was the best approach to take. An in-depth exploration of the patient's case history and assessment outcomes would provide a deeper and richer understanding of DBS for TRD.

There are five categories of case study design namely: 1. Explanatory, 2. Descriptive, 3. Illustrative, 4. Exploratory and, 5. Meta-evaluation. This case study design is based on a descriptive approach (Zucker, 2009). The study is inductive in nature as a single case study will be explored and utilised to develop an enhanced understanding of DBS for TRD (Boyer, 2010). The design in itself is based upon the subject of analysis: the DBS procedure and the patient's neuropsychological outcomes pre-and-post DBS. It will provide the patient's case history, a brief description of the neurosurgical procedure and stimulation parameters, BDI-11 scores and the neuropsychological assessments performed pre-and-post operatively at four timelines (baseline, 6, 9 and 12 months). Therefore, the study can be classified as a longitudinal study as the patient was assessed at four timelines over a period of 12 months. A noteworthy strength of the case study methodology is the capacity to cope with various data sources. The researcher chose the methodology that is best suited to answer the research question while considering theoretical and pragmatic issues.

The research is also viewed as a retrospective review of participant demographic information and neuropsychological assessment scores with an additional presentation of mood-related outcomes. Retrospective research allows for the analysis of data that is already in existence that was collected for non-research purposes (Gearing, Mian, Barber, & Ickowicz, 2006). There are various advantages for using retrospective reviews such as: having access to a large amount of valuable data, enhanced objectivity due to the data being collected separately from the research postulations and assumptions, and the ability to test hypotheses that may have been formulated even before the data has been collected. In addition, retrospective reviews are less time and resource intensive allowing it to be completed while results are still current (Gearing et al., 2006).

This methodology has its limitations. Data that is not collected concurrently and in line with the research aim may be incomplete or ambiguous and would thus affect the quality of the research and the formulation. The validity of the research endeavour may be affected by unclear information that is obtained from patient reports. Retrospective reviews also lack a control group or premorbid data which would not allow inference of causality (Gearing et al., 2006).

Common methodological practice dictates that single case studies with measurable performance scores require a Reliable Change Index technique to determine if clinically meaningful change is reliable and significant. In this case study the RCI was not calculated because a normative data set that matches the patient's demographics, exact test-retest time interval and comparative stability coefficients was not available.

3.3 Participant

The sampling strategy that was applied is termed "purposive sampling". The patient was selected for the DBS procedure due to the presence of specific characteristics and was selected for this study due to being the only known patient at this time to undergo DBS of the BNST procedure in the country. This allowed for a detailed description of the variable under investigation to be provided.

The participant is one of the first patients in the country to undergo this novel procedure for TRD. She was informed of the research by the psychiatrist and psychologist and was asked to volunteer for the study. She was informed that if she consented to participate in the study her neuropsychological performance scores and mood scores, DBS parameter and procedural information would be reviewed for the purposes of this investigation. She was asked to sign the consent form which allowed the researcher access to information regarding the mood rating scores, DBS procedure (diagnostic radiological brain scans) and neuropsychological assessment scores over a period of 1 year.

3.4 Criteria for Participant Selection

The patient was screened by a psychiatrist, neurologist, psychologist (specialising in neuropsychology) and neurosurgeon to determine the eligibility for the procedure. Selection criteria for the surgical procedure included: failure to respond to antidepressants, psychotherapy or ECT despite adequate dosage, duration and compliance with treatment and willingness to comply with long-term follow-up. The patient met these psychiatric and neurosurgical criteria for DBS candidacy and completed a comprehensive baseline neuropsychological assessment prior to DBS. The DBS procedure was conducted on 12 October 2013 and the target site was the bed nucleus of the stria terminalis (BNST) (bilaterally). Post-neuropsychological assessments were administered at 6, 9 and 12 months. Information with regard to

mood ratings and DBS parameters such as pulse width, voltage and frequency were also monitored during these timelines.

3.5 Informed Consent

The research proposal was approved by the Small Committee, Departmental Research Committee, Cluster Research Committee, and the Research Ethics Committee (RESCOM) at the University of Pretoria. The patient signed an informed consent based on the guidelines stipulated by the University of Pretoria.

3.6 Deep Brain Stimulation Procedure

Deep Brain Stimulation (DBS) is a neurosurgical procedure which involves the stereotactic implantation of electrodes which sends electrical impulses to specific neuroanatomical areas of the brain (Anderson et al., 2012). The area is stimulated by means of a stimulator device, similar to a heart pacemaker, which is implanted subcutaneously below the clavicle. Surgical implantation may occur under local or general anaesthesia.

A hole that is approximately 14mm in diameter is drilled into the skull and the electrode is stereotactically implanted (National Institute of Neurological Disorders and Stroke, 2015). The system consists of the implanted pulse generator (IPG), the lead and the extension. The IPG is a neurostimulator that is battery-powered and is sheathed in titanium. The IPG sends electrical impulses to the brain to alter neural activity at the target site. The lead is an insulated coiled wire that is placed in one or two nuclei of the brain. Leads are placed in accordance with the symptoms being treated. The IPG and the lead are connected via the extension which is an insulated wire below the skin that travels from the head, to the side of the neck and behind the ear to the IPG. The IPG is placed subcutaneously below the clavicle or the abdomen (NINDS, 2015). A neurologist or trained technician is able to calibrate the IPG in order to optimize results (Volkmann, Herzog, Kopper, & Deuschl, 2002).

3.7 Measurement Instruments

The following measurement instruments were administered by the neuropsychologist pre-and-post DBS. A brief description of the measuring instruments are outlined

below. For a full description of the tests see Lezak, Howieson, Bigler, and Tranel (2012) and Strauss, Sherman, and Spreen, (2006).

3.7.1 Repeatable Battery for the Assessment of Neuropsychological Status

The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) is an individually administered battery, utilised to measure cognitive decline or improvement in five cognitive domains. These include: immediate memory (list learning and story memory), visuospatial/construction abilities (figure copy and line orientation), language (picture naming and semantic fluency), attention (digit span and coding) and delayed memory (list recall, list recognition, story memory and figure recall). Each index score is expressed as an age-adjusted standard score with a mean of 100 and standard deviation of 15 (Randolf, 1998). Split-half reliability of this test and the average reliability of the total scale score are both high at r=.80 and r=.86-.94 respectively. In this study parallel forms of the RBANS were administered. The test also boasts an interscorer reliability of r=0.85. The RBANS index scores have adequate test-retest reliability ranging from r=0.65 to r=0.78 for indexes with a relatively better reliability over time for the Total Scale score (r=0.88). Randolf (1998) provides the overall intercorrelation of index scores for each of the six standardization groups and states that the overall pattern of correlations shows that the different index scores measure distinct cognitive constructs. The content and format of the RBANS are similar in nature to frequently used clinical assessments such as the WAIS-II and WMS-III.

3.7.2 Stroop Test

The Stroop test (ST) measures the executive functions of selective attention and cognitive flexibility. This is accomplished by measuring the ease with which a person is able to shift his/her perceptual set to adhere to changing demands and suppress habitual and typical responses in favour of atypical responses while reading various colour names (Golden & Freshwater, 1998). Reliability for word, colour and colour-word are high at r=.90, r=.83 and r=.91 respectively. Internal consistency reliability is moderate to high r=.71 to r=.84. The interference score correlates well with other measures of attention and is moderately related to other measures of response inhibition. Factorial validity has been shown for several factors such as working

memory, conceptual abilities, processing speed and elements of planning (Strauss et al., 2006).

