Leeza Petrov
Mr. Robinson
Biology 582
February 10, 2017

Shocking New Advancements: Deep Brain Stimulation as an Experimental Procedure for Treatment-Resistant Major Depressive Disorder

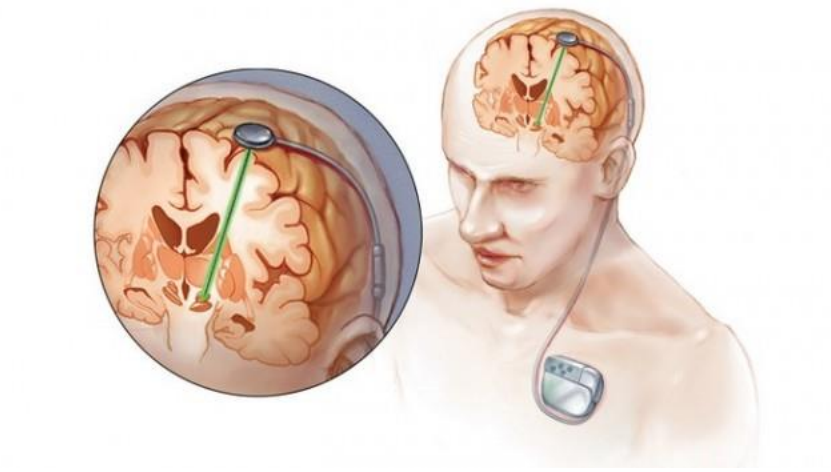
This paper discusses and evaluates deep brain stimulation as a surgical treatment for Major depressive disorder. This treatment has been found successful in small case studies but proves too experimental to serve as a front-line treatment at the present moment.

Major depressive disorder (MDD) affects 6% of the worldwide adult population (Otte, 2016). The Diagnostic and Statistical Manual of Mental Disorders, created by the American Psychiatric Association, characterizes MDD as exhibiting "markedly diminished interest in activities," "insomnia or hypersomnia," "diminished ability to concentrate," "inappropriate guilt," and "feelings of worthlessness" (Otte, 2016). MDD has both physical and psychological effects and is an incredibly debilitating disease leading to chronic disability and a 20-fold increased risk of death by suicide (Otte, 2016). Studies cited by Otte (2016) find that MDD has a clear effect on cognition, mood, and pleasure, as well as increasing risk of heart disease, cancer, Alzheimer disease, and obesity. Although it is a devastating disorder, researchers have not found an established causal mechanism for MDD. Genetic and epigenetic contribution to MDD is approximated to 35% (Otte, 2016), but a slew of environmental factors complicates researchers' understanding of this disease. What propagates and causes MDD is certainly unknown, and current psychiatric drugs are not universally effective. Founded on the basis of neurological alterations found in the brain of MDD patients, a new surgical treatment is being developed aiming to treat patients on an individualized basis.

Although researchers have found strong correlations between certain symptoms and the presence of MDD, the vast majority of etiological (causal) questions remain unanswered. However, some biological foundations of this disorder have been discovered in recent years. MDD has been shown to increase levels of cortisol, a steroid hormone in the body which is released during the stress response. This increased cortisol inhibits the induction of neuroplasticity, or the brain's ability to rewire itself and form new connections (Sale, 2008). Decreased plasticity could result in a decrease in neurogenesis (the growth of adult neurons from stem cells), which would naturally occur as a response to stress. Therefore, although the exact mechanism is unknown, it is understood that neurogenesis and neuroplasticity play key roles in the brain's 'resilience.' This is a potential explanation for why these pathways degrade in treatment-resistant depressed individuals (Otte, 2016). More pathophysiological symptoms include a decrease in hippocampal and other regional volumes, and inflammation in the central nervous system (Otte 2016). Similar to the increase in cortisol, a causal relationship between decreased regional brain volumes and MDD has not been determined. An analysis of 143 individual studies concluded that the volumes of the basal ganglia, hippocampus, and thalamus (determined with structural MRI analysis) were significantly decreased in patients with MDD (Otte, 2016). These three regions are part of the limbic system of the brain, a series of structures

