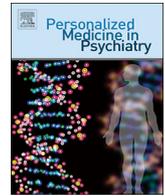




Contents lists available at ScienceDirect

# Personalized Medicine in Psychiatry

journal homepage: [www.elsevier.com/locate/pmip](http://www.elsevier.com/locate/pmip)

## Putative novel neuromodulatory treatments for affective disorders – What might emerge?



Hannah M. Kilian<sup>a</sup>, Dora M. Meyer<sup>a</sup>, Thomas E. Schlaepfer<sup>a,b,\*</sup>

<sup>a</sup> Department of Interventional Biological Psychiatry, Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, Germany

<sup>b</sup> Departments of Psychiatry and Mental Health, The Johns Hopkins University, Baltimore, MD, USA

A considerable amount of research investigating the pathophysiology of psychiatric diseases led to a better understanding of neurochemical, neuroanatomical, environmental and genetic bases of affective and compulsive disorders [1]. In the last decades, biological components of psychiatric diseases became important and neural network models have been developed. These network models describe psychiatric diseases as a dysfunction of specific brain circuits. Particularly, networks mediating mood and reward responses play an important role in major depressive disorder (MDD) and in obsessive compulsive disorder (OCD) as well [2,3]. Research from different disciplines has led to novel conceptualizations of the underlying neurobiology of affective disorders in the term of a network of tightly integrated and reciprocally connected centers processing affective stimuli. Those centers communicate both chemically and electrically. Therefore new emerging treatments can be developed using specific chemical and electrical stimulation to regulate those circuits. In this article, we focus on deep brain stimulation (DBS) with an open-loop as well as closed-loop system, highlight new insights from optogenetics as well as magnetogenetics, demonstrate new developments in ablative surgery techniques like focused ultrasound and introduce the new field of temporal interference.

Famm and colleagues [4] describe a future where the majority of medical treatments will use electrical impulses to repair lost function and restore health. Already, devices treating disease conditions with electrical stimulation could be implemented targeting disease-specific neural circuits but not specific cells within those circuits. To create devices controlling action potentials in individual neurons interdisciplinary teams need to be established in the future [4]. Their perspective is interesting because all the authors are working at a pharmaceutical manufacturer, highlighting a concept shift from pharmacology to neuromodulation.

We believe that DBS is the most promising modality of targeted neuromodulation regarding its efficacy and the ability to precisely verify predetermined hypotheses, today. DBS is an invasive treatment that requires a neurosurgical procedure for the bilateral implantation of electrodes into specific, well selected brain targets. This treatment is

approved for movement disorders, especially Parkinson's disease (PD), dystonia and essential tremor showing high effects at controlling motor symptoms [5]. Until today, more than .000 patients with movement disorders are treated with DBS. Recently, DBS has been actively researched as a treatment option for psychiatric diseases, especially MDD and has been associated with rapid and sustained antidepressant effects [6,7]. Different brain targets associated with the brain reward circuit have been investigated so far. In brief, the following targets have successfully been used for DBS in MDD: subgenual cingulate cortex (Cg25) [8], anterior limb of the capsule interna (ALIC) [9], nucleus accumbens (NAcc) [10], ventral capsule (Vc)/ventral striatum (Vs) [11] and the superolateral branch of the medial forebrain bundle (sIMFB) [12].

The sIMFB has been proposed as a more effective DBS target for MDD as it is neuroanatomically and functionally connected with other DBS targets described and evaluated in depression (SCC, ALIC and NAcc) [13]. The results of sIMFB DBS in treatment-resistant depression (TRD) showed rapid antidepressant effects one week after stimulation onset in two independent unblinded non-randomized trials [12,14]. These promising results have been replicated in a larger randomized controlled trial (RCT) describing comparable acute effects in 16 patients [15]. Besides these acute effects, sIMFB DBS could be associated with sustained antidepressant efficacy up to five years after stimulation onset [16,17]. Blinded discontinuation of stimulation after continuous stimulation of six to twelve months was associated with an aggravation of depressive symptoms emphasizing the idea that permanent stimulation is needed to maintain response [8,9]. Although these data are promising, two RCTs one stimulating Vc/Vs [18] and one stimulating Cg25 [19] showed controversial results. Both studies failed to show superiority of DBS to sham stimulation at short-time because they were terminated after a futility analysis in a subgroup of patients. Among other reasons, the study design has been put forward as a major problem [20]. The RCT trial investigating sIMFB DBS did not show a significant difference between active and sham stimulation eight weeks after stimulation onset either [15]. Nonetheless, there was a trend showing an increase of depressive symptoms in the sham control group after eight weeks. This observation seems interesting in the light of the

\* Corresponding author at: Department of Interventional Biological Psychiatry, Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, Germany.

E-mail address: [Thomas.schlaepfer@uniklinik-freiburg.de](mailto:Thomas.schlaepfer@uniklinik-freiburg.de) (T.E. Schlaepfer).

