Preclinical Studies Modeling Deep Brain Stimulation for Depression

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Abstract

Deep brain stimulation (DBS) is currently being investigated for the treatment of depression. Results of early clinical trials have been very promising, but the mechanisms responsible for the effects of DBS are still unknown. This article reviews behavioral findings of stimulation applied to different brain targets in rodents, with a particular focus on the ventromedial prefrontal cortex. Mechanisms and substrates involved in the antidepressant-like effects of DBS, including the role of local tissue inactivation, the modulation of fiber pathways in the vicinity of the electrodes, as well as the importance of the serotonergic system and brain derived neurotrophic factor are discussed.

Keywords

Animal models; deep brain stimulation; depression; fiber pathways; psychiatry; radiofrequency lesions; serotonin

Deep brain stimulation (DBS) has been investigated for the treatment of depression with promising clinical results (1–11). Although preclinical research using electrical stimulation to study behavior has been conducted for over 50 years, results from animal studies did not comprise the rationale for the current use of DBS in depression. Experiments in animal models to investigate substrates and mechanisms responsible for the antidepressant-like effects of DBS were only conducted after the initial clinical trials were published (2,7,8,10–12).

This article provides an overview of current findings and some of the emerging concepts from experiments with DBS in models of depression, with a particular focus on results obtained with ventromedial prefrontal cortex (vmPFC) stimulation in rodents.

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Dr. Hamani is a consultant to St. Jude Medical. Dr. Nobrega reports no biomedical financial interests or potential conflicts of interest.

Supplementary material cited in this article is available online.

Choosing a Stimulation Target

The medial surface of the frontal cortex in rodents has been subdivided into four cytoarchitectural regions: the agranular frontal cortex, anterior cingulate cortex (AC), prelimbic cortex (PL), and infralimbic cortex (IL) (Figure 1A) (13–15). Alternatively, it has also been subdivided into dorsal and ventral “systems,” according to functional role as well as afferent and efferent projections (15). The dorsal system includes the frontal agranular cortex, AC, and dorsal PL and seems to be involved in the control of eye and head movements (14–16). The ventral system, comprises the IL and ventral aspects of the PL (vPL), projects mainly to the amygdala, hypothalamus, insula, and brainstem and has been suggested to play a role in autonomic control (17–20). Vertes (21) proposed an alternative subdivision of the medial prefrontal cortex (PFC) in dorsal (frontal agranular cortex and AC) and ventral regions (PL and IL). To mimic the effects of subgenual cingulum (SCG) DBS in rodents, we have been applying stimulation to the vmPFC (12,22–26), including IL and vPL.

Overall, the limits of the vPL are hard to delineate. However, if an arbitrary line is traced dividing the PL into dorsal and ventral halves, the approximate anteroposterior, mediolateral, and dorsoventral dimensions of the vmPFC (including IL and vPL) would be $1.3 \times 1 \times 1.3$ mm, with an estimated volume of approximately $1.7\text{--}1.9\text{ mm}^3$. In most of our studies, the electrode tips were .25 mm in diameter and .75 mm in height (22,26). This would be equivalent to a cylinder with dorsal-ventral dimensions and volume that are 6 and 2.5 times smaller than the ones estimated for the vmPFC. Under these circumstances, it is easy to imagine that the current delivered would not only influence the IL and PL but also areas adjacent to the target. The rationale for selecting such a large target was to mimic the clinical scenario, in which stimulation electrodes are not located in a specific Brodmann area (BA) but in a broader subgenual region, including BAs 32, 24, 25, and 10 (25,27). To investigate the contribution of specific vmPFC regions to the antidepressant-like effects of DBS, we have recently implanted rodents with smaller exposed tip electrodes into either the vPL or the IL. Overall, we found that the antidepressant-like effects of stimulation were more pronounced after PL stimulation in the forced swim test (FST) (Figure 1B) (22). As in most of our studies, the tips of the electrodes were implanted in the border between the IL and PL; the vPL was likely the primary structure influenced by stimulation.

In addition to the vmPFC, targets recently studied in animal models include the nucleus accumbens (NAc) (28,29), lateral habenula (LHb) (30), and ventral tegmental area (VTA) (31).

Choosing Stimulation Parameters

In clinical practice, stimulation frequency, pulse width, and amplitude can all be adjusted, leading to seemingly countless possible combinations of parameters. At present, the ideal settings for obtaining an antidepressant response in humans are still unclear. Commonly used parameters include 3–8 volts/mAmps, 130 Hz, and 90 μ sec pulse width (2,3,5). We have recently conducted experiments in rodents to characterize the most effective stimulation parameters for obtaining an antidepressant-like effect with vmPFC DBS in the FST (22). We found that high-frequency stimulation (130 Hz) at currents approximating

those used in humans when the charge density is considered (i.e., 100–300 μA) yielded optimal results (22). Of note, increasing the current above that range was associated with a worsening of the response. This is of importance, because a commonly used step to improve outcome in humans is to increase current, provided that no side effects are observed. Our results suggest that, above a certain threshold, this might not necessarily be the best approach.

Preclinical studies have also investigated the effects of intermittent patterns or trains of stimulation in different behavioral paradigms (29,31,32). These were set to mimic the physiological firing properties of local neuronal populations (31) or the way other neuromodulation strategies are clinically administered to patients (29). As an example, vPL or NAc stimulation at settings commonly used during transcranial magnetic stimulation induces an antidepressant-like response in animals undergoing chronic mild stress (cycles of 100 pulses at 20 Hz followed by 20-sec pauses) (29) (Table 1).

As conducted today, DBS has only been applied bilaterally in patients. An intriguing finding from our laboratory was that left unilateral vmPFC stimulation seemed to be as effective as bilateral DBS (22). From a clinical perspective, this would be of interest, because morbidity after unilateral procedures might be potentially reduced. In a recent study, the outcome of a single patient undergoing bilateral SCG stimulation has been reported (33). After experiencing a significant improvement during the first postoperative year, an alternate activation of either the right or left electrodes was attempted (33). The antidepressant effects of DBS were significantly more pronounced after right-sided stimulation (33). Despite the differences in stimulated hemisphere, this clinical note and our animal data suggest that unilateral DBS might be effective in controlling depressive states. Imperative in the future will be to assess anatomical and functional hallmarks that are particular to each cortical hemisphere and might be associated with a good clinical outcome.

