

## Review

# Deep Brain Stimulation of the Human Reward System for Major Depression—Rationale, Outcomes and Outlook

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Deep brain stimulation (DBS) as a putative approach for treatment-resistant depression (TRD) has now been researched for about a decade. Several uncontrolled studies—all in relatively small patient populations and different target regions—have shown clinically relevant antidepressant effects in about half of the patients and very recently, DBS to a key structure of the reward system, the medial forebrain bundle, has yielded promising results within few days of stimulation and at much lower stimulation intensities. On the downside, DBS procedures in regions are associated with surgical risks (eg, hemorrhage) and psychiatric complications (suicidal ideation, hypomania) as well as high costs. This overview summarizes research on the mechanisms of brain networks with respect to psychiatric diseases and—as a novelty—extrapolates to the role of the reward system in DBS for patients with treatment-resistant depression. It further evaluates relevant methodological aspects of today's research in DBS for TRD. On the scientific side, the reward system has an important yet clearly under-recognized role in both neurobiology and treatment of depression. On the methodological side of DBS research in TRD, better animal models are clearly needed to explain clinical effects of DBS in TRD. Larger sample sizes, long-term follow-up and designs including blinded sham control are required to draw final conclusions on efficacy and side effects. Practical research issues cover study design, patient tracking, and the discussion of meaningful secondary outcome measures.

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## INTRODUCTION

Major depression is a disorder that taxes many patients with their lives (Blair-West *et al*, 1999) and all with their quality of life (QoL) (Whiteford *et al*, 2013). The impact of this disorder on individual patients has not been lost on physicians who over history tried to develop treatments with sustained antidepressant efficacy. These efforts were not without positive outcomes—today the majority of depressed patients respond to combinations of psychotherapy and pharmacotherapy, in more resistant cases electroconvulsive therapy adds considerable benefit (Lisanby, 2007). FDA-approved neuromodulatory treatments for treatment-resistant depression (TRD) are vagus nerve stimulation, transcranial magnetic stimulation (TMS) and only very recently deep TMS (Lozano and Lipsman, 2013; Schlaepfer *et al*, 2010).

There is however, a sizable proportion of patients who do not benefit significantly from currently available treatments. Given the intense suffering of patients and the lack of efficacious treatments, it is understandable that many invasive and desperate treatments for psychiatric disorders were tried without scientific hypotheses and evaluation (Hariz *et al*, 2010). In 1937, electroconvulsive therapy was introduced by Cerletti and Bini initially as a treatment for psychotic patients (Shorter and Healy, 2007), a treatment which—by way of thorough scientific evaluation—developed into perhaps the most effective methods for TRD (Doshi, 2011).

Lesional psychosurgery for mental disorders—including anxiety disorders and depression—was promoted in the mid-1930s by Moniz with help of the neurosurgeon Lima (Moniz, 1994). Lesion surgery utilizing a stereotactic technology evolved in the mid-1940s. Scientists saw a need for more confined and less-destructive focal lesions than the ones created with the frontal lobotomy procedures that had been introduced by Moniz and were later further developed and clearly too deliberately applied by the neurologist Walter Freeman. This very need for circumscribed lesions in a first step led to the development of the stereotactic dorsomedial thalamotomy (Hariz *et al*, 2010; Spiegel *et al*, 1947) after the thalamus had been identified as a target

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structure with degeneration studies on postmortem brains from frontal lobotomy. At that time, Papez had just recently published his seminal paper that essentially summarized previous work and localized emotions to specific brain regions (Meyer *et al*, 1947; Papez, 1995). In the following decades, other stereotactic lesion surgeries were developed, which were among other disorders applied for the treatment of anxieties and depression: (1) anterior capsulotomy, (2) anterior cingulotomