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Long Term Antidepressant Effects of Deep Brain Stimulation for Treatment Resistant Depression – A Research Protocol

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Abstract

Introduction: Individuals with treatment resistant depression (TRD) are those with severe major depressive disorder who fail to respond to conventional pharmacological treatment. As a result, novel technologies in the field of neuromodulation have been investigated to alleviate depressive symptoms in this population. One such neuromodulation therapy is deep brain stimulation (DBS), in which electrodes are neurosurgically implanted into target regions of the brain associated with depression, such as the subgenual anterior cingulate cortex (sgACC). While previous studies have explored the use of DBS as a therapy for TRD, few studies with adequate statistical power have explored the sustained antidepressant effects of DBS when targeting the sgACC of the brain.

Methods: This study aims to explore the long-term effects in DBS patients for TRD by measuring changes in cerebral blood flow and cerebral metabolic rate in the sgACC, and its correlation to changes in self-reported depressive symptoms. Forty-five participants will be enlisted into this study. Psychometric evaluation and positron-emission topography imaging will be conducted prior to neurosurgery. Electrodes will be implanted into the sgACC, with extension wires attaching the electrodes to the internal pulse generator. In the six-week blinded phase, progressive increases in stimulation will be administered within the blinded group and sham stimulation in controls. The three-month open label phase will administer the same degree of high-frequency biphasic stimulation to the control and blinded groups and assess depression scores, neuroimaging, and adverse events. After cessation of active stimulation, a one-year, three-year, seven-year, and ten-year follow-up will monitor changes in antidepressant effects of DBS using simple linear contrasts and paired-sample t-tests.

Expected Results: This study expects to find a sustained antidepressant response marked by decreases in sgACC metabolism and cerebral blood flow, and a reduction in self-report depression scores.

Discussion: The use of DBS shows promise as a successful treatment intervention with sustained long-term effects for individuals with TRD. Additional secondary outcomes to be expected are improved quality of life and health behaviours.

Conclusion: Though minor fluctuations are expected due to the presence of comorbidities, this study expects to showcase the long-term efficacy of deep brain stimulation for treatment resistant depression.

Keywords: treatment-resistant depression; deep brain stimulation; neuromodulation; sham stimulation; longitudinal study; high-frequency stimulation

Introduction

Major depressive disorder (MDD) is a multifactorial psychiatric condition involved with significant functional impairment to psychosocial outcomes and quality of life (QoL). It is marked by its primary symptom of anhedonia (reduced hedonic capacity), however, the range of cognitive (impaired memory, slowed thinking and motor movements, difficulty concentrating, poor decision making or prioritization), mood (sadness, apathy, low self-esteem, diminished confidence, guilt or worthlessness, suicidal ideation), and physical symptoms (lethargy, decreased activity, difficulty sleeping or insomnia, fatigue, disrupted sleep patterns, agitation or restlessness, weight loss, anorexia, low libido) experienced within MDD can vary between individuals [1,2]. The average lifetime prevalence of MDD is 12% globally; this rate is doubled in women compared to men due to the differences in hormonal and childbirth effects, psychosocial stressors, and behavioural models of learned helplessness [3]. These poor outcomes are exacerbated with limited clinical resources, resulting in economic and social burdens. As a result, MDD acts as the global leading cause of disability and ranks third in the global burden of disease [4].

Extensive clinical research has been aimed to designing effective treatments for this condition [3]. Conventional methods of care for MDD involve pharmaceutical interventions and cognitive-behavioural therapy. Antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) are considered the first line of care when a patient is newly diagnosed with MDD [3]. However, up

to 30% of individuals fail to respond to these conventional treatment methods [5]. When this occurs, the individual's MDD diagnosis is referred to as treatment resistant depression (TRD).

TRD is a common phenomenon observed within individuals diagnosed with MDD in which standard-dose pharmaceutical care, psychiatric care, and other conventional forms of treatment illicit unsuccessful responses from the individuals [6]. Despite the lack of a standardized definition for TRD criteria within the medical community, it acts a major contributor to the global burden of disease for MDD. Its high burden is attributed to its rampant prevalence, early symptom onset — predominantly during late adolescents — inadequate or undertreatment, high exposure to hereditary and environmental stressors, with severe underdiagnoses and a lack of prioritisation of prevention strategies for relapse despite a high frequency [7]. Furthermore, in the United States alone, it was estimated in the year 2020 that TRD represented the total annual burden of medicated-treated MDD at 47.2% despite its unsuccessfulness, which contributes to the high burden of health care (56.6%; $25.8 billion USD), unemployment burden (47.7%; $8.7 billion USD), and productivity burden (32.2%; $9.3 billion USD). The extensive healthcare and economic costs of TRD reinforce the need for effective treatment measures that do not exacerbate burden of disease for these individuals, both financially and physiologically [8].

Neuromodulation is a novel therapeutic intervention being investigated for the use of treating TRD, in which individuals receive electrical stimulation to influence depolarization and hyperpolarization of neurons using low-electrical voltages on localized areas of the brain to overcome electrical imbalances of neurological activity [9]. While previous research has highlighted the success of neuromodulatory therapies in treating movement-based disorder (tremors, Parkinson's disease), little research has explored its usage in neurological disorders and specifically treatment-resistant psychiatric disorders. Different neuromodulation therapies include transcranial direct current stimulation (tDCS) which is a non-invasive technique typically used for schizophrenia, addiction, depression [10-12]; transcranial magnetic stimulation (TMS), a non-invasive technique for medication refractory depression, schizophrenia, stroke rehabilitation [13,14]; electroconvulsive therapy (ECT), a neurosurgical procedure that initiates a brief seizure using electrical currents through the brain, and typically used to treat conditions such as catatonia, agitation and aggression in dementia, schizophrenia, and epilepsy [15-18]; and deep brain stimulation (DBS).

Deep brain stimulation (DBS) is a neurosurgical procedure in which electrodes ("leads") are implanted into targeted brain regions which are stimulated using low-electrical voltages to manipulate neuronal activity. This procedure is reserved for treating a variety of neurological conditions such as Parkinson's disease and tremors, or treatment-resistant psychiatric disorders, such as obsessive-compulsive disorder (OCD) and major depressive disorder (MDD). Unlike other neuromodulation techniques, such as ECT, which has been associated with persistent memory and other cognitive deficits, adverse events in DBS have been demonstrated to be both rare and transient [19-21]. Luo and colleagues' investigation on the usage of DBS in resolving TRD through specific regional targeting in rat models is one example from the limited studies that explore the usage of DBS for TRD [22]. While studies involving DBS to human *in vitro* brain splices [23] and rodent pre-clinical studies have been extensively explored, in vivo human studies in the efficacy of utilizing DBS specifically in the treatment of TRD is lacking. The purpose of this research is to determine the potency of DBS in treating TRD in humans.

