TOKARZEWSKA, Agata, ORCZYK, Jakub, OŁOWNIA, Aleksandra & MAŁYSZEK, Maciej. Use of deep brain stimulation for treatment-resistant depression - review of main stimulation targets. Journal of Education, Health and Sport. 2023;13(5):18-26. eISSN 2391-8306. DOI http://dx.doi.org/10.12775/JEHS.2023.13.05.002
https://apcz.umk.pl/JEHS/article/view/42665
https://zenodo.org/record/7700283

The journal has had 40 points in Ministry of Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of December 21, 2021. No. 32343.
Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical Culture Sciences (Field of Medical sciences and health sciences); Health Sciences (Field of Medical Sciences and Health Sciences).
Punkty Ministerialne z 2019 - aktualny rok 40 punktów. Załącznik do komunikatu Ministra Edukacji i Nauki z dnia 21 grudnia 2021 r. Lp. 32343. Posiada Unikatowy Identyfikator Czasopisma: 201159.
Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 19.02.2023. Revised: 22.02.2023. Accepted: 04.03.2023. Published: 05.03.2023.

Use of deep brain stimulation for treatment-resistant depression – review of main stimulation targets

Agata Tokarzewska
Uniwersytet Medyczny w Lublinie
https://orcid.org/0000-0001-9539-1697
Jakub Orczyk
Uniwersytet Medyczny w Lublinie
https://orcid.org/0000-0002-4201-545X
Aleksandra Ołownia
Uniwersytet Medyczny w Lublinie
https://orcid.org/0000-0001-6164-6639
Maciej Małyszek
Uniwersytet Medyczny w Lublinie
https://orcid.org/0000-0002-9338-3623

Abstract

Deep brain stimulation (DBS) is an innovative method using neuromodulation in treatment of various diseases, most commonly used in Parkinson's disease, tremor and dystonia. Due to method's minimally invasive nature and very low incidence of severe adverse effects, the research upon its use in other indications is conducted. Treatment-resistant depression (TRD) is one of these emerging indications. Currently available data regarding the matter concentrate mainly of electrode placement within seven particular structures of the brain: the subgenual anterior cingulate cortex, the ventral capsule/ventral striatum, the lateral habenula, the nucleus accumbens, the inferior thalamic peduncle, the bed nucleus of the stria terminalis and the medial forebrain bundle. It is yet to be determined which stimulation targets bring the most optimal effect. Published clinical trials give basis to theorize that stimulation of each DBS target results in different neurotransmitter modulation. Antidepressant effects vary also depending on stimulation parameters and overall duration. The aim of this review is to compare various targets for stimulation and underlying physiological mechanisms in therapy of TRD. It is needed to keep in mind that there is still high demand on well-designed, randomized, double-blind trials on bigger groups of patients in order to exclude potential inconsistency between results of clinical research.
Key words: Deep brain stimulation, Treatment-resistant depressive disorder, Major depressive disorder,

Introduction and purpose

Major depression is a chronic, recurring disease, associated not only with lower quality of everyday functioning, but also estimated shorter life expectancy and suicidal tendencies. Depression makes for a vast financial burden for healthcare worldwide mainly for its recurrent character and with even up to 30% patients being refractory to the standard treatment [1][2][3]. World Mental Health survey conducted in 2011 shows that 14,6% and 11,1% of population of high-income and low-income countries respectively suffer from this disease [4], whereas according to Global Burden of Disease conducted by Institute for Health Metrics and Evaluation in 2017 depression is currently second most prevalent psychiatric disease, with over 4,2% of European population afflicted [5]. Although there are many various means of treatment, it is proven that only a third of patients responds to the first-line pharmacological treatment, whilst even up to 30% patients remain unresponsive towards conventional medications and psychotherapy, resulting in treatment-resistant depression (TRD) [3][6].

Moreover, even in case of patients responsive to conventional therapy, there is a chance of relapse, with high probability of not benefitting from standard treatment anymore [2]. Such statistics generate an urgent need for development of alternative ways of depression treatment, with emphasis put on non-pharmacological interventions, such as transcranial magnetic stimulation, electroconvulsive therapy, epidural cortical stimulation and deep brain stimulation (DBS). The last method mentioned brings promise due to its minimally invasive character and low incidence of severe adverse effects. DBS is currently successfully used as a therapeutic method for tremor, dystonia and Parkinson disease, and, due to its relative safety, the studies to expand its use to other conditions are conducted [7]. The purpose of this paper is to elucidate and summarize current state of knowledge regarding appliance of DBS in TRD treatment.

Description of the state of knowledge

So far as in case of neurological diseases we are capable of determining exact anatomical location of lesion, in psychiatric illnesses we face the problem concerning connections between particular functional areas. Neuroimaging studies present functional locations which take part in development and maintenance of the symptoms of major depression. Studies conducted with use of DBS in depression treatment concentrate on seven main regions: subgenual anterior cingulate cortex (sACC), the ventral capsule/ventral striatum (VC/VS), the nucleus accumbens (NAcc), the lateral habenula (LHb), and the inferior thalamic peduncle (ITP), the medial forebrain bundle (MFB) and the bed nucleus of the stria terminalis (BNST) [8][9].