3.7.3 Controlled Oral Word Association Test

The Controlled Oral Word Association Test (COWAT) measures verbal fluency. The test administered used a three-letter set of F, A, and S. The participant is required to name as many words beginning with one of the letters as possible in 1 minute (Benton, Hamsher, Rey, & Sivan, 1994). The procedure is then repeated for the remaining two letters. Internal consistency reliability for this test was high r=.83. Test-retest reliability was also shown to be high r=.74 (Strauss et al., 2006).

3.7.4 Tower of London

The Tower of London (TOL) is a problem-solving task that measures the executive function of mental planning ability. In the task the participant is asked to mentally plan a sequence of moves to match a set of discs to a goal and then to complete the moves one by one (Culbertson & Zillmer, 2001). Split-half reliability at r=.72 and internal consistency reliability at r=.69 are moderate to high for this test. Test-retest reliability for the Total Move score is within the moderate to high level (r=0.80) suggesting that the scores are relatively stable over time. The Total Correct score fell short of significance at (r=0.42). The TOL assessment is deemed valid in terms of its predictability, however, it should be utilised in conjunction with order neuropsychological measures. Consistent findings suggest that the TOL showcases high construct validity as constructs assess are robust and clinically significant. Results also indicate that the test boasts convergent and discriminant validity as a measure of executive functioning (Strauss et al., 2006).

3.7.5 Delis-Kaplan Executive Function System (Trail making test)

The Delis-Kaplan Executive Function System, Trail Making Test (DKEFS-TMT) is a visual-motor sequencing task that measures the executive function of set-shifting flexibility. It involves 5 conditions: visual scanning, number sequencing, letter sequencing, number-letter switching and motor speed. In the Visual Scanning condition, examinees cross out all the 3s that appear on the response sheet. In the Number Sequencing condition, examinees draw a line connecting the numbers 1–16 in order; distractor letters appear on the same page. The Letter Sequencing condition

requires examinees to connect the letters A through P, with distractor numbers present on the page. In the Number-Letter Switching condition, examinees switch back and forth between connecting numbers and letters (i.e., 1, A, 2, B, etc., to 16, P). Examinees may perform poorly on the Number-Letter Switching task due to and impairment in one or more core component skills needed to perform the task. Therefore, performance on each of the baseline tasks is distributed out from performance on the Number-Letter Switching condition by computing a series of contrast measures.

For each contrast score, the completion-time scaled score for a component task (Condition 1, 2, 3, and 5) or the Number-Letter Sequencing composite is subtracted from the completion-time scaled score on the Number-Letter Switching task. A new scaled score with a mean of 10 and standard deviation of 3, is obtained for each scaled-score difference. The contrast scores show whether or not an examinee is demonstrating disproportionate impairment in cognitive flexibility relative to one of the four baseline component abilities, or to the combined baseline abilities measured by Conditions 2 and 3. Last, a Motor Speed condition is administered in which examinees trace over a dotted line connecting circles on the page as quickly as possible, in order to gauge their motor drawing speed (Delis, Kaplan, & Kramer, 2001). Reliability for this test has generally been shown to be moderate at r=.65. Internal consistency and test-retest reliability was found to be adequate (r=.70-r=.79) (Delis, Kramer, Kaplan, & Holdnack, 2004).

3.7.6 Beck's Depression Inventory-II

The Beck's Depression Inventory-II (BDI-II) is a multiple-choice self-report inventory that measures the severity of depression. There are 21-items which are scored and used for the clinical diagnosis of depression. Each answer is scored on a scale value of 0-3 with higher scores indicating more severe depressive symptoms. The internal consistency reliability and test-retest reliability of this test are both very high at r= .92 and r=.93 respectively. The test-retest reliability is high at r=.93 (Beck, Steer, & Brown, 1996). BDI-II total scores were correlated with several other psychological tests and evidence of convergent and discriminant validity was found. Intercorrelations among 21 BDI-II items were calculated and provided evidence for highly intercorrelated factors (factorial validity) (Strauss et al., 2006).

3.7.7 Beck's Anxiety Inventory

The Beck Anxiety Inventory is a 21-item, multiple-choice self-report inventory that measures the severity of anxiety. The inventory measures the emotional, physiological and cognitive symptoms of anxiety. Each item is a description of a symptom of anxiety in terms of subjectivity, neurophysiology, autonomic responses and panic-related symptoms (Beck & Steer, 1990). Each answer is scored on a scale value of 0-3 with higher scores indicating more severe anxiety symptoms. The BAI is considered reliable with an internal consistency ranging from .92 to .94 and test-retest reliability as .75. The BAI possesses convergent and discriminant validity for inpatients and outpatients (Osman et al., 2002).

3.8 Data Collection

There are six primary data sources that are utilised in the case study methodology. These include: documentation, archival records, semi-structured interviews, direct observation, participant-observation and physical artefacts (Yin, 2003). This research endeavour made use of documentation in the form of case history, neurosurgical information as well as neuropsychological and mood assessments. The data being utilised was previously collected by the neuropsychologist and will be analysed by the researcher. These sources provided a representation of the research question under investigation. Comparison of the data yields valuable insight into the neuropsychological outcomes of DBS for TRD.

3.9 Descriptive Data Review

This study will attempt to describe and report the pre-and-post neuropsychological outcomes of the Deep Brain Stimulation (DBS) procedure. Gerring (2007) argued that the case study method allows the research to be flexible in that data can be collected and analysed both qualitatively and quantitatively making this method suitable for novel research questions.

The data related to the period from 2013 till 2014. Numerical data was collected in the form of neuropsychological and mood assessment scores, data was interpreted through comparison of obtained scores with published normative data. Korzilius (2010) argues that numerical data, when used in a case study, can be interpreted in the same

way that qualitative textual data is interpreted in order to give meaning to the data. Scores were tabulated and the data was presented as a descriptive table. Inferences were made based on the patient's case history and assessment results.

3.10 Ethical Considerations

The research endeavour was approved by the various committees of the University of Pretoria. Written informed consent was requested from the participant to utilize information regarding the procedure (diagnostic radiological brain scans), mood related scores as well as neuropsychological assessment scores for a period of 1 year. The consent form highlighted that participation in this research was completely voluntary and all data accessed would not have any personal identifiers to ensure confidentiality of information. The data was provided to the researcher in the form of raw scores with no identifiable markers. Thus ensuring anonymity. The neuropsychologist granted permission for the researcher to utilise the data. The methodology fell within the parameters approved by the Ethics committee at the inception of the study. The data was be securely stored in password protected files and in a secured data storage room in the department of psychology for 15 years. The researcher stringently adhered to the ethical guidelines outlined by the university ethics committee.

3.11 Conclusion

Due to the novelty of this procedure globally and in the South African context, this approach is uniquely suited to address the research question under exploration. Unlike quantitative research, which requires large samples in order to perform statistical analysis, the case study method allows for a comprehensive description and exploration of the neuropsychological outcomes of the DBS procedure without sacrificing pertinent contextual information. However, this technique has been criticized due to issues relating to the generalizability of findings. The following chapter presents the patient's case history and the review of neuropsychological and mood outcomes.

Chapter 4

Review

In this chapter the results of the study are reviewed and discussed. Firstly, the patient's case will be reviewed. A brief history will be provided as well as information regarding the DBS procedure. Secondly, the results of the neuropsychological and mood assessments administered pre-and-post DBS will be reported.

4.1 History

The patient is a 36 year old, English speaking female with a tertiary education. She experienced a 13 year history of recurrent episodes of major depression and five psychiatric admissions. She fulfilled the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, revised, criteria for Major Depressive Disorder (MDD) (American Psychiatric Association, 2013). The patient's life has been significantly altered over the past decade. She does not participate in her premorbid interests, she has isolated herself from her former social relationships, and approximately 6 years ago she left her occupation as an educator. The patient has been married for 7 years and has no children. In terms of her predisposing factors for MDD, she disclosed that her family had a history of depression and anxiety, however, no history of dementia within her family was revealed.