Previous neuropathological studies involving ^{18}F-fluorodeoxy-D-glucose Positron Emission Tomography (^{18}F-FDG PET) scans were used to determine the status of brain metabolism changes in neuropsychiatric conditions. In a study conducted by Bak and colleagues, ^{18}F-FDG PET (BiographmCT 128 scanner) was used 60 minutes after injecting patients with 185 mBq of ^{18}F-FDG intravenously [24]. Each scan was conducted from the vertex to the skull for 10 minutes, and imaging was reconstructed using iterative reconstructive algorithms with attenuated correction to visualize brain metabolism. The results of these scans indicated a decrease in dorsomedial prefrontal cortex (PFC) and dorsal-anterolateral PFC activity by assessing the cerebral metabolic rate (CMR) of glucose in depressive patients [24]. A particular region of interest was the posterior subgenual anterior cingulate cortex (sgACC) of the ventromedial PFC, typically referred to as Brodmann area 25. The sgACC is one of the most interconnected components of the amygdala-ACC network, with its primary role pertaining to regulating emotional arousal and autonomic states [25]. The executive functions of the sgACC area are considered top-down and often described as "hot" executive functions due to their pertinence towards emotional processing (fear, emotional regulation, gratification, reward and punishment) [26]. Previous studies investigating the role of the sgACC in mood disorders found the mean grey matter volume of this region was reduced and the cerebral metabolic rate was increased compared to neighbouring regions of the PFC [27,28]. This region also displayed the largest difference in cerebral blood flow. The difference observed was visualized using a 5 mm FWHM camera for magnitude of variance and displayed a decrease in normalized metabolism [24]. Associated depressive symptoms have been associated with the increased cerebral blood flow (CBF) of the sgACC, despite the overall hypometabolism of the neocortex. This increased CBF has been theorized to be the cause of the maladaptive emotional regulation seen in MDD and TRD, with traditionally successful antidepressant effects resulting in an increased CMR of the neocortex and decrease CBF of

the sgACC area [27,29]. Thus, targeting the sgACC area allows researchers to quantify the efficacy of DBS for treating TRD by measuring the changes in CBF within the sgACC and CMR of the neocortex.

Targeting subcortical white matter has been shown to produce better clinical outcomes within animal studies involving rodents and infralimbic (IL) cortex-targeted DBS. The IL cortex is considered homologous to the posterior sgACC in human brains both structurally and functionally [30]. The IL cortex has been seen to project to the same cortical and subcortical areas as the sgACC, relating to emotion, visceromotor control, and memory [31,32]. Therefore, the applicability of rodent-designed studies offers a promising recourse of utilizing the sgACC area to target TRD in human studies. Luo & Kiss's research in positron electrode neuromodulation in the IL white matter recorded rapid long-lasting effects resulting in plastic changes in the layer-5 pyramidal neurons [33]. If the findings of this research can be applied to the human homologue of the IL, this means DBS stimulation can result in potentially long-lasting antidepressant effects by inducing neuroplasticity in individuals with TRD. Human studies targeting the sgACC white matter should undergo neuroimaging prior to electrical stimulation and use 18-F-FDG PET scans to observe changes in CMR and CBF over the course of treatment.

Currently, there is a gap in longitudinal studies with adequate sample power to confidently draw associations between DBS treatment in effective long-term clinical outcomes in patients with TRD. Though previous studies exist that follow DBS patients naturalistically over the course of 3-9 years [34], these studies rather pertain to different targeted regions of the brain, such as the ventral anterior limb of internal capsule (vALIC), superolateral medial forebrain bundle (MFB), and the nucleus accumbens (nACC) [30,34,35], to smaller sample sizes, or to smaller follow-up times [36-38]. This study aims to bridge this gap by offering clinical evidence over a longitudinal period of time to measure the effectiveness of sgACC-targeted DBS treatment in relieving depressive symptoms and providing long-term antidepressant effects in individuals with TRD. This will be achieved through restimulation of sgACC neurons and subsequently normalizing abnormal CMR and CBF in depressive patients.

Primary Outcome

The primary outcome of this study is to observe a percentage change improvement in the Hamilton Depression Rating Scale (HDRS-17) compared to baseline results and increased CMR within the sgACC region. Baseline HDRS-17 is characterized by the screening score obtained 4 weeks prior to DBS surgery. CMR baseline refers to the mean CMR as visualized using 18-F-FDG-PET scanning 4 weeks prior to DBS surgery. Baseline HDRS-17 scores should be a minimum of 18 to meet the eligibility criteria.

Methods

Participants

Patients will be recruited through clinical referrals detailing previous TRD intervention attempts, patient registries, as well as through advertisements in relevant community message boards. Patients will be invited to the study if they meet the following inclusion criteria: exhibit a minimum of four symptoms of major depression according to the DSM-V, are currently experiencing a depressive episode for at least 12 months, have a maximum Global Assessment Functioning of 50, have an HDRS-17 score of at least 18, have undergone a minimum of four 4-week courses of pharmacological treatment with little-to-no improvement (exhibiting symptoms of moderate depression after treatment course), are capable of undergoing neurosurgical treatment involving general anesthesia, MRI, and PET scans, and are between the ages of 20-65 years. Although DBS surgery does not have an absolute age range, this demographic was selected as treatment efficacy was reported to be lower in patients above the age of 65 years old [39]. Patients below the age of 20, or who have experienced alleviation of depression symptoms with pharmacological intervention, have a history of angina, coronary vascular disease, hypertension, diabetes, and/or increased risk of perioperative complications will be excluded from the study. Signed informed consent will be obtained from each patient prior to data collection.

Sample Size

A double-blind, sham-controlled study of 45 patients with TRD will be included in the study and given DBS treatment to the white matter of the sgACC region of the cortex. This sample size was calculated using the standard deviation of sgACC CMR in patients with MDD (SD = 8.5) using previous experimental evidence within literature [40] and the calculated Z score with a significance level of a = 0.05. The effect size of this experiment was calculated as 0.588, thus the sample size for adequate study power requires a minimum of 45 participants.

Measures and Procedure

Recruited participants will undergo pre-operative screening by a trained research coordinator and a licensed psychiatrist for eligibility criteria (see Appendix 1.0). Informed consent will be obtained once participants have been deemed eligible for this experiment. The study will be divided into two phases: the blinded phase and the open label phase. The blinded phase will occur 8 weeks post-operation for a duration of 12 weeks, in which participants in the sham group will have their stimulators turned off (receiving no electrical transmissions) and participants in the case group will have their stimulators turned on (receiving electrical stimulation). Participants will be blinded to the status of their stimulators, as a means to ameliorate potential participant biases in DBS therapy

efficacy [31]. The distribution of the sham and case group will be randomized in a 1:1 ratio.

The open-label phase will occur for a duration of 8-weeks (week 12 to week 20, post-operative), in which DBS treatment will be administered to participants. Participants will visit the clinic to receive electrical stimulation. Short term immediate effects of the stimulation will be recorded quantitatively, using CMR levels, fMRI/PET brain activity measured with ^{18}F-FDG biomarkers, and changes in the psychiatric depression rating scale scores (see Appendix 1.0). Long-term observations will be collected at the end of the treatment course for comparison of data. Additionally, a one-year, three-year, and ten-year follow-up will be used to analyze the efficacy of DBS for long-term antidepressant clinical outcomes. To prevent participants from discovering blinding status through sensations associated with electrical stimulation, non-contact voltage testing should be used to administer the charges [41].