Subgenual anterior cingulate cortex

sACC, also referred to as Brodmann area 25, is considered to be strongly associated with general feeling of sadness, including anhedonia occurring during major depressive episode. According to Mayberg et al. mood changes in healthy subjects towards sadness or happiness are marked by increase or decrease of cerebral bloodflow within this area, respectively [10]. sACC anatomically and functionally co-creates neural networks prone to malfunctions in the course of major depression. These networks also consist of medial frontal cortex, dorsal medial thalamus, hypothalamus, anterior medial temporal lobe, brainstem nuclei and nucleus accumbens [11][12]. New approach towards pathophysiology of depressive disorder suggests vast role of so-called Default Mode Network (DMN), i.e. a group of brain regions activated during individual's internal mental processes, such as autobiographical memory and interoception [13]. sACC projections are considered important components within limbic and subcortico-cortical neural networks involved in DMN [14]. In terms of technical appliance of DBS, according to Riva-Posse et al. there are three major pathways most likely influencing the final outcome of the stimulation. The first one consists of connection between sACC and medial frontal cortex, with forceps minor and medial aspect of the uncinate fascicle in between. The second way connects sACC mainly with rostral and dorsal anterior cingulate cortex, whilst the third one, short and descending, reaches nucleus caudate, accumbens, putamen and thalamus [15]. For trials regarding other therapeutic methods, popular unit used was cerebral metabolic rate of glucose (CMRGlc). Research shows that increased CMRGlc within sACC in the course of TRD enhances chance of successful outcome of treatment by cingulotomy and accelerated high-frequency transcranial magnetic stimulation [16][17].

The open-laben trial conducted by Mayberg et al. concerned 6 patients with TRD, with minimum entry score of 20 on the 17 item Hamilton Depression Rating Scale (HDRS), who received bilateral sACC DBS. Directly following the electrode implantation, all the patients reported occurrence of sudden chance in perception, including "sudden calmness or lightness", "disappearance of the void", sharpened sense of sight and perception of colour, and increased interest. At end-point after 6 months antidepressant response classified as >50% reduction in HDRS score was noted in 4 out of 6 patients, whereas 3 out of 6 patients went into remission [18]. Results of follow-up study also proved encouraging – average response rates after 1, 2 and 3 years were 62,5%, 46,2% and 75%, respectively, with average result in total of 64,3% [19]. Extended follow-up conducted by Lozano et al. added 14 more patients to the initial group of 6. Response rate after one month and six months into the study was evaluated as 35% and 60%, respectively, with remission rate being 10% and 35% accordingly. The positive effects were maintained up to follow-up in 12th month of the study. Adverse effects occurred unitary and included irritability, pain at pulse generator site, wound infection requiring reinsertion of the hardware, perioperative headaches and perioperative seizure, whereas 7 out of 20 patients had no adverse effects [20]. Due to promising results, there was a need to broaden the research in order to evaluate efficacy and safety of the therapy. That is why a prospective, multicentre, double-blinded, randomised, sham-controlled trial involved 90 participants. The main mean to evaluate the results and compare them between the groups was >40% reduction of the Montgomery-Åsberg Depression Rating Scale (MADRS) score. Even despite patients showing statistically significant improvement in global functioning at 6-months endpoint, there was no statistically significant difference between the stimulation group and the control group (20% and 17%, respectively). By 12 months into the research, response did not increase statistically, but it did increase numerically, reaching 30% and 27% in stimulation and control group, respectively, with remission rate remaining stable (18% and 7% for stimulation and control group, respectively). Non-satisfying results were, however, further explained with probability of misplacement of electrodes or wrong points of stimulation [3][21].

Ventral capsule/ventral striatum

Increased interest in research revolving around VC/VS DBS in TRD was a result of successful therapies involving VC/VS in OCD treatment. The methods used were capsulotomy and said DBS. In both cases patients suffered both from treatment-refractory OCD and major depression – in both cases alleviation of depression symptoms were noted [22][23]. In order to exclude improvement in depression symptoms as an additional effect of amelioration of OCD, there was a need of independent studies concentrating on major depression, TRD specifically. There was a strong physiological basis to such approach. VS is functionally connected with many areas, including caudate, mid and superior prefrontal cortex and anterior cingulate cortex, with this resulting in higher anhedonia risk and suicidality, respectively [24]. By means of tractography it was elucidated that the anterior limb of the internal capsule is broadly connected with brainstem, medial temporal lobe, frontal lobe, hypothalamus, thalamus and nucleus accumbens. Malfunctions within these connections also increase predisposition to display of depressive symptoms. Depressive effect is associated with lesser activation within VS as a response to positive stimuli in subjects with major depression [24][25][26].

The open-label multi-centre study conducted by Malone et al. included 15 patients with highly refractory depression who underwent bilateral VC/VS DBS. Leads were placed in a way that was supposed to mimic dorso-ventral trajectory of the anterior limb of the ventral capsule. The results of the treatment were evaluated using HDRS and MADRS scales, and response was defined as >50% reduction of points in depression scales given in relation to the pre-operative baseline. For MADRS responder rates evaluated at 3 months, 6 months and the last follow-up were 53,3%, 46,7%, and 53,3%, respectively, whilst for HDRS they were 46,7%, 40%, and 53,3%, respectively [27]. On the contrary, the study conducted by Dougherty et al., consisting of 16-week-long double-blind, sham-controlled, randomized phase and followed by open-label phase, did not show as promising results. The 16-week-long sham-controlled phase results failed to meet the predefined study outcome measures. Responders in stimulation group and control group were 20% and 14,3% of patients, respectively. Moreover, there was no difference between cognitive functions of the patients in both groups noted. The MADRS score improvement in the said groups was 19,6% and 24,6%, respectively. At 12 months, during the open-label phase, the mean improvement of MADRS score relative to the baseline was 24,4%. There were also significant adverse effects which occurred during the study, 71 effects in 22 subjects in total, including i.e. worsening depression, suicidal ideation, infection of the post-operative area and suicidal attempts [28]. Bergfeld et al. presented different approach towards the results. In this case 25 patients took part in an open-label study followed by a double-blind crossover phase. After the first phase full response was attained in 40% of patients, partial response was attained in 20% of patients, whilst final remission rate was 20%. The placebo effect occurrence was excluded during active-sham study phase, especially in terms of noticed reduction of depressive symptoms. The authors of the publication noted that the difference in results in comparison to the preceding research may be conditioned by multiple factors, including, among others, slightly different positioning of the electrodes or different approach to the DBS optimization [29]. There is also a note-worthy difference between these two studies, considering difference in gender ratio, with 57% of male participants in Dougherty et al. study and 32% of male patients in Bergfeld et al. study [8]. Moreover, Kubu et al. in randomised double-blind trial performed on 25 patients suggested that age of the patient might be a factor modifying the cognitive outcome of the therapy [30]. The outcome of the study might be influenced by different factors, including need of adjustments of electrodes placement basing on individual anatomical variations or more flexibility regarding assessment of used combinations of stimulation parameters [28][31].

