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Neural Circuits in Emotional Regulation in Treatment Resistant Depression and Deep Brain Stimulation Therapy

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Abstract: As one of the most debilitating mental disorders, treating patients with treatment resistant depression (TRD) is still a challenge in psychiatric medicine with conventional methods. Deep brain stimulation (DBS), which has been proved successful in many neurological diseases, also showed its great potential in treating some psychiatric disorders, including depression. However. since it was first investigated in treating TRD, over two decades has passed and this technology is still not able to benefit more severe depressive patients. This article starts by reviewing what has already been knowing about emotional neural regulation mechanisms in depression pathophysiology. Then the article looks into deep brain stimulation therapy at different brain targets in treating depressive disorder. Adaptive deep brain stimulation technology is not new to some other neurogenic disorders but still new to in treating depressive disorder. With the great advances in neural science and artificial intelligence research, adaptive deep brain stimulation with brain-machine interface would lead to personalized treatment with higher efficiency and safety.

Keywords: treatment resistant depreesion, deep brain stimulation,emotion neural circuits, adaptive deep brain stimulation, artificial intelligence, brain-machine interface

1. Introduction

Major depressive disorder (MDD) is one of the incapacitating psychiatric disorders. According to 2021 National Survey on Drug Use and Health (NSDUH), 21.0 million adults in the U.S. are estimated had at least one major depressive episode, which accounted as 8.3% of all the U.S. adult population. Among those population, 14.5 million aged 18 or older reported to have at least one major depressive episode with severe impairment in 2021, which indicated 5.7% of all the U.S. adult population [1]. Mental disorders have been among the leading causes of the global health-related burden with depressive disorder ranked the top 25 leading causes of burden worldwide according to the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2019. SARS-CoV-2 global pandemic (COVID-19) significantly associated with approximately 27.6% increase of major depressive disorder globally, which accounted an additional 53.2 million new cases in 2020 [2].

Even though there are some effective treatment methods to improve the symptoms of depressive disorder, but one subset of MDD named as treatment-resistant depression (TRD) does not respond to conventional and first-line therapies. The rate of those depression patient were not responded to conventional treatment at all is as high as 50% [3].

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As there are relatively few medical advancements that have been made in treating the depression, many novel therapies have been under investigation. These includes Ketamine and psychedelics, anti-inflammatories, as well as rapid acting antidepressants. Non-pharmacological therapeutic methods include psychotherapy, different level brain stimulations, such as electroconvulsive therapy, repetitive transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), vagus nerve stimulation (VNS), and magnetic seizure therapy, etc. However, for patients with TRD, most of them do not respond to these treatments, which has made alternative therapies an urgent need. Deep brain stimulation (DBS), which has been proved effectiveness in treating neurogenic movement disorders, is now extending to the field of psychiatric. With promising efficacy which has already been demonstrated in clinical, the future of DBS in treating TRD will be built upon advancement of neuroimaging technology, as well as better understanding of neural circuits underlying physiology of depression.

2. Neural Circuits in Emotion Regulation

Major depressive disorder (MDD) as one of the most prevailing and disabilitating psychiatric disorders characterized by aberrant emotion regulation. Diverse neural circuits are contributing in normal emotion and mood regulation. While higher level cognitive structures are in charge of encoding and decoding contextual information, the lower level limbic structures trigger all kinds of emotional expression [4]. These observed neural and behavioral demonstration together constitute emotions management and control. Dysfunctional cognitive process usually leads to some specific abnormalities related to MDD, such as biased attention, rumination, and altered information processing and memory. Neural activities control the intensity, duration, and type of different kinds of emotion experiences as well as its expression [5].