Considerations on Study Design and Stimulation Timeframe

Important questions in terms of study design include when to stimulate the animals and for how long. In the clinical scenario, results obtained while patients are receiving active stimulation are often compared with those observed during sham stimulation or preoperative assessments. In preclinical studies, the decision as to whether animals should receive DBS before, during, or after behavioral assessments is largely dependent on the task and the specific behavior under investigation. Deep brain stimulation given during behavioral assessments has two main advantages. First, it more closely mimics the clinical scenario. Second, it allows the study of direct effects of stimulation on the behavior of interest. However, a disadvantage of this approach is that stimulation might impact different physiological domains, sometimes precluding a controlled assessment of the target behavior—for example, in cases where DBS might induce changes in general locomotor activity. In such cases, various control experiments might be necessary to ascertain the effects of stimulation in each particular domain. In our studies we have generally opted for applying DBS before and after but not during behavioral testing.

Additional design issues that need to be considered include carry-over and the so-called “insertional” or “microlesion” effects. Carry-over effects refer to the persistence of DBS-induced behavioral and/or neurochemical effects after stimulation is discontinued (23,34). Insertional or microlesion effects are said to occur when behavioral, neurochemical, or metabolic responses are seen after the mere insertion of electrodes into the target, in the absence of stimulation (35–38). Establishing whether animals present DBS carry-over effects is important, because this might interfere with behavioral findings, particularly in studies involving multiple longitudinal measurements or in crossover designs (i.e., animals receiving active followed by sham stimulation or the inverse treatment) (23,34). When carry-over effects are suspected, one might consider testing independent groups of animals or including washout periods in the study (i.e., a phase in which no stimulation is delivered), thus allowing animals to return to their baseline physiological and/or behavioral state before undergoing the next stimulation session. We have found interesting evidence of carry-over effects in longitudinal DBS experiments (26), although it remains to be determined whether those are caused by physical (i.e., insertional and or microlesion) or functional effects.

Selecting an Animal Model

The selection of an animal model is an important step, because no model adequately mimics all aspects of the respective disease states in humans (12,39,40). An ideal model would have predictive validity (a response to treatment similar to that observed in the clinic), face validity (similar phenomenology between model and disease), and construct validity (a strong theoretical rationale). Because most animal models do not meet all of these requirements, one often has to choose the most suitable experimental preparation to answer specific questions or combine different models to generate more definitive conclusions.

DBS Effects in the FST

Perhaps the most commonly used screener to test the efficacy of antidepressant interventions is the FST (41–50). In the FST, an anti-depressant-like effect occurs when an intervention decreases immobility during a swimming session. An important feature of the test is the short timeframe (days) required to observe antidepressant-type responses. This does not reflect the typical clinical pattern, where improvement often takes several days or weeks to emerge. It also makes the FST model unsuitable for the study of chronic mechanisms of antidepressant interventions.

Although recognizing that the FST might not model all features of depressive states and their treatment, we have used a modified version of this paradigm (45,51) to study the antidepressant-like activity of DBS due to its strong predictive validity. We found that rats treated with vmPFC DBS in between swimming sessions had a 30%–45% decrease in immobility scores, as compared with control subjects that did not have electrodes implanted (23) (Figure 2A, Table 1). These results were not due to a simple increase in motor activity, because both groups had a similar performance in an open field (23). Similar to rats, DBS-treated mice have also shown a significant antidepressant-like effects in the FST as compared with control subjects and sham-treated rats with electrodes implanted that did not receive stimulation (Figure 2B, Supplement 1). An aspect that is worth mentioning is that, in our experience, tricyclic antidepressants seem to be more reliable control drugs for the

effects of DBS in the FST than selective serotonin re-uptake inhibitors (SSRIs). This is similar to previous reports showing that SSRIs are only effective in the FST when given to the animals in a chronic fashion (51).

In addition to the vmPFC, an antidepressant-like response in the FST has also been recorded after LHb (32) or VTA stimulation (31) in naïve and Flinders rats, respectively (Table 1).

DBS Effects in the Chronic Mild Unpredictable Stress Model

Another commonly used animal model, particularly when chronic mechanisms of antidepressant treatments are considered, is chronic mild unpredictable stress (CUS). The key outcome measure is a decrease in preference for sucrose solutions over water, which is taken to reflect an anhedonic-like state induced by CUS (39,52). The vmPFC or NAc DBS applied for a few weeks significantly rescued sucrose preference in stressed animals (26,29) (Figure 2C, Table 1).

DBS Effects in Other Animal Models

Also used to investigate potential antidepressant-like effects of DBS is the learned helplessness model. A common learned helplessness paradigm involves one session of inescapable stress (e.g., foot-shock), followed 1 to a few days later by 1–3 daily sessions of escapable shocks in consecutive days (53,54). In our laboratory, vmPFC DBS was given after the inescapable stress session and then between the escapable shock sessions (23). In contrast to the positive effects of DBS in the FST and CUS paradigms, no differences in helplessness (latency to escape or avoid shocks) or the number of animals classified as helpless have been recorded in animals receiving DBS as compared with control subjects (23). Additional experiments are needed to test whether DBS improves escape and avoidance latencies in animals receiving yoked versus controllable stress, because the vmPFC seems to play an important role in the degree of controllability an organism has over a stressful situation (55).

We have also begun to explore the effects of vmPFC DBS in a novelty suppressed feeding paradigm. In this test, rats are placed in a novel environment and the latency to consume a food reward is measured. In our laboratory, animals given DBS had shorter latencies to consume the reward as compared with control subjects that did not have electrodes implanted (23). We note, however, that these experiments were preliminary and involved a small number of animals.

Finally, we have recently tested the effects of vmPFC stimulation in mice undergoing the tail suspension test (TST) (Supplement 1). In contrast to the FST, a reduction in immobility scores has not been observed during this test. This might be surprising given the apparent conceptual similarities between the FST and TST and their similar sensitivity to various antidepressant interventions. Whether different mouse strains vary in susceptibility to vmPFC DBS remains to be demonstrated.

Differences in behavioral response according to DBS target have also been demonstrated by other investigators. Stimulation of the LHb not only improved the number of escape responses (lever presses) but also decreased the time required for completion of a learned

helplessness test (32). Ventral tegmental area stimulation in Flinders rats increased sucrose self-administration, improved social interaction, and increased exploratory behavior in a novelty suppressed feeding test (31). In the open field, both NAc and LHb stimulation increased exploratory behavior in naïve and Kyoto Wistar rats (28,30).