Lateral habenula

The lateral habenula plays important role in perception of reward-related situations. The LHb impulsation is proven to be increased when information regarding omission of the reward is received. It is caused by inhibition of dopaminergic impulsation within ventral striatum, which is activated as a response to anticipation and reception of positive events [32]. Overally, it is also bound to down regulation of serotoninergic and noradrenergic systems and impacts the hypothalamic-pituitary-adrenal axis [33]. Since LHb activation occurs due to detrimental stimulus, is hypothesized that it can associate with some of depression symptoms, including increased pain sensitivity and lowered anticipation of the reward [34]. Due to that, a hypothesis was formulated, according to which deep brain stimulation of LHb should target cessation of its impulsation. Antidepressant effects are bound with increased levels of norepinephrine within medial frontal cortex and hippocampus, as well as elevated levels of serotonin in striatum [33].

There is, however, little data regarding the matter. Meng et al. conducted a study on rats, where depressed animals were divided into the groups of DBS stimulation, sham stimulation, pharmacological treatment and no treatment. At day 21 of the trial horizontal activity was statistically significantly improved in animals undergoing DBS treatment in comparison to sham-stimulated group and control group. At 28 days into the study, both horizontal and vertical activity were increased in the group. It was also noticed that increase of the level of monoamines within blood samples and brain tissues of depressed rats was the highest within group undergoing DBS treatment among all the groups, including group treated pharmacologically [35]. Sartorius et al. conducted the first study on human subject in 2008. The DBS treatment of LHb resulted in full remission of

symptoms of depression in patient who remained therapy-resistant for 9 years. There was, however, no immediate effect to the stimulation, characteristic for DBS of other functional brain areas mentioned in this paper, which may indicate higher chance of neuroplasticity of mood-regulatory circuits in process of recovery [36]. Analogous study was conducted by Wang et al. in 2019. Bilateral DBS procedure within lateral habenula in 34-year-old male patient resulted in amelioration of sleep quality, mood and overall quality of life. On the contrary to previous research, however, there was a notice of acute antidepressant effect of the procedure. The differences may be due to type of patient participating (in 2008 study there was a 64-year-old female patient), as well as different stimulation parameters used [37]. There is still a vast need of conducting more research in this area, in order to obtain more repetitive results on bigger groups.

Nucleus accumbens

On the contrary to sACC and VC/VS, nucleus accumbens is associated with sense of pleasure and reward. There is strong evidence for higher impulsation rates within NAcc as a response to a reward with the opposite effect with being punished. What additionally speaks for role of NAcc in depression is the fact that it structurally and functionally correlates with sense of anhedonia – in patients with major depression NAcc is smaller in size, and thus, its activation in response to pleasure is weaker [38]. The target mechanism for DBS in this case is enhancement of NAcc function.

The study conducted by Bewernick et al. showed 50% response rate in patients who underwent NAcc-DBS within 12 months postsurgery. For one month period 30% of patients went into remission. Similar results were achieved as measured both with HDRS and MADRS. Interestingly, both responders and non-responders throughout the study showed significant reduction of anxiety level, as measured with Hamilton Anxiety Scale (HAMA) [39]. Throughout the study, no worsening of symptoms or progression of cognitive impairment were observed. The main target was met, as it is shown by a survey conducted among patients, concerning activities considered pleasant. Thus, it seems to be possible to modulate particular depressive symptoms, targeting specific brain areas with DBS [39]. Millet et al. designed a pilot multicentre, prospective, non-comparative open study involving 4 patients with TDR, who underwent NAcc DBS, which was switched to caudate nucleus DBS for months 5 to 9 of the trial. Although none of the patients throughout nine-month follow-up could be classified as responsive (>50% decrease in HDRS score) or in remission, there was still a noticeable mood improvement in 3 out of 4 patients in extension phase of the study. There were also more promising results achieved by DBS of NAcc than DBS of caudate nucleus. Moreover, authors point that the better target for DBS would be nucleus accumbens' shell instead of the core, as it is closer related to limbic system [40].

Inferior thalamic peduncle

The ITP consists of neurofibers binding the dorsomedial part of thalamus to the orbitofrontal cortex, which is said to play a big role in so-called non-reward attractor depression theory [3][41]. Research shows that stereotactic tractotomy leading to lesions within the ITP causes the improvement of depressive symptoms, mainly due to interruption in inhibitory effect of thalamo-orbitofrontal system [42][43]. Primarily DBS stimulation of ITP was hypothesized to be prone of activation of the glutamatergic system in relation to arousal, along with cholinergic system [43].