The major neural systems involved in common neural network of brain regions that have been involved in the emotion regulation shared common path ways for specific emotions. The neural mechanisms involved in generating the expressive and affective components of emotion responses involve various brain structures. For example, brainstem nuclei and subcortical structures, specifically hypothalamus and amygdala, play essential roles in generating both the physical expression and visceral feelings associated with emotions [4, 6, 7]. These structures are regulated to ensure synchronization of emotional responses. Lower-level cortical regions like the nucleus accumbens (NAc) on the other hand are responsible for mediating feelings of reward [8]. Anterior cingulate cortex (ACC) plays a key role in processing aversion [9]. The insular cortex (IC) is involved in generating complex emotional states by integrating visceral sensations with motivational inputs from other cortical regions [10]. Dysfunction in these circuits, as seen in autonomic failure, can result in a reduced capacity to experience emotions. This comprehensive understanding of the neural mechanisms behind emotions sheds light on the intricate processes that give rise to our emotional experiences.

Emotions in the human brain are modulated by contextual information through a process known as cognitive reappraisal [11, 12]. It emphasizes the role of various higher-level cortical structures, such as the medial prefrontal cortex (mPFC), dorsolateral prefrontal cortex (dlPFC), vertrolateral prefrontal cortex (vIPFC), dorsomedial prefrontal cortext (dmPFC), and temporal poles, in regulating emotions based on context [12]. The mPFC is involved in self-referential processing and and cognitive reappraisal, while the dlPFC inhibits subcortical limbic structures and mediates attention shifts [13]. The vlPFC is responsible for valuation and goal-setting, while the dmPFC links emotion regulation with the salience and default mode networks. Additionally, the temporal poles assess emotional significance by integrating contextual cues.A bidirectional communication between these higher-level structures and subcortical limbic structures explains how bottom-up signals from

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subcortical regions can impact higher-level cognitive processes, as seen in individuals with depression [12, 13].

In the context of major depressive disorder (MDD), research has revealed abnormalities within the neural systems responsible for emotion regulation. Various neuroscientific techniques, such as fMRI, PET, EEG, VBM, stimulation studies, lesion studies, and connectivity studies, have contributed to our understanding of these abnormalities. Specifically, individuals with MDD exhibit heightened and prolonged amygdala activation in response to negative stimuli, which contributes to the persistent processing of negative information and enhanced memory for such events [14]. Additionally, MDD is associated with abnormalities in regions linked to rumination, including increased activity in the medial prefrontal cortex (mPFC) during rumination and altered activity within the default mode network [15].

Furthermore, inhibitory control deficits are observed in depression, partly due to impaired functioning of higher-level cortical regions such as the left dorsolateral prefrontal cortex (dlPFC) hypoactivity and right dlPFC hyperactivity [16]. The ventrolateral prefrontal cortex (vlPFC), involved in valuation, also shows reduced function in individuals with MDD, leading to negative attentional bias and difficulties in cognitive reappraisal. Functional connectivity changes are evident, with decreased connectivity between subcortical limbic structures and prefrontal cortical regions. However, there's increased connectivity between the amygdala and temporal poles, potentially serving as a compensatory mechanism. Additionally, the dorsomedial prefrontal cortex (dmPFC) plays a pivotal role in regulating communication between emotion regulation, salience, and default mode networks and is associated with emotional integration difficulties in MDD [17]. Reward and motivation circuits are impaired in depressed individuals, characterized by reduced reactivity of the prefrontal cortex and nucleus accumbens (NAc) to rewarding stimuli, as well as diminished brain structure volumes related to reinforcement learning [18]. These findings collectively highlight the neural underpinnings of emotion regulation abnormalities in MDD.

3. DBS Brain Targets and Neural Circuitries Influenced

For severely treatment resistant depression patients, when all other treatment methods have failed, some novel approaches have been tested and used clinically. Less invasive methods such as transcranial magnetic stimulation, transcranial direct current stimulation (tDCS) and, transcranial alternating current stimulation (tACS), as well as vagus nerve stimulation (VNS) have all been investigated but with relatively low response and remission rates for severely TRD patients [19]. An invasive method, deep brain stimulation (DBS), has been paid more and more attention with its remarkable clinical effects. Through a stereotactically implanted electrodes into specific brain regions, electrical generated pulses are given under the control of a subcutaneous implantable pulse generator.