The following symptoms were experienced by the patient during her depressive episodes: daily moderate to severe depressed mood, anhedonia, blunted affect and cognitive problems. Her neurovegetative symptoms included: decreased energy, variable appetite and a non-existent libido. In addition to these symptoms, the patient experienced difficulty in coping with stressful situations. The patient reported that she experiences difficulty with spontaneous laughter and also feels unmotivated in terms of decision-making and planned events. When asked to describe her premorbid functioning she reported that she was inventive, optimistic about life, physically active and that she had a career that was meaningful to her. Additionally, symptoms of generalized anxiety disorder (GAD) preceded her diagnosis of MDD, however medication has subsequently decreased her anxiety. The patient did not report suicidal ideation or any suicide attempts.

In terms of her cognitive functioning the patient reported: poor attention and concentration, and issues with short-term memory and decision-making.

This array of symptoms were resistant to pharmacotherapy. Various combinations of mood stabilizers were prescribed to the patient. She attended eleven sessions of electroconvulsive therapy (ECT) in July 2011 and March 2012. A vagus nerve stimulator was implanted and adjusted to the maximum recommended stimulation according to the University of Arizona review. In addition, she also received ketamine infusions with no success. In 2013, the patient was proposed for psychosurgery after being evaluated by an ad hoc committee (psychiatrist, neuropsychologist and neurosurgeon). She discontinued her medication after the DBS procedure, however, on the 8 May 2014 she was placed on Solium (50-100mg) for insomnia.

4.2 Neurosurgical Procedure

The procedure took place on the 12 October 2013. The bed nucleus of the stria terminalis (BNST) was targeted bilaterally using stereotactic frame-based MRI, surgical planning software and microelectrode recording. The DBS electrodes were implanted bilaterally spanning the grey-white matter of the BNST. The electrodes were then connected to the implantable pulse generator and placed subcutaneously below the clavicle. MRI and high-resolution computed tomography was utilised post-operatively to evaluate the contact location within the BNST.

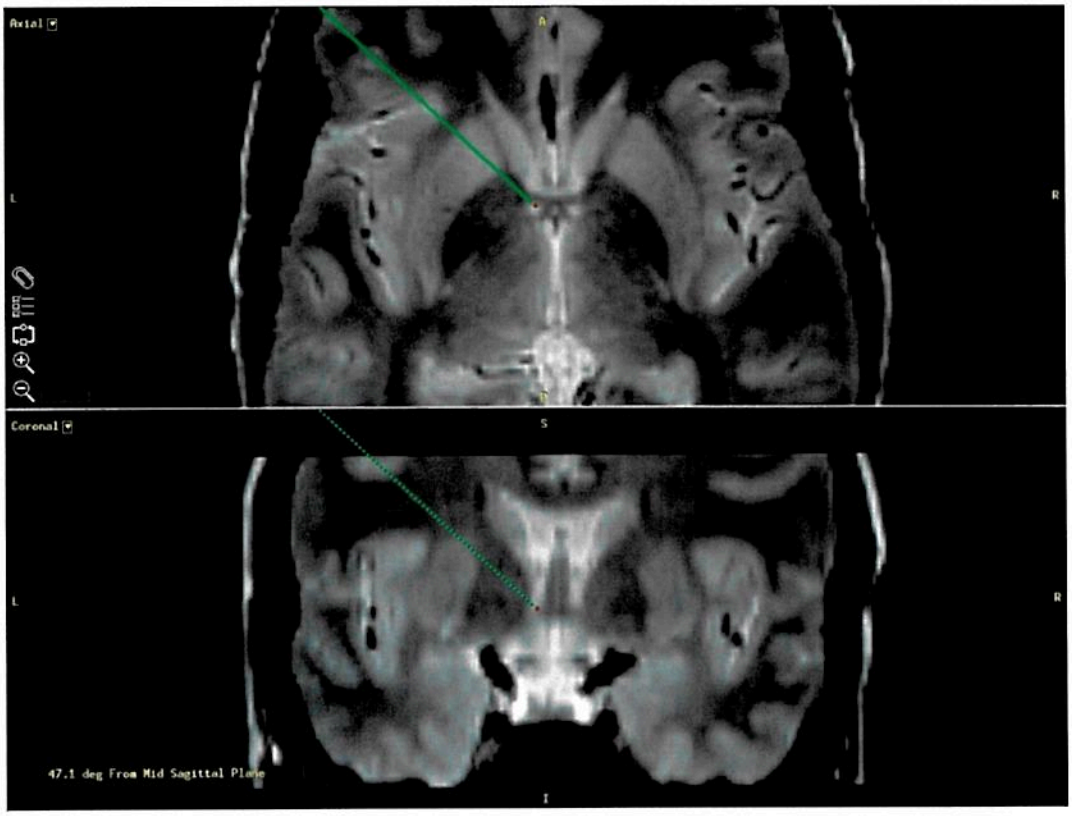

Figure 4.1: Left Bed Nucleus of the Stria Terminalis

4.3 Stimulation Parameters

TABLE 1: Stimulation parameters

The stimulation parameters utilised during the Deep Brain Stimulation (DBS) procedure are outlined below.

DATE	BILATERAL			
	Left	**Right**	**PULSE WIDTH**	**FREQUENCY**
16-10-2013	0 – C+; 6 VOLTS	8 – C+; 4 VOLTS	90	130Hz
08-11-2013	0-1+; 8 VOLTS	8-9+; 7.5VOLTS	90	130Hz
09-01-2014	0-1+; 7.5 VOLTS	8-9+, 6.5 VOLTS	110	130Hz
30-01-2014	0-C+; 5.5 VOLTS	8-C+; 3.5 VOLTS	210	130Hz
12-02-2014	0-1-C+; 3.5	8-9-C+; 3.5 VOLTS	210	130Hz
08-05-2014	0-1-C+; 3.5	8-9-C+; 3.5 VOLTS	180	130Hz
17-07-2014	0-1+; 3.5	8-9+; 3.5VOLTS	210	130Hz
21-08-2014	0-1, 3VOLTS	8-9+; 3.5VOLTS	210	130Hz
01-09-2014	SWITCHED OFF	8-9+; 3.5VOLTS	210	130Hz

Note: Pulse width is represented in milliseconds

Four days after surgery in October 2013, bipolar electrical stimulation of the electrodes was carried out with a frequency of 130Hz, pulse width of 90 milliseconds and amplitude of (left=0-6V) and (right=8-4V). In November 2013, 1 month post-DBS, stimulation to the left BNST was increased to (0.1-8V) and (8.9-7.5V) to the right BNST while keeping the pulse width and frequency constant. The amplitude was then decreased on the left electrode to 7.5V and then 5.5V and was also decreased on the right side to 6.5V and 3.5 V in January 2014. The frequency remained constant during this time, however, the pulse with was increased to 120 milliseconds and then to 210 milliseconds. For the next 6 months, from February to July 2014, frequency remained constant at 130Hz and amplitude remained bilaterally constant at 3.5V. However, the pulse width was decreased from 210 milliseconds to 180 milliseconds in May 2014. The amplitude of the left electrode was decreased to 3V in August 2014 with the right electrode, frequency and pulse width remaining constant. In September 2014 the left electrode was switched off and the right electrode remained constant at 3.5V with a frequency of 130Hz and 210 milliseconds.