Mechanisms Involved in the Effects of vmPFC Stimulation in the FST

Commonly proposed mechanisms of high-frequency stimulation (HFS) include functional inactivation of local neuronal populations and modulation of structures at a distance from the stimulated target (i.e., through activation of fiber pathways nearby the electrodes) (56–58). The latter effect might lead to distal neurotransmitter release and the induction of plastic changes in systems and substrates implicated in the antidepressant effects of drugs.

In an initial series of experiments, we investigated whether inactivation or lesion of the vmPFC could induce antidepressant-like effects similar to that observed with DBS. Three methods were used, namely radiofrequency (RF) lesions, ibotenic acid (IBO) lesions, and focal injections of muscimol (23). The former technique injures all cytoarchitectonic elements near the probes; ibotenic acid destroys primarily neuronal cell bodies while sparing afferents to the target and en passant fiber pathways; muscimol, a gamma-aminobutyric acid (GABA)_A ergic agonist, inhibits local cells expressing GABA_A receptors. We found that none of these treatments induced a significant antidepressant-like effect in the FST, although a 20%–25% reduction in immobility scores was noticed after muscimol injections and radiofrequency lesions (23). Other groups conducting similar experiments have shown a significant increase in immobility scores after PL and IL muscimol injections (59,60). Although these findings suggest that target inactivation might contribute to the effects of vmPFC DBS, the smaller magnitude of the observed response as compared with DBS (23) does imply that this was not the sole mechanism responsible for the effects of stimulation.

In the clinical scenario, common RF targets for the treatment of patients with depression include the anterior cingulate gyrus (cingulotomy) and the anterior limb of the internal capsule (capsulotomy). No clinical trials have been conducted comparing positive and adverse effects of DBS versus RF lesions in humans. In a recent study, however, a patient who failed cingulotomy has been reported to benefit from superior cervical ganglia DBS (61). We have conducted a series of studies to address whether lesions in regions analogous to commonly used clinical targets induce antidepressant-like responses. One week before the FST, different groups of animals were treated with RF lesions in the anterior cingulate cortex or white matter fibers running close to the fornix minor above the NAc (Supplement 1). Neither intervention induced a significant antidepressant-like response in the FST, although both lesioned groups had some reduction in immobility scores as compared with sham-treated control subjects (Figure 3C).

Another mechanism suggested to play a role in the antidepressant effects of DBS is modulation of fiber pathways in the vicinity of the electrodes. This has been shown to influence activity in brain regions at a distance from the stimulated target, leading to neurotransmitter release and inducing plastic changes in systems and substrates thought to be involved in the mechanisms of antidepressant treatments (56,57). In a recent study, the trajectory of white matter tracts running from prefrontal/orbitofrontal cortical regions to

subcortical structures has been characterized in nonhuman primates with the use of tract tracing techniques (62). A functional organization of components from medial to lateral areas in the PFC and orbitofrontal cortex has been identified in tracts such as the uncinate fascicle and the internal capsule. With computer modeling, the volume of tissue activated has been studied showing potential fiber projections and regions that could be influenced by stimulation in different targets. Along these lines, studies have also begun to emerge with diffusion tensor imaging and tractography in humans (62). Once we understand potential fiber pathways influenced by DBS, data may be integrated with PET scans and postoperative imaging studies showing where the electrodes are placed and which areas are activated in each individual patient (27). Through this approach we might determine the fiber pathways and regions influenced by stimulation and assess anatomical substrates that might potentially correlate with a positive clinical outcome.

We have obtained further evidence in rodents suggesting that fiber pathways in the vicinity of the electrodes might be responsible for the effects of DBS. As described in the preceding text, IBO primarily injure cell bodies while preserving afferent projections and en passant fibers. Taking advantage of this property, we implanted electrodes in animals in the same location where IBO was injected to assess whether the modulation of spared fiber tracts could contribute to the antidepressant-like outcome of vmPFC DBS in the FST. Confirming our hypothesis, we found that animals receiving vmPFC IBO + DBS had a significant reduction in immobility as compared with control subjects (23) (Figure 3B). One caveat related to these results, however, is that glial cells are not only spared but also increase in number after IBO administration (63,64). This is important in light of recent evidence suggesting that PFC glia might be involved in mechanisms of depressivelike behavior and antidepressant treatments in rats (65,66). Furthermore, adenosine and glutamate released by glial cells have been shown to contribute to the mechanisms of thalamic DBS in vitro (67). At present, there is still no conclusive evidence supporting a role for glia in the antidepressant-like effects of vmPFC DBS. Future research is still needed to address this issue.

Neural substrates of DBS have also been investigated in animals undergoing stimulation in the LHb. In a recent in vitro study, LHb stimulation was shown to induce a significant decrease in synaptic transmission in cells projecting to the VTA (32). Along this line, LHb muscimol injections induce a significant antidepressant-like response in congenitally helpless animals (68). Altogether, these results suggest that LHb DBS might induce a functional inactivation of neuronal populations near the electrodes, which might induce a behavioral effect similar to that recorded with local muscimol injections. However, this does not exclude the involvement of other potential substrates in the antidepressant-like effects of LHb DBS.

Neurochemical Substrates Involved in the Antidepressant-Like Effects of DBS

Neural substrates commonly implicated in mechanisms of antidepressant therapies include the monoaminergic system, neurotrophins, and neurogenesis (69–72). The effects of DBS on

the former two have been investigated in greater detail. Plastic changes induced by DBS in the context of depression have not been extensively studied to date. Evidence suggesting that the serotonergic system might be involved in the mechanisms of vmPFC stimulation comes from two sources. First, rats bearing serotonin (5-HT)-depleting raphe lesions do not respond to DBS in the FST or CUS (23,26) (Figure S2A, B in Supplement 1). Second, vmPFC stimulation induces a marked increase in 5-HT release in various brain regions (23,73) (Figure S2C Supplement 1). This surge has been hypothesized to occur due to the modulation of prefrontal projections to the raphe, a structure involved in 5-HT synthesis and release (22,24,74). If this is proven to be the case, it will provide an alternative mechanism for influencing the serotonergic system, complementary to medications that block the 5-HT transporter (e.g., SSRIs) or 5-HT reuptake (e.g. tricyclic antidepressants) (24). Similar to the vmPFC, DBS in the LHb has been shown to increase hippocampal monoamine levels, including 5-HT and norepinephrine (30). In contrast, norepinephrine and dopamine levels were reduced in Kyoto rats treated with stimulation of the NAc (28).