Psychometric Evaluation (Appendix 1.0)

A full diagnostic evaluation will be conducted with each patient with a licensed psychologist leading evaluation. Researchers will observe scores after all tests results have been collected to assess each patient's level of severity of depression, alongside note for any existing comorbidities to consider when analyzing the results of this study. The Minnesota Multiphasic Personality Inventory 2nd edition (MMPI-II) [42], Raskin Depression Rating Score (RDRS) [43], and Hamilton Depression Rating Scale (HDRS-17) [44] will be used for psychological evaluation. Patients with scores greater than 18 on the HDRS-17, greater than 8 on the RDRS, and a T-score greater than 70 on the depression (D-) category of the MMPI-II test will be included in the study. T-scores greater than 70 are considered statistically significant and therefore indicative of active depressive symptoms within participants [45].

Neuroimaging

Procedures relating to neurological imaging were designed in reference to previous similar studies [24,28]. Prior to DBS therapy, neurological imaging will be conducted for a post-assessment comparison of changes in CMR. An ^{18}F-FDG-PET scanner will be used to collect low resolution images (full width, half maximum 17mm imaging) in the region of interest, i.e., the sgACC of the prefrontal cortex. Prior to ^{18}F-FDG-PET scanning, patients will be required to fast for 6 hours. Blood glucose levels should be stabilized for 30 minutes at <150.0 mg/dl prior to injecting 185 mBQ of 18-F-FDG intravenously to allow for uptake into circulation. Scans will occur for 10 minutes from the vertex of the skull to the base. After all scans are completely, iterative reconstruction will allow for visualization of CMR in localized brain regions. CMR will be measured per voxel and calculated by dividing each voxel to the local variance. Pre-operative CMR mean scores will be recorded for statistical comparison post-operatively.

Neurosurgical Procedure

The neurosurgical procedures preceding DBS treatment will be divided into two stages: stage 1 will consist of mapping electrode trajectories and inserted, whereas stage 2 will implant the pulse generator and extension wires. These procedures are designed in reference to previous neurosurgical procedures of DBS [28,46]. Stage 1 of the neurosurgical DBS procedure involves implantation of the electrodes into the targeted sgACC region of the brain. Patients will undergo surgery whilst conscious and under general anesthesia. The procedure will begin by fixing a Leksell stereotactic to the patient's head to utilize in a frameless stereotactic neuronavigational system. Five bone marker screws, MRI, and CT scans will be used to map out the best electrode trajectory for stimulation to the sgACC [46].

Once the stereotactic has been established, the patient's head will be clipped in preparation for the surgery, disinfected with betadine solution, and placed in a semi-recumbent position. The target of DBS therapy is the sgACC, 7 cm right of the midline, 43 cm anterior to the anterior commissure, and 6 cm dorsal to the horizontal plane (7; 43; 6 stereotaxic spatial coordinates) [28]. Stereotaxic navigation and MRI imaging will be used to aid in insertion of the guide cannula 1.5 cm above the sgACC. Identification of the dorsal-ventral borders and the electrophysiological signature of the sgACC are collected from microelectrodes to determine an effective tract. Macroelectrodes are then permanently placed into the sgACC tract and clinical simulations are tested to determine side effects and efficacy. The fixing of the electrode is verified using an intraoperative fluoroscopy before closing the incision.

Stage 2 of the neurosurgical procedure occurs 10-14 days following Stage 1, in which the neurostimulator is implanted and connected to the target electrodes of the sgACC using extension wires. Patients will be under general anesthesia for this procedure. Distal ends of the sgACC electrodes will hook into subcutaneous extension wires travelling behind the ear towards the clavicle, where the secondary incision will be made. A subfascial pocket for the internal pulse generator will be implanted 3 cm below the clavicle and connected to the extension wires. Test clinical stimulations are conducted to determine proper conduction. Post-operatively, patients will be allowed discharge after two nights of inpatient surveillance. After 6-8 weeks, the patient can return to clinic and DBS therapy can initiate [46].

DBS Electrical Transmission

Further parameters of DBS have been informed based on findings from animal studies. Luo and Kiss's investigation on applying high frequency stimulation (HSF) to rats is of particular relevance to this present study, as it explores the difference in clinical outcomes when white matter is targeted over grey matter in the rat brain

homologue to the sgACC area [33]. Utilizing this study as a reference, as many other DBS studies have done with alternative animal study literature, can assist in the creation of target parameters for electrical transmission. Based on Kiss and Luo's study, high frequency stimulation (HFS= 130 Hz) has been seen to produce more effective results in the sgACC region. There have been no observed differences in delivering stimulation unilaterally on the left-side of the brain compared to bilaterally. However, targets to white matter have been reported as more clinically effective at treating depression in rats than targeting grey matter [33].

With this knowledge, this study will target subcortical white matter in stimulation trains of 10/30/60 seconds at a frequency of 130 Hz and 0.1 µs PW square-wave biphasic pulses to achieve the best clinical outcomes whilst minimizing the risk of electric-induced damage to the neural tissue. The charge-balanced HSF biphasic pulses should be orthodromic to prevent induction of spreading depolarization in the neural tissue. Continuous monophasic pulse sequences will not be applied in this study due to their increased risk of irreversible reactions or tissue damage reported in previous literature [47].

Expected Results

Statistical Analysis

Paired-sample t-tests will be used to compare scores on the HDRS-17, RDRS, and MMPI-II scores obtained from baseline to corresponding scores at the 8-week, 12-week, 20-week, and 1-year follow-up. Simple linear contrasts will be used during the longitudinal phase of this study to assess changes in the antidepressant effects during the one-year, three-year, seven-year, and ten-year follow-up. CBF changes observed in ^{18}F-FDG-PET scans will also be compared with paired-sample t-tests. All data will be presented as mean ± SD. Normality will be tested using a Shapiro-Wilk test prior to data analysis. A 95% confidence interval will be reported. Non-parametric data will be analyzed using Wilcoxon Signed-Rank and Kruskal Wallis tests. Statistical significance will be considered at $p < 0.05$. All analyses will be conducted using IBM SPSS software.

Administration of Stimulation Parameters

After a full recovery is made from postoperative patients, patients will undergo the blinded phase of the study, in which the blinded group will be administered progressive increases in voltage between 0.0-9.0 Volts, 10-130 Hz biweekly. By this design, the blinded group will experience 120 Hz and 6.0 Volts by week 12 of the study, when the open-label phase begins. From here, both groups will be administered equivalent dosage of treatment (10/30/60 seconds, 130 Hz, 0.1 µs PW square-wave biphasic pulses) and act as their own controls. Researchers will be comparing HDRS-17, RDRS, and MMPI-II scores at week 8 (postoperative), week 12 (end of blinded phase), week 20 (end of open-label phase), and one-year postoperative. Additionally, each assessment will measure changes in the CBF of the sgACC area using ^{18}F-FDG/PET scanning. Both psychiatric scores and neuroimaging results should continue to be followed-up at the three-, five-, eight-, and ten-year mark, as to assess the long-term efficacy of DBS in TRD.

Adverse Events

Several studies reported a commonality of adverse events that occurred during the course of the study, some of which were a direct consequence of DBS, whilst others did not have any evidence of causation. Common adverse events included hospitalization due to a variety of medical reasons (e.g., psychiatric worsening, suicidal ideation, homolytic uremic syndrome, pancreatitis, colon cancer), hardware infections due to technical complications, seizures, lead problems, and mortality [48-52]. Kennedy et al.'s study reported two patients who were hospitalized due relapse and worsening of depressive symptoms (including suicide ideation) following DBS cessation but were not directly attributed to end of treatment [50]. The frequency of TRD and comorbidities added to the higher rates of adverse events, with most hospitalizations and mortalities reported occurring due to non-psychiatric related conditions, such as a knee-replacement surgery, homolytic uremic syndrome, and colon cancer – and not due to DBS itself. None of these adverse events had evidence of relation to DBS malfunctioning, hardware concerns, or other stimulation related causes. Though previous studies have drawn associations between suicidality and DBS [50], they have been exclusively observed in patients with Parkinson's disease and therefore do not represent the same stimulated brain regions as DBS for TRD. Nevertheless, suicidal ideation is an important factor to consider when assessing the high mortality risk associated with DBS interventions.