<https://doi.org/10.1016/j.pmip.2019.07.002>

effect that insertion effects have been described in PD as well [21]. It is assumed that eight weeks are not sufficient to show a significant difference between both groups regarding the influences of electrode insertion and placebo. Irrespective of brain target, acute antidepressant effects after surgery were observed even in the sham group. These effects need to be studied in more detail and should be taken into account in the planning of larger RCTs. The first pilot trial (FORESEE I; registered @clinicaltrials.gov with Identifier NCT01095263) and one gateway trial (FORESEE II; registered @clinicaltrials.gov with Identifier NCT01778790) have been completed investigating the efficacy of sMFB DBS in MDD with promising results paving the way for a third multicenter, randomized, sham-controlled and double blind study currently recruiting up to 50 patients with TRD (registered @clinicaltrials.gov with Identifier NCT03653858). In summary, the results of studies investigating sMFB DBS support the hypothesis of network dysfunctions in TRD and the idea of DBS restoring and regulating the function of this dysfunctional network [2,12,22].

Despite its therapeutic effects, there is still uncertainty on underlying biological mechanisms of DBS [23,24]. Functional abnormalities might be reversed due to inhibition of neuronal networks or activation of neurons. It is hypothesized, that DBS may suppress pathological states, modulate pathological brain activity or lead to a recalibration of functional states. In studies investigating NAcc DBS in TRD, stimulation was associated with acutely decreased hypometabolism in the prefrontal cortex (PFC) and acutely increased metabolism in the Vs [10,25]. Furthermore, different neurotransmitter systems (e.g. dopamine) seem to play an important role in the effects of DBS. Studies investigating dopamine following sMFB DBS in rodents reported a significant increase in dopamine D2 receptors in the PFC [26] and an increase of dopamine release in the Vs acutely after onset of stimulation [27].

Additionally, precise predictors of response are lacking. It might very well be that ‘one size fits them all’ is likely in DBS but nonetheless some patients appear not to respond to this treatment. In the currently used open-loop DBS systems, stimulation parameters have to be adapted manually by the physician at clinical visits. Once, stimulation parameters are set by the physician, DBS delivers a constant level of stimulation regardless of different disease states. Due to the reason that the symptomatology of mental disorders is not static and that the severity of symptoms may fluctuate over time (days/months/years), a constant stimulation may not be the most efficient option. Furthermore, efficacy of therapeutic parameters may diminish over time, acute responses do not guarantee sustained therapeutic effects and parameter adaptation relies on the subjective experience of both the patient and clinician. Clinicians may have to repeat a trial-and-error based process several times to find the stimulation parameters with the best clinical outcome for the individual patient. This trial and error procedure in order to find the most efficient stimulation parameters currently is inevitable in open-loop DBS systems. Additionally, the stimulation parameters cannot be adapted acutely in response to aggravation of disease symptoms [3,28]. Together, all these factors may complicate optimized stimulation in open-loop DBS systems. Steps towards an individualized treatment and personalized medicine with a better treatment selection for individual patients as well as automatic parameter adaptation considering the different disease states seem relevant for the development of future DBS systems.

Closed-loop/adaptive DBS systems can be one of those steps. There are several logical possibilities that make the development of closed-loop stimulation systems mandatory. Closed-loop control systems rely on sensor feedback. In those systems, an adaptation of stimulation parameters following changes of biological brain states (neurochemical changes, changes in electrical brain activity) is possible as an acute response without the need of a clinical visit. Studies focusing on the development and implementation of closed-loop systems use anatomical as well as physiological approaches [29]. While the anatomical approach rather describes ways to place the electrode individually

relative to the individual brain, the physiological approach deals with the challenge to identify brain-responsive biomarkers.

In MDD treatment with antidepressants an effect called antidepressant tachyphylaxis (‘poop-out’) is described [30]. Despite continuation of a previously effective treatment, approximately 25% of patients experience a recurrence of depressive symptoms. This effect is associated with the development of tolerance after chronic exposure to antidepressants. A permanent adaptation of DBS parameters in response to changes in biological markers might prevent this effect although there is no evidence for recurrence of symptoms despite maintenance of DBS until today. DBS to the sMFB is associated with lasting antidepressant effects over more than five years and permanent adaptation of stimulation parameters was not necessary in order to sustain antidepressant efficacy [16,17]. Interestingly, a discontinuation of sMFB DBS has been associated with a recurrence of depressive symptoms within days [31]. However, habituation to stimulation parameters has been described in a sample of patients with essential tremor treated with DBS of the nucleus ventralis intermedius [32]. In this study, immediate effects following the adaptation and optimization of stimulation parameters diminished ten weeks later due to a habituation of the tremor network to DBS. Closed-loop systems with permanently changing stimulation parameters may prevent relapse of symptoms, habituation or tolerance development.