4.4 Mood and Neuropsychological Assessment Scores

Testing was conducted before surgical implantation (baseline), and at 6, 9 and 12 months post-operatively.

TABLE 2 Longitudinal Mood and Neuropsychological Assessment Scores

Assessment	Baseline	6 Months	9 Months	12 Months
RBANS				
Immediate Memory	87	100	100	126
Visuospatial/Construction	87	92	96	96
Language	85	104	96	116
Attention	91	75	88	94
Delayed Memory	91	97	97	101
Total Scale	84	90	94	108
STROOP TEST				
C/W	34	43	37	60
Interference	34	41	31	58
DKEFS (TMT)				
Visual Scanning	12	13	13	13
Switching	5	11	9	11
Motor Speed	11	10	13	13
COWAT				
Phonemic	31	40	39	44
TOWER OF LONDON				
Total Move	76	106	100	108
Total Correct	72	90	90	102
Total Problem Solving	82	110	102	106
BECK'S DEPRESSION INVENTORY	29	5	17	4
BECK'S ANXIETY INVENTORY	21	15	18	3

Note: RBANS scores represent raw scores converted to index scores. Stroop test scores represent raw scores converted to T-Scores. DKEFS and TOL scores represent raw scores converted to scaled scores.

4.5 Review of Longitudinal Mood Assessments Over 12 Months

4.5.1 Beck's Depression Inventory-II

Clinically significant decreases in depressed mood and anxiety were noted in the patient. At baseline the patient's BDI-II score indicated that she was severely depressed. At 6 months post-DBS the patient's score indicated that she was minimally depressed. However, at 9 months the patient's score increased and signified that she had gone from a minimally depressed state to a mildly depressed state. The patient's depressed mood fluctuated between baseline and 9 months post-DBS, however, 12 months post-DBS she showcased a significant decrease in her score which indicated that she was now classified as minimally depressed. Based on the patient's decrease in the BDI-II scores from baseline to 12 months, the patient was classified as responsive to treatment (Beck et al., 1996).

4.5.2 Beck's Anxiety Inventory

At baseline the patient's Beck's Anxiety Inventory-II (BAI-II) score indicated that she was experiencing moderate anxiety. At 6 months the patient's score classified her as mildly anxious. At 9 months the patient's score increased and she was classified once again as moderately anxious. However, the 12 month period saw a significant decrease in her BAI-II score and she was classified as having minimal anxiety.

4.6 Review of Longitudinal Neuropsychological Assessments Over 12 Months

4.6.1 Repeatable Battery for the Assessment of Neuropsychological Status

Results of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) were compared with normative data reported by Randolph (1998). A score of 100 is classified as average for each index. At baseline the patient performed below the norm on all indexes and her scores were classified as low average. Among the indexes at baseline the patient's scores on attention and delayed memory were the highest. The patient's total scale score was also classified as low average at baseline. At 6 months the patient's scores on immediate memory and language improved to an average classification, however, visuospatial/construction, attention, delayed memory and her total scale score, which also improved in terms of scores, remained in the low

average classification. At this interval a noticeable decline in the patient's attention score occurred and her attention score was classified as borderline.

At 9 months the patient's immediate memory and delayed memory scores did not change and remained average, her visuospatial/construction score improved but this improvement was not striking and her score remained in the low average range. The patient's language score decreased and her score was classified as low average at 9 months after an improvement to average at 6 months. It is interesting to note that at 9 months when other indexes appeared to decrease, attention appeared to noticeably increase, however it remained in the low average range.

At 12 months her performance on the immediate memory index showed a marked increase and her score was classified as superior. Her performance on the visuospatial/construction index remained in the low average classification as her score did not change from 9 months to 12 months. The patient's language score increased noticeably and her score was classified as high average. Her performance on the delayed memory index improved from a low average to average classification. In terms of her total scale score, the patient's score improved from a low average to average classification. The patient's performance pattern on the attention index was consistently below average. Despite being the patient's highest scores at baseline, the attention index was consistently below average and did not show marked improvement at 12 months.

An examinee's level of education may influence his or her test performance on the RBANS (Randolf, 1998). Norms have been provided for examinees based on education levels. At baseline the patient scored below the norm in all indexes for an individual with tertiary education, with her total score significantly below the norm (M=103.7). At 6 months and 9 months she continued to score below the norm, for a person with her educational level, on all indexes excluding language which improved to within normative limits (M=102.8). It is also interesting to note that at 9 months the patient's attention score decreased to below the baseline score. At 12 months the patient's overall performance was within normative limits (M=103.7), however, she scored below the norm in visuospatial/construction (M=103.3) and attention (M=103.8).

In terms of performance pattern for memory, the patient's immediate memory improved to within normative levels, however, delayed memory did not showcase marked improvement. Issues with delayed memory may impact all cognitive functions assessed by the RBANS (Beatty, Mold, & Gontkovsky, 2003). Overall, the patient's memory improvements were inconsistent and the memory score pattern appeared to affect delayed memory more than immediate memory.

The visuospatial/construction index involves the copying of a complex figure and assessing the orientation of lines. The language index involves the testing of naming and semantic fluency. The attention index contains the digit span sub-test and a written coding test. These tasks which involve greater motor skill (copying the complex figure), greater processing speed (semantic fluency) or both greater motor skill and greater processing speed (coding) were all impaired at baseline and only language showcased improvement at 12 months. In addition to this, low scores on visuospatial/construction tasks indicate difficulties with processing and may occur in patients with attention problems (Arnett, 2013).

4.6.2 Stroop Test

The patient's ST scores were compared to normative data presented by Golden and Freshwater (1998). Diminished performance on the ST has been documented in depressed patients (Moritz et al., 2002). At baseline the patient exhibited impaired performance on the ST with a colour-word score below the normative limit for a person of her age and education level (M=45) and an interference score that was below the norm. Low colour-word scores indicate problems with selective attention whereas low interference scores indicate issues with cognitive flexibility. At 6 months the patient's scores on both the colour-word and interference tasks improved to normative limits, however, both scores were very close to 40 which literature states may be a sign of prefrontal pathology or emotional turmoil. This suggests that the patient's performance resembled the profile of an individual experiencing depressive symptoms (Golden & Freshwater, 1998). At the 9 month interval the patient's scores decreased to below normative limits. At 12 months the patient showcased high scores when compared to the norm showing a greater ability to inhibit conflicting responses.

4.6.3 Delis-Kaplan Executive Function System-Trail Making Test

Results of the DKEFS-TMT were compared to normative data provided by Delis, Kaplan, & Kramer (2001). At baseline, the patient scored within the norm limits (M=10, SD=3) for both visual scanning and motor speed. However, she displayed marked impairment in her switching abilities (M=10, SD=3).

At 6 months the patient's scores improved to within normative limits with the patient's switching score showing the greatest improvement. At 9 months the patient's visual scanning score remained the same and her motor speed score increased, however, her switching score appeared to decrease to below normative levels. At 12 months all scores were within normative levels for all three conditions. However, at 12 months the patient's score on the switching condition remained the lowest score and visual scanning and motor speed remained constant with no improvement. Overall, the patient's visual scanning scores remained constant from 6 to 12 months, the patient's switching score appeared to fluctuate from 6 to 12 months and the patient's motor speed scores showcased improvement from 6 months to 12 months.