Brain-derived neurotrophic factor (BDNF), a neurotrophin involved in synaptic transmission and plasticity (75–81), has been closely associated with the pathophysiology of mood disorders. The BDNF levels are significantly reduced in rodents undergoing stress and in patients with depression (82–84). Commonly used antidepressant treatments (e.g., SSRIs and electroconvulsive therapy) reverse this pattern in rats (29,84,85). BDNF is also important for stress resiliency. Low hippocampal BDNF levels are associated with vulnerability to stress and depressive-like behavior (86,87), whereas injection of BDNF into the hippocampus of rodents increases stress resilience (88). An increase in hippocampal BDNF has been reported in rodents undergoing CUS (26,29) and in Flinders rats (31) after vmPFC, NAc, and VTA but not dorsal prelimbic stimulation. Moreover, BDNF levels in the hippocampus and striatum of stressed rats respectively receiving PFC or NAc stimulation, have been shown to correlate with an improvement in sucrose preference (29). We have recently shown that, in contrast to these findings, 5-HT-depleted animals undergoing CUS have a complete abolishment of a DBS despite normal hippocampal BDNF levels (26). Further investigation is clearly necessary to elucidate the role of BDNF in the antidepressant- and anti-anhedonic-like effects of DBS.

Summary and Conclusions

Promising results of open label trials using DBS for depression have encouraged investigation of basic mechanisms underlying the antidepressant effects of this novel therapy. Animal models can offer important insights in this context, as suggested by a number of specific findings reviewed in the preceding text relating to putative neurochemical and neuroanatomical mechanisms underlying these effects.

On the behavioral side, we note that results obtained with DBS have not been homogeneous across tests. For instance, an antidepressant-like response after vmPFC stimulation has been observed in the FST and CUS models but not in learned helplessness paradigms and the TST. This suggests some degree of specificity on the behaviors influenced by stimulation and might have interesting implications. As an example, differences in response between medications and stimulation in particular tests, such as those noted with the use of SSRIs

and DBS in the FST, might provide an important venue for the study of specific mechanisms involved in the antidepressant-like response of distinct therapies.

One caveat of the currently published preclinical studies is that they have been largely conducted in untreated animals. This is in contrast to the clinical scenario, in which surgery is only offered to patients who are “treatment-resistant.” Although it is reasonable to assume that interventions that work in treatment-resistant sub-populations should also be expected to work in the wider nonresistant population, the next step might indeed be to implement DBS in treatment-resistant preclinical models. Although at present there are no widely accepted animal models of treatment resistance, work in this direction might begin by focusing on animals that respond poorly to drug treatments in various tests.

In terms of mechanisms data published to date suggest that a DBS-induced modulation of fiber pathways might play a role in the antidepressant-like effects of stimulation in humans (62). Preclinical studies are consistent with these findings but also show that a functional target inactivation might be important. As for the neurochemical substrates, the integrity of the 5-HT system seems to be critical for antidepressant-like effects of vmPFC DBS (23,26). Not only does vmPFC DBS induce 5-HT release but animals bearing 5-HT-depleting raphe lesions do not respond to DBS in the FST and CUS paradigms. BDNF is another substrate that might also play a role in the mechanisms of DBS but only in animals with an intact 5-HT system. Substrates that still need to be explored are hippocampal neurogenesis and the role of glial cells. Investigating the mechanisms responsible for a DBS response in different models might help us differentiate the role played by distinct mechanisms in the acute and chronic effects of this therapy.

Overall, preclinical studies have shown good predictive validity for the study of DBS in the FST and CUS. In these tests, the antidepressant-like effects of DBS have been recorded in targets known to induce antidepressant-like effects in humans at settings that approximate those used in humans (22,29). Although a great degree of caution is necessary when translating data from animals to humans, current results clearly suggest that preclinical studies have predictive validity and might be used to investigate mechanisms and substrates of the antidepressant-like effects of DBS and possibly provide clues to improve the clinical application of this technique (58).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Experimental work conducted by the authors was supported in part with funds from Brain and Behavior Research Foundation (National Alliance for Research on Schizophrenia and Depression), the Ontario Mental Health Foundation, and the Canadian Institutes for Health Research. We wish to thank all the collaborators involved in our studies (Luciene Covolan, Deborah Suchecki, Debora C. Hipolide, Andres Lozano, Marcus L. Brandão, Paul J. Fletcher, and Francisco Gonzalez-Lima) and students (Francisco P. Dubiela, Carlos E. Macedo, Fabio Tescarollo, Uilton Martins, Jason Schumake, and Silvia Isabella). We are particularly indebted to Mustansir Diwan, Roger Raymond, and Danilo C. Machado for their superb work and dedication.