According to different depression symptoms, the brain targets for DBS varies but mainly targeting circuits related to two primary diagnostic criteria for MDD: negative affect and anhedonia. In general, targeting subcallosal cingulated cortex (SCC) and the lateral habenula (LHb) is aiming to improve negative emotions, while targeting areas like ventral capsule and ventral striatum (vALIC and VC/VS), the medial forebrain bundle (MFB), and the inferior thalamic peduncle (ITP) is to improve anhedonia [20].

The first most known region for DBS targeting is the subcallosal cingulated (SCC), known as Cg25 or Brodmann area 25, based on neuroimaging data indicating its relevance to mood regulation in depression. Activating this region can provoke sad mood as well as suppress response to antidepressants [21]. Not only this region closely interacts with areas that process emotions and motivation, but also is connected to antidepressant targets for non-invasive neuromodulation [22-24]. Initial studies showed promising results, with a proof-of-concept study demonstrating significant improvement in four out of six extreme TRD patients following 6 months of open-label SCC DBS.

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A larger study of 20 patients reported a 60% response rate and a 50% remission rate after one year, with most depression symptoms improving over time [26]. Subsequent open-label studies indicated remission rates ranging from 33% to 58% with chronic stimulation, and even patients who had relapsed after other treatments showed positive responses. Importantly, no adverse effects were observed with acute or long-term SCC DBS, and there were no cognitive impairments reported [27]. However, in a randomized controlled trial (RCT) known as BROADEN trial, the investigation of DBS of the SCC region was aborted prematurely because the unmet response rate after six months. Although the study result has never been published, it raised a meaningful question about the selection qualification of candidate, as well as the criteria to evaluate the clinic outcome regarding DBS efficacy in TRD treatment [28, 29].

Besides SCC, the lateral habenula (LHb) area communicate between the forebrain and monoaminergic systems in the midbrain and hindbrain, which showed its connection with negative mood and depression [30]. Research found that increased LHB blood flow and hypermetabolism have caused depressive symptoms, while smaller volume of LHb is specific to MDD patients [31, 32] . Stimulation in this region demonstrated depression remission in a patient with TRD over 12 months, and this result persisted at the last follow-up [33]. Importantly, the exclusion of placebo effects was supported by severe relapses in patients upon accidental or planned discontinuation of stimulation, followed by rapid onset within a week and gradual remission taking two to three months after reinitiating stimulation [34]. However, the precision of targeting of selective LHb white matter connections in human DBS trials remains challenging [20].

Ventral internal capsule/ventral striatum (VC/VS), along with nucleus accumbens (NAc), or ventral anterior limb of the internal capsule (vALIC) are sharing one neural trajectory [20]. Since this neural circuitry exhibits a substantial overlap with the reward-related circuitry believed to be associated with the anhedonia symptoms of major depressive disorder [35, 36]. Therefore, it's became another brain target after showing its promising clinical results in treating obsessive-compulsive disorder (OCD) patients [37, 38]. The hyperactive VC/VS is also associated with depression [39]. Studies found the lesioning or capsulotomy of the VC/VS has improved depression symptoms, which triggering the trials of DBS targeting this brain areas in TRD patients [40]. The pilot study of VC/VS DBS in TRD patients has demonstrated significant response and remission rates. However, a subsequent double-blind trial failed to establish statistically significant efficacy [28]. While acute stimulation in both VC/VS and nucleus accumbens (NAc) DBS showed mood and anxiety changes, these effects were manageable with parameter adjustments and didn't co rrelate with long-term outcomes [19]. Focusing on the NAc, given its role in reward-seeking behavior and anhedonia in depression, initial testing showed promising results in TRD, with acute symptom return upon discontinuation of stimulation, which reversed upon reinitiation [43, 44]. Importantly, no negative neuropsychological effects were found in these studies.