Lozano et al.'s [49] study showcased similar occurrences of adverse events as Kennedy et al. [50], with the addition of worsened mood and irritability, headaches or pain at the site of the pulse generator postoperatively, perioperative seizures, and wound infections. Seven of the twenty patients did not experience any adverse effects, and there were no reported cases of hypomania in any of these patients.

Overall, the occurrence of adverse events caused by DBS are predominantly associated with neurosurgical complications and risks, or consequences of comorbidities. There were no significant reporting of DBS directly causing any serious adverse effects in patients.

Discussion

This study is designed to assess the long-term implications and efficacy in DBS for TRD. Previous studies with similar designs rather had smaller sample sizes, thus lacking statistical power, or limited patient follow-ups to 12 months post-final administration of DBS [38,49,53]. In continuing patient follow-up years after DBS cessation, this

study aims to answer how DBS specifically holds permanence in beneficial antidepressant treatment and observe the occurrence of subsequent adverse events as a result of DBS treatment. Furthermore, the results of this study allow researchers and practitioners to determine the long-term efficacy and safety of DBS prior to offering it as a reliable therapy for a larger population demographic. In establishing this study in a larger sample, this study will be able to observe a diverse range of individuals and examine different clinical manifestations of DBS treatment in individuals.

Previous studies utilizing DBS with less statistical power were used to inform potential expected results from DBS treatment. High frequency stimulation of the sgACC area using DBS is believed to decrease HDRS-17, RDRS, and MMPII scores to reflect a positive therapeutic effect in TRD patients. Additionally, elevations in CBF and CMR activity within individuals with TRD are believed to decrease towards normal levels within the sgACC and surrounding areas. In decreasing CBF in the sgACC, DBS is predicted to successfully restabilize hyperactive metabolic activity within the region, contributing to the mood irregularities within TRD and other mood disorders.

In a clinical study by Mayberg and colleagues [53], six patients of both unipolar and bipolar TRD were administered double-blinded active stimulation or sham stimulation. Sham stimulation used 0 Volts or subthreshold stimulation which did not elicit behavioural changes. When randomized acute trials of electrical stimulation was administered to patients (1-5 minutes), consistent behavioural improvements were reported compared to depressive baselines. Notably, longer durations and stimulation (1-3 hours of active stimulation) marked lingering beneficial behaviours (e.g., increased motor speed, volume, prosody and changes in positive and negative affect rating scores) after the cessation of stimulation. No adverse effects were observed with these longer stimulations [53].

Meanwhile, Zhang et al. [54] discovered a 49% reduction in depression and anxiety symptoms alongside significant improvements in health status, functional impairment, and QoL. These improvements were maintained throughout the duration of the 12-month study [54]. Additionally, improvements in the secondary outcomes associated with severe MDD symptoms, such as impaired sleep quality (42% improvement) [55], poor QoL [4], and poor general health (75% improvement) were observed, predominantly within the first month [54].

Mayberg et al. [53] also showcased a >50% decrease in HDRS-17 score 1-week post-treatment. After two weeks, this decreased HDRS-17 score was mostly sustained, though there were increases in HDRS-17 scores from initial success, in all but two participants [53]. This substantial increase can be ascribed to the cessation of stimulation at the two-week period, in which additional studies where DBS targeted various different brain regions and white matter pathways (vALIC, MFB, nACC) have also reported the possibility of relapse in patients [9,30,35]. By the six-month follow-up, all patients experienced decreases in HDRS-17 scores, with only one patient experiencing minor reductions (<50%) [53]. Of these 5 patients, 2 experienced clinical remission (absolute HDRS score of <8) [53].

Furthermore, changes in the sgACC were observed using PET scans that were realigned and spatially normalized into three-dimensional space respective to the anterior commissure. At baseline, regional CBF in the sgACC was reported at an elevated level in the five TRD patients relative to baseline controls. Decreases in CBF were observed between the third and sixth month. Additionally, CBF was seen to increase in the prefrontal cortex (BA9/46), premotor (BA6), dorsal anterior cingulate (BA24), and anterior insula blood. Bilateral reduction within these regions have been associated with depressive symptoms, thus increased CBF within these regions displays promise of the anti-depressive effectiveness of DBS-centered interventions for TRD [48,56,57]. Lozano et al. further verifies these results using ^{18}F-FDG-PET imaging to measure changes in CBF and CBR in the sgACC [49]. Decreases in metabolic activity in the orbital (BA11), medial frontal cortex (BA10/9/8), and insula were reported, alongside increases in the lateral prefrontal cortex (BA11/47), parietal (BA40) anterior midcingulate (BA24), and posterior cingulate (BA23). Reductions in CBF of the sgACC were especially apparent at 6 months, in which both white matter and the adjacent caudal subcallosal grey matter was also seen to decrease in CMR [58].

Mayberg et al. showcases the efficacy of sustained decreases in HDRS reduction through sgACC DBS [53]. The fluctuations in HDRS scores invites questioning of potential cofactors, such as comorbidities, that may have impacted patient outcomes. Interestingly, two of the patients whom initially experienced large increases in HDRS scores with the cessation of all electrical stimuli in DBS, actually achieved two of the lowest HDRS scores (HDRS-17, 6-month: $n_3 = 9$; $n_5 = 6$), with patient five achieving clinical remission [53]. This longitudinal outcome may act as evidence to showcase fluctuations in patient scores are acute in the adjustment period towards achieving patient remission. These results offer promise of accomplishing clinical outcomes in patients who initially do not respond effectively to sgACC-DBS.

In the present study, changes in CBF over the duration of sgACC-DBS therapy will be analyzed relative to baseline, in which elevated levels of sgACC blood flow and bilateral decreases in the BA9/46, BA6, BA24, and anterior insula blood flow levels are expected to be observed. This would be consistent to previous studies measuring CBF in depressed patients' pre-treatment [48,56,57]. The decrease in sgACC blood flow after 3-months of DBS correlates with the reduced HDRS-17 scores, drawing associations between elevated CBF and depressive symptoms within patients; the continued reduction of sgACC blood flow in

this area thus acts as a reliable predictor of DBS efficacy in achieving desired patient outcomes. This effect also compares to successful outcomes in conventional pharmaceutical therapeutic approaches, in which reduced CBF to the sgACC and increased CMR to the BA9/46, BA6, BA24, and anterior insula also promoted effective patient results and sustained antidepressant outcomes [59]. However, unlike antidepressants, patients of DBS therapy sustained these CBF and CMR changes 6-months postop, when active stimulation to the targeted area had ceased [48]. These results indicate the neurobiological basis for DBS efficacy. If this present study succeeds in replicating these results with a larger sample power and longer longitudinal follow-ups, DBS may pose as an effective and permanent treatment to depression.