In terms of her contrast scores, at baseline the number-letter switching vs visual scanning was below normative limits (score=4). This was also the case with number-letter switching vs motor speed (score=4) at baseline. At 6 months her number-letter vs visual scanning score and number-letter vs motor speed score improved to within normative levels (M=10, SD=3) (scaled score=8 and scaled score=7 respectively). At 9 months the patient's number-letter switching vs visual scanning contrast score was below normative limits. However, the number-letter switching vs motor speed contrast score increased to within normative levels. This indicates that the patient may be exhibiting disproportionate impairment in cognitive flexibility relative to one of the four baseline component skills or the combined skills. At 12 months the patients number-letter switching vs visual scanning and number-letter switching vs motor-speed contrast scores increased further to within normative levels (scaled score=8).

On Condition 4 (Switching) at baseline and 6 months post-DBS, no set-loss errors were made. At 9 months one sequencing error and two set loss errors were made. At 12 months two sequencing errors were made. Sequencing errors indicate difficulty with divided attention and set loss errors indicate problems with shifting sets rather

than issues with maintaining sets. This may indicate difficulties with cognitive flexibility rather than sustaining focused attention. These results may link with the calculation of contrast scores which suggests that poor performance on core component skills required for Conditions 2 and 3 (Number sequencing and Letter sequencing respectively) cannot solely account for the impaired performance in executive functioning.

4.6.4 Controlled Oral Word Association Test

Based on the normative data provided by Strauss et al. (2006) the patient scored below the 20th percentile at baseline. When considering the patient's educational background, such as the fact that she obtained tertiary education, her verbal fluency score should have been in the above average range. Her baseline score thus resembles the profile of a person suffering from the detrimental cognitive effects of depression. At 6 and 9 months the patient's scores were in the 40th percentile indicating that performance was in the low average range. The patient's score at 12 months was in the average range indicating that improvement had occurred from baseline to 12 months.

Phonemic fluency is processed in the pre-frontal area, specifically the left inferior frontal gyrus (Hirshorn & Thompson-Schill, 2006). Frontal functioning is one area that has been shown to be negatively affected by depression (Lin et al, 2014; Snyder, 2013).

4.6.5 Tower of London

The patient's TOL scores were compared to normative data provided by (Culbertson & Zillmer, 2001). At baseline the patient's TOL Total Move standard score of 76 was classified as a borderline score for young adults of a comparable age which indicates deficiencies in executive planning, and issues with attentional allocation, response inhibition, working memory and cognitive flexibility. The patient's Total Correct standard score of 72 was also in the borderline range indicating impairment in working memory. According to Culbertson and Zillmer (2001) the inattentive adult is likely to earn a low Total Correct score. The Total Problem-Solving standard score was 82 was within the low average range for a person of that age indicating overall problems with executive planning in relation to problem-solving speed.

At 6 months the patient's TOL Total Move standard score increased substantially as her score of 76 at baseline improved to 106 which is in the average range for young adults of a comparable age. The patient's Total Correct standard score of 90 was also in the average range indicating improvement in working memory. The patient's performance on the Total Problem-Solving standard score was 110 indicating that she improved to a high average range for a person of that age

At the 9 month interval the patients Total Move score decreased to 100, and her Total Problem Solving score decreased to 102. Despite the fact that the scores remained in the average range, these scores are important as they are linked with score reduction that was witnessed on the other measures administered to the patient at 9 months. It is also important to note that the patient's Total Correct score (90), which was her lowest score at baseline (72), did not decrease at 9 months but remained the same.

The patient's scores at 12 months were placed within the average range for Total Move (108), Total Correct (102) and Total Problem-Solving (106) for a young adult of a comparable age. The Total Correct score increased noticeably at this time with a 12 point increase in her score.

4.7 Conclusion

All scores were tabulated for ease of reference and compared to normative data. The above analysis indicated that there were significant improvements from baseline to 12 months post-DBS in the cognitive domains being measured when compared to the normative data. In addition, the above analysis indicated that there were significant changes in mood symptoms from baseline to 12 months post-DBS based on the norms.

Chapter 5 elaborates on the results presented above in view of current neuropsychological knowledge and includes an interpretation and discussion of the patient's overall neuropsychological outcomes post-DBS.

Chapter 5

Discussion

The purpose of this study was to review the pre-and-post neuropsychological outcomes of the Deep Brain Stimulation (DBS) procedure for a patient with Treatment Resistant Depression (TRD). To the researcher's knowledge, this is the first case review in a South African context to document the neuropsychological outcomes of bed nucleus of the stria terminalis (BNST) DBS for TRD. This chapter will discuss the findings presented in the previous chapter in light of existing neuropsychological literature and will also elaborate on pertinent results for the purpose of theoretical discussion. This chapter will conclude with a brief overview of the limitations of this project, recommendations for future research, and a conclusion.

5.1 Main Findings

There are various somatic interventions that are currently being utilised to alleviate the symptoms of TRD such as electroconvulsive therapy (ECT) and vagus nerve stimulation (VNS). However, what these somatic interventions have in common is a concern that the techniques are associated with adverse cognitive effects (McNeely et al., 2008). Major Depressive Disorder (MDD) has been reported to be associated with cognitive impairment (Baune et al., 2010). Therefore, it is unsurprising that existing evidence argues that the population diagnosed with TRD already suffers from cognitive impairment (McNeely et al., 2008). This notion was corroborated in the current study as the patient's baseline performance on all cognitive measures, despite her education level, were classified as borderline and below average when compared to the available norms for an individual of her age.

The Diagnostic and Statistical Manual (5th ed.) lists poor concentration and difficulty with decision making as two cognitive symptoms experienced by individuals suffering from MDD (American Psychiatric Association, 2013). Literature regarding cognition in depressive disorders consistently implicate issues with attention, processing speed, executive functions and working memory (Doumas, Smolders, Brunfaut, Bouckaert, & Krampe, 2012; Elderkin et al., 2010; Marazziti, Consoli, Pichetti, Carlini, & Faravelli, 2010; Nakano et al., 2008; Rosenberg, Mielke, Xue, & Carlson, 2010; Weiland-Fiedler et al., 2004). Studies have also reported the negative effects of depression on verbal

fluency (Reischies & Neu, 2000) and visuospatial/construction abilities (Arnett, 2013). In this study the patient's attention, visuospatial/construction abilities and verbal fluency deficits were evident which corroborates the cognitive patterns of depressed patients that has been found in literature.

The current study found that DBS of the BNST for TRD was well-tolerated with no neuropsychological impairments observed when the patient's performance was compared to the appropriate age and education normative group. Deep Brain Stimulation (DBS) of the BNST did not exacerbate existing cognitive impairment nor introduce novel cognitive impairment to the patient. Unlike ablative techniques, DBS has the advantage of being adjustable, and therefore was less likely to cause the cognitive impairment that has been reported with other techniques. Moreover, it was found that baseline performance which was in the below average to clinically impaired range improved to the average or above average range at 12 months post-DBS. No consistent pattern of decline was observed on any cognitive measure post-surgery or after onset and maintenance of DBS which lends support for the cognitive safety of the DBS procedure. Cognitive domains that were negatively affected such as attention and visuospatial/construction abilities appeared to improve as time progressed. Despite attention and visuospatial/construction abilities remaining in the low average range, a clinical improvement from baseline was still evident.

5.2 Cognitive Improvement Hypotheses

At the 12 month period of ON stimulation, abnormal mood assessment scores and neuropsychological performance improved to normative levels. The first hypothesis put forward to explain this improvement in cognitive performance is the idea that depression-associated cognitive deficit might have been improved by DBS with the progressive reduction of depressive symptom severity (Aouizerate et al., 2004). This notion postulates that cognitive impairment is secondary to mood symptoms and therefore it suggests that if mood symptoms are alleviated then cognition will improve as a result.