The medical forebrain bundle (MFB) is also playing a key function in the reward circuit. Targeting this area is believed to generate a more precise anti-anhedonia effects. Stimulation has shown promising results in treating TRD in several studies. In the first open-label study with 8 TRD patients, high response rates were observed at 6 weeks (85.7%) and 1 year (75% response, 50% remission) [45, 46]. Long-term follow-ups of these patients and another cohort (N=21) demonstrated significant response and remission rates at 6 months, 2 years, and 5 years [47]. Additional studies reported promising response and remission rates in open-label phases but no significant differences in blinded conditions, highlighting the need for further research to understand the underlying mechanisms and optimize MFB DBS for sustained antidepressant effects and minimal side effects [48].

The inferior thalamic peduncle (ITP) is another targeting area. Dorsomedial thalamus and the orbitofrontal cortex are connected by ITP and demonstrated hypermetabolism [49]. Stimulation ITP

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with DBS also demonstrated remission at 12 months [50]. There was not significant difference compared with VC/VS stimulation in 7 TRD patients [51].

4. Closed-loop Adaptive DBS with BCI and Machine Learning

Despite the promising clinical outcomes in DBS to treat TRD patients, side effects from conventional open loop continuous stimulation are not uncommon. With deeper understanding of electrophysiology bio-marker in the brain circuitry, and recent advances achieved in brain-machine interface technology, closed-loop adaptive DBS could optimize stimulation parameters according to the sensing readouts collected from intracranial recordings. The challenges in adaptive DBS design came from two areas. First is choosing a reliable and accessible biomarkers in patients with TRD. Second challenge is the complexity of depression clinical symptoms in TRD. In one case report, this closed-loop adaptive DBS was used in a TRD patient. After conducting a period of stimulus-response mapping of emotion circuitry through implanted stereoelectroencephalography (SEEG) electrodes, researchers found amygdale gamma power was a indicator of high depressive symptom states recorded several times a day. In this case, VC/VS site was chosen to stimulate bilaterally. With the implantation of electros to give deep brain stimulation, another set of leads were implanted into amygdale to receive and detect biomarker. This set of close-loop DBS was able to detect 400 depressive biomarker episodes, which led to six second stimulations. The clinical results also showed rapidly improved both symptom severity and depression. The success of this case has brought a promising future for personalized depression-specific biomarker with closed-loop DBS therapy for TRD [52].

Personalized DBS therapy can benefit greatly from deep machine learning. Through computational algorithm training, brain-machine interface may identify multiple electrophysiological biomarkers with variables, as well as subtle patterns. From more accurate and immediate detection, more efficient stimulation could be given to target specific symptoms and result in patient-tailored treatments [53].

5. Discussion

Despite a promising future of DBS in the treatment of TRD patients, this therapy is still not popularized as it should be. To make this therapy benefit more people, some questions still need to be clarified and answered. Adverse effects associated with DBS is one of the most concerning problems since it's not only an invasive therapy, but also has machine related malfunction to create risks. Acuracy targeting in the brain area require highly cooperative multidisciplinary team including neurosurgery and imagine. Dysphagia, swollen eyes, and incision site pain are all concerning directly related to surgery. Unplanned discontinuation of machine due to battery or machenical resons not only could cause relapse of symtomes but also scuicidal ideation. Also some stimulation related adverse effects such as hypermania or hypomania and even worsening depression were also reported. Safety of this therapy is still the major area to continue work on. Effectiveness of DBS in depression still need to be further proved by excluding skewed clinic outcomes from possible placebo effects. It require more double-blind placebo-controlled trial to build solid outcome data. More proper clinical outcome evaluation systems are also needed to catch up with DBS therapy. The conventional HRDS and MADRS are designed and used to evalue antidepressant effects of treatment therapies but not for circuitry specific intervention from DBS. A alternative measuring system works for DBS on selective neural circuitry should consider elements such as symptom subdimensions.