Secondary outcomes observed in previous studies are indicative of potential consequences of the alteration of hyperactive sgACC activity. The results of these studies include an improvement of patient QoL, health behaviours, and sleep disturbances. These results are relevant due to the association between depression and these secondary factors. Poor QoL is defined as an individual's self-perception of their positionality in their own life, society, and value systems in association with their standards and objectives. In depression, poor QoL is marked by a reduced satisfaction in life, poor living environment, comorbidities [58], and various lacking factors in the social determinants of health [60]. A naturalistic prospective study on the QoL in DBS for depression showcased long-term efficacy of sgACC-targeted DBS [34]. This study naturalistically followed patients who had received DBS for TRD over the course of 6-9 years. The results indicated that positive outcomes for QoL improved up until the 7.5-year mark, in which reduction had begun to manifest. This observation further validates the conclusions of Kennedy et al. [50] and Raymaeker et al. [61], who also discovered significant and prolonged improvements in QoL. All three studies notably remarked the raised satisfaction and daily functioning of TRD patients during the follow-up period.

Health behavioural improvement were also observed in Zhang et al.'s study [54]. Health behaviours consist of intentional or unintentional actions, daily routines and behaviours that impact and individual's health outcomes, morbidities, and mortalities [62]. Examples of these behaviours particularly pertaining to depression include substance use, diet, physical activity, and sleep disturbances [55,63-65]. Thus, the results discovered in Zhang et al.'s study are reflective of substantial improvements in depression for TRD patients, further validating the efficacy of sgACC-DBS as a therapeutic treatment [54]. Improved general health status, predominantly in the first month (75% improvement) with sustained progression (91% at 12-month follow-up) has also reflected successful antidepressant secondary outcomes [54]. However, in regard to measuring dietary improvements towards positive health outcomes in DBS treatment for TRD, no such associations have been drawn in past studies. Additionally, previous literature observing secondary outcomes in DBS treatment have not specifically observed the correlation between sgACC-DBS in treating TRD and changes in substance use dependency. Future studies designed to discover associations between TRD behavioural outcomes and substance use changes would be a beneficial exploration to solidify the impacts of neuronal dysfunction and increased risk of substance use dependency.

This proposed study has various strengths. Foremost, its recruitment of a wide and diverse demographic increases the generalizability of the results, allowing a multitude of populations to be represented within the data. Diversifying the sample also allows for the detection of several cofactors that require investigation or highlight complications in future DBS studies. This allows for modifications to be made that improve the overall design of DBS treatment, increase safety and efficacy, and increase specificity of the targeted nuclei and subsequent outcomes. Moreover, the use of the HDRS-17, RDRS, and MMPII-II offers a valid and scientifically credible source of psychiatric screening conducted by a licensed psychiatrist. These diagnostic tools act as the gold-standard for depression screening, which ensures the inclusion criteria is met with a high degree of accuracy. Additionally, the use of all three diagnostic tools takes an extensive approach to examining changes in depression scale scores, where previous studies typically utilize HDRS-17 scores in isolation. This study also seeks to fulfill a gap within neuromodulation studies for DBS, which lack the dearth and power required to assess the sustained efficacy of DBS treatment for TRD. All previous studies measuring long-term outcomes in DBS rather lacked significant statistical power due to small sample sizes, did not target the sgACC area, or did not measure for the treatment of TRD. The result of this study incorporates all three missing factors to account for long-term efficacy and safety.

However, this study does contain some limitations that should be considered in conduction and analysis. Though the efficacy of DBS offers promise in justifying this limitation, the invasiveness of the procedure still acts as a deterrent and the primary risk in developing complications during treatment. All adverse events but one linked to the DBS treatment in previous studies were linked to neurosurgical complications, infections on electrodes or internal pulse generators, or malfunctioning material requiring re-surgery [49]. Though the number of studies reporting this adverse event are scarce, there have been observations of memory loss from DBS [66], a consequence of ECT that this present study aims to avoid in using DBS. Furthermore, conducting the double-blind design of this study may prove difficult, as neurosurgical procedures are often too invasive to ethically administer sham stimulation for a long duration of the study. Thus, placebo effects and control observations are limited to a small duration of this longitudinal study.

Future Prospects

Future initiative in the field of neuromodulation for TRD should focus on longer follow-up periods, extending up to 10 years, to verify the results of this present study in the efficacy and sustained antidepressant impacts of sgACC-DBS. These studies should screen for the development of adverse events relating to DBS, rather directly (malfunctioning equipment, sgACC neural stimulation causing spreading depression, infections, seizures, psychiatric worsening) [47,49] or indirectly (worsening of comorbidities that impact individual morbidity and mortality, unsuccessful treatment prompting suicidal ideation) [50]. In assessing longitudinal adverse events, researchers and practitioners will gain a better understanding on the ethical consequences of DBS, and whether these risks outweigh the significant benefit of long-term antidepressant treatment.

Longitudinal studies should also explore the underlying mechanisms behind the success of DBS. While a basic understanding of how neuromodulation produces effective neural activity regulation, animal studies have recently begun investigating the role of neuroplasticity through neuromodulation, and how its mechanisms are foundational to neuromodulatory therapy [67,68].

Neuroplasticity is defined as the brain's susceptibility to physiological changes through experience, in which new networks will form or old networks will reform based on an individual's lifetime exposures [68]. The hippocampal and dentate gyrus regions of the brain are known to be highly neuroplastic, which is in congruence to their function of memory encoding and consolidation [68]. Studies involving neuromodulation to assess neuroplasticity have been conducted, such as Falowski and associates' study on the effects of DBS on the neuroplasticity of the nACC within rats [69]. Longitudinal studies involving could further explore how neuroplasticity is sustained with DBS cessation over the course of time. Furthermore, understanding the physiological and morphological mechanisms behind DBS's success can help researchers understand the biological basis of why neuromodulatory therapy fails to illicit beneficial responses in some individuals.

Although DBS is an effective treatment, the necessity of neurosurgery makes it an invasive therapy that reduces accessibility and increases the frequency of adverse events. As the field of neuromodulation continues to be explored and generalized, establishing safer protocols that minimizes the level of invasiveness, complications, and risk of adverse events should be the foremost priority of all future studies.

Conclusions

The use of sgACC-DBS offers a potential long-term treatment for TRD with minimal and rare adverse effects. Compared to other forms of neuromodulation, DBS offers the safest, most effective therapeutic approach to individuals that are nonresponsive to pharmacological treatments. Furthermore, sgACC DBS studies for TRD has observed significant clinical findings in the link between neurostimulation and neuroplasticity of the brain. This stimulation-induced neuroplasticity offers insights into the mechanism of action for electro-neurological changes in targeted brain regions and overall functionality of the brain. In examining stimulation-induced neuroplastic effects, researchers can begin establishing networks that collaborate into manifesting depressive symptoms in people with TRD to further understand why the pharmaceutical mechanisms fail to elicit successful responses in these individuals. In establishing a foundational connection between successful DBS and neuroplastic effects in targeted regions, researchers can observe potential hereditary indicators or biomarkers that can predict the efficacy of certain treatments of people with MDD to minimize the adverse effects of therapeutics, maximize the antidepressant efficacy, duration, and overall QoL of these individuals. Overall, the connection between DBS and neuroplasticity opens a novel field of exploration in how the effects of electrical stimulation impact neurogenesis within the brain.