References

1. 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; 64:461–467. [PubMed: 18639234]
2. Mayberg HS, Lozano AM, Voon V, McNeely HE, Seminowicz D, Hamani C, et al. Deep brain stimulation for treatment-resistant depression. *Neuron*. 2005; 45:651–660. [PubMed: 15748841]
3. Holtzheimer PE, Kelley ME, Gross RE, Filkowski MM, Garlow SJ, Barrocas A, et al. Subcallosal cingulate deep brain stimulation for treatment-resistant unipolar and bipolar depression. *Arch Gen Psychiatry*. 2012; 69:150–158. [PubMed: 22213770]
4. Kennedy SH, Giacobbe P, Rizvi SJ, Placenza FM, Nishikawa Y, Mayberg HS, et al. Deep brain stimulation for treatment-resistant depression: Follow-up after 3 to 6 years. *Am J Psychiatry*. 2011; 168:502–510. [PubMed: 21285143]
5. Lozano AM, Giacobbe P, Hamani C, Rizvi SJ, Kennedy SH, Kolivakis TT, et al. A multicenter pilot study of subcallosal cingulate area deep brain stimulation for treatment-resistant depression. *J Neurosurg*. 2012; 116:315–322. [PubMed: 22098195]
6. Puigdemont D, Pérez-Egea R, Portella MJ, Molet J, de Diego-Adelino J, Gironell A, et al. Deep brain stimulation of the subcallosal cingulate gyrus: Further evidence in treatment-resistant major depression. *Int J Neuropsychopharmacol*. 2011;1–13.
7. Jimenez F, Velasco F, Salin-Pascual R, Hernandez JA, Velasco M, Ciales JL, et al. A patient with a resistant major depression disorder treated with deep brain stimulation in the inferior thalamic peduncle. *Neurosurgery*. 2005; 57:585–593. discussion 585–593. [PubMed: 16145540]
8. Schlaepfer TE, Cohen MX, Frick C, Kosel M, Brodessa D, Axmacher N, et al. Deep brain stimulation to reward circuitry alleviates anhedonia in refractory major depression. *Neuropsychopharmacology*. 2008; 33:368–377. [PubMed: 17429407]
9. 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; 67:110–116. [PubMed: 19914605]
10. Malone DA Jr, Dougherty DD, Rezai 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; 65:267–275. [PubMed: 18842257]
11. Sartorius A, Kiening KL, Kirsch P, von Gall CC, Haberkorn U, Unterberg AW, et al. Remission of major depression under deep brain stimulation of the lateral habenula in a therapy-refractory patient. *Biol Psychiatry*. 2010; 67:e9–e11. [PubMed: 19846068]
12. Hamani C, Nobrega JN. Deep brain stimulation in clinical trials and animal models of depression. *Eur J Neurosci*. 2010; 32:1109–1117. [PubMed: 21039950]
13. Neafsey EJ. Prefrontal cortical control of the autonomic nervous system: Anatomical and physiological observations. *Prog Brain Res*. 1990; 85:147–165. discussion 165–146. [PubMed: 2094892]
14. Neafsey EJ, Bold EL, Haas G, Hurley-Gius KM, Quirk G, Sievert CF, et al. The organization of the rat motor cortex: A microstimulation mapping study. *Brain Res*. 1986; 396:77–96. [PubMed: 3708387]
15. Neafsey EJ., Terberry, RR., Hurley, KM., Ruit, KG., Frystak, RJ. Anterior cingulate cortex in rodents: Connections, visceral control functions, and implications for emotion. In: Vogt, BA., Gabriel, M., editors. *Neurobiology of the Cingulate Cortex and Limbic Thalamus: A Comprehensive Handbook*. Boston, Basel, Berlin: Birkhäuser; 1993. p. 216-223.
16. Sinnamon HM, Galer BS. Head movements elicited by electrical stimulation of the anteromedial cortex of the rat. *Physiol Behav*. 1984; 33:185–190. [PubMed: 6505061]
17. Cassell MD, Wright DJ. Topography of projections from the medial prefrontal cortex to the amygdala in the rat. *Brain Res Bull*. 1986; 17:321–333. [PubMed: 2429740]
18. Hurley KM, Herbert H, Moga MM, Saper CB. Efferent projections of the infralimbic cortex of the rat. *J Comp Neurol*. 1991; 308:249–276. [PubMed: 1716270]
19. Saper CB. Convergence of autonomic and limbic connections in the insular cortex of the rat. *J Comp Neurol*. 1982; 210:163–173. [PubMed: 7130477]

20. van der Kooy D, McGinty JF, Koda LY, Gerfen CR, Bloom FE. Visceral cortex: A direct connection from prefrontal cortex to the solitary nucleus in rat. *Neurosci Lett*. 1982; 33:123–127. [PubMed: 6185887]
21. Vertes RP. Interactions among the medial prefrontal cortex, hippocampus and midline thalamus in emotional and cognitive processing in the rat. *Neuroscience*. 2006; 142:1–20. [PubMed: 16887277]
22. Hamani C, Diwan M, Isabella S, Lozano AM, Nobrega JN. Effects of different stimulation parameters on the antidepressant-like response of medial prefrontal cortex deep brain stimulation in rats. *J Psychiatr Res*. 2010; 44:683–687. [PubMed: 20096858]
23. Hamani C, Diwan M, Macedo CE, Brandao ML, Shumake J, Gonzalez-Lima F, et al. Antidepressant-like effects of medial prefrontal cortex deep brain stimulation in rats. *Biol Psychiatry*. 2010; 67:117–124. [PubMed: 19819426]
24. Hamani C, Diwan M, Raymond R, Nobrega JN, Macedo CE, Brandao ML, et al. Electrical brain stimulation in depression: Which target(s)? *Biol Psychiatry*. 2011; 69:e5–e6. author reply e7–e8. [PubMed: 21145040]
25. 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; 69:301–308. [PubMed: 21145043]
26. Hamani C, Machado DC, Hipolide DC, Dubiela FP, Suchecki D, Macedo CE, et al. Deep brain stimulation reverses anhedonic-like behavior in a chronic model of depression: Role of serotonin and brain derived neurotrophic factor. *Biol Psychiatry*. 2012; 71:30–35. [PubMed: 22000731]
27. Hamani C, Mayberg H, Snyder B, Giacobbe P, Kennedy S, Lozano AM. Deep brain stimulation of the subcallosal cingulate gyrus for depression: Anatomical location of active contacts in clinical responders and a suggested guideline for targeting. *J Neurosurg*. 2009; 111:1209–1215. [PubMed: 19480538]
28. Falowski SM, Sharan A, Reyes BA, Sikkema C, Szot P, Van Bockstaele EJ. An evaluation of neuroplasticity and behavior after deep brain stimulation of the nucleus accumbens in an animal model of depression. *Neurosurgery*. 2011; 69:1281–1290. [PubMed: 21566538]
29. Gersner R, Toth E, Isserles M, Zangen A. Site-specific antidepressant effects of repeated subconvulsive electrical stimulation: Potential role of brain-derived neurotrophic factor. *Biol Psychiatry*. 2010; 67:125–132. [PubMed: 19880094]
30. 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; 1422:32–38. [PubMed: 21978548]
31. Friedman A, Frankel M, Flaumenhaft Y, Merenlender A, Pinhasov A, Feder Y, et al. Programmed acute electrical stimulation of ventral tegmental area alleviates depressive-like behavior. *Neuropsychopharmacology*. 2009; 34:1057–1066. [PubMed: 18843267]
32. Li B, Piriz J, Mirrione M, Chung C, Proulx CD, Schulz D, et al. Synaptic potentiation onto habenula neurons in the learned helplessness model of depression. *Nature*. 2011; 470:535–539. [PubMed: 21350486]
33. Guinjoan SM, Mayberg HS, Costanzo EY, Fahrner RD, Tenca E, Antico J, et al. Asymmetrical contribution of brain structures to treatment-resistant depression as illustrated by effects of right subgenual cingulum stimulation. *J Neuropsychiatry Clin Neurosci*. 2010; 22:265–277. [PubMed: 20686133]
34. Tellez-Zenteno JF, McLachlan RS, Parrent A, Kubu CS, Wiebe S. Hippocampal electrical stimulation in mesial temporal lobe epilepsy. *Neurology*. 2006; 66:1490–1494. [PubMed: 16554495]
35. Tasker RR. Deep brain stimulation is preferable to thalamotomy for tremor suppression. *Surg Neurol*. 1998; 49:145–153. discussion 153–144. [PubMed: 9457264]
36. Pourfar M, Tang C, Lin T, Dhawan V, Kaplitt MG, Eidelberg D. Assessing the microlesion effect of subthalamic deep brain stimulation surgery with FDG PET. *J Neurosurg*. 2009; 110:1278–1282. [PubMed: 19301972]
37. Kesner RP. Brain stimulation: Effects on memory. *Behav Neural Biol*. 1982; 36:315–367. [PubMed: 6135412]

