**Deep Brain Stimulation’s Effect On Depression**

*A review article discussing the effects of depression and how Deep Brain Stimulation(DBS) is helping.*

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**ABSTRACT**

Depression is growing a problem with rates rising from 3.33% in 1991 to 7.06% in 2001. (Saveanu R. V., et. al. 2009) with suicide being a major concern and consequence. Subgenual Cingulate Deep Brain Stimulation (SCG-DBS) is new method of helping depressed patients and in this review, we look at the neurotransmitters that are involved in depression and how SGC-DBS can help it. Based on the results, thirty-three percent of participants had a positive response to SGC-DBS after the 24-month follow-up until the last observation at 28-months and 4 years. Based on the study, it seems SGC-DBS has limited to none side effects, but unless the tragic memories of a person are dealt with, progress will not to be made. SGC-DBS paired with therapy may be a way to permanently cure depression.

**INTRODUCTION:**

**Is Depression Taking a Toll?**

Depression is a common mental disorder. It is a growing a problem with rates rising from 3.33% in 1991 to 7.06% in 2001. (Saveanu R. V., et. al. 2009). Another example of depression taking a toll is in number of depressive female to male ratio. According to a study published in Psychological Science in the Public Interest, Women are 20% more likely to get/inherent depression, unlike their male counterparts, who is 10% more likely; this is due to factors such as: pregnancy, birth, and hormonal changes. A more serious implication of depression is its effect on children. Evidence of this include, One out of ten Chinese children displays symptoms of severe depression, and this proportion closely matches depression estimates for U.S. children (Society for Science & the Public), Maternal mothers whom are depressed are more likely to give birth to unhealthy, and/or premature babies (Li. et al. 2009; Orr. et al. 2002), with an increased risk of hospitalization (Chung et al., 2004), and 4-8% of adolescents will experience depression, and up to 25% will continue to experience depression by the end of their adolescence (Bylund & Reed 2007).

Depression has serious consequences with suicide being its a major concern and consequence. The World Health Organization (WHO) states that over 300 million people are affected by depression, and that a little under 800,000 people die from suicide every year causing suicide to be the second leading cause of death among 15 to 29-year-olds. Not only is it the second leading cause of death in 15 to 29 years old, but over a million people have died from suicide every year and the rates have increased by 60% in some countries over the last 45 years (WHO, 2013). According to a study done by The Journal of Affective Disorders, 58% of all MDD patients experienced suicidal ideation, and among them, 15% has attempted suicide. Like stated before, a serious implication of depression is its effect on children, a study done by Holzera et al., shows that suicide of youths in juvenile facilities are higher than those in the general population with female youths more likely to attempt suicide compared to males. Based on these facts alone the impact of depression not only on kids, but on adults as well is tremendous and needs to be examined.

Deep Brain Stimulation (DBS) is new method of helping depressed patients and in this review, we will look at the neurotransmitters that are involved depression and how DBS can help it.

**Pathophysiology of Depression**

**Serotonin (5HT):** The ability of 5HT to bind to its receptors differentiates depressive people to non-depressive people. For example, there is evidence that shows the binding potential of serotonin-1A (5HT1A) receptor in depressed patients was significantly decreased in the Raphe Nuclei. In a study done by Lopez et al. (1998), it was found that postmortem subjects had decreased 5HT1A receptor mRNA levels (that correlated with receptor density) by 31% to 49% across hippocampal subfields. The Binding potential also decreased in neocortical areas agrees; for example, Bowen et al (1989), observed that 5HT1A receptor decreased 24.5% in the temporal polar cortex, 24.2% in frontal opercula cortex, and 28.8% in superior parietal cortex.

The “TRP-5-HT deficiency hypothesis of major depression” is the dysfunction of 5HT neurotransmission in patients with major depression. Patients with major depressive disorder had lower levels of tryptophan (TRP) in the plasma that is available for Serotonin synthesis, also physiological changes in plasma TRP concentrations might impact 5HT levels, due to the ability of TRP to cross the blood-brain barrier (Fava & Sonino, 2010). The evidence that supports this hypothesis was done by Baranyi A. et al. (2017), showing that TRP concentration was significantly lower in patients with MDD in comparison to the controls (t: −3.93; df = 116, p < 0.001).

**Hypothalamic-pituitary-adrenal (HPA):** The hyperactivation of cortisol (CRH) is mediated by 5HT signaling. In a study done by Kageyama et al. (1998), their results gave evidence that CRH release were mediated by 5-HT1A and 5-HT3 receptors. More evidence showed that the serotonergic part of the raphe nucleus expressed CRH receptors (Chalmers et al. 1995), while intracerebroventricular and intraraphe administrations of CRH constrained 5HT activity in the neurons of the raphe nucleus in rats (Price et al. 1998). This leads many neuroscientists to believe that 5HT and CRH to be biphasic.

**Subgenual** **cingulate (cg25):** The anterior cingulate cortex’s use of emotional behavior in neuroimaging studies has been increasing, due a recent discovery by Dreverts WC. et al. (1997). He discovered that the anterior cingulate cortex’s (ACC) gray region was significantly reduced in size in familial bipolar disorder and (MDD). It is important to note that neuroimaging studies have not yet found significant differences between mood disordered individuals and health individuals in respect to the whole brain, but many researchers have reported gray matter loss in other portions of the anterior or posterior cingulate cortex. Nevertheless, the anterior subgenual anterior cingulate cortex (sgACC) and more dorsal regions of the perigenual anterior cingulate cortex (pgACC) are more affected in studies concerning emotions, depression, and mood disorders. In a multitude of studies, it showed that the tissue near the sgACC and pgACC junction had an increase of hemodynamic activity during tasks involving emotions, such as: Inducing sadness in women (Mayberg HS. et al. 1999), Exposing people to traumatic memories (Rauch SL. & Dreverts WC. 2008), and using words as sad or happy targets in an emotional go/no-go study (Elliot R. et al. 2000). In mood disorders, sgACC activity has been shown to positively correlate with depressive symptoms (Osuch EA. et al 2000).