The second hypothesis that has been argued is based on the notion that DBS stimulates pathological areas implicated in depression and therefore the regulation of the BNST was responsible for the improved cognitive performance and not the

reduction in depressive symptoms. Deep Brain Stimulation (DBS) may have enhanced cognitive processes via the "neural jamming effect" (Lozano et al., 2008), which argues that DBS may regulate and amend pathological activity in the neural circuit that is stimulated, by controlling spontaneous neural signalling of the altered processes found in depression. This effect could have altered transmission by means of neuron flood out which may "normalize" information flow through distal neural pathways (Mori et al., 2005).

Therefore, when considering the idea that DBS stimulation may affect distal regions to the stimulation site via white matter tracts (Johansen-Berg et al., 2008), and the postulation that anatomical links exist between the BNST and areas such as the NAcc (that have been shown to produce antidepressant effects when stimulated), it can be hypothesized that cognitive performance could have been enhanced by the indirect stimulation and regulation of additional areas. Thus, it can be suggested that the spread of current to these pathways may account for the mood and cognitive improvements noted post-DBS (Serra-Blasco et al., 2015).

Jimenez et al. (2005) argued that it is doubtful that improvement occurred due to spontaneous remission as this form of remission is unlikely to occur in TRD where the patient has suffered long-standing depression (Jimenez et al, 2005). Moreover, there was a return of depressive symptoms and cognitive impairment at 9 months that improved once electrical stimulation was adjusted which suggests that improvement occurred due to one of the above hypotheses and not due to spontaneous remission.

5.3 Bed nucleus of the Stria Terminalis as a Target Site

The bed nucleus of the stria terminalis (BNST) has been linked with stress and reward responses as well as modulating coping mechanisms during stressful situations. Excitatory as well as inhibitory limbic information is funnelled through the BNST. The BNST has been associated with longer-duration and sustained increases in anxiety-like behaviour. It is a major output pathway of the amygdala which includes the shell of the NAcc (Walker, Toufexis, & Davis, 2003).

The BNST is interconnected with various regions that are centrally involved in cognitive functioning (Crestani et al., 2013). The hippocampus is crucial for spatial

learning and declarative memory and attention, working memory and executive functions engage the prefrontal areas (Grubert et al., 2011). The combination of post-mortem and neuroimaging studies suggest that structural and functional deficits exist in subcortical regions such as the thalamus, amygdala, striatum, hypothalamus and brainstem during depression (Grubert et al., 2011). The BNST, with its projections to these areas, may serve as an optimal stimulation site when considering the notion that distal areas may be regulated through stimulation (Crestani et al., 2013). Millet et al. (2014) suggests that it might be relevant to stimulate the shell of the NAcc, as it is more closely related to the limbic system, in order to interact with neuroanatomical structures which are known to be involved in the pathophysiology of depression. The NAcc has been shown to be a promising stimulation site due to its effects on the reward and pleasure centre (Millet et al., 2014).

Therefore, the BNST may also be involved in the symptomatic expression of TRD. Whether its involvement is direct or indirect through its connection to the NAcc and the amygdala, stimulation to the BNST was associated with significant improvements in mood and cognitive functioning at 12 months post-DBS. Furthermore, the improvements that were found in various cognitive functions such as attention, memory and verbal fluency, which have different neuroanatomical structures and locations, bolsters current theories that suggest that specific sets of brain areas are transiently fused together as functional units in order to enable cognitive functioning (Hirsch, Moreno, & Kim, 2001 as cited in Grubert et al., 2011).

5.4 Stimulation Hypothesis

An anomaly was noted at 9 months where the patient's performance on all cognitive measures as well as mood assessments declined to average or below average performance. The alteration of stimulation parameters that was made at 7 months provides one hypothesis that can be considered to explain this decline. The pulse width was decreased to 180 milliseconds at the 7 month interval and was then increased to 210 milliseconds at the 9 month interval.

Ramasubbu et al. (2013) argued that stimulation utilising longer pulse widths was associated with short-term clinical improvement. Research indicates that shorter pulse width with higher amplitude stimulation (up to 9V) and longer pulse widths with lower amplitude may generate equivalent benefits. The decrease of pulse width at 7 months

to 180 milliseconds and subsequent increase of pulse width at 9 months to 210 milliseconds may account for the patient's increased depression and anxiety scores as well as decreased cognitive performance. Research shows that response to chronic stimulation is delayed yet progressive (Ramasubbu et al., 2013), therefore, when considering that DBS has a delayed response it is plausible that the decline in cognitive functioning and enhanced depressive symptoms could be a result of the altered stimulation parameters at 7 months.

Another noteworthy finding in the present study was the fact that the alteration in stimulation parameters at 7 months that is hypothesized to have caused a decline in other indexes, appears to have improved attention, visuospatial/construction and motor speed scores. Therefore, it can be hypothesized that shorter pulse widths with a higher frequency may promote adequate stimulation for the improvement of attention and visuospatial/construction abilities.

In addition to the encouraging cognitive improvements noted in the patient's assessment scores, the patient experienced sustained mood improvement from stimulation of the BNST. The effect of the treatment on the patient's clinical symptoms at 12 months was clinically significant. Stimulation of the BNST appears to have been involved in the decrease of anxiety and depressive symptoms experienced by the patient. At 9 months the patient appeared to experience increased depression and anxiety. Although a definitive link cannot be presented, this finding may lend support to the above-mentioned notion that poor neuropsychological outcomes are a result of the return of depressive symptoms. However, both suppositions are still plausible.

5.5 Medication Hypothesis

The patient was placed on Solian (50-100mg) for insomnia 7 months post-DBS. Solian contains amisulpride which is an atypical antipsychotic and is generally used to treat schizophrenia. Amisulpride affects dopamine which is known to be involved in regulating mood and behaviour. It works by blocking dopamine receptions and prevents excessive activity of dopamine in order to control illness. Solian is known to cause abnormal movements of the hands, legs, face, neck and tongue such as twitching and rigidity as well as sleepiness, restlessness and agitation (SANOFI, 2015). Another hypothesis to explain the decline in scores witnessed at 9 months is

the notion that cognitive decline could be attributed to the side effects of the medication administered to her at 7 months.

5.6 Cognitive Domains

Various cognitive domains were assessed in this study. Available research argues that cognitive deficits occur when more demanding tasks are administered such as measures of cognitive flexibility relative to less challenging assessments (Harvey et al., 2004). These deficits may resolve once a patient recovers from depression (Aouizerate et al., 2004). However, Serra-Blasco et al. (2015) argues that cognitive deficits link with the illness rather than the mood state and therefore improvements may be related directly to the treatment rather than mood improvements. In this study it is important to note that at the 9 month assessment interval, mood outcomes and cognitive performance appeared to decline simultaneously which may lend support to the argument that cognitive improvement is associated with an improvement in mood.

5.6.1 Attention

Depressive symptoms are associated with significant deficits in attention and executive functioning issues specifically and these problems may persist during remission or in the absence of depressive symptoms (Rock et al., 2013). At the 12 month interval the patient continued to showcase impairment in attention. A study conducted by Grubert et al. (2011) found similar results when assessing attention in ten patients suffering from TRD who were stimulated at the NAcc. Attention was measured using the d2 attention-burden test and it was found that performance improved over time but at the 12 month period performance remained below average compared to normative data.

Two hypotheses have been put forth regarding this finding:

Firstly, attention is a multi-modal concept that is linked with many facets. The information processing model states that attention is not a single entity but a concept that includes a variety of processes. Research has predominantly found four factors that explain 80% of the variance across a variety of assessments utilised to measure attention including: focused attention, encoding, shifting, and sustained attention (Levine et al., 2008). Attention is also argued to be a distinctive cognitive domain that

can be measured with neuropsychological assessments based on deductive theories (Levine et al., 2008).