characterized as being the emotional center of the brain. The diminished emotional response often found in patients with MDD could be caused by the decreased volume of these brain regions, as a smaller volume means fewer neurons are firing, which produces a smaller response than anticipated (Otte, 2016). Finally, inflammation in the central nervous system has been established as a risk factor for the development of MDD. The immune system releases inflammatory cytokines, which are proteins involved with cell signaling (Otte, 2016). These cytokines reach the brain through two main cellular pathways. First, cytokines have direct passage through the blood-brain barrier, a covering of the brain capillaries that selectively allows certain substances from the bloodstream into the central nervous system (Reece, 2014). In addition, cytokines can trigger a signaling cascade and send messages through the vagus nerve, a cranial nerve connected to most major bodily areas and serves to regulate vital body functions (Parker, 2013). These inflammatory stimuli trigger certain responses in the CNS that elicit behavioral changes, including a sad mood, fatigue, and anhedonia, or the inability to feel pleasure (Slavich 2014). The aforementioned anatomical foundations of MDD have prompted researchers to explore beyond traditional psychoactive drug therapies. Consequently, work in this field has resulted in the development of direct neuromodulatory treatments which are both more individualized and therefore more effective. These experimental surgical treatments ultimately have the potential to drastically increase the quality of life for MDD patients. .

Deep brain stimulation (DBS) – the process of providing direct electrical current to certain neurons/neural networks—has emerged as an especially promising treatment, especially in cases of otherwise treatment-resistant MDD. Traditionally, neuromodulation is used to treat motor diseases, commonly Parkinson's disorder. For instance, a 2011 study found that bilateral deep brain stimulation of the globus pallidus internus and subthalamic nucleus reduced dyskinesias (involuntary movements) and tremors in patients (Lyons 2011). The general process of the surgery, with a different target area, has proved a promising area of research for treatment of non-motor diseases. The National Institute of Mental Health explains the procedure of DBS as a localized invasive surgery where, under local anesthetic, two holes are drilled into the head and electrodes are fed in and placed to specific areas of the brain (2016). The patient is kept awake in order to confirm brain function during this procedure. The electrodes are then connected to wires that run from the patient's head to the chest, and are attached to a generator inside the chest. Said generator provides continual electrical impulses (NAMI 2016). Although it is not completely



<u>Figure 1:</u> Deep Brain Stimulation Surgery, Electrode and Generator Placement ("Deep Brain Stimulation," 2013).

understood how these electrical impulses reduce depression, the current hypothesis is that this generator acts similarly to a pacemaker; the pulses "reset" the malfunctioning area of the brain (NAMI 2016). See Figure 2. for a diagram of the surgery. Other neuromodulatory treatments for MDD include electroconvulsive therapy, where noninvasive electrical current induces seizures in the brain (Lipsman, 2014). In addition, a newer alternative to monoamine-modulating medications (such as MAOIs) is repetitive transcranial magnetic stimulation, a noninvasive procedure which stimulates cortical neurons with magnetic field pulses to increase firing rates in certain areas (Lipsman, 2014). However, only deep brain stimulation has been proven to have "target-specific effects on both firing rates and patterns" (Lipsman, 2014).

Three primary clinical trials have established themselves as landmarks in the research of DBS as a treatment for MDD. The efficacy of these trials are measured through a quantitative scale, as it is otherwise difficult for researchers to standardize results. Traditionally, the Hamilton (HDRS) or Montgomery-Aspberg (MADRS) Depression Rating Scales are used to measure the levels of remission. Both are questionnaires designed to assess the severity of and potential change in depressive symptoms ("The Hamilton Rating Scale," 1997). They encompass topics including suicide, feelings of guilt, insomnia, and psychomotor retardation. The clinician administering assigns a numerical score to certain responses given by the patient. The higher a score, the more severe a case of MDD. ("The Hamilton Rating Scale," 1997). However, while the HDRS was initially the 'gold standard' of measuring MDD symptoms, it has fallen out of favor with some researchers. Arguing that the HDRS places too much emphasis on insomnia as opposed to suicidal thoughts and gestures, scientists have turned to the MADRS. Because a theoretical antidepressant could show statistical efficacy with the HDRS while actually increasing suicidal thoughts, the MADRS is designed to underscore mood changes in a patient ("The Hamilton Rating Scale," 1997). Through these survey methods, a researcher can determine the efficiency of a certain treatment.