**Deep Brain Stimulation (DBS)**

DBS is a relatively new procedure for mental illnesses, such as: treatment resistant major depressive disorder (TR-MDD), MDD, etc. and has been studied by a few researchers (e.g., Delaloye and Holtzheimer). According to a study done by Lozano et al. (2008), Cg25 stimulation has led to favorable responses in approximately 50% of participants suffering from severe TR-MDD; also, a study done by Holtzheimer et al. (2012) reported a one-year response rate of 62% and 36%. In theory, bilateral DBS electrodes or a neurostimulator is inserted into the brain, shocks of high and low frequency are administered, and signals different neurotransmitters in the brain to release excitatory neurotransmitters such as 5HT within the brain.

 Merkl A. et al. (2017) conducted a study with fifteen participants, later dropping to eight, suffering from TR-MDD. The participants were stereotactically implanted with quadripolar electrode in the subgenual cingulate **(**SCG) bilaterally. Results were based off Hamilton depression rating scale- 24 item (HAMD-24), which were obtained in all participants before, for a baseline, and after DBS, for an outcome parameter. To evaluate efficiency of DBS, responses were measured as a 50% reduction in the HAMD-24, and partial response was defined as 25% reduction in the HAMD-24 and remission measurements were recorded as HAMD-24 score of 10 or less. Participant evaluation took place weekly until three months after DBS placement.

 The average HAMD-24-score at 6, 12, and 24 months, compared to the baseline, were 34%, 25%, and 37%. At four and eight weeks, the HAMD-24-score had no significant group difference in both delayed and active stimulation, there was also no significant improvements compared to the baseline. At three months, two participants in the delayed group had a 50% response with percentage changes of 43%, 13%, 3%, 50% and mean of 25 ± 10.03.

At six month, three out of the four participants in the delayed group fulfilled the HAMD-24 response with a percentage change of 75%, 63%, 68%. One out of participants in the active group fulfilled the HAMD-24 with a partial change (37%). One of the participants, who was later removed, had a 62% improvement in the HAMD-24-score at the 6-month follow-up. Apparent reductions in the raw HAMD-24-score were not seen until 12 months after with the mean score (mean score= 24.14 ± 10.32) showing a significant decrease compared to the baseline, same with average HAMD-24-score for 24 months. The average (mean= 20.66 ± 10.98) HAMD-24-score at the 24-month follow-up had significant decrease compared to the baseline. (fig 1&2)

 Another parameter Merkl A. et al. tested was BDI scores. BDI scores were observed similarly to the HAMD-24 scores. At four weeks, there was a significant difference between groups and a significant difference compared to the baseline scores. Out of the six participants, who completed protocol, the average BDI score had a significantly decrease at 24-months. Beck depression inventory (BDI) scores continued to improve after 24-months (40%).  (fig 1&2)

**Discussion**

Based on the results, thirty-three percent of participants had a positive response to Subgenual cingulate Deep Brain Stimulation (SGC-DBS) after the 24-month follow-up until the last observation at 28-months and 4 years. HAMD-24 and BDI scores improved after 6-months, which gives evidence that SGC-DBS has notable and significant difference in the long-term. The SGC-DBS did not have any severe consequences/side effects, and if any, it was easy fixed by adjusting the DBS settings. Participants were treated with antidepressants and supportive therapy to help with any issues or problems. During the study, participants had notable fluctuations in the severity of their depression. It is unclear to the case of the fluctuations but it is certain that it was not caused by the SGC-DBS, but perhaps due to stressors in life.

**Conclusion:**

**What Is The Next Step**

 Based on the study, it seems SGC-DBS has limited to none side effects, and if any, they were easy and simple to fix, and it provides long-term relief to TR-MDD patients. It is hard to treat a mental illness that is caused by genetics and environmental factors. Inserting electrodes in the brain and sending electrical shocks to produce more excitatory neurotransmitter can help, but unless the tragic memories of a person is dealt with, progress will not to be made. SGC-DBS paired with therapy may be a way to permanently cure depression.

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***Fig 1.*** *Abbreviations: p-value for non-parametric t-test (Wilcoxon for dependent samples, two- tailed); a absolute improvement. “-c”: missing data. SD = Standard Deviation; HAMD = Hamilton Depression Rating Scale, MDD = Major Depressive Disorder, N = number, BDI = Beck Depression Inventory; Rating Scale; SD = standard deviation, Values are mean ± SD if not otherwise specified; BL = Baseline; improvement = Mean change of HAMD-scores compared to BL. # Two patients requested explanation of electrodes and DBS-device before 24-months rating. \* significant p < .05; a = Wilcoxon test baseline vs 6-Months. (Merkl A. et al. 2017)*

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***Fig 2.*** *The delayed onset group started DBS-ON after four weeks which was a double-blind rating period. After a period of 8 weeks the trial was open-label. bANOVA for repeated measures (main factor time) with simple contrasts between follow-up visits versus baseline and in-between factor (randomization delayed onset versus active); interaction effect not significant at any time point (p-value not shown). \*\*significant: p < .01; \*significant: p < .05; SD = Standard Deviation; BDI = Beck Depression Inventory; HAMD = Hamilton Depression Rating Scale; Values are mean ± SD if not otherwise specified; #n = 7; §n = 6; BL = baseline. (Merkl A. et al. 2017)*

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