38. Kesner RP, Wilburn MW. A review of electrical stimulation of the brain in context of learning and retention. *Behav Biol.* 1974; 10:259–293. [PubMed: 4592638]
39. Willner P. Validity, reliability and utility of the chronic mild stress model of depression: A 10-year review and evaluation. *Psychopharmacology (Berl).* 1997; 134:319–329.
40. Nestler EJ, Hyman SE. Animal models of neuropsychiatric disorders. *Nat Neurosci.* 2010; 13:1161–1169. [PubMed: 20877280]
41. Cryan JF, Markou A, Lucki I. Assessing antidepressant activity in rodents: Recent developments and future needs. *Trends Pharmacol Sci.* 2002; 23:238–245. [PubMed: 12008002]
42. Cryan JF, Slattery DA. Animal models of mood disorders: Recent developments. *Curr Opin Psychiatry.* 2007; 20:1–7. [PubMed: 17143074]
43. Cryan JF, Valentino RJ, Lucki I. Assessing substrates underlying the behavioral effects of antidepressants using the modified rat forced swimming test. *Neurosci Biobehav Rev.* 2005; 29:547–569. [PubMed: 15893822]
44. Detke MJ, Lucki I. Detection of serotonergic and noradrenergic antidepressants in the rat forced swimming test: The effects of water depth. *Behav Brain Res.* 1996; 73:43–46. [PubMed: 8788475]
45. Detke MJ, Rickels M, Lucki I. Active behaviors in the rat forced swimming test differentially produced by serotonergic and noradrenergic antidepressants. *Psychopharmacology (Berl).* 1995; 121:66–72. [PubMed: 8539342]
46. Kral SE, Senanayake SS, Pekary AE, Sattin A. Vagus nerve stimulation (VNS) is effective in a rat model of antidepressant action. *J Psychiatr Res.* 2004; 38:237–240. [PubMed: 15003428]
47. Li B, Suemaru K, Cui R, Araki H. Repeated electroconvulsive stimuli have long-lasting effects on hippocampal BDNF and decrease immobility time in the rat forced swim test. *Life Sci.* 2007; 80:1539–1543. [PubMed: 17306836]
48. Porsolt RD, Anton G, Blavet N, Jalfre M. Behavioural despair in rats: A new model sensitive to antidepressant treatments. *Eur J Pharmacol.* 1978; 47:379–391. [PubMed: 204499]
49. Porsolt RD, Le Pichon M, Jalfre M. Depression: A new animal model sensitive to antidepressant treatments. *Nature.* 1977; 266:730–732. [PubMed: 559941]
50. Temel Y, Boothman LJ, Blokland A, Magill PJ, Steinbusch HW, Visser-Vandewalle V, et al. Inhibition of 5-HT neuron activity and induction of depressive-like behavior by high-frequency stimulation of the subthalamic nucleus. *Proc Natl Acad Sci U S A.* 2007; 104:17087–17092. [PubMed: 17942692]
51. Cryan JF, Page ME, Lucki I. Differential behavioral effects of the antidepressants reboxetine, fluoxetine, and moclobemide in a modified forced swim test following chronic treatment. *Psychopharmacology (Berl).* 2005; 182:335–344. [PubMed: 16001105]
52. Willner P, Mitchell PJ. The validity of animal models of predisposition to depression. *Behav Pharmacol.* 2002; 13:169–188. [PubMed: 12122308]
53. Martin P, Puech AJ. Antagonism by benzodiazepines of the effects of serotonin-, but not norepinephrine-, uptake blockers in the learned helplessness paradigm in rats. *Biol Psychiatry.* 1996; 39:882–890. [PubMed: 9172709]
54. Martin P, Soubrie P, Puech AJ. Reversal of helpless behavior by serotonin uptake blockers in rats. *Psychopharmacology (Berl).* 1990; 101:403–407. [PubMed: 2362957]
55. Amat J, Baratta MV, Paul E, Bland ST, Watkins LR, Maier SF. Medial prefrontal cortex determines how stressor controllability affects behavior and dorsal raphe nucleus. *Nat Neurosci.* 2005; 8:365–371. [PubMed: 15696163]
56. Lozano AM, Dostrovsky J, Chen R, Ashby P. Deep brain stimulation for Parkinson's disease: Disrupting the disruption. *Lancet Neurol.* 2002; 1:225–231. [PubMed: 12849455]
57. Vitek JL. Mechanisms of deep brain stimulation: Excitation or inhibition. *Mov Disord.* 2002; 17(Suppl 3):S69–72. [PubMed: 11948757]
58. Hamani C, Temel Y. Deep brain stimulation for psychiatric disease: Contributions and validity of animal models. *Sci Transl Med.* 2012
59. Scopinho AA, Scopinho M, Lisboa SF, Correa FM, Guimaraes FS, Joca SR. Acute reversible inactivation of the ventral medial prefrontal cortex induces antidepressant-like effects in rats. *Behav Brain Res.* 2010; 214:437–442. [PubMed: 20600346]