In study conducted by Jimenez et al. the patient underwent stimulator implantation targeting the ITP. The study consisted of period of acute stimulation a week after implantation followed by chronic phase with double-blind stage in months from 8th to 20th. There was acute improvement of patient's state directly after implantation, however it probably resulted from haemorrhage formulated during electrodes insertion, since it may have caused lesions within ITP area. Due to stimulation itself patient's state was ameliorating progressively, with changes such as improvement in manual praxis, abstractive thinking and verbal and non-verbal memory [44]. A few years later Raymaekers et al. compared results of DBS of two targets: ITP and BNST in parallel patient groups. At the end of optimization for ITP and BNST leads, response was elucidated in 4 out of 7 patients and 6 out of 7 patients, respectively for each DBS target. The crossover phase of the study was, however, not substantiated statistically, due to small sample size being one of the limitations of the study [45].

Bed nucleus of the stria terminalis

Bed nucleus of stria terminalis plays major role in stress response regulation, since it is an output pathway of amygdala. Its mechanism of action is meant to modulate feeling of anxiety, mainly through serotoninergic neurotransmission [46]. Although there were very few studies regarding the matter, their results appear promising, including previously mentioned trial by Raymaekers et al. [45][46]. A case report of a patient with coexisting major depression and anorexia nervosa showed gradual amelioration of the condition due to DBS treatment. At first the patient underwent implantation of electrodes within medial forebrain bundle, yet after 10 months trial was ceased due to deterioration of vision. Two years after the first procedure, the patient was re-operated, with electrodes reaching BNST applied. In this case the alleviation of major depression was gradual and profound, with significant decrease in MADRS, HAM-D and HAMA scores, allowing the patient to return to family and social life [47]. A sample group of 5 female patients with TRD took part in study conducted by Fitzgerald et al. Basing on HRDS score, the response rate at 6 months, 12 months and last follow-up was 20%, 40% and 60%, respectively [48]. Bigger group was examined by Neumann et al., with patients

with TRD and obsessive-compulsive disorder taking part. Out of 19 patients in total, 7 patients with TRD had DBS electrodes implanted in sACC area, 7 patients with TRD had them implanted in BNST area, along with 5 OCD patients undergoing DBS of BNST. The study, however, concentrated on spectral recordings of the stimulation rather than psychiatric outcome specifically. The main difference was noted mainly within α-frequency range, which peaked for patients with TRD for both DBS targets, remaining absent in OCD patients. Moreover, there was no significant difference between α-frequency ranges in both DBS targets in patients with TRD. The conducted spectral measurements correlated significantly with self-reported amelioration of depressive symptoms, evaluated using BDI and HDMS scales [49].

Medial forebrain bundle

The medial forebrain bundle is divided into two parts, reaching different areas of the limbic system. Both parts consecutively reach ventral tegmental area, the dentate nucleus of the cerebellum, the upper pons, retrobulbar area, and then the periaqueductal grey. In the end inferomedial MFB reaches lateral hypothalamus, whilst superolateral MFB goes into anterior limb of the internal capsule [50]. It is hypothesized that due to the well-developed net of connections MFB takes part in formation of panic, seeking, and reward, thus taking part in pathophysiology of depression, when these systems do not function properly [51]. It is supported by the findings of reduced fractional anisotropy of MFB in patients with major depression [52].

A few studies regarding efficacy of DBS of superolateral MFB in patients with TRD were conducted, bringing rather spectacular results. In study by Bewernick et al., after 12 months of consecutive DBS, 75% of patients taking part in the trial (6 out of 8 patients) were classified as responders, basing on MADRS score. Out of non-responders, one was classified as responsive for 4 months, whereas the other did not reach responsiveness at all. The alleviation of depressive symptoms was noticeable throughout the study by improvements of BDI, HAMA and HDRS scores each month comparing to the baseline [53]. In single-centre study with double-blinded phase by Coenen et al. all 16 patients were responsive to the treatment, as indicated by reduction of MADRS score. Averagely, responsiveness was achieved within 61% of months spent in the trial. Moreover, at the 12-month endpoint of the study, 8 out of 16 patients went into remission. During double-blinded phase there were no differences in cognitive domains between sham and active stimulation groups. There was also no effect noticed for most cognitive domains in both groups throughout entire study, with an exception for verbal learning and language IQ, which significantly improved between baseline and endpoint [54].

As much as DBS of MFB is an undoubtedly promising method of TDR treatment, vast controversy concerns exact mechanism of action of stimulation in this case. Basing on animal models it was suggested that in this case DBS works by increasing the number of dopaminergic receptors within prefrontal cortex and hippocampal dopamine transporters [55]. However, it remained unclear whether changes in dopamine levels in examined rats were casual for behavioural changes observed throughout the study, and whether this data is even applicable for explanation of human neurocircuitry [56]. This uncertainty is additionally built-up by research by Bregman et al., who noticed that dopamine axons are not myelinated either in humans or in rats, thus they cannot be recruited using standard stimulation parameters for DBS. Moreover, during experiments on rats, no additional dopamine release was registered during MFB DBS protocol. Such data indicates a need of more thorough exploration of mechanism of action of MFB DBS [56][57].

Summary

In conclusion, although DBS brings promising results in many studies, taking into consideration various target areas within the brain, we need to keep in mind that it still remains an experimental method. Research papers available describe trials which in most cases concern singular patients or small groups, often with unsuccessfully conducted double-blinded phase. There is a need of reaching higher repeatability of the results on larger sample groups in order to clarify future use of the treatment. It is undeniable, however, that DBS is much safer, reversible method, with smaller chance of adverse effects than previously used lesioning of particular brain areas. Once there is more evidence of effectiveness of the therapy and exact mechanism of action is elucidated, it will be more probable for DBS to become an important tool in treatment of TRD.