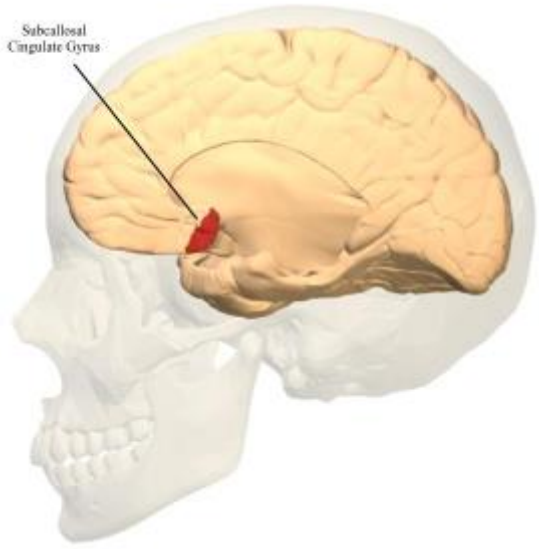


Figure 3: Location of Subcallosal Cingulate Gyrus ("Medial View," 2011)

The first cortical area determined to have an effect on MDD is the subcallosal cingulate gyrus (SCG), determined in a clinical trial carried out by Lozano, et al. in 2008. The SCG is a node in a network that includes cortical structures like the thalamus, hypothalamus, and other areas of the limbic system. See *Figure 3.* for the location of the SCG in the brain. Furthermore, it has been determined that blood flow in the SCG increases when subjects are asked to recite "autobiographic sad scripts," or sad experiences that had occurred to the patients (Lozano, 2008). General increased activity in the SCG has been found in depressed patients through fMRI scans. The goal of stimulating neurons through DBS here is to override the current rate of function and consequently decrease the activity of the SCG (returning it to normal levels) through electrical stimulation (Lozano, 2008). By 'resetting'

function of the SCG with these impulses, several other connections in the brain, including a link to the prefrontal cortical area (involved in executive cognitive processes) and the amygdala (associated with emotional responses), are regulated as well (Lozano, 2008). In this study, 20 patients underwent bilateral DBS of the SCG. One month after surgery, 35% of patients saw a 50% reduction of their Hamilton score, and 10% of the patients scored a 7 or below, which is the criteria for 'normal' or non-depressed individuals, as compared to a score of twenty or above indicating a certain degree of depression (Lozano, 2008). A landmark case in MDD research, the SCG is now the most common area selected for bilateral DBS. The results of this and other studies concluded that the benefits described above were maintained at 6 and 12 months post-surgery (Lozano, 2008); thus the efficacy of SCG stimulation is evident with minimal side effects.

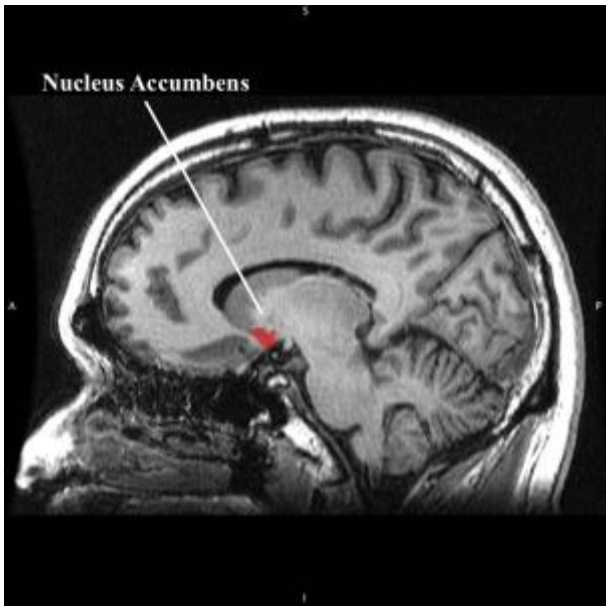


Figure 4: Location of Nucleus Accumbens ("Sagittal MRI slice with highlighting indicating the nucleus accumbens," 2011).

A more recent study in DBS involved bilateral stimulation to the nucleus accumbens (NAc). Conducted by Bewernick, et al. in 2010, the goal of stimulating the NAc was to reduce anhedonia—the inability to feel pleasure—in depressed patients (Bewernick, 2010). The nucleus accumbens is located in the ventral striatum, a critical association area for the brain's reward system; the NAc is believed to be involved in mediating motivational processes such as incentive, aversion, and pleasure (Bewernick, 2010). Moreover, the NAc is generally located near the limbic system. See Figure 4. for the location of the NAc in the brain. As mentioned above, certain structures in the limbic system had decreased volume in MDD patients. A potential outcome of stimulating this area would be the reinforcement and repeated strengthening of certain neuronal connections, ameliorating an otherwise underactive and hypometabolic area (Bewernick, 2010). Ten patients were selected for this clinical trial. The mean HDRS score in the whole sample decreased from 32.5 to 23.8 after one month of stimulation, approaching the benchmark score of 20 (which indicates a diagnosis of MDD). 12 months post-surgery, half of the patients were evaluated and researchers found an average 50% reduction of their Hamilton scores (Bewernick, 2010) No worsening of symptoms, recurrence of new symptoms, or cognitive impairments were observed in any of the patients (Bewernick, 2010). By targeting one specific symptom of MD—in this instance, anhedonia—this case study innovated the accuracy of DBS and allowed researchers to selectively address certain symptoms; effectively creating a more individualized treatment of MDD.