In epilepsy, responsive closed-loop cortical DBS is approved in the US since 2013 and represents a personalized approach providing on-demand stimulation responding to intracranial patterns of electrocorticography [33]. Additionally, vagal nerve stimulation (VNS) has been developed as an adaptive treatment for epilepsy, too. The VNS system is responsive to tachycardia because heart rate changes precede electrographic and clinical changes during seizure [33]. Closed-Loop systems have successfully been implemented in the treatment of pain syndromes with spinal cord electrical stimulation sensing the patient’s body activity and position [28]. In PD, first developments for closed-loop systems have been implemented as well, offering ways to reduce stimulation-induced adverse effects (such as dyskinesia), prolong battery life of the generator and maintain stimulation parameters with changes in patient’s condition [34,35]. Swann and colleagues (2018) could demonstrate the feasibility of adaptive DBS in two patients with PD using basal ganglia signals for feedback control. Therapeutic efficacy was comparable to effects with open-loop DBS but energy savings were substantial in the adaptive DBS condition [36].

Before closed-loop systems can be implemented in psychiatric disorders it is necessary to understand the system mechanisms and to identify biomarkers. Lo et al. (2017) describe the identification of meaningful biomarkers for the titration as the biggest challenge for the development of closed-loop systems. Despite decades of research on the underlying mechanisms of depression, the electrical signature of psychiatric symptoms is still largely unknown [3,34].

First approaches to quantitatively characterize complex neural networks and brain states in psychiatric diseases have been realized through the System-Based Neurotechnology for Emerging Treatments (SUBNETS) project funded by the Defense Advanced Research Project Agency (DARPA) [37,38]. The goal of this program is the identification of predictive biomarkers indicating changes in psychiatric symptom states, to deliver a safe and targeted neural stimulation realized in an adaptable closed-loop treatment for neuropsychiatric diseases and to apply therapies that incorporate near real-time recording, analysis and stimulation. Recently, promising data have been published describing a decoding technology that allows to predict mood state variations from neural activity [39]. Neurophysiological correlates of mood-state changes could be found enabling continuous electrocorticography in patients with epilepsy implanted with intracranial electrodes for seizure localization [40] and a combination of electroencephalography and machine learning methods could help to discover a brain subnetwork correlating with self-reported mood changes [41]. Roads to a better understanding of biological mechanisms underlying psychiatric

diseases are urgently needed but seem to be very challenging considering the long history of research for biomarkers in psychiatric disorders [42].

Optogenetic tools currently represent one way to get new insights into biomarkers of psychiatric diseases as well as for the future development in neurosciences, basic neurobiology and the neural mechanisms involved in psychiatric diseases [43]. Optogenetics as a research area contribute to a better understanding of the mode of action of DBS, the therapeutic effects of DBS and the development of more effective antidepressant treatments [34,44,45]. Optogenetics constitute a groundbreaking technology and a new neuromodulation approach that allows a precise control (activation or inhibition) or monitoring of neural activity with light. To enable optical modulation of selected cells, optogenetics involve lasers and fiber optics for light delivery as well as genetic tools (genes called microbial opsins) to encode light-activated proteins that allow a transmission of action potentials through ion channels. By this biological technique, specific cells or pathways of interest become sensitive to light enabling the activation or inhibition of neural circuitries in a very precise way [46,47].

Optogenetic studies in rodents already lead to a better insight into the mode of action of DBS in PD [48,49] and showed first progress in treating refractory epilepsy on the level of preclinical models [45]. Despite this success in neurological disorders, a clinical application for psychiatric disorders is far more challenging due to fact that causal roles of specific neuronal circuits still need to be elucidated in psychiatric disorders [50]. Optogenetic studies investigating neuronal pathways and functional anatomy of neuronal populations in psychiatric diseases already contributed to a better understanding of neural circuits underlying addictive disorders, fear, anxiety and depression. Optogenetics significantly improved the knowledge of healthy brain activity and connections as well as neuronal changes in psychiatric disorders [45]. Yet, the transition of this new technology from the preclinical model into the human model as a putative treatment for neurological and psychiatric diseases is still far away. A main problem herewith will be the development of safe viral vectors. However, ideas exist that combine optogenetic tools with adaptive closed-loop systems. Grosenick et al. [51] describe a closed-loop and activity-guided optogenetic control method with a structured, time-varying light stimulus that is automatically modulated based on the difference between desired and measured outputs (behavioral, electrophysiological or readouts of activity). They conclude that optogenetics with a closed-loop control theory applied to optogenetic stimulation could help to understand how circuits change with optical stimulation and learning.

In 2010, Covington and colleagues could demonstrate antidepressant-like effects in response to optogenetic stimulation of the mPFC in mice, restoring normal social interaction via optogenetic stimulation [52]. Furthermore, a susceptible, depression-like phenotype could be triggered via optogenetic induction of phasic firing in ventral tegmental area (VTA) dopamine neurons. An inhibition of the VTA-NAcc projection could rapidly cause resilience whereas activation of VTA neurons projecting to the NAcc induced susceptibility even in mice that were resilient previously [53]. Considering these results, Schlaepfer and colleagues (2014) speculate that sMFB DBS increases the tonic dopamine output from the VTA and by that increases synaptic dopamine in NAcc and the PFC leading to the clinically described antidepressant effects [2]. Insights generated through studies investigating optogenetic stimulation may help to better understand the mechanisms of sMFB DBS in depression and psychiatric illness in general.