Based on the notion that attention is a multi-faceted concept, it is argued that a single measure may not have been not sufficient to measure all aspects of attention and therefore a wider range of assessments should be utilised. The reported results may indicate that tests use a simple model of attention that does not differentiate between functions such as processing speed and the ability to select relevant stimuli and resist distraction (Egeland et al., 2003).

It is suggested that the measurement of attention in the current study may not have been adequate to capture all facets of attention that may have improved or declined. The conclusions reached regarding attention may be restricted due to the different nature of assessment measures or confounded by other cognitive processes required by each of the measures. The neuroanatomical substrates of attention and the definition of attention are poorly understood and therefore the measurement instruments utilised to assess attention require further investigation (Levine et al., 2008).

The second hypothesis that can be put forth is the notion that the decreased pulse width with unadjusted amplitude may have led to inadequate stimulation of the BNST resulting in the patient experiencing increased stress and anxiety symptoms. In addition to studies showcasing the effect of depressive symptoms on cognition (see 2.3.3), anxiety has been shown to affect attention and concentration among other cognitive domains to a large degree (Eysenck, Derakshan, Santos, & Calvo, 2007; Ashcraft & Moore, 2009). The attentional control theory suggests that anxiety decreases efficient functioning of the goal-directed attentional system (attention influenced by goals and knowledge) and increases the degree that processing is influenced by the stimulus-driven attentional system (attention to salient and conspicuous stimuli) (Eysenck et al., 2007).

Anxiety enhances the attention given to threat-related stimuli in addition to decreasing attentional control. Worrisome thoughts consume the limited amount of attentional resources that working memory possesses and therefore less attention can be given to tasks that are occurring concurrently. Inhibition and shifting are the two core

executive functions are responsible for the adverse effects of anxiety on processing efficiency. With that in mind anxiety may not impair the quality of assessment performance when compensatory strategies such as increased effort are utilised (Eysenck et al., 2007). Qualitative data about the patient's functioning can be gauged from the errors made on the TMT (Kortte, Horner, & Windham, 2002). Errors related to perseveration and errors of impulsivity are an indication of the patient's issues with cognitive flexibility and shifting from numbers to letters (Ruffolo, Guilmette, & Willis, 2000). Errors may also highlight compromised accuracy in the participants' haste to complete the test quickly as performance is scored on time to complete (Ruffolo et al., 2000). Set-loss errors on Condition 4 may highlight problems related to cognitive flexibility rather than sustaining focused attention.

The patient's performance on the DKEFS-TMT revealed that at 9 months, when she experienced a decrease in all her other scores, she began making errors which indicated issues with divided attention and shifting which could relate to issues with cognitive flexibility. The patient's performance pattern on the switching tasks such as the ST interference task, and the DKEFS-TMT switching condition, where examinees are expected to disengage their attention from salient stimuli, replicated the performance pattern on the RBANS attention index and may bolster the notion that the patient's anxiety was preventing her from ignoring salient stimuli. This suggests that the patient's attentional and executive processes were impaired and that it affected certain tasks that require these resources specifically. It is interesting to note that these issues occurred at 9 months after the reduction in pulse width was made at 7 months which bolsters the argument that a lower pulse width resulted in inadequate stimulation and may have caused the impairment in performance.

However, at the 12 month interval the patient's score on attention remained below baseline despite a decrease in her anxiety scores as well as increased pulse width which then lends additional support to the notion that the assessment utilised to measure attention may not have measured all aspects of attention that could have increased or decreased.

5.6.2 Memory

Studies have looked at the effects of somatic interventions on memory and have found that retrograde and anterograde memory deficits have been reported with ECT.

Retrograde amnesia has been shown to persist for up to 3 months in some cases (Moreines et al., 2011). Cognitive impairment's such as memory decline following somatic interventions is one of the primary concerns which eventually led to the investigation of DBS for psychiatric disorders (Blumberger & Mulsant, 2013; McNeely et al., 2008).

In the present study no declines in memory were found after onset and maintenance of DBS. The patient's immediate memory index on the RBANS which is used to assess verbal learning and short-term memory exhibited markedly improved performance. The patient's delayed memory which assesses visual memory through the recollection of a complex figure also improved, however, it did not improve as prominently as immediate memory. These findings lends support to the notion that DBS is a safer option due to the fact that it is adjustable, reversible and localized (Anderson et al., 2012).

Deep Brain Stimulation (DBS)-related enhancement of memory has been reported in a variety of studies (Suthana & Fried, 2014). Suthana and Fried (2014) analysed several studies which illustrated the potential of DBS to improve episodic learning and memory. Deep Brain Stimulation (DBS) of the medial temporal lobe (MTL) which includes the amygdala and other regions outside the MTL such as the anterior nucleus of the thalamus and hypothalamus that have efferent and afferent connections to the hippocampus have been shown to improve memory. Hamani et al. (2008) explored memory enhancement after DBS and found that DBS to the hypothalamus with higher stimulation parameters allowed for the production of more vivid autobiographical memories as well as the augmentation of verbal learning and memory. The BNST has projections to the amygdala, thalamus and hypothalamus and therefore the positive improvements in memory that were found in the present study lends support to the postulation that DBS improves memory (Crestani et al., 2013; Suthana & Fried, 2014).

5.6.3 Executive Functions

Executive function is a term given to a complex set of processes that have been generally defined as the inherent capability to react and adjust to novel situations (Lezak et al., 2004; Strauss et al., 2006). Executive functions are involved in planning and the allocation of attentional resources to allow for goal-directed behaviour to be initiated, continued and monitored effectively in order to achieve goals. According to

Lezak et al. (2004) it involves volition, planning, purposive action and effective performance. Executive dysfunction may manifest in assessment performance as impaired initiation, planning and organisation, impaired inhibition and shifting, poor working memory, cognitive inflexibility, perseveration, problems with generating and implementing strategies, issues with correcting errors and the utilisation of feedback as well as negligence (Strauss et al., 2006). This definition then suggests that executive functioning is an integral component of the assessments that were administered to the patient such as the ST where habitual responses needed to be suppressed in order to generate a correct response (Jahanshahi et al., 2000). The prefrontal lobes in systematic interaction with cortical and subcortical areas are centrally involved in executive functioning (Culbertson & Zillmer, 2001). Impaired executive functioning has been identified when other neuromodulatory techniques are utilised and MDD has been shown to be associated with poor executive functioning (Grubert et al., 2011).

Three functions support the overall executive functioning of an examinee: working memory, prospective memory, and interference control. Provisional memory involves the usage of retrospective information in order to formulate and structure goal-directed behaviour. The prospective function allows for the preparation and execution of goal-directed behaviour which is moderated by possible limitations or predicted contingencies. Goal-directed behaviour is protected by interference control (in the formation and implementation stages) from disruptions by intrusions (Strauss et al., 2006).

Working memory is understood as the limited capacity, situational-specific, future-focused and transient processing system that allows the individual to internalize, maintain, and manipulate mental representations in order to guide behaviour when external cues or aides are absent. The critical performance component of the TOL is spatial working memory. The TOL taps executive functions such as problem solving, response inhibition, schema's which are the internal mental representations needed to guide behaviour (working memory). Both spatial and object working memory processes are linked to the Total Correct Score (Culbertson & Zillmer, 2001).