However, one limitation of the previous two studies is that neither included a 'sham' control. In other words, the patients were not granted a placebo "stimulation" and knew that the generator was turned on and administering electrical impulses (Bewernick, 2010). According to

Bewernick, her team abandoned a placebo-based design after stimulation was discontinued accidentally (for example, the generator exhausted its battery in one patient) without the patient or researcher's knowledge and symptoms of depression worsened rapidly (2010). However, the placebo effect cannot be completely eliminated and this lack of patient-blinding could mitigate the results of these studies.

A very recent development in neuromodulatory treatments of MDD occurred in 2016, when Fenoy, et al. examined the effects of DBS on the medial forebrain bundle (MFB). The MFB is a significant structure in the brain's reward system (Fenoy, 2016). It is most strongly associated with dopaminergic (involving dopamine) pathways and is connected to the NAc (mentioned above) and other nodes to create a large network controlling hedonic and reward-mediated behavior (Fenoy, 2016). See Figure 5 for the location of the MFB in the brain. Other studies have concluded that increased cell firing and strengthening these pathways have regulated depressive behavior (Fenoy, 2016). Fenoy conducted a clinical trial examining 4 patients over a 52-week period. This was a single-blind study which also included a sham stimulation in order to address the concerns expressed with the previous trials. While there was no change in mood during the sham stimulation, 3 out of the 4 patients had over a 50% decrease on the Montgomery Aspberg Scale at just 7 days post stimulation (Fenoy, 2016). The Montgomery Aspberg was in this study to more objectively measure suicidal thoughts and ideas – a more pressing symptom of depression to the researchers – as opposed to the HDRS. At 26 weeks, the patients had over an 80% decrease in their scores. The MADRS scores were supplemented by interviews from an objective viewpoint (eg: a spouse or close friend) to give qualitative data about the daily quality of life for the patients (Fenoy, 2016). While this is a study with an incredibly small sample size, the results are promising for a study with a larger scope to reach further conclusions.

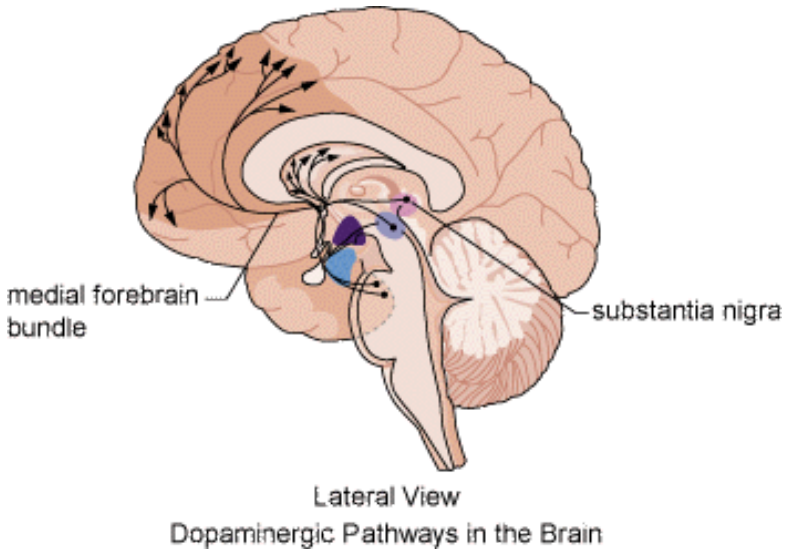


Figure 4: Location of Medial Forebrain Bundle ("Dopaminergic Pathways in the Brain," 2001).