60. Slattery DA, Neumann ID, Cryan JF. Transient inactivation of the infralimbic cortex induces antidepressant-like effects in the rat. *J Psychopharmacol.* 2011; 25:1295–1303. [PubMed: 20530589]
61. Neimat JS, Hamani C, Giacobbe P, Merskey H, Kennedy SH, Mayberg HS, et al. Neural stimulation successfully treats depression in patients with prior ablative cingulotomy. *Am J Psychiatry.* 2008; 165:687–693. [PubMed: 18519534]
62. Lehman JF, Greenberg BD, McIntyre CC, Rasmussen SA, Haber SN. Rules ventral prefrontal cortical axons use to reach their targets: Implications for diffusion tensor imaging tractography and deep brain stimulation for psychiatric illness. *J Neurosci.* 2011; 31:10392–10402. [PubMed: 21753016]
63. Klein S, Koch M, Schwabe K. Neuroanatomical changes in the adult rat brain after neonatal lesion of the medial prefrontal cortex. *Exp Neurol.* 2008; 209:199–212. [PubMed: 17967454]
64. Schulz JB, Wree A, Schleicher A, Zilles K. Plasticity in the rat hippocampal formation following ibotenic acid lesion of the septal region: A quantitative [¹⁴C]deoxyglucose and acetylcholinesterase study. *J Cereb Blood Flow Metab.* 1992; 12:1007–1021. [PubMed: 1400640]
65. Banasr M, Duman RS. Glial loss in the prefrontal cortex is sufficient to induce depressive-like behaviors. *Biol Psychiatry.* 2008; 64:863–870. [PubMed: 18639237]
66. Banasr M, Chowdhury GM, Terwilliger R, Newton SS, Duman RS, Behar KL, et al. Glial pathology in an animal model of depression: Reversal of stress-induced cellular, metabolic and behavioral deficits by the glutamate-modulating drug riluzole. *Mol Psychiatry.* 2010; 15:501–511. [PubMed: 18825147]
67. Tawfik VL, Chang SY, Hitti FL, Roberts DW, Leiter JC, Jovanovic S, et al. Deep brain stimulation results in local glutamate and adenosine release: Investigation into the role of astrocytes. *Neurosurgery.* 2010; 67:367–375. [PubMed: 20644423]
68. Winter C, Vollmayr B, Djodari-Irani A, Klein J, Sartorius A. Pharmacological inhibition of the lateral habenula improves depressive-like behavior in an animal model of treatment resistant depression. *Behav Brain Res.* 2011; 216:463–465. [PubMed: 20678526]
69. Krishnan V, Nestler EJ. The molecular neurobiology of depression. *Nature.* 2008; 455:894–902. [PubMed: 18923511]
70. Sahay A, Hen R. Adult hippocampal neurogenesis in depression. *Nat Neurosci.* 2007; 10:1110–1115. [PubMed: 17726477]
71. Duman RS, Monteggia LM. A neurotrophic model for stress-related mood disorders. *Biol Psychiatry.* 2006; 59:1116–1127. [PubMed: 16631126]
72. Mongeau R, Blier P, de Montigny C. The serotonergic and noradrenergic systems of the hippocampus: Their interactions and the effects of antidepressant treatments. *Brain Res Brain Res Rev.* 1997; 23:145–195. [PubMed: 9164669]
73. Juckel G, Mendlin A, Jacobs BL. Electrical stimulation of rat medial prefrontal cortex enhances forebrain serotonin output: Implications for electroconvulsive therapy and transcranial magnetic stimulation in depression. *Neuropsychopharmacology.* 1999; 21:391–398. [PubMed: 10457536]
74. Gabbott PL, Warner TA, Jays PR, Salway P, Busby SJ. Prefrontal cortex in the rat: Projections to subcortical autonomic, motor, and limbic centers. *J Comp Neurol.* 2005; 492:145–177. [PubMed: 16196030]
75. Spedding M, Gressens P. Neurotrophins and cytokines in neuronal plasticity. *Novartis Found Symp.* 2008; 289:222–233. discussion 233–240. [PubMed: 18497106]
76. Alleva E, Francia N. Psychiatric vulnerability: Suggestions from animal models and role of neurotrophins. *Neurosci Biobehav Rev.* 2009; 33:525–536. [PubMed: 18824030]
77. Cirulli F, Francia N, Berry A, Aloe L, Alleva E, Suomi SJ. Early life stress as a risk factor for mental health: Role of neurotrophins from rodents to non-human primates. *Neurosci Biobehav Rev.* 2009; 33:573–585. [PubMed: 18817811]
78. Lipsky RH, Marini AM. Brain-derived neurotrophic factor in neuronal survival and behavior-related plasticity. *Ann N Y Acad Sci.* 2007; 1122:130–143. [PubMed: 18077569]
79. Binder DK. Neurotrophins in the dentate gyrus. *Prog Brain Res.* 2007; 163:371–397. [PubMed: 17765730]

80. Bramham CR, Messaoudi E. BDNF function in adult synaptic plasticity: The synaptic consolidation hypothesis. *Prog Neurobiol.* 2005; 76:99–125. [PubMed: 16099088]
81. Kaplan GB, Vasterling JJ, Vedak PC. Brain-derived neurotrophic factor in traumatic brain injury, post-traumatic stress disorder, and their comorbid conditions: Role in pathogenesis and treatment. *Behav Pharmacol.* 2010; 21:427–437. [PubMed: 20679891]
82. Shimizu E, Hashimoto K, Okamura N, Koike K, Komatsu N, Kumakiri C, et al. Alterations of serum levels of brain-derived neurotrophic factor (BDNF) in depressed patients with or without antidepressants. *Biol Psychiatry.* 2003; 54:70–75. [PubMed: 12842310]
83. Smith MA, Makino S, Kvetnansky R, Post RM. Stress and glucocorticoids affect the expression of brain-derived neurotrophic factor and neurotrophin-3 mRNAs in the hippocampus. *J Neurosci.* 1995; 15:1768–1777. [PubMed: 7891134]
84. Nibuya M, Morinobu S, Duman RS. Regulation of BDNF and trkB mRNA in rat brain by chronic electroconvulsive seizure and antidepressant drug treatments. *J Neurosci.* 1995; 15:7539–7547. [PubMed: 7472505]
85. Altar CA, Whitehead RE, Chen R, Wortwein G, Madsen TM. Effects of electroconvulsive seizures and antidepressant drugs on brain-derived neurotrophic factor protein in rat brain. *Biol Psychiatry.* 2003; 54:703–709. [PubMed: 14512210]
86. Blugeot A, Rivat C, Bouvier E, Molet J, Mouchard A, Zeau B, et al. Vulnerability to depression: From brain neuroplasticity to identification of biomarkers. *J Neurosci.* 2011; 31:12889–12899. [PubMed: 21900567]
87. Taliaz D, Stall N, Dar DE, Zangen A. Knockdown of brain-derived neurotrophic factor in specific brain sites precipitates behaviors associated with depression and reduces neurogenesis. *Mol Psychiatry.* 2010; 15:80–92. [PubMed: 19621014]
88. Taliaz D, Loya A, Gersner R, Haramati S, Chen A, Zangen A. Resilience to chronic stress is mediated by hippocampal brain-derived neurotrophic factor. *J Neurosci.* 2011; 31:4475–4483. [PubMed: 21430148]

Figure 1.