The current study supports the argument that DBS is linked with improvement in executive functions. Grubert et al. (2011) found executive functions to improve from

below average to average after DBS. The psychological mechanisms underlying the ST include working memory, processing speed, semantic activation and the ability to strengthen one characteristic over another (Golden & Freshwater, 1998). The TOL recruits complex executive functions such as planning, working memory, attention allocation, response modulation and inhibition, self-monitoring and cognitive flexibility. Tower of London (TOL), ST and DKEFS performance are supported by frontal and frontal-striatal circuits. In this study the patient's ability to inhibit and switch responses in the ST and the DKEFS number-letter switching task showed a marked improvement from baseline to 12 months as her scores improved from a below average classification to an average classification. The patient's ability to plan, problem-solve and execute correctly showed clinically significant improvement post-DBS when compared to classifications provided by authors. Therefore, when compared to other brain stimulation treatments such as ECT which were found to be associated with executive functioning deterioration stimulation of the BNST not only resulted in no evidence of cognitive deterioration but even improvement in executive functioning.

Strauss et al. (2006) stated that the clinical, diagnostic and interpretive value of the results of a neuropsychological assessment is dependent upon the ability of the assessments being administered to reliably and validly assess the applicable domains. The executive function assessments are not without their criticisms. The ST is one of the most widely used assessments to examine attention and response inhibition, however, the interference task has only mildly acceptable reliability. In addition, the DKEFS is criticized for as not being a theoretically driven instrument which does not assess all aspects of executive functioning (Strauss et al., 2006).

Furthermore, the theoretical model underlying Golden's interference score used for adults has been questioned as it assumes that the brain adds word reading to the colour-naming process to produce the word on the colour-word card. This assumes that the time to read a colour-word item is an additive function of the time it takes to read a word and the time that it takes to name a colour. However, research into the stroop effect has stated that it is not about addition but rather about inhibition and suppression. Based on this it is suggested that the interference score reflects the time to suppress the reading of a word plus the time to name a colour (Strauss et al., 2006).

5.6.4 Verbal Fluency

In the current study verbal fluency was shown to improve from a below average range to an average range. In terms of gender, men tend to perform better on visuospatial/construction tasks and women tend to perform better in language and memory tasks (Beatty et al., 2003). An extensive literature review revealed that there is very little information available on verbal fluency in MDD.

Phonemic fluency involves both verbal ability and executive control. Individuals are required to retrieve words from their language which requires them to access their mental lexicon and they also need to focus on the task, select specific words and avoid repetition which involves executive control (Shao, Janse, Visser, & Meyer, 2014). Executive control involves the regulation of thoughts and direction of behaviour towards a goal. The three chief components are purported to be: updating, shifting and inhibition of dominant responses. Updating involves the continual monitoring and tracing of working memory representations and shifting involves the switching between tasks or mental sets. In the letter fluency task words are retrieved from a phonemic category, which is not usually done in everyday speech production and suppression of the semantically related words must occur thereby forcing individuals to resort to novel retrieval strategies. Issues with either verbal ability or executive control should manifest as poor verbal fluency (Shao et al., 2014). Therefore, an improvement in executive functioning would be linked with an improvement in verbal fluency (Lezak et al., 2004). In the current study the patient's executive functioning improved, as evidenced by her improved scores in the DKEFS-TMT, ST and TOL. Thus, it can be hypothesized that her improvement in verbal fluency may be related to her improvement in executive functioning. However, the current study does not have enough statistical evidence to definitively make this link.

5.6.5 Visuospatial/Construction

Evidence of the impact of depression on visuospatial/construction abilities has been inconsistent (Arnett, 2013). Wefel, Hoyt, and Massman (1999) found that depression had a negative impact on the Weschler block design subtest, whereas more recently Arnett (2013) found that depression did not have an impact on the block design subtest or clock drawing assessment. visuospatial/construction deficits may be a result of impaired executive functioning that is required for the logical and systematic approach

needed in order to complete the Figure copy task of the RBANS (Baune et al., 2010; Randolf, 1998).

The patient continued to display impairment in visuospatial/construction abilities despite an improvement in executive functioning. Therefore, it can be argued that the residual visuospatial/construction deficits may not be a result of impaired executive processes but of some other overlapping cognitive process. The hypotheses discussed above regarding the lack of improvement in attention may also apply to the finding that visuospatial/construction abilities remained impaired at the 12 month period. The delayed effect during the change in parameters could be the result of rearrangement in the regulatory process of different neurotransmitters induced by DBS.

5.7 Interpreting Cognitive Effects

It is important to bear in mind that individual neuroanatomy, fibre pathways, clinical factors and electrode placements may be associated with differences in cognitive performance experienced by the patient (Moreines et al., 2011). When interpreting the cognitive effects of DBS practice effects, and methodological variations amid studies must be considered.

Practice effects can be understood as improvements in assessment scores that can be attributed to earlier test exposure (Moreines et al., 2011). One strategy utilised to buffer practice effects is the use of alternate forms of a particular test, however, it has been found that this strategy does not completely remove the influence of these effects. In this study alternate forms of the RBANS were utilised in order to decrease practice effects. The Stroop Colour-Word test is an assessment where repeated exposure is expected to improve performance. Therefore, when interpreting such tests a lack of improvement may indicate cognitive impairment.

Significant methodological differences between studies may, in part, contribute to cognitive findings (Moreines et al., 2011). Variations in stimulation parameters and testing conditions, have important implications and should be controlled for when interpreting cognitive results and comparing such results to other studies. In addition, disparities in neuropsychological batteries being used may be a source of great variability in cognitive performance.

5.8 Limitations

The encouraging results of this novel study must be viewed in light of methodological limitations. The aim of this study is not to generalise any findings, but to gain a deeper understanding of DBS for TRD for a specific patient and to allow for potential prospective studies. Given that the study is a single case review, the generalizability of the findings is limited. A specific test battery was chosen in order to limit practice effects, however, some impact of repeated testing may have affected the results. In addition, statistical analysis were not conducted to determine the reliability of clinically significant changes. Furthermore, the results were obtained at various intervals in which the patient's performance could have been potentially mediated by external and contextual factors.

5.9 Recommendations for Future Research

The current results are promising. Aside from the decline in cognitive functioning at 9 months, there appears to be no sign of cognitive impairment due to DBS and chronic stimulation appears to be associated with improvement in cognitive functioning for this specific patient. Although the findings were limited to a certain extent, the results add credibility to the hypothesis that states that DBS has no adverse effects cognitive functionality in patients with TRD and therefore warrants further investigation in a South African context. Future studies with larger samples, healthy controls, double-blind on-off stimulation controls and utilising a broader range of neuropsychological assessments would be pertinent in confirming the above results and allowing results to be generalizable to the TRD population. Furthermore, utilising a larger sample may allow for correlations between cognitive performance and mood outcomes to be statistically analysed which may allow for more definitive answers to be provided regarding the cause of cognitive improvement. In addition to this, follow-up sessions could allow for blinded discontinuation studies in order to investigate if stimulation to this particular site resulted in long-term neuronal changes to see if a level of sustained improvement has been reached.

5.10 Conclusion

In conclusion, the aim of this descriptive study was to explore the pre-and-post neuropsychological outcomes of the DBS procedure for TRD. The study found that stimulation of the BNST did not lead to cognitive deterioration in the patient receiving

DBS for TRD. Furthermore, after the DBS procedure the patient's performance improved relative to available norms when various cognitive domains were assessed. This study contributes to the overall body of knowledge on DBS. The study also found that the BNST is a pioneering study that provides an in-depth look into the first known DBS procedure for TRD conducted in South Africa. It also provides a detailed review of a particular case. Treatment for TRD usually entails the use of medications with probable side-effects as well as long-term psychotherapy. Deep Brain Stimulation (DBS) may be especially suited to treat TRD when taking into account the severity and poor prognosis of the disorder.

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