6. Conclusion

Every day, there are many people globally are suffering from depression who are not able get relief from conventional pharmacological treatment. This has brought huge burden to the person self as

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well as the family around. Deep brain stimulation is not a new technology, and has been used in more and more other neurogenic diseases. The future development of DBS in treat TRD with optimized stimulation relies on continuous understanding of the neural physiology of emotion regulation, advanced imaging technology, and machine learning combined with engineering innovation. Even though it has been over decades since the first successful case of DBS in treating TRD, the broader application of using DBS therapy is still facing many barriers. Limited use of optogenetic technology and functional imaging studies makes precision targeting in the brain a challenge. With the fast developing era of artificial intelligence and neural science, mental illnesses such as treatment resistant depression may have a brighter future.

References

[1] *B. R. Bloem, M. S. Okun, and C. Klein, "Parkinson's disease," The Lancet, vol. 397, no. 10291, pp. 2284–2303, Jun. 2021, doi: 10.1016/S0140-6736(21)00218-X.*

[2] *D. F. Santomauro et al., "Global prevalence and burden of depressive and anxiety disorders in 204 countries and territories in 2020 due to the COVID-19 pandemic," The Lancet, vol. 398, no. 10312, pp. 1700–1712, Nov. 2021, doi: 10.1016/S0140-6736(21)02143-7.*

[3] *Gaynes BN, Asher G, Gartlehner G, et al., "Definition of Treatment-Resistant Depression in the Medicare Population".*

[4] *C. Park et al., "The neural systems of emotion regulation and abnormalities in major depressive disorder," Behav. Brain Res., vol. 367, pp. 181–188, Jul. 2019, doi: 10.1016/j.bbr.2019.04.002.*

[5] *X. Gu, P. R. Hof, K. J. Friston, and J. Fan, "Anterior Insular Cortex and Emotional Awareness," J. Comp. Neurol., vol. 521, no. 15, pp. 3371–3388, Oct. 2013, doi: 10.1002/cne.23368.*

[6] *F. Kurth, K. Zilles, P. T. Fox, A. R. Laird, and S. B. Eickhoff, "A link between the systems: functional differentiation and integration within the human insula revealed by meta-analysis," Brain Struct. Funct., vol. 214, no. 5–6, pp. 519–534, Jun. 2010, doi: 10.1007/s00429-010-0255-z.*

[7] *J. Olds and P. Milner, "Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain," J. Comp. Physiol. Psychol., vol. 47, no. 6, pp. 419–427, Dec. 1954, doi: 10.1037/h0058775.*

[8] *S. H. Journée, V. P. Mathis, C. Fillinger, P. Veinante, and I. Yalcin, "Janus effect of the anterior cingulate cortex: Pain and emotion," Neurosci. Biobehav. Rev., vol. 153, p. 105362, Oct. 2023, doi: 10.1016/j.neubiorev.2023.105362.*

[9] *C. Lu et al., "Insular Cortex is Critical for the Perception, Modulation, and Chronification of Pain," Neurosci. Bull., vol. 32, no. 2, pp. 191–201, Feb. 2016, doi: 10.1007/s12264-016-0016-y.*

[10] *"Cognitive Reappraisal - an overview | ScienceDirect Topics." Accessed: Sep. 23, 2023. [Online]. Available: https://www.sciencedirect.com/topics/psychology/cognitive-reappraisal*

[11] *Y.-X. Wang and B. Yin, "A new understanding of the cognitive reappraisal technique: an extension based on the schema theory," Front. Behav. Neurosci., vol. 17, 2023, Accessed: Sep. 23, 2023. [Online]. Available: https://www.frontiersin.org/articles/10.3389/fnbeh.2023.1174585*