These three studies, amongst others, have yielded encouraging results regarding the efficacy of DBS as a MDD treatment. While not without fault, these clinical trials have proved to be a worthwhile area of research for refractory depression. The specificity of the targeted brain areas, as well as the far-reaching effects, makes DBS an effective solution for patients who have not responded to SGAs and other antidepressants. Although SGAs have been developed to increase selectivity of treatment, the mechanism of targeting a certain 'type' of receptors or

neurotransmitters still proves too general for a significant portion of patients. MDD is a complicated disease: there is a myriad of ways that genetic and epigenetic predispositions can interact with environmental factors (Otte, 2016). For patients that have resisted these general forms of treatment, DBS offers an individualized alternative method of targeting their disease. For example, through coupling PET scans and fMRIs, Fenoy et al. was able to determine individual target sites for each of the patients involved in the trial. (2016). This level of patient-specific care enables doctors to target and ameliorate the symptoms that affect their patients the most, and consequently raise their standard of living. In the case of Bewernick's trial, the specific stimulation of the NAc and regulation of the reward pathway eliminated anhedonia in her patients, making their MDD significantly less debilitating (2010).

In contrast with DBS, the current pharmaceutical front-line treatments for MDD are known as second-generation antipsychotic drugs, or SGAs. They are known as second-generation because they arose out of careful re-development of initial antidepressant medication. Older antipsychotics include monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs). MAOIs inhibit an enzyme which removes the neurotransmitters dopamine, serotonin, and norepinephrine from the brain ("Monoamine oxidase inhibitors," 2016). TCAs, similarly, block the re-uptake of serotonin and norepinephrine from the brain. Low levels of these neurotransmitters have been associated with MDD (Otte, 2016). However, the limited tolerability and questionable safety of these early anti-depressants led to the development of treatments that selectively target receptors, rather than impacting 2-3 neurotransmitters at once (Wang, 2016).

Consequently, new SGAs do not have a 'blanket effect,' but in turn, are able to more effectively solve the multifactorial manifestations of MDD. One example is Brexiprazole, a dopamine receptor activator which is commonly used as an adjunctive therapeutic treatment (Wang, 2016). By increasing the quantity of dopamine receptors (receptors of an excitatory neurotransmitter), Brexiprazole strengthens many dopamine pathways in the brain, including those linked in the reward circuit, thereby eliminating anhedonia by increasing the rate of activity in these pathways (Wang, 2016). On a broader scale, SGAs in general have proved effective as both augmentation and primary therapies. An analysis by Papakostas et al. examining the efficacy of four different SGAs (aripiprazole, olanzapine, quetiapine, and risperidone) concluded that all four drugs had "statistically significant effects on remission [of MDD]" (Wang 2016). However, despite their general success, a factor that significantly complicates pharmaceutical treatments is the "pleomorphic" nature of MDD (Otte, 2016). Although there are generalized symptoms like those listed in the Diagnostic and Statistical Manual of Mental Disorders, MDD manifests itself differently in each individual. MDD is characterized by Christian Otte as having "considerable variation in remission and chronicity" (2016). The downside to most antipsychotic treatments, even SGAs, is that they are significantly less individualized than the physiopathology of MDD in a patient. This leads to the occurrence of treatment resistant depression, often known as refractory depression. Treatment resistance is defined as an inadequate response to at least one course of antidepressant trials (Fava 2003); approximately 30% of patients do not remit from major depressive disorder after several pharmaceutical treatment attempts (Otte 2016). Consequently, diagnostic re-evaluations and modifications of treatment plans must occur – in some cases, without any amelioration in symptoms for the patient.

However, when considering the efficacy of DBS as compared to the current pharmaceutical treatments, the question of 'which is a better treatment?' becomes incredibly nuanced. On one hand, one must take into account the cost and time-consuming nature of DBS. This procedure is accompanied with risks similar to any other invasive brain surgery, including brain hematomas, bleeding, or stroke, infection, or changes in mood or movement patterns (NAMI, 2016). Because this is a relatively new procedure, long term benefits and risks are still unknown. In addition, the individualized nature of DBS treatment for MDD is not cost-effective. PET and fMRI scans, as well as other surgical costs, are expensive and not feasible to perform for every patient diagnosed with MDD. Although a patient-specific nature makes DBS effective, it unfortunately makes DBS unreasonable as a primary or first-line treatment simply because of its cost.

However, despite these drawbacks, DBS remains to be a significantly promising and worthwhile research area, and should not be ruled out as a treatment entirely. Even early innovations in this surgery to treat MDD have produced effective results with minimal side effects. Although by no means should an invasive and costly surgery be considered the first line of defense for patients diagnosed with MDD, this procedure should remain a viable option for those whose depression does not respond to pharmaceutical or psychotherapeutic treatment. Furthermore, innovations in neuromodulation could affect other disciplines; initially, the procedure of DBS was intended solely to address motor diseases, so developments in either discipline could aid its counterpart. In the future, if research continues, DBS will likely become more fine-tuned, less dangerous, less costly, and more accessible to the public – and hopefully becoming a front-line treatment for patients with treatment-resistant major depressive disorder.