References

1. Ranjan M, Ranjan N, Deogaonkar M, Rezai A. Deep Brain Stimulation for Refractory Depression, Obsessive-Compulsive Disorder and Addiction. Neurol India [serial online] 2020 [cited 2022 Dec 8];68, Suppl S2:282-7. Available from: https://www.neurologyindia.com/text.asp?2020/68/8/282/302459
2. Filkowski MM, Sheth SA. Deep Brain Stimulation for Depression: An Emerging Indication. Neurosurg Clin N Am. 2019 Apr;30(2):243-256. doi: 10.1016/j.nec.2018.12.007. Epub 2019 Feb 18. PMID: 30898275.
3. Dandekar MP, Fenoy AJ, Carvalho AF, Soares JC, Quevedo J. Deep brain stimulation for treatment-resistant depression: an integrative review of preclinical and clinical findings and translational

implications. Mol Psychiatry. 2018 May;23(5):1094-1112. doi: 10.1038/mp.2018.2. Epub 2018 Feb 27. PMID: 29483673.
4. Bromet E, Andrade LH, Hwang I, Sampson NA, Alonso J, de Girolamo G, de Graaf R, Demyttenaere K, Hu C, Iwata N, Karam AN, Kaur J, Kostyuchenko S, Lépine JP, Levinson D, Matschinger H, Mora ME, Browne MO, Posada-Villa J, Viana MC, Williams DR, Kessler RC. Cross-national epidemiology of DSM-IV major depressive episode. BMC Med. 2011 Jul 26;9:90. doi: 10.1186/1741-7015-9-90. PMID: 21791035; PMCID: PMC3163615.
5. IHME, 2020. Global health data exchange. URL: http://ghdx.healthdata.org/ gbd-results-tool.
6. Rush AJ, Trivedi MH, Wisniewski SR, Stewart JW, Nierenberg AA, Thase ME et al. Bupropion-SR, sertraline, or venlafaxine-XR after failure of SSRIs for depression. N Engl J Med 2006; 354: 1231–1242.
7. Krauss, J. K., Lipsman, N., Aziz, T., Boutet, A., Brown, P., Chang, J. W., … Lozano, A. M. (2020). Technology of deep brain stimulation: current status and future directions. Nature Reviews Neurology. doi:10.1038/s41582-020-00426-z
8. Drobisz D, Damborská A. Deep brain stimulation targets for treating depression. Behav Brain Res. 2019 Feb 1;359:266-273. doi: 10.1016/j.bbr.2018.11.004. Epub 2018 Nov 8. PMID: 30414974.
9. La Torre D, Della Torre A, Chirchiglia D, Volpentesta G, Guzzi G, Lavano A. Deep brain stimulation for treatment-resistant depression: a safe and effective option. Expert Rev Neurother. 2020 May;20(5):449-457. doi: 10.1080/14737175.2020.1749049. Epub 2020 Apr 4. PMID: 32223454.
10. Mayberg HS, Liotti M, Brannan SK, McGinnis S, Mahurin RK, Jerabek PA, Silva JA, Tekell JL, Martin CC, Lancaster JL, Fox PT. Reciprocal limbic-cortical function and negative mood: converging PET findings in depression and normal sadness. Am J Psychiatry. 1999 May;156(5):675-82. doi: 10.1176/ajp.156.5.675. PMID: 10327898.
11. Hamani C, Mayberg H, Stone S, Laxton A, Haber S, Lozano AM. The subcallosal cingulate gyrus in the context of major depression. Biol Psychiatry. 2011 Feb 15;69(4):301-8. doi: 10.1016/j.biopsych.2010.09.034. Epub 2010 Dec 8. PMID: 21145043.
12. Drevets WC, Savitz J, Trimble M. The subgenual anterior cingulate cortex in mood disorders. CNS Spectr. 2008 Aug;13(8):663-81. doi: 10.1017/s1092852900013754. PMID: 18704022; PMCID: PMC2729429.
13. Hamed Ekhtiari, Padideh Nasseri, Fatemeh Yavari, Azarkhsh Mokri, John Monterosso, Chapter 7 - Neuroscience of drug craving for addiction medicine: From circuits to therapies, Editor(s): Hamed Ekhtiari, Martin Paulus, Progress in Brain Research, Elsevier, Volume 223, 2016, Pages 115-141, ISSN 0079-6123, ISBN 9780444635457,
14. Greicius MD, Flores BH, Menon V, Glover GH, Solvason HB, Kenna H, Reiss AL, Schatzberg AF. Resting-state functional connectivity in major depression: abnormally increased contributions from subgenual cingulate cortex and thalamus. Biol Psychiatry. 2007 Sep 1;62(5):429-37. doi: 10.1016/j.biopsych.2006.09.020. Epub 2007 Jan 8. PMID: 17210143; PMCID: PMC2001244.
15. Riva-Posse P, Choi KS, Holtzheimer PE, McIntyre CC, Gross RE, Chaturvedi A, Crowell AL, Garlow SJ, Rajendra JK, Mayberg HS. Defining critical white matter pathways mediating successful subcallosal cingulate deep brain stimulation for treatment-resistant depression. Biol Psychiatry. 2014 Dec 15;76(12):963-9. doi: 10.1016/j.biopsych.2014.03.029. Epub 2014 Apr 13. PMID: 24832866; PMCID: PMC4487804.
16. Dougherty DD, Weiss AP, Cosgrove GR, Alpert NM, Cassem EH, Nierenberg AA, Price BH, Mayberg HS, Fischman AJ, Rauch SL. Cerebral metabolic correlates as potential predictors of response to anterior cingulotomy for treatment of major depression. J Neurosurg. 2003 Dec;99(6):1010-7. doi: 10.3171/jns.2003.99.6.1010. PMID: 14705729.
17. Baeken C, Marinazzo D, Everaert H, Wu GR, Van Hove C, Audenaert K, Goethals I, De Vos F, Peremans K, De Raedt R. The Impact of Accelerated HF-rTMS on the Subgenual Anterior Cingulate Cortex in Refractory Unipolar Major Depression: Insights From 18FDG PET Brain Imaging. Brain Stimul. 2015 Jul-Aug;8(4):808-15. doi: 10.1016/j.brs.2015.01.415. Epub 2015 Feb 7. PMID: 25744500.
18. Mayberg HS, Lozano AM, Voon V, McNeely HE, Seminowicz D, Hamani C, Schwalb JM, Kennedy SH. Deep brain stimulation for treatment-resistant depression. Neuron. 2005 Mar 3;45(5):651-60. doi: 10.1016/j.neuron.2005.02.014. PMID: 15748841.
19. Kennedy SH, Giacobbe P, Rizvi SJ, Placenza FM, Nishikawa Y, Mayberg HS, Lozano AM. Deep brain stimulation for treatment-resistant depression: follow-up after 3 to 6 years. Am J Psychiatry. 2011 May;168(5):502-10. doi: 10.1176/appi.ajp.2010.10081187. Epub 2011 Feb 1. PMID: 21285143.
20. Lozano AM, Mayberg HS, Giacobbe P, Hamani C, Craddock RC, Kennedy SH. Subcallosal cingulate gyrus deep brain stimulation for treatment-resistant depression. Biol Psychiatry. 2008 Sep 15;64(6):461-7. doi: 10.1016/j.biopsych.2008.05.034. Epub 2008 Jul 18. PMID: 18639234.