[12] *J. Zhao et al., "The VLPFC versus the DLPFC in Downregulating Social Pain Using Reappraisal and Distraction Strategies," J. Neurosci., vol. 41, no. 6, pp. 1331–1339, Feb. 2021, doi: 10.1523/JNEUROSCI.1906-20.2020.*

[13] *C. M. Tyng, H. U. Amin, M. N. M. Saad, and A. S. Malik, "The Influences of Emotion on Learning and Memory," Front. Psychol., vol. 8, 2017, Accessed: Sep. 23, 2023. [Online]. Available: https://www.frontiersin.org/articles/10.3389/fpsyg.2017.01454*

[14] *X. Zhu, Q. Zhu, H. Shen, W. Liao, and F. Yuan, "Rumination and Default Mode Network Subsystems Connectivity in First-episode, Drug-Naive Young Patients with Major Depressive Disorder," Sci. Rep., vol. 7, p. 43105, Feb. 2017, doi: 10.1038/srep43105.*

[15] *S. C. Trifu, A. C. Trifu, E. Aluaş, M. A. Tătaru, and R. V. Costea, "Brain changes in depression," Rom. J. Morphol. Embryol., vol. 61, no. 2, pp. 361–370, 2020, doi: 10.47162/RJME.61.2.06.*

[16] *"Neural Circuitry of Impaired Emotion Regulation in Substance Use Disorders | American Journal of Psychiatry." Accessed: Sep. 23, 2023. [Online]. Available: https://ajp.psychiatryonline.org/doi/10.1176/appi.ajp.2015.15060710*

[17] *S. J. Russo and E. J. Nestler, "The Brain Reward Circuitry in Mood Disorders," Nat. Rev. Neurosci., vol. 14, no. 9, p. 10.1038/nrn3381, Sep. 2013, doi: 10.1038/nrn3381.*

[18] *S. Delaloye and P. E. Holtzheimer, "Deep brain stimulation in the treatment of depression," Dialogues Clin. Neurosci., vol. 16, no. 1, pp. 83–91, Mar. 2014.*

[19] M. Figee, P. Riva-Posse, K. S. Choi, L. Bederson, H. S. Mayberg, and B. H. Kopell, "Deep Brain Stimulation for Depression," Neurother. J. Am. Soc. Exp. Neurother., vol. 19, no. 4, pp. 1229–1245, Jul. 2022, doi: 10.1007/s13311-022-01270-3.

[20] H. S. Mayberg et al., "Reciprocal limbic-cortical function and negative mood: converging PET findings in depression and normal sadness," Am. J. Psychiatry, vol. 156, no. 5, pp. 675–682, May 1999, doi: 10.1176/ajp.156.5.675.

[21] C. Hamani, H. Mayberg, S. Stone, A. Laxton, S. Haber, and A. M. Lozano, "The subcallosal cingulate gyrus in the context of major depression," Biol. Psychiatry, vol. 69, no. 4, pp. 301–308, Feb. 2011, doi: 10.1016/j.biopsych.2010.09.034.

[22] P. Riva-Posse et al., "Defining critical white matter pathways mediating successful subcallosal cingulate deep brain stimulation for treatment-resistant depression," Biol. Psychiatry, vol. 76, no. 12, pp. 963–969, Dec. 2014, doi: 10.1016/j.biopsych.2014.03.029.

[23] S. H. Siddiqi et al., "Brain stimulation and brain lesions converge on common causal circuits in neuropsychiatric disease," Nat. Hum. Behav., vol. 5, no. 12, pp. 1707–1716, Dec. 2021, doi: 10.1038/s41562-021-01161-1.

[24] S. H. Kennedy et al., "Deep brain stimulation for treatment-resistant depression: follow-up after 3 to 6 years," Am. J. Psychiatry, vol. 168, no. 5, pp. 502–510, May 2011, doi: 10.1176/appi.ajp.2010.10081187.