The optogenetic approach in principal is very promising and might allow overcoming limitations of molecular and chemistry based drug designs. Optogenetic stimulation itself may develop as a new therapeutic option for the clinical use in humans providing the knowledge to establish circuit-centric therapeutics [44,50]. It is proposed that studies in nonhuman primates (NHPS) rather than in rodents would be the better model for human brain functions and disorders [54]. Today,

optogenetic stimulation is not yet applicable as a treatment option for humans regarding the following limitations: viral vectors need to be delivered to discrete brain regions, limited ability to direct cell type specificity, greater volume of tissue due to larger size of the brain, light delivery to cells by genetic introduction of light-sensitive proteins with reducing brain tissue damage and in vivo assessment of opsin expression level need to be developed. Nonetheless, an optogenetic-driven circuit-centric strategy could help to refine DBS protocols [50]. In future, optogenetic stimulation potentially could help to exert more selective stimulatory or inhibitory effects compared to DBS [44].

Finally, a different putative treatment option for the clinical use in humans could be the development of magnetogenetics [55]. This approach might be interesting due to the fact that optogenetics require genetic alteration and intracranial delivery of light which makes them currently infeasible for the clinical use in humans. The basic idea of magnetogenetics is to manipulate neurons with magnetic stimuli relying on an inducible, genetically encoded molecule that might activate neurons in a temporally precise and robust way [55]. Wheeler and colleagues [56] described a method that couples ferritin (a paramagnetic protein) directly to the calcium channel (TRPV4) making it sensitive to the application of a strong static magnetic field resulting in a magnetic activation. There are still a number of major issues that need to be resolved before an implementation of this technique will become possible in humans. The major advantage compared to optogenetics would be that no intracranial surgery is needed.

Non-invasive treatments that are currently feasible for the treatment of psychiatric diseases include ablative surgery techniques. One of these techniques is the Gamma Knife Radiation Surgery (GKRS) [57]. This ablation technique utilizes ionizing radiation to provide a radiation dose sufficient to cause neuronal cell death in specific brain areas without the need for an open surgery. One randomized, double-blind, sham-controlled study using GKRS for capsulotomy with the isocenters targeted to the ventral border of the anterior limb of the internal capsule included 16 OCD patients [58]. At 12 months follow-up, 25% of the active treatment group responded (response > 35% reduction in the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS)) and response rates were increased at the last follow-up (54 months: 62.5% responders). Disadvantages and possible risks of GKRS include the need for radiation, the latency to the clinical and radiographic effects, the necessity of repetitive treatments as well as problems with lesion accuracy [57]. Additionally, there are some concerns regarding untoward long-term histological developments after GKRS (e.g. radiation necrosis) [59]. While this is worrisome it is unclear how this is actually related to clinical effects.

Recently, focused ultrasound has been proposed as a non-invasive method for neuromodulation in neurological and psychiatric diseases. Compared to GKRS ultrasound has the advantage that there is no need for radiation exposure and that it can be used at different intensities. Ultrasound is defined as sound waves that are higher than the audible range of human hearing (> 20 KHz) and can be used as a diagnostic, surgical, neuromodulation and drug delivery tool. Therapeutic ultrasound uses similar instrumentation as it is known from the diagnostic ultrasound tools using the instrumentation at a higher power [60]. MR-guided focused ultrasound is available in two different modalities: thermal/high-intensity focused ultrasound (HIFU) or nonthermal/low-intensity focused ultrasound (LIFU).

HIFU is a non-invasive ablation technique that generates precise lesions in the brain through the intact skull following a sufficient increase in temperature in an irreversible way. This technique is conducted under real-time MRI guidance and with a specially designed helmet. For now, approximately 1000 patients with movement disorders have been treated with focused ultrasound ablation worldwide [61]. Besides this application, focused ultrasound as a surgical tool has been used in neuropathic pain, brain tumors, stroke and psychiatric disorders [60]. Two studies published data on overall 15 patients with OCD treated with bilateral thermal capsulotomy ablating the ALIC

(representing a DBS brain target for depression, too) with MR-guided focused ultrasound [62]. At six-month follow-up mean improvement of OCD symptoms was 33% (measured with Y-BOCS) and mean reduction of depressive symptoms was 61.1% (measured with Hamilton Depression Rating Scale (HAM-D)). Clinical symptoms decreased significantly over a time period of 24 months with 54.5% (6/11) responders at this time point [63]. Currently one single case, a patient diagnosed with MDD, who was treated with thermal ablation of the ALIC via MR-guided focused ultrasound has been demonstrated [64]. Directly one week after the treatment, depressive symptoms decreased significantly and continued to be significantly reduced 12 months after the treatment compared to baseline. Two clinical trials (registered at clinicaltrials.gov with identifier NCT02348411 and NCT02685488) are currently underway investigating antidepressant effects of lesioning ALIC in TRD patients [65].