Antidepressant-like effects of deep brain stimulation (DBS) in different prefrontal cortical targets. **(A)** In rodents the medial surface of the frontal cortex has been divided in frontal, anterior cingulate (AC), prelimbic (PL), and infralimbic cortices (IL). On the basis of cytoarchitectural features and anatomical projections, the IL and ventral PL (ventromedial prefrontal cortex) have been suggested to be homologous to the human subgenual cingulum. **(B)** Antidepressant-like effects of DBS in the forced swim test have been observed after PL stimulation ($p = .05$). Animals treated with IL DBS had a nonsignificant decrease in immobility scores as compared with control subjects ($p = .1$). Numbers in parentheses represent animals/group. *Statistically significant compared to controls. Aca, anterior commissure; Acb, nucleus accumbens; AgM, agranular cortex medial; AgL, agranular cortex lateral; CC, corpus callosum; CI, claustrum; CP, caudate putamen; DPC, dorsal peduncular cortex; Ins, insula; MO, medial orbital cortex; Pir, piriform cortex; SI, primary somatosensory cortex; SII, somatosensory cortex; V, ventricle; tt, tenia tecta. Reprinted from Hamani *et al.* (22), with permission from Elsevier, copyright 2010.

Figure 2.

Outcome of ventral medial prefrontal cortex deep brain stimulation (DBS) in the forced swim test and chronic unpredictable mild stress. **(A)** In rats undergoing forced swim test, the predominant behavior (immobility, swimming, or climbing) during the 5 min of the second swimming session was scored every 5 sec (maximal score of 60). **(B)** In mice, immobility time was recorded during a 5-min swimming session. In both rats and mice, animals receiving ventral medial prefrontal cortex DBS had a significant reduction in immobility, the hallmark of an antidepressant-like response, as compared with control subjects ($p = .01$). Part **(C)** of the figure may be divided in two, before and after surgery (arrow). Before surgery, rats exposed to chronic unpredictable mild stress had a significant reduction in the sucrose preference index (SPI). DBS (8 hours/day) was commenced on the third postoperative week and continued for 2 weeks (horizontal bar). On the first week after stimulation onset, SPI in stressed animals receiving DBS ($n = 9$) was significantly higher than that recorded in the stress alone group ($n = 9$; $p < .002$). Differences were accentuated on the second week of stimulation ($p < .0001$ vs. stress alone) with SPI in DBS-treated stressed animals reaching levels comparable to those of nonstressed control subjects. In all experiments, numbers in parentheses represent animals/group. *Statistically significant compared to controls in **A** and **B**, and statistically significant compared to stressed controls in **C**. Reprinted from Hamani *et al.* (23,26), with permission from Elsevier, copyright 2010 and 2012.

Figure 3.

Outcome of radiofrequency (RF) and ibotenic acid (IBO) lesions in the forced swim test (FST). Photomicrographs of animals that underwent bilateral ventromedial prefrontal cortex (vmPFC) (A), fornix minor (C, upper panel), and cingulate RF lesions (C, lower panel). Neither vmPFC RF nor IBO lesions (A, B) induced a significant antidepressant-like response in the FST. (B) When animals bearing vmPFC IBO lesions received stimulation at the same site, however, a significant reduction in immobility scores was observed, as compared with IBO-treated nonstimulated rats ($p < .001$) or control subjects ($p = .02$). (C) A significant antidepressant-like response has not been recorded in animals previously treated with fornix minor (fibers) or cingulate RF lesions. In all panels, numbers in parentheses represent animals/group. Scale bars in A and C = 1 mm. Reprinted from Hamani *et al.* (23), with permission from Elsevier, copyright 2010.

Table 1

Stimulation Targets, Parameters, and Overall Results of Preclinical Studies Investigating the Antidepressant-Like Effects of DBS in Rodents

Author (reference)	Target	Stimulation Parameters	Electrode Configuration	Results
Friedman <i>et al.</i> (31)	VTA	300 μ A, 10-Hz bursting pattern with 2 bursts/sec (5 spikes each), 180-msec pause after each burst	Bipolar unilateral stimulation for 20 min before tests Electrodes with .08 mm in diameter	Flinders rats Antidepressant-like response in the FST and sucrose self-administration Increase in social interaction and exploratory behavior in a novelty exploration test
Hamani <i>et al.</i> (22,23)	vmPFC	100–300 μ A, 90 μ sec, 130 Hz	Bilateral monopolar stimulation for 6 hours in between swimming sessions Electrodes with .125 or .25 mm in diameter	Antidepressant-like response in the FST Reduced latency to eat in the NSF No effect on locomotor activity or LH
Gersner <i>et al.</i> (29)	vPL NAc	400 μ A, 200 μ sec, cycles of 100 pulses during 5 sec (20 Hz) followed by 20-sec pauses	Left unilateral stimulation 10 min/day for 10 days	Anti-anhedonic-like effect in the CUS No effect on locomotor activity, Morris Water maze or the FST
Li <i>et al.</i> (32)	LHb	Trains of 130 Hz with 40-msec pauses at 150 or 300 μ A	FST; bipolar unilateral stimulation given 1 hour after and 1 hour before swimming sessions LH; stimulation given for 1 hour after baseline testing and for 1 hour immediately before LH sessions Electrodes with .8 mm in diameter	Antidepressant-like effects in the FST and LH
Meng <i>et al.</i> (30)	LHb	80–100 μ A, 150 Hz, .3 msec	Bipolar stimulation 30 min/day for 28 days	Increased in vertical and horizontal activity in the open field
Falowski <i>et al.</i> (28)	NAc	2V, 120 Hz, 200 msec	Intermittent (3 hours/day for 2 weeks) or constant (24 hours/day for 2 weeks) bipolar right stimulation Electrodes with .25 mm in diameter	Increased exploratory activity in the open field
Hamani <i>et al.</i> (26)	vmPFC	200 μ A, 90 μ sec, 130 Hz	Bilateral monopolar stimulation 6 hours/day for 2 weeks Electrodes with .25 mm in diameter	Anti-anhedonic-like effects in the CUS

CUS, chronic unpredictable mild stress; FST, forced swim test; LH, learned helplessness; LHb, lateral habenula; NAc, nucleus accumbens; NSF, novelty suppressed feeding; vmPFC, ventromedial prefrontal cortex; vPL, ventral prelimbic cortex; VTA, ventral tegmental area.