[25] M. Sobstyl, A. Kupryjaniuk, M. Prokopienko, and M. Rylski, "Subcallosal Cingulate Cortex Deep Brain Stimulation for Treatment-Resistant Depression: A Systematic Review," Front. Neurol., vol. 13, 2022, Accessed: Sep. 23, 2023. [Online]. Available: https://www.frontiersin.org/articles/10.3389/fneur.2022.780481

[26] T. Morishita, S. M. Fayad, M. Higuchi, K. A. Nestor, and K. D. Foote, "Deep brain stimulation for treatment-resistant depression: systematic review of clinical outcomes," Neurother. J. Am. Soc. Exp. Neurother., vol. 11, no. 3, pp. 475–484, Jul. 2014, doi: 10.1007/s13311-014-0282-1.

[27] P. E. Holtzheimer et al., "Subcallosal cingulate deep brain stimulation for treatment-resistant depression: a multisite, randomised, sham-controlled trial," Lancet Psychiatry, vol. 4, no. 11, pp. 839–849, Nov. 2017, doi: 10.1016/S2215-0366(17)30371-1.

[28] Y. Yang, H. Wang, J. Hu, and H. Hu, "Lateral habenula in the pathophysiology of depression," Curr. Opin. Neurobiol., vol. 48, pp. 90–96, Feb. 2018, doi: 10.1016/j.conb.2017.10.024.

[29] F. A. Henn and B. Vollmayr, "Stress models of depression: forming genetically vulnerable strains," Neurosci. Biobehav. Rev., vol. 29, no. 4–5, pp. 799–804, 2005, doi: 10.1016/j.neubiorev.2005.03.019.

[30] K. Ranft, H. Dobrowolny, D. Krell, H. Bielau, B. Bogerts, and H.-G. Bernstein, "Evidence for structural abnormalities of the human habenular complex in affective disorders but not in schizophrenia," Psychol. Med., vol. 40, no. 4, pp. 557–567, Apr. 2010, doi: 10.1017/S0033291709990821.

[31] A. Sartorius et al., "Remission of major depression under deep brain stimulation of the lateral habenula in a therapy-refractory patient," Biol. Psychiatry, vol. 67, no. 2, pp. e9–e11, Jan. 2010, doi: 10.1016/j.biopsych.2009.08.027.

[32] C. Zhang et al., "Bilateral Habenula deep brain stimulation for treatment-resistant depression: clinical findings and electrophysiological features," Transl. Psychiatry, vol. 12, no. 1, p. 52, Feb. 2022, doi: 10.1038/s41398-022-01818-z.

[33] E. J. Nestler, "Role of the Brain's Reward Circuitry in Depression: Transcriptional Mechanisms," Int. Rev. Neurobiol., vol. 124, pp. 151–170, 2015, doi: 10.1016/bs.irn.2015.07.003.

[34] S. J. Rizvi, D. A. Pizzagalli, B. A. Sproule, and S. H. Kennedy, "Assessing anhedonia in depression: Potentials and pitfalls," Neurosci. Biobehav. Rev., vol. 65, pp. 21–35, Jun. 2016, doi: 10.1016/j.neubiorev.2016.03.004.

[35] B. D. Greenberg, S. L. Rauch, and S. N. Haber, "Invasive circuitry-based neurotherapeutics: stereotactic ablation and deep brain stimulation for OCD," Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol., vol. 35, no. 1, pp. 317–336, Jan. 2010, doi: 10.1038/npp.2009.128.

[36] B. Aouizerate et al., "Deep brain stimulation of the ventral caudate nucleus in the treatment of obsessive-compulsive disorder and major depression. Case report," J. Neurosurg., vol. 101, no. 4, pp. 682–686, Oct. 2004, doi: 10.3171/jns.2004.101.4.0682.

[37] K. Quevedo et al., "Ventral Striatum Functional Connectivity during Rewards and Losses and Symptomatology in Depressed Patients," Biol. Psychol., vol. 123, pp. 62–73, Feb. 2017, doi: 10.1016/j.biopsycho.2016.11.004.