LIFU does not directly lead to a lesion but has the potential as a new non-invasive, highly spatially and very precise focused neuromodulation technique instead of having ablative effects by thermal coagulation. Applying ultrasound at sublesional temperatures affords to modulate the brain activity in a reversible way. This allows the examination of clinical effects and can precede the step of generating an irreversible lesion. Leinenga (2016) summarize that neural activity can be altered through the targeting of electrical stimulation to restore function, relieve symptoms or probe the function of brain circuits in behavior [60]. A “first-in-man” clinical trial has been conducted in one patient suffering from post-traumatic disorder of consciousness 19 days post-injury showing rapid improvements in the Coma Recovery Scale Revised [66]. Furthermore, the effect of transcranial ultrasound on mental states in a healthy human control group already could be demonstrated [67]. Improvements in subjectively assessed mood were reported ten minutes and 40 min after subthermal LIFU compared to sham in 31 chronic pain patients [68]. In a sample of adults with mild to moderate depressive symptoms worry (measured with the PSWQ) was significantly reduced after five days of receiving LIFU compared to adults receiving a sham stimulation [69]. They described that LIFU could reduce Default Mode Network resting state connectivity and could increase connectivity within the Cognitive Control Network. The authors assume that LIFU to the right inferior frontal gyrus (rIFG) affects mood via reducing perseverative thinking. In 2017, Sanguinetti and colleagues reported that LIFU to the rIFG in healthy volunteers possibly changes brain connectivity. This change may be associated with changes in mood [70].

In conclusion, focused ultrasound potentially is an effective, safe and promising technology for both ablative as well as non-ablative applications. Rapid effects on neurophysiological outcomes could be demonstrated and a modulation of neural networks involved in psychiatric disorders seems possible. In future, focused ultrasound may develop as a promising non-invasive alternative to invasive DBS. Before focused ultrasound can be applied for the clinical use, a lot of work remains investigating parameter estimation and careful testing is necessary [71].

Another application possibility of ultrasound consists in its ability to transiently open the blood brain barrier (BBB) for drug delivery. The permeability of the BBB can be increased via ultrasound permitting molecules that normally fail to cross the intact BBB due to their size to enter the brain [72]. Tsai [73] formulated the hypothesis that focused ultrasound could increase the brain derived neurotrophic factor (BDNF) levels and neurogenesis in the hippocampus. Compelling evidence that BDNF is involved in the pathogenesis and recovery of MDD led to thoughts about its therapeutic application. It might very well be that modulation of the BBB by focused ultrasound might represent an alternative strategy for the treatment of MDD via regulating BDNF levels.

Another idea of noninvasive deep brain stimulation has currently been described by Grossmann and colleagues (2017) and uses temporally interfering electrical fields [74]. Temporal interference (TI) describes a novel strategy of electrical brain stimulation applying high-

frequency oscillating electric fields at both sites outside the brain differing in their frequency by a small amount and thereby causing interference phenomena. This technique allows stimulation of deep regions of the brain without stimulating overlying neurons at the cortex and without invasive surgery. There is still a lot of research needed investigating the efficacy of TI stimulation. Particularly, future studies need to explore how strong electric fields affect the brain, how a small focal volume may be achieved and if electric fields may have effects beyond a brief transient change in the neural activity. The authors conclude that addressing all the unanswered questions TI may have the potential to develop as a new strategy to stimulate deep regions of the brain non-invasively and be studied in human clinical trials.

It is promising, that despite the obvious dearth of novel pharmacological treatments several new possible avenues of the development of putative treatments for psychiatric disorders with a biological approach exist, as described above. The main driving factor of this development is a novel conceptualization of MDD as dysfunctions in a discrete brain network, processing affective stimuli, rather than mere dysfunctions of synaptic transmitters. This novel conceptualization became possible via studies using brain imaging methods investigating the pathophysiology of psychiatric diseases. The development of new emerging treatments for psychiatric disorders is still a major issue due to the fact that a lot of patients are treatment-resistant to conventional methods. To enable the above described biological approaches for the clinical use in humans, interdisciplinary teams including among others psychiatrists, neurosurgeons, physicians and engineers need to be established and have to work closely together.

#### Declaration of Competing Interest

All authors declare that they have no conflicts of interest relating to this study.

#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.pmip.2019.07.002>.