List of Abbreviations Used

BA6: premotor cortex
BA9/46: prefrontal cortex
BA10/9/8: medial frontal cortex
BA11: orbital cortex
BA11/47: lateral prefrontal cortex
BA23: posterior cingulate
BA24: dorsal anterior cingulate
BA40: parietal cortex
CBF: cerebral blood flow
CMR: cerebral metabolic rate
DBS: deep brain stimulation
^{18}F-FDG: 18-fluorodeoxyglucose
fMRI: functional magnetic resonance imaging
FWHM: far width high magnitude
HDRS-17, HDRS: Hamilton Depression Rating Scale
HSF: high frequency stimulation
Hz: hertz
IF cortex: infralimbic cortex
MDD: major depressive disorder
MFB: superolateral medial forebrain bundle
MMPI-II: Minnesota multiphasic personality inventory
nACC: nucleus accumbens
PET: positronemission topography
PFC: prefrontal cortex
PW: pulse-width
QoL: quality of life
RDRS: Raskin depression score
sgACC: subgenual anterior cingulate cortex
TRD: treatment resistant depression
vALIC: ventral anterial limb of internal capsule
WHOQOL-BREF: World Health Organization Quality of Life

Conflicts of Interest
The author declares that they have no conflict of interests.

Ethics Approval and/or Participant Consent
No consent or ethics approval was required for this protocol. When undergoing the study, participants will be screened for their adherence to the inclusion criteria. All study objectives, protocols, experimental procedures, and potential risks and adverse events will be overviewed with each participant prior to beginning any experimental procedures. Participants will be informed of their ability to withdraw from the study at any given time without any repercussions. Signed written consent will be obtained from each participant.

Authors' Contributions
GKM: made substantial contributions to the design of the study, the literature search of data as well as interpretation and analysis of predicted results, drafted the manuscript, revised the manuscript critically, and gave final approval of the version to be published.

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References
[1] Pizzagalli DA, Iosifescu D, Hallet LA, Ratner KG, Fava M. Reduced hedonic capacity in major depressive disorder: Evidence from a probabilistic reward task. Journal of Psychiatric Research. 2008; 43(1):76-87. https://doi.org/10.1016/j.jpsychires.2008.03.001
[2] Christensen MC, Wong CMJ, Baune BT. Symptoms of major depressive disorder and their impact on psychosocial functioning in the different phases of the disease: Do the perspectives of patients and healthcare providers differ? Frontiers in Psychiatry. 2020 Apr 24;11. https://doi.org/10.3389/fpsyt.2020.00280
[3] Bains N, Abdijadid S. Major depressive disorder [Internet]. StatPearls Publishing; 2023 [cited 2023 Jul 20]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK559078/
[4] Cho Y, Lee JK, Kim DH, Park JH, Choi M, Kim HJ, et al. Factors associated with quality of life in patients with depression: A nationwide population-based study. PLoS One. 2019;14(7):e0219455. http://dx.doi.org/10.1371/journal.pone.0219455
[5] Rabin JS, Davidson B, Giacobbe P, Hamani C, Cohn M, Illes J, et al. Neuromodulation for major depressive disorder: Innovative measures to capture efficacy and outcomes. Lancet Psychiatry. 2020;7(12):1075–80. http://dx.doi.org/10.1016/s2215-0366(20)30187-5
[6] Souery D, Papakostas GI, Trivedi MH. Treatment-resistant depression [Internet]. Journal of Clinical Psychiatry. 2006 Jan 1;67:16. Available from: https://www.psychiatrist.com/read-pdf/21622/
[7] Greden JF. The burden of disease for treatment-resistant depression [Internet]. Journal of Clinical Psychiatry [cited 2023 Jul 20]. 2001 Jan 1;62:26-31. Available from: https://www.psychiatrist.com/wp-content/uploads/2021/02/11361_burden-disease-treatment-resistant-depression.pdf
[8] Zhdanava M, Pilon D, Ghelerter I, Chow W, Joshi K, Lefebvre P, et al. The prevalence and national burden of treatment-resistant depression and major depressive disorder in the United States. The Journal of Clinical Psychiatrist. 2021 Mar 16; 82(2):20m13699. https://doi.org/10.4088/JCP.20m13699
[9] Johnson MD, Lim HH, Netoff TI, Connolly AT, Johnson N, Roy A, et al. Neuromodulation for brain disorders: Challenges and opportunities. IEEE Transactions on Biomedical Engineering. 2013; 60(3): 610–24. https://doi.org/10.1109/TBME.2013.2244890
[10] Agarwal SM, Shivakumar V, Bose A, Subramaniam A, Nawani H, Chhabra H, et al. Transcranial direct current stimulation in schizophrenia. Clinical Psychopharmacology and Neuroscience. 2013; 11(3):118–25. https://doi.org/10.9758/cpn.2013.11.3.118
[11] Yokoi Y, Narita Z, Sumiyoshi T. Transcranial direct current stimulation in depression and psychosis: A systematic review. Clinical EEG and Neuroscience. 2017;49(2):93–102. https://doi.org/10.1177/1550059417732247
[12] Lapenta OM, Marques LM, Rego GG, Comfort WE, Boggio PS. tDCS in addiction and impulse control disorders. The Journal of ECT. 2018;34(3):182–92. https://doi.org/10.1097/yct.0000000000000541
[13] Figiel GS, Epstein C, McDonald WM, Amazon-Leece J, Figiel L, Saldivia A, et al. The use of rapid-rate transcranial magnetic stimulation (rTMS) in refractory depressed patients. The Journal of Neuropsychiatry and Clinical Neurosciences. 1998;10(1):20–5. https://doi.org/10.1176/jnp.10.1.20
[14] Hoyer EH, Celnik PA. Understanding and enhancing motor recovery after stroke using transcranial magnetic stimulation. Restorative Neurology and Neuroscience. 2011;29(6):395–409. https://doi.org/10.3233/rnn-2011-0611
[15] Lloyd JR, Silverman ER, Kugler JL, Cooper JJ. Electroconvulsive therapy for patients with catatonia: Current perspectives. Neuropsychiatr Dis Treat. 2020;16:2191–208. http://dx.doi.org/10.2147/ndt.s231573

[16] Van Den Berg JF, Kruithof HC, Kok RM, Verwijk E, Spaans H-P. Electroconvulsive therapy for agitation and aggression in dementia: A systematic review. The American Journal of Geriatric Psychiatry. 2018;26(4):419–34. https://doi.org/10.1016/j.jagp.2017.09.023

[17] Grover S, Sahoo S, Rabha A, Koirala R. ECT in schizophrenia: A review of the evidence. Acta Neuropsychiatrica. 2018;31(03):115–27. https://doi.org/10.1017/neu.2018.32

[18] Lunde ME, Lee EK, Rasmussen KG. Electroconvulsive therapy in patients with epilepsy. Epilepsy & Behavior. 2006;9(2):355–9. https://doi.org/10.1016/j.yebeh.2006.06.013

[19] Bailine SH, Rifkin A, Kayne E, Selzer JA, Vital-Herne J, Blieka M, et al. Comparison of bifrontal and bitemportal ECT for major depression. The American Journal of Psychiatry. 2000;157(1):121-3. https://doi.org/10.1176/ajp.157.1.121