[38] B. D. Greenberg et al., "Three-year outcomes in deep brain stimulation for highly resistant obsessive-compulsive disorder," Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol., vol. 31, no. 11, pp. 2384–2393, Nov. 2006, doi: 10.1038/sj.npp.1301165.

[39] T. E. Schlaepfer et al., "Deep brain stimulation to reward circuitry alleviates anhedonia in refractory major depression," Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol., vol. 33, no. 2, pp. 368–377, Jan. 2008, doi: 10.1038/sj.npp.1301408.

[40] B. H. Bewernick, S. Kayser, V. Sturm, and T. E. Schlaepfer, "Long-Term Effects of Nucleus Accumbens Deep Brain Stimulation in Treatment-Resistant Depression: Evidence for Sustained Efficacy," Neuropsychopharmacology, vol. 37, no. 9, Art. no. 9, Aug. 2012, doi: 10.1038/npp.2012.44.

[41] B. H. Bewernick, S. Kayser, S. M. Gippert, C. Switala, V. A. Coenen, and T. E. Schlaepfer, "Deep brain stimulation to the medial forebrain bundle for depression- long-term outcomes and a novel data analysis strategy," Brain Stimulat., vol. 10, no. 3, pp. 664–671, 2017, doi: 10.1016/j.brs.2017.01.581.

[42] T. E. Schlaepfer, B. H. Bewernick, S. Kayser, B. Mädler, and V. A. Coenen, "Rapid effects of deep brain stimulation for treatment-resistant major depression," Biol. Psychiatry, vol. 73, no. 12, pp. 1204–1212, Jun. 2013, doi: 10.1016/j.biopsych.2013.01.034.

[43] B. H. Bewernick et al., "Deep brain stimulation of the supero-lateral branch of the medial forebrain bundle does not lead to changes in personality in patients suffering from severe depression," Psychol. Med., vol. 48, no. 16, pp. 2684–2692, Dec. 2018, doi: 10.1017/S0033291718000296.

[44] V. A. Coenen et al., "Superolateral medial forebrain bundle deep brain stimulation in major depression: a gateway trial," Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol., vol. 44, no. 7, pp. 1224–1232, Jun. 2019, doi: 10.1038/s41386-019-0369-9.

[45] F. Velasco, M. Velasco, F. Jiménez, A. L. Velasco, and R. Salin-Pascual, "Neurobiological background for performing surgical intervention in the inferior thalamic peduncle for treatment of major depression disorders," Neurosurgery, vol. 57, no. 3, pp. 439–448; discussion 439-448, Sep. 2005, doi: 10.1227/01.neu.0000172172.51818.51.

[46] F. Jiménez et al., "A patient with a resistant major depression disorder treated with deep brain stimulation in the inferior thalamic peduncle," Neurosurgery, vol. 57, no. 3, pp. 585–593; discussion 585-593, Sep. 2005, doi: 10.1227/01.neu.0000170434.44335.19.

[47] S. Raymaekers, L. Luyten, C. Bervoets, L. Gabriëls, and B. Nuttin, "Deep brain stimulation for treatment-resistant major depressive disorder: a comparison of two targets and long-term follow-up," Transl. Psychiatry, vol. 7, no. 10, p. e1251, Oct. 2017, doi: 10.1038/tp.2017.66.

[48] K. W. Scangos et al., "Closed-loop neuromodulation in an individual with treatment-resistant depression," Nat. Med., vol. 27, no. 10, Art. no. 10, Oct. 2021, doi: 10.1038/s41591-021-01480-w.

[49] A. M. Oliveira, L. Coelho, E. Carvalho, M. J. Ferreira-Pinto, R. Vaz, and P. Aguiar, "Machine learning for adaptive deep brain stimulation in Parkinson's disease: closing the loop," J. Neurol., Aug. 2023, doi: 10.1007/s00415-023-11873-1.