21. Holtzheimer, P. E., Husain, M. M., Lisanby, S. H., Taylor, S. F., Whitworth, L. A., McClintock, S., … Mayberg, H. S. (2017). Subcallosal cingulate deep brain stimulation for treatment-resistant depression: a multisite, randomised, sham-controlled trial. The Lancet Psychiatry, 4(11), 839–849. doi:10.1016/s2215-0366(17)30371-1
22. Zhan S, Liu W, Li D, Pan S, Pan Y, Li Y, Lin G, Sun B. Long-term follow-up of bilateral anterior capsulotomy in patients with refractory obsessive-compulsive disorder. Clin Neurol Neurosurg. 2014 Apr;119:91-5. doi: 10.1016/j.clineuro.2014.01.009. Epub 2014 Jan 24. PMID: 24635934.
23. Aouizerate B, Cuny E, Martin-Guehl C, Guehl D, Amieva H, Benazzouz A, Fabrigoule C, Allard M, Rougier A, Bioulac B, Tignol J, Burbaud P. Deep brain stimulation of the ventral caudate nucleus in the treatment of obsessive-compulsive disorder and major depression. Case report. J Neurosurg. 2004 Oct;101(4):682-6. doi: 10.3171/jns.2004.101.4.0682. PMID: 15481726.
24. Hwang JW, Xin SC, Ou YM, Zhang WY, Liang YL, Chen J, Yang XQ, Chen XY, Guo TW, Yang XJ, Ma WH, Li J, Zhao BC, Tu Y, Kong J. Enhanced default mode network connectivity with ventral striatum in subthreshold depression individuals. J Psychiatr Res. 2016 May;76:111-20. doi: 10.1016/j.jpsychires.2016.02.005. Epub 2016 Feb 13. PMID: 26922247; PMCID: PMC4838997.
25. Gutman DA, Holtzheimer PE, Behrens TE, Johansen-Berg H, Mayberg HS. A tractography analysis of two deep brain stimulation white matter targets for depression. Biol Psychiatry. 2009 Feb 15;65(4):276-82. doi: 10.1016/j.biopsych.2008.09.021. Epub 2008 Nov 14. PMID: 19013554; PMCID: PMC4423548.
26. Epstein J, Pan H, Kocsis JH, Yang Y, Butler T, Chusid J, Hochberg H, Murrough J, Strohmayer E, Stern E, Silbersweig DA. Lack of ventral striatal response to positive stimuli in depressed versus normal subjects. Am J Psychiatry. 2006 Oct;163(10):1784-90. doi: 10.1176/ajp.2006.163.10.1784. PMID: 17012690.
27. Malone DA Jr, Dougherty DD, Rezai AR, Carpenter LL, Friehs GM, Eskandar EN, Rauch SL, Rasmussen SA, Machado AG, Kubu CS, Tyrka AR, Price LH, Stypulkowski PH, Giftakis JE, Rise MT, Malloy PF, Salloway SP, Greenberg BD. Deep brain stimulation of the ventral capsule/ventral striatum for treatment-resistant depression. Biol Psychiatry. 2009 Feb 15;65(4):267-75. doi: 10.1016/j.biopsych.2008.08.029. Epub 2008 Oct 8. PMID: 18842257; PMCID: PMC3486635.
28. Dougherty DD, Rezai AR, Carpenter LL, Howland RH, Bhati MT, O'Reardon JP, Eskandar EN, Baltuch GH, Machado AD, Kondziolka D, Cusin C, Evans KC, Price LH, Jacobs K, Pandya M, Denko T, Tyrka AR, Brelje T, Deckersbach T, Kubu C, Malone DA Jr. A Randomized Sham-Controlled Trial of Deep Brain Stimulation of the Ventral Capsule/Ventral Striatum for Chronic Treatment-Resistant Depression. Biol Psychiatry. 2015 Aug 15;78(4):240-8. doi: 10.1016/j.biopsych.2014.11.023. Epub 2014 Dec 13. PMID: 25726497.
29. Bergfeld IO, Mantione M, Hoogendoorn ML, Ruhé HG, Notten P, van Laarhoven J, Visser I, Figee M, de Kwaasteniet BP, Horst F, Schene AH, van den Munckhof P, Beute G, Schuurman R, Denys D. Deep Brain Stimulation of the Ventral Anterior Limb of the Internal Capsule for Treatment-Resistant Depression: A Randomized Clinical Trial. JAMA Psychiatry. 2016 May 1;73(5):456-64. doi: 10.1001/jamapsychiatry.2016.0152. PMID: 27049915.
30. Kubu CS, Brelje T, Butters MA, Deckersbach T, Malloy P, Moberg P, Tröster AI, Williamson E, Baltuch GH, Bhati MT, Carpenter LL, Dougherty DD, Howland RH, Rezai AR, Malone DA Jr. Cognitive outcome after ventral capsule/ventral striatum stimulation for treatment-resistant major depression. J Neurol Neurosurg Psychiatry. 2017 Mar;88(3):262-265. doi: 10.1136/jnnp-2016-313803. Epub 2016 Sep 22. PMID: 27659923.
31. Morishita T, Fayad SM, Higuchi MA, Nestor KA, Foote KD. Deep brain stimulation for treatment-resistant depression: systematic review of clinical outcomes. Neurotherapeutics. 2014 Jul;11(3):475-84. doi: 10.1007/s13311-014-0282-1. PMID: 24867326; PMCID: PMC4121451.
32. Matsumoto M, Hikosaka O. Lateral habenula as a source of negative reward signals in dopamine neurons. Nature. 2007 Jun 28;447(7148):1111-5. doi: 10.1038/nature05860. Epub 2007 May 23. PMID: 17522629.
33. Sartorius A, Henn FA. Deep brain stimulation of the lateral habenula in treatment resistant major depression. Med Hypotheses. 2007;69(6):1305-8. doi: 10.1016/j.mehy.2007.03.021. Epub 2007 May 10. PMID: 17498883.
34. Shelton L, Pendse G, Maleki N, Moulton EA, Lebel A, Becerra L, Borsook D. Mapping pain activation and connectivity of the human habenula. J Neurophysiol. 2012 May;107(10):2633-48. doi: 10.1152/jn.00012.2012. Epub 2012 Feb 8. PMID: 22323632; PMCID: PMC3362277.
35. Meng H, Wang Y, Huang M, Lin W, Wang S, Zhang B. Chronic deep brain stimulation of the lateral habenula nucleus in a rat model of depression. Brain Res. 2011 Nov 8;1422:32-8. doi: 10.1016/j.brainres.2011.08.041. Epub 2011 Aug 22. PMID: 21978548.