References

Bewernick, B. H., Hurlemann, R., & Matusch, A. (2010, January 15). Nucleus accumbens deep brain stimulation decreases ratings of depression and anxiety in treatment-resistant depression. *Biological Psychiatry*, *67*(2), 110-116. http://dx.doi.org/10.1016/j.biopsych.2009.09.013.

Deep brain stimulation [Image]. (2013, July 2). Retrieved from https://www.extremetech.com/extreme/160203-deep-brain-stimulation-the-bleeding-edge-of-neurohacking-and-transhumanism

Dopaminergic pathways in the brain [Illustration]. (2001). Retrieved from http://www.ablongman.com/html/psychplace_acts/synapse/dopamine.html

Fava, M. (2003, April 15). Diagnosis and definition of treatment-resistant depression. *Biological Psychiatry*, *53*(8), 649-659. Retrieved from PubMed database.

Fenoy, A. J., Schulz, P., & Selvaraj, S. (2016, October). Deep brain stimulation of the medial forebrain bundle: Distinctive responses in resistant depression. *Journal of Affective Disorders*, *203*, 143-151. http://dx.doi.org/10.1016/j.jad.2016.05.064

Hall, G. (2011). *Sagittal MRI slice with highlighting (red) indicating the nucleus accumbens* [Photograph]. Retrieved from https://en.wikipedia.org/wiki/Nucleus_accumbens#/media/File:Nucleus_accumbens_sag.jpg

The Hamilton rating scale for depression. (n.d.). Retrieved February 9, 2017, from UMass HealthNet website: http://healthnet.umassmed.edu/mhealth/HAMD.pdf

Lipsman, N., & Sankar, T. (2014, January 7). Neuromodulation for treatment-refractory major depressive disorder. *Canadian Medical Association Journal*, *186*(1), 33-39. http://dx.doi.org/10.1503

Lozano, & Mayberg. (2008, September 15). Subcallosal cingulate gyrus deep brain stimulation for treatment-resistant depression. *Biological Psychiatry*, *64*(6), 461-467. http://dx.doi.org/10.1016

Lyons, M. K. (n.d.). Deep brain stimulation: Current and future clinical applications. *Mayo Clinic Proceedings*. Retrieved from PubMed database.

Mayo Clinic Staff. (2016, June 8). Monoamine oxidase inhibitors (MAOIs). Retrieved February 8, 2017, from Mayo Clinic website: http://www.mayoclinic.org/diseases-conditions/depression/in-depth/maois/art-20043992

Mayo Clinic Staff. (2016, June 18). Tricyclic antidepressants and tetracyclic antidepressants. Retrieved February 9, 2017, from Mayo Clinic website: http://www.mayoclinic.org/diseases-conditions/depression/in-depth/antidepressants/art-20046983

Meidal view [Image]. (2011, November). Retrieved from https://en.wikipedia.org/wiki/Brodmann_area_25#/media/File:Brodmann_area_25_medial.jpg

The National Institute of Mental Health. (2016, June). Brain stimulation therapies - deep brain stimulation. Retrieved December 16, 2016, from National Institute of Mental Health website: https://www.nimh.nih.gov/health/topics/brain-stimulation-therapies/brain-stimulation-therapies.shtml#part_152881

Otte, C., & Gold, S. M. (2016). Major depressive disorder. *Nature*. http://dx.doi.org/10.1038/nrdp.2016.65

Reece, J. B., Urry, L. A., Cain, M. L., Wasserman, S. A., Minorsky, P. V., Jackson, R., & Campbell, N. A. (2014). *Campbell biology* (10th ed.). Boston: Pearson.

Salgado, S., & Kaplitt, M.G. (2015). The nucleus accumbens: A comprehensive review. *Stereotactic and Functional Neurosurgery*, *93*(2). https://dx.doi.org/10.1159/000368279

Slavich, G., & Irwin, M. (2014). From stress to inflammation and major depressive disorder: A social signal transduction theory of depression. *Psychol Bull*. http://dx.doi.org/10.1037/a0035302

Wang, S.-M., & Han, C. (2016). Second generation antipsychotics in the treatment of major depressive disorder: An update. *Chonnam Medical Journal*. http://dx.doi.org/10.4068/cmj.2016.52.3.159