[20] Lisanby SH, Maddox JH, Prudic J, Devanand DP, Sackeim HA. The effects of electroconvulsive therapy on memory of autobiographical and public events. Archives of General Psychiatry. 2000; 57(6): 581–90. https://doi.org/10.1001/archpsyc.57.6.581

[21] Hitti FL, Yang AI, Cristancho MA, Baltuch GH. Deep brain stimulation is effective for treatment-resistant depression: A meta-analysis and meta-regression. Journal of Clinical Medicine. 2020; 9(9):2796. https://doi.org/10.3390/jcm9092796

[22] Luo F, Kiss ZH. Cholinergics contribute to the cellular mechanisms of deep brain stimulation applied in rat infralimbic cortex but not white matter. European Neuropsychopharmacology. 2021; 45:52–8. https://doi.org/10.1016/j.euroneuro.2021.02.019

[23] Anderson T, Hu B, Pittman Q, Kiss ZH. Mechanisms of deep brain stimulation: An intracellular study in rat thalamus. The Journal of Physiology. 2004; 559(1):301–13. https://doi.org/10.1113/jphysiol.2004.064998

[24] Bak J, Lee SM, Kwon YJ, Shim SH, Kim JI. The normalization of brain ^{18}F-fluorodeoxy-D-glucose positron emission tomography hypometabolism following electroconvulsive therapy in a 55-year-old woman with treatment-resistant late onset depression: A case report. Clinical Psychopharmacology and Neuroscience. 2017; 15(1):82–6. https://doi.org/10.9758/cpn.2017.15.1.82

[25] Kelly EA, Thomas VK, Indraghanty A, Fudge JL. Perigenual and subgenual anterior cingulate afferents converge on common pyramidal cells in amygdala subregions of the macaque. The Journal of Neuroscience. 2021;41(47):9742–55. https://doi.org/10.1523/jneurosci.1056-21.2021

[26] Salehinejad MA, Ghanavati E, Rashid MH, Nitsche MA. Hot and cold executive functions in the brain: A prefrontal-cingular network. Brain and Neuroscience Advances. 2021;5. https://doi.org/10.1177/23982128211007769

[27] Talbot P, Cooper S. Anterior cingulate and subgenual prefrontal blood flow changes following tryptophan depletion in healthy males from neuropsychopharmacology. 2006; 31:1757–67. https://doi.org/10.1038/sj.npp.1301022

[28] Drevets WC, Savitz J, Trimble M. The subgenual anterior cingulate cortex in mood disorders. CNS Spectrums. 2008 Aug; 13(8):663-81. https://doi.org/10.1017/s1092852900013754

[29] Ge R, Downar J, Blumberger DM, Daskalakis ZJ, Vila-Rodriguez F. Functional connectivity of the anterior cingulate cortex predicts treatment outcome for rTMS in treatment-resistant depression at 3-month follow-up. Brain Stimulation. 2020;13(1):206–14. https://doi.org/10.1016/j.brs.2019.10.012

[30] Fenoy AJ, Quevedo J, Soares JC. Discontinuation of deep brain stimulation to the medial forebrain bundle leads to depression relapse: Considerations when reinstating stimulation. Molecular Psychiatry. 2023. https://doi.org/10.1038/s41380-023-01947-x

[31] Alexander L, Clarke HF, Roberts AC. A focus on the functions of area 25. Brain Sciences. 2019; 9(6):129. https://doi.org/10.3390/brainsci9060129

[32] Alexander L, Jelen LA, Mehta MA, Young AH. The anterior cingulate cortex as a key locus of ketamine's antidepressant action. Neuroscience and Biobehavioral Reviews. 2021; 127:531–54. https://doi.org/10.1016/j.neubiorev.2021.05.003

[33] Luo F, Kiss ZH. Cholinergics contribute to the cellular mechanisms of deep brain stimulation applied in rat infralimbic cortex but not white matter. European Neuropsychopharmacology. 2021; 45:52–8. https://doi.org/10.1016/j.euroneuro.2021.02.019

[34] Bergfeld IO, Mantione M, Hoogendoorn ML, Ruhé HG, Notten P, van Laarhoven J, et al. Deep brain stimulation of the ventral anterior limb of the internal capsule for treatment-resistant depression: A randomized clinical trial. JAMA Psychiatry. 2016; 73(5):456–64. https://doi.org/10.1001/jamapsychiatry.2016.0152

[35] Wu Y, Mo J, Sui L, Zhang J, Hu W, Zhang C, et al. Deep brain stimulation in treatment-resistant depression: A systematic review and meta-analysis on efficacy and safety. Frontiers in Neuroscience. 2021; 15. https://doi.org/10.3389/fnins.2021.655412

[36] Merkl A, Aust S, Schneider G-H, Visser-Vandewalle V, Horn A, Kühn AA, et al. Deep brain stimulation of the subcallosal cingulate gyrus in patients with treatment-resistant depression: A double-blinded randomized controlled study and long-term follow-up in eight patients. J Affect Disord. 2018;227:521–9. http://dx.doi.org/10.1016/j.jad.2017.11.024

[37] Eitan R, Fontaine D, Benoît M, Giordana C, Darmon N, Israel Z, et al. One year double blind study of high vs low frequency subcallosal cingulate stimulation for depression. Journal of Psychiatric Research. 2018; 96:124–34. https://doi.org/10.1016/j.jpsychires.2017.09.026

[38] Puigdemont D, Pérez-Egea R, Portella MJ, Molet J, de Diego-Adeliño J, Gironell A, et al. Deep brain stimulation of the subcallosal cingulate gyrus: Further evidence in treatment-resistant major depression. Int J Neuropsychopharmacol. 2012;15(1):121–33. http://dx.doi.org/10.1017/s1461145711001088

[39] Hanna JA, Scullen T, Kahn L, Mathkour M, Gouveia EE, Garces J, et al. Comparison of elderly and young patient populations treated with deep brain stimulation for Parkinson's disease: Long-term outcomes with up to 7 years of follow-up. Journal of Neurosurgery. 2019; 131(3):807-12. https://thejns.org/view/journals/j-neurosurg/131/3/article-p807.xml

[40] Kennedy BL, Morris RL, Pedley LL, Schwab JJ. The ability of the symptom checklist SCL-90 to differentiate various anxiety and depressive disorders. Psychiatry Quartery. 2001 Sept; 72:277–88. https://doi.org/10.1023/A:1010357216925

[41] Mosley PE, Windels F, Morris J, Coyne T, Marsh R, Giorni A, et al. A randomised, double-blind, sham-controlled trial of deep brain stimulation of the bed nucleus of the stria terminalis for treatment-resistant obsessive-compulsive disorder. Translational Psychiatry. 2021; 11(190). https://doi.org/10.1038/s41398-021-01307-9

[42] Butcher JN, Atlis MM, Hahn J. The Minnesota multiphasic personality inventory-2 (MMPI-2). In: Comprehensive Handbook of Psychological Assessment. John Wiley & Sons, Inc; 2004. p. 30–8.