36. Sartorius A, Kiening KL, Kirsch P, von Gall CC, Haberkorn U, Unterberg AW, Henn FA, Meyer-Lindenberg A. Remission of major depression under deep brain stimulation of the lateral habenula in a therapy-refractory patient. Biol Psychiatry. 2010 Jan 15;67(2):e9-e11. doi: 10.1016/j.biopsych.2009.08.027. PMID: 19846068.
37. Wang Z, Cai X, Qiu R, Yao C, Tian Y, Gong C, Zhang Y, Xu B, Zhang D, Zang Y, Liu J, Peng B, Li L. Case Report: Lateral Habenula Deep Brain Stimulation for Treatment-Resistant Depression. Front Psychiatry. 2021 Jan 13;11:616501. doi: 10.3389/fpsyt.2020.616501. PMID: 33519557; PMCID: PMC7838359.
38. Wacker J, Dillon DG, Pizzagalli DA. The role of the nucleus accumbens and rostral anterior cingulate cortex in anhedonia: integration of resting EEG, fMRI, and volumetric techniques. Neuroimage. 2009 May 15;46(1):327-37. doi: 10.1016/j.neuroimage.2009.01.058. Epub 2009 Feb 6. PMID: 19457367; PMCID: PMC2686061.
39. Bewernick BH, Hurlemann R, Matusch A, Kayser S, Grubert C, Hadrysiewicz B, Axmacher N, Lemke M, Cooper-Mahkorn D, Cohen MX, Brockmann H, Lenartz D, Sturm V, Schlaepfer TE. Nucleus accumbens deep brain stimulation decreases ratings of depression and anxiety in treatment-resistant depression. Biol Psychiatry. 2010 Jan 15;67(2):110-6. doi: 10.1016/j.biopsych.2009.09.013. PMID: 19914605.
40. Millet B, Jaafari N, Polosan M, Baup N, Giordana B, Haegelen C, Chabardes S, Fontaine D, Devaux B, Yelnik J, Fossati P, Aouizerate B, Krebs MO, Robert G, Jay T, Cornu P, Vérin M, Drapier S, Drapier D, Sauleau P, Peron J, Le Jeune F, Naudet F, Reymann JM. Limbic versus cognitive target for deep brain stimulation in treatment-resistant depression: accumbens more promising than caudate. Eur Neuropsychopharmacol. 2014 Aug;24(8):1229-39. doi: 10.1016/j.euroneuro.2014.05.006. Epub 2014 May 20. PMID: 24950819.
41. Rolls ET. A non-reward attractor theory of depression. Neurosci Biobehav Rev. 2016 Sep;68:47-58. doi: 10.1016/j.neubiorev.2016.05.007. Epub 2016 May 12. PMID: 27181908.
42. KNIGHT G. STEREOTACTIC TRACTOTOMY IN THE SURGICAL TREATMENT OF MENTAL ILLNESS. J Neurol Neurosurg Psychiatry. 1965 Aug;28(4):304-10. doi: 10.1136/jnnp.28.4.304. PMID: 14338119; PMCID: PMC495909.
43. Velasco M, Velasco F, Jiménez F, Carrillo-Ruiz JD, Velasco AL, Salín-Pascual R. Electrocortical and behavioral responses elicited by acute electrical stimulation of inferior thalamic peduncle and nucleus reticularis thalami in a patient with major depression disorder. Clin Neurophysiol. 2006 Feb;117(2):320-7. doi: 10.1016/j.clinph.2005.10.023. Epub 2006 Jan 3. PMID: 16403484.
44. Jiménez F, Velasco F, Salin-Pascual R, Hernández JA, Velasco M, Criales JL, Nicolini H. A patient with a resistant major depression disorder treated with deep brain stimulation in the inferior thalamic peduncle. Neurosurgery. 2005 Sep;57(3):585-93; discussion 585-93. doi: 10.1227/01.neu.0000170434.44335.19. PMID: 16145540.
45. Raymaekers S, Luyten L, Bervoets C, Gabriëls L, Nuttin B. Deep brain stimulation for treatment-resistant major depressive disorder: a comparison of two targets and long-term follow-up. Transl Psychiatry. 2017 Oct 31;7(10):e1251. doi: 10.1038/tp.2017.66. PMID: 29087373; PMCID: PMC5682606.
46. Lebow MA, Chen A. Overshadowed by the amygdala: the bed nucleus of the stria terminalis emerges as key to psychiatric disorders. Mol Psychiatry. 2016 Apr;21(4):450-63. doi: 10.1038/mp.2016.1. Epub 2016 Feb 16. Erratum in: Mol Psychiatry. 2021 Aug;26(8):4561. PMID: 26878891; PMCID: PMC4804181.
47. Blomstedt P, Naesström M, Bodlund O. Deep brain stimulation in the bed nucleus of the stria terminalis and medial forebrain bundle in a patient with major depressive disorder and anorexia nervosa. Clin Case Rep. 2017 Mar 31;5(5):679-684. doi: 10.1002/ccr3.856. PMID: 28469875; PMCID: PMC5412827.
48. Sobstyl M, Kupryjaniuk A, Prokopienko M, Rylski M. Subcallosal Cingulate Cortex Deep Brain Stimulation for Treatment-Resistant Depression: A Systematic Review. Front Neurol. 2022 Apr 1;13:780481. doi: 10.3389/fneur.2022.780481. PMID: 35432155; PMCID: PMC9012165.
49. Neumann WJ, Huebl J, Brücke C, Gabriëls L, Bajbouj M, Merkl A, Schneider GH, Nuttin B, Brown P, Kühn AA. Different patterns of local field potentials from limbic DBS targets in patients with major depressive and obsessive compulsive disorder. Mol Psychiatry. 2014 Nov;19(11):1186-92. doi: 10.1038/mp.2014.2. Epub 2014 Feb 11. PMID: 24514569; PMCID: PMC4813757.
50. Coenen VA, Panksepp J, Hurwitz TA, Urbach H, Mädler B. Human medial forebrain bundle (MFB) and anterior thalamic radiation (ATR): imaging of two major subcortical pathways and the dynamic balance of opposite affects in understanding depression. J Neuropsychiatry Clin Neurosci. 2012 Spring;24(2):223-36. doi: 10.1176/appi.neuropsych.11080180. PMID: 22772671.