#### References

- [1] Holtzheimer III PE, Nemeroff CB. Emerging treatments for depression. *Expert Opin Pharmacother* 2006;7:2323–39.
- [2] Schlaepfer TE, Bewernick BH, Kayser S, Hurlmann R, Coenen VA. Deep brain stimulation of the human reward system for major depression—rationale, outcomes and outlook. *Neuropsychopharmacology* 2014;39:1303–14.
- [3] Widge AS, Ellard KK, Paulk AC, Basu I, Yousefi A, Zorowitz S, et al. Treating refractory mental illness with closed-loop brain stimulation: progress towards a patient-specific transdiagnostic approach. *Exp Neurol* 2017;287:461–72.
- [4] Famm K, Litt B, Tracey KJ, Boyden ES, Slaoui M. Drug discovery: a jump-start for electroceuticals. *Nature* 2013;496:159–61.
- [5] Lozano AM, Lipsman N, Bergman H, Brown P, Chabardes S, Chang JW, et al. Deep brain stimulation: current challenges and future directions. *Nature Rev Neurol* 2019;15:148–60.
- [6] Schlaepfer TE, Bewernick BH. Deep brain stimulation for major depression. In: Lozano A, Hallett M, editors. *Handbook of Clinical Neurology*. Elsevier; 2013. p. 235–43.
- [7] Zhou C, Zhang H, Qin Y, Tian T, Xu B, Chen J, et al. A systematic review and meta-analysis of deep brain stimulation in treatment-resistant depression. *Prog Neuro-Psychopharmacol Biol Psychiatry* 2018;82:224–32.
- [8] Mayberg HS, Lozano AM, Voon V, McNeely HE, Seminowicz D, Hamani C, et al. Deep brain stimulation for treatment-resistant depression. *Neuron* 2005;45:651–60.
- [9] Bergfeld IO, Mantione M, Hoogendoorn ML, Ruhé HG, Notten P, van Laarhoven J, et al. Deep brain stimulation of the ventral anterior limb of the internal capsule for treatment-resistant depression: a randomized clinical trial. *JAMA* 2016;73:456–64.
- [10] Bewernick BH, Hurlmann R, Matusch A, Kayser S, Grubert C, Hadrysiewicz B, et al. Nucleus accumbens deep brain stimulation decreases ratings of depression and anxiety in treatment-resistant depression. *Biol Psychiatry* 2010;67:110–6.
- [11] Malone DA, Dougherty DD, Rezaei AR, Carpenter LL, Friehs GM, Eskandar EN, et al. Deep brain stimulation of the ventral capsule/ventral striatum for treatment-resistant depression. *Biol Psychiatry* 2009;65:267–75.
- [12] Schlaepfer TE, Bewernick BH, Kayser S, Mädl B, Coenen VA. Rapid effects of deep brain stimulation for treatment-resistant major depression. *Biol Psychiatry* 2013;73:1204–12.