[43] Fish J. Raskin rating scale. In: Encyclopedia of Clinical Neuropsychology. Cham: Springer International Publishing; 2018. p. 2936–7. http://dx.doi.org/10.1007/978-3-319-57111-9_1960

[44] Hamilton M. Rating depressive patients. The Journal of Clinical Psychiatry. 1980; 41(12):21–4. https://pubmed.ncbi.nlm.nih.gov/7440521/

[45] Floyd AE, Gupta V. Minnesota multiphasic personality inventory [Internet]. StatPearls Publishing; 2023 [cited 2023 Jul 20]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK557525/

[46] Dallapiazza RF, De Vloo P, Fomenko A, Lee DJ, Hamani C, Munhoz RP, et al. Considerations for patient and target selection in deep brain stimulation surgery for Parkinson's disease. In: Parkinson's Disease: Pathogenesis and Clinical Aspects. Codon Publications; 2018. p. 145–60. https://doi.org/10.15586/codonpublications.parkinsonsdisease.2018.ch8

[47] Yuan Y, Zheng L, Feng Z, Yang G. Different effects of monophasic pulses and biphasic pulses applied by a bipolar stimulation electrode in the rat hippocampal CA1 region. BioMedical Engineering OnLine. 2021; 20(25). https://doi.org/10.1186/s12938-021-00862-y

[48] Mayberg HS. Modulating dysfunctional limbic-cortical circuits in depression: Towards development of brain-based algorithms for diagnosis and optimised treatment. British Medical Bulletin. 2003; 65:193–207. https://doi.org/10.1093/bmb/65.1.193

[49] Lozano AM, Mayberg HS, Giacobbe P, Hamani C, Craddock RC, Kennedy SH. Subcallosal cingulate gyrus deep brain stimulation for treatment-resistant depression. Biological Psychiatry. 2008; 64(6):461–7. https://doi.org/10.1016/j.biopsych.2008.05.034

[50] Kennedy SH, Giacobbe P, Rizvi SJ, Placenza FM, Nishikawa Y, Mayberg HS, et al. Deep brain stimulation for treatment-resistant depression: Follow-up after 3 to 6 years. The American Journal of Psychiatry. 2011; 168(5): 502–10. https://doi.org/10.1176/appi.ajp.2010.10081187

[51] Holtzheimer PE, Kelley ME, Gross RE, Filkowski MM, Garlow SJ, Barrocas A, et al. Subcallosal cingulate deep brain stimulation for treatment-resistant unipolar and bipolar depression. Archives of General Psychiatry. 2012; 69(2): 150–8. https://doi.org/10.1001/archgenpsychiatry.2011.1456

[52] Crowell AL, Riva-Posse P, Holtzheimer PE, Garlow SJ, Kelley ME, Gross RE, et al. Long-term outcomes of subcallosal cingulate deep brain stimulation for treatment-resistant depression. The American Journal of Psychiatry. 2019; 176(11), 949–56. https://doi.org/10.1176/appi.ajp.2019.18121427

[53] Mayberg HS, Lozano AM, Voon V, McNeely HE, Seminowicz D, Hamani C, et al. Deep brain stimulation for treatment-resistant depression. Neuron. 2005; 45(5): 651–60. https://doi.org/10.1016/j.neuron.2005.02.014

[54] Zhang C, Zhang Y, Luo H, Xu X, Yuan T, Li D, et al. Bilateral habenula deep brain stimulation for treatment-resistant depression: Clinical findings and electrophysiological features. Translational Psychiatry. 2022 Feb 3; 12(52). https://doi.org/10.1038/s41398-022-01818-z

[55] Nutt D, Wilson S, Paterson L. Sleep disorders as core symptoms of depression. Dialogues in Clinical Neuroscience. 2008; 10(3): 329–36. https://doi.org/10.31887/DCNS.2008.10.3/dnutt

[56] Kimbrell TA, Dunn RT, George MS, Danielson AL, Willis MW, Repella JD, et al. Left prefrontal-repetitive transcranial magnetic stimulation (rTMS) and regional cerebral glucose metabolism in normal volunteers. Psychiatry Res Neuroimaging. 2002;115(3):101–13. https://doi.org/10.1016/s0925-4927(02)00041-0

[57] Rigucci S, Serafini G, Pompili M, Kotzalidis G, Tatarelli R. Anatomical and functional correlates in major depressive disorder: The contribution of neuroimaging studies. World J Biol Psychiatry. 2009;1–16. https://doi.org/10.1080/15622970903131571

[58] Hansson L. Quality of life in depression and anxiety. International Review of Psychiatry. 2002; 14(3); 185–9. https://doi.org/10.1080/09540260220144966

[59] Gouveia FV, Hamani C. Deep brain stimulation as a treatment for depressive disorder. Brazilian Journal of Psychiatry. 2020; 42(4): 342–3. https://doi.org/10.1590/1516-4446-2019-0780

[60] Jang BN, Lee HJ, Joo JH, Park EC, Jang SI. Association between health behaviours and depression: Findings from a national cross-sectional study in South Korea. BMC Psychiatry. 2020; 20(238). https://doi.org/10.1186/s12888-020-02628-7

[61] Raymaekers S, Luyten L, Bervoets C, Gabriels L, Nuttin B. Deep brain stimulation for treatment-resistant major depressive disorder: A comparison of two targets and long-term follow-up. Translational Psychiatry. 2017; 7:e1251. https://doi.org/10.1038/tp.2017.66

[62] Short SE, Mollborn S. Social determinants and health behaviors: Conceptual frames and empirical advances. Curr Opin Psychol. 2015; 5:78–84. https://doi.org/10.1016/j.copsyc.2015.05.002

[63] Jerstad SJ, Boutelle KN, Ness KK, Stice E. Prospective reciprocal relations between physical activity and depression in female adolescents. Journal of Consulting and Clinical Psychology. 2010; 78(2):268–72. https://doi.org/10.1037/a0018793

[64] McMartin SE, Jacka FN, Colman I. The association between fruit and vegetable consumption and mental health disorders: Evidence from five waves of a national survey of Canadians. Preventive Medicine. 2013; 56(3-4): 225–30. https://doi.org/10.1016/j.ypmed.2012.12.016

[65] Choi WS, Patten CA, Gillin JC, Kaplan RM, Pierce JP. Cigarette smoking predicts development of depressive symptoms among U.S. adolescents. Annals of Behavioral Medicine. 1997; 19(1): 42–50. https://doi.org/10.1007/BF02883426

[66] McNeely HE, Mayberg HS, Lozano AM, Kennedy SH. Neuropsychological impact of Cg25 deep brain stimulation for treatment-resistant depression: Preliminary results over 12 months. The Journal of Nervous and Mental Disease. 2008; 196(5):405–10. https://doi.org/10.1097/NMD.0b013e3181710927

[67] Marufa SA, Hsieh TH, Liou JC, Chen HY, Peng CW. Neuromodulatory effects of repetitive transcranial magnetic stimulation on neural plasticity and motor functions in rats with an incomplete spinal cord injury: A preliminary study. PLOS One. 2021; 16(6):e0252965. https://doi.org/10.1371/journal.pone.0252965

[68] Urakubo H, Honda M, Tanaka K, Kuroda S. Experimental and computational aspects of signaling mechanisms of spike-timing-dependent plasticity. HFSP Journal. 2009; 3(4): 240–54. https://doi.org/10.2976/1.3137602

[69] Falowski SM, SharanA, Reyes BA, Sikkema C, Szot P, Van Bockstaele EJ. An evaluation of neuroplasticity and behavior after deep brain stimulation of the nucleus accumbens in an animal model of depression. Neurosurgery. 2011. 69(6):1281–90. https://doi.org/10.1227/NEU.0b013e3182237346

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