51. Waraczynski MA. The central extended amygdala network as a proposed circuit underlying reward valuation. Neurosci Biobehav Rev. 2006;30(4):472-96. doi: 10.1016/j.neubiorev.2005.09.001. Epub 2005 Oct 21. PMID: 16243397.
52. Bracht T, Horn H, Strik W, Federspiel A, Schnell S, Höfle O, Stegmayer K, Wiest R, Dierks T, Müller TJ, Walther S. White matter microstructure alterations of the medial forebrain bundle in melancholic depression. J Affect Disord. 2014 Feb;155:186-93. doi: 10.1016/j.jad.2013.10.048. Epub 2013 Nov 5. PMID: 24252169.
53. Bewernick BH, Kayser S, Gippert SM, Switala C, Coenen VA, Schlaepfer TE. Deep brain stimulation to the medial forebrain bundle for depression- long-term outcomes and a novel data analysis strategy. Brain Stimul. 2017 May-Jun;10(3):664-671. doi: 10.1016/j.brs.2017.01.581. Epub 2017 Feb 9. PMID: 28259544.
54. Coenen VA, Bewernick BH, Kayser S, Kilian H, Boström J, Greschus S, Hurlemann R, Klein ME, Spanier S, Sajonz B, Urbach H, Schlaepfer TE. Superolateral medial forebrain bundle deep brain stimulation in major depression: a gateway trial. Neuropsychopharmacology. 2019 Jun;44(7):1224-1232. doi: 10.1038/s41386-019-0369-9. Epub 2019 Mar 13. PMID: 30867553; PMCID: PMC6785007.
55. Dandekar MP, Luse D, Hoffmann C, Cotton P, Peery T, Ruiz C, Hussey C, Giridharan VV, Soares JC, Quevedo J, Fenoy AJ. Increased dopamine receptor expression and anti-depressant response following deep brain stimulation of the medial forebrain bundle. J Affect Disord. 2017 Aug 1;217:80-88. doi: 10.1016/j.jad.2017.03.074. Epub 2017 Apr 5. PMID: 28395208.
56. Bregman T, Reznikov R, Diwan M, Raymond R, Butson CR, Nobrega JN, Hamani C. Antidepressant-like Effects of Medial Forebrain Bundle Deep Brain Stimulation in Rats are not Associated With Accumbens Dopamine Release. Brain Stimul. 2015 Jul-Aug;8(4):708-13. doi: 10.1016/j.brs.2015.02.007. Epub 2015 Mar 10. PMID: 25835354.
57. Fenoy AJ, Quevedo J, Soares JC. Deep brain stimulation of the "medial forebrain bundle": a strategy to modulate the reward system and manage treatment-resistant depression. Mol Psychiatry. 2022 Jan;27(1):574-592. doi: 10.1038/s41380-021-01100-6. Epub 2021 Apr 26. PMID: 33903731.