- [13] Coenen VA, Schlaepfer TE, Maedler B, Panksepp J. Cross-species affective functions of the medial forebrain bundle—implications for the treatment of affective pain and depression in humans. *Neurosci Biobehav Rev* 2011;35:1971–81.
- [14] Fenoy AJ, Schulz P, Selvaraj S, Burrows C, Spiker D, Cao B, et al. Deep brain stimulation of the medial forebrain bundle: distinctive responses in resistant depression. *J Affect Disord* 2016;203:143–51.
- [15] Coenen VA, Bewernick BH, Kayser S, Kilian H, Boström J, Greschus S, et al. Superolateral medial forebrain bundle deep brain stimulation in major depression—a gateway trial. *Neuropsychopharmacology* 2019;44:1224–32.
- [16] 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 Stimulation* 2017;10:664–71.
- [17] Schlaepfer T, Bewernick B, Kilian H, Coenen V. T128. Deep brain stimulation to the super-lateral part of the medial forebrain bundle (sLMFB) is associated with sustained efficacy in major depression for more than five years. *Neuropsychopharmacology* 2017;42:S375.
- [18] Dougherty DD, Rezaei AR, Carpenter LL, Howland RH, Bhati MT, O'Reardon JP, et al. A randomized sham-controlled trial of deep brain stimulation of the ventral capsule/ventral striatum for chronic treatment-resistant depression. *Biol Psychiatry* 2015;78:240–8.
- [19] Holtzheimer PE, Husain MM, Lisanby SH, Taylor SF, Whitworth LA, McClintock S, et al. Subcallosal cingulate deep brain stimulation for treatment-resistant depression: a multisite, randomised, sham-controlled trial. *Lancet Psychiatry* 2017;4:839–49.
- [20] Schlaepfer TE. Deep brain stimulation for major depression—Steps on a long and winding road. *Biol Psychiatry* 2015;78:218–9.
- [21] Tykocki T, Nauman P, Koziara H, Mandat T. Microlesion effect as a predictor of the effectiveness of subthalamic deep brain stimulation for Parkinson's disease. *Stereotact Funct Neurosurg* 2013;91:12–7.
- [22] 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;24:223–36.
- [23] Udupa K, Chen R. The mechanisms of action of deep brain stimulation and ideas for the future development. *Prog Neurobiol* 2015;133:27–49.
- [24] Lozano AM, Lipsman N. Probing and regulating dysfunctional circuits using deep brain stimulation. *Neuron* 2013;77:406–24.
- [25] Schlaepfer TE, Cohen MX, Frick C, Kosel M, Brodesser D, Axmacher N, et al. Deep brain stimulation to reward circuitry alleviates anhedonia in refractory major depression. *Neuropsychopharmacology* 2008;33:368–77.
- [26] Dandekar MP, Luse D, Hoffmann C, Cotton P, Peery T, Ruiz C, et al. Increased dopamine receptor expression and anti-depressant response following deep brain stimulation of the medial forebrain bundle. *J Affect Disord* 2017;217:80–8.
- [27] Klanker M, Feenstra M, Willuhn I, Denys D. Deep brain stimulation of the medial forebrain bundle elevates striatal dopamine concentration without affecting spontaneous or reward-induced phasic release. *Neuroscience* 2017;364:82–92.
- [28] Grahm PJ, Mallory GW, Khurram OU, Berry BM, Hachmann JT, Bieher AJ, et al. A neurochemical closed-loop controller for deep brain stimulation: toward individualized smart neuromodulation therapies. *Front Neurosci* 2014;8:169.
- [29] Herman AB, Widge AS. Dynamic network targeting for closed-loop deep brain stimulation. *Neuropsychopharmacology* 2019;44:219–20.
- [30] Targum SD. Identification and treatment of antidepressant tachyphylaxis. *Innov Clin Neurosci* 2014;11:24–8.
- [31] Kilian HM, Meyer DM, Bewernick BH, Spanier S, Coenen VA, Schlaepfer TE. Discontinuation of superolateral medial forebrain bundle deep brain stimulation for Treatment-Resistant depression leads to critical relapse. *Biol Psychiatry* 2019;85:e23–4.
- [32] Barbe MT, Liebhart L, Runge M, Pauls KAM, Wojtecki L, Schnitzler A, et al. Deep brain stimulation in the nucleus ventralis intermedia in patients with essential tremor: habituation of tremor suppression. *J Neurol* 2011;258:434–9.
- [33] Hartshorn A, Jobst B. Responsive brain stimulation in epilepsy. *Therapeutic Adv Chronic Dis* 2018;9:135–42.
- [34] Lo M-C, Widge AS. Closed-loop neuromodulation systems: next-generation treatments for psychiatric illness. *Int Rev Psychiatry* 2017;29:191–204.
- [35] Mohammed A, Bayford R, Demosthenous A. Toward adaptive deep brain stimulation in Parkinson's disease: a review. *Neurodegenerative Dis Manage* 2018;8:115–36.
- [36] Swann NC, de Hemptinne C, Thompson MC, Miciocovic S, Miller AM, Ostrem JL, et al. Adaptive deep brain stimulation for Parkinson's disease using motor cortex sensing. *J Neural Eng* 2018;15:046006.
- [37] DARPA: SUBNETS Aims for Systems-Based Neurotechnology and Understanding for the Treatment of Neuropsychological Illnesses. Available online: <https://www.darpa.mil/news-events/2013-10-25> (accessed on 4 March 2019).
- [38] DARPA: Systems-Based Neurotechnology for Emerging Therapies (SUBNETS). Available online: <https://www.darpa.mil/program/systems-based-neurotechnology-for-emerging-therapies> (accessed on 4 March 2019).
- [39] Sani OG, Yang Y, Lee MB, Dawes HE, Chang EF, Shaneci MM. Mood variations decoded from multi-site intracranial human brain activity. *Nat Biotechnol* 2018;36:954–61.
- [40] Rao VR, Sellers KK, Wallace DL, Lee MB, Bijanzadeh M, Sani OG, et al. Direct electrical stimulation of lateral orbitofrontal cortex acutely improves mood in individuals with symptoms of depression. *Curr Biol* 2018;28(3893–3902):E4.
- [41] Kirkby LA, Luongo FJ, Lee MB, Nahum M, Van Vleet TM, Rao VR, et al. An amygdala-hippocampus subnetwork that encodes variation in human mood. *Cell* 2018;175(1688–1700):E14.
- [42] Abi-Dargham A, Horga G. The search for imaging biomarkers in psychiatric disorders. *Nat Med* 2016;22:1248–55.
- [43] Deisseroth K. Optogenetics and psychiatry: applications, challenges, and opportunities. *Biol Psychiatry* 2012;71:1030–2.
- [44] Lobo MK, Nestler EJ, Covington III HE. Potential utility of optogenetics in the study of depression. *Biol Psychiatry* 2012;71:1068–74.
- [45] Touriño C, Eban-Rothschild A, de Lecea L. Optogenetics in psychiatric diseases. *Curr Opin Neurobiol* 2013;23:430–5.
- [46] Duebel J, Marazova K, Sahel J-A. Optogenetics. *Curr Opin Ophthalmol* 2015;26:226–32.
- [47] Deisseroth K. Optogenetics: 10 years of microbial opsins in neuroscience. *Nat Neurosci* 2015;18:1213–25.
- [48] Gradinaru V, Mogri M, Thompson KR, Henderson JM, Deisseroth K. Optical deconstruction of parkinsonian neural circuitry. *Science* 2009;324:354–9.
- [49] McIntyre CC, Mori S, Sherman DL, Thakor NV, Vitek JL. Electric field and stimulating influence generated by deep brain stimulation of the subthalamic nucleus. *Clin Neurophysiol* 2004;115:589–95.
- [50] Shirai F, Hayashi-Takagi A. Optogenetics: applications in psychiatric research. *Psychiatry Clin Neurosci* 2017;71:363–72.
- [51] Grosenick L, Marshal JH, Deisseroth K. Closed-loop and activity-guided optogenetic control. *Neuron* 2015;86:106–39.
- [52] Covington HE, Lobo MK, Maze I, Vialou V, Hyman JM, Zaman S, et al. Antidepressant effect of optogenetic stimulation of the medial prefrontal cortex. *J Neurosci* 2010;30:16082–90.
- [53] Chaudhury D, Walsh JJ, Friedman AK, Juarez B, Ku SM, Koo JW, et al. Rapid regulation of depression-related behaviours by control of midbrain dopamine neurons. *Nature* 2013;493:532–6.
- [54] Galvan A, Stauffer WR, Acker L, El-Shamayleh Y, Inoue K-I, Ohayon S, et al. Nonhuman primate optogenetics: recent advances and future directions. *J Neurosci* 2017;37:10894–903.
- [55] Nimpf S, Keays DA. Is magnetogenetics the new optogenetics? *EMBO J* 2017;36:1643–6.
- [56] Wheeler MA, Smith CJ, Ottolini M, Barker BS, Purohit AM, Grippo RM, et al. Genetically targeted magnetic control of the nervous system. *Nat Neurosci* 2016;19:756–61.
- [57] Volpini M, Giacobbe P, Cosgrove GR, Levitt A, Lozano AM, Lipsman N. The history and future of ablative neurosurgery for major depressive disorder. *Stereotact Funct Neurosurg* 2017;95:216–28.
- [58] Lopes AC, Greenberg BD, Canteras MM, Batistuzzo MC, Hoexter MQ, Gentil AF, et al. Gamma ventral capsulotomy for obsessive-compulsive disorder: a randomized clinical trial. *JAMA* 2014;311:1066–76.
- [59] Okun MS, Stover NP, Subramanian T, Gearing M, Wainer BH, Holder CA, et al. Complications of gamma knife surgery for Parkinson disease. *Arch Neurol* 2001;58:1995–2002.
- [60] Leinenga G, Langton C, Nisbet R, Götz J. Ultrasound treatment of neurological diseases—current and emerging applications. *Nature Rev Neurol* 2016;12:161–74.
- [61] Krishna V, Sammartino F, Rezaei A. A review of the current therapies, challenges, and future directions of transcranial focused ultrasound technology: advances in diagnosis and treatment. *JAMA* 2018;75:246–54.
- [62] Jung H, Kim S, Roh D, Chang J, Chang W, Kweon E, et al. Bilateral thermal capsulotomy with MR-guided focused ultrasound for patients with treatment-refractory obsessive-compulsive disorder: a proof-of-concept study. *Mol Psychiatry* 2015;20:1205–11.
- [63] Kim SJ, Roh D, Jung HH, Chang WS, Kim C-H, Chang JW. A study of novel bilateral thermal capsulotomy with focused ultrasound for treatment-refractory obsessive-compulsive disorder: 2-year follow-up. *J Psychiatry Neurosci* 2018;43:327–37.
- [64] Kim M, Kim C-H, Jung HH, Kim SJ, Chang JW. Treatment of major depressive disorder via magnetic resonance-guided focused ultrasound surgery. *Biol Psychiatry* 2018;83:e17–8.
- [65] Meng Y, Suppiah S, Mithani K, Solomon B, Schwartz ML, Lipsman N. Current and emerging brain applications of MR-guided focused ultrasound. *J Ther Ultrasound* 2017;5:26.
- [66] Monti MM, Schnakers C, Korb AS, Bystritsky A, Vespa PM. Non-invasive ultrasonic thalamic stimulation in disorders of consciousness after severe brain injury: a first-in-man report. *Brain Stimul* 2016;9:940–1.
- [67] Sanguinetti J, Smith EE, Dieckman L, Vanuk J, Hameroff S, Allen JJ. Transcranial ultrasound for brain stimulation: Effects on mood. *Psychophysiology* 2013;50:S46.
- [68] Hameroff S, Trakas M, Duffield C, Annabi E, Gerace MB, Boyle P, et al. Transcranial ultrasound (TUS) effects on mental states: a pilot study. *Brain Stimulation* 2013;6:409–15.
- [69] Reznik SJ, Sanguinetti J, Allen JJ. Transcranial ultrasound (TUS) reduces worry in a five-day double-blind pilot study Barcelona, Spain International Brain Stimulation Conference. 2017.
- [70] Sanguinetti J, Allen JJ. Transcranial ultrasound improves mood and affects resting state functional connectivity in healthy volunteers. *Brain Stimulation: Basic, Translational, Clin Res Neuromodulation* 2017;10:426.
- [71] Bowary P, Greenberg BD. Noninvasive focused ultrasound for neuromodulation: a review. *Psychiatric Clin* 2018;41:505–14.
- [72] Munoz F, Aurup C, Konofagou EE, Ferrera VP. Modulation of brain function and behavior by focused ultrasound. *Curr Behav Neurosci Rep* 2018;5:153–64.
- [73] Tsai S-J. Transcranial focused ultrasound as a possible treatment for major depression. *Med Hypotheses* 2015;84:381–3.
- [74] Grossman N, Bono D, Dedic N, Kodandaramaiah SB, Rudenko A, Suk H-J, et al. Noninvasive deep brain stimulation via temporally interfering electric fields. *Cell* 2017;169(1029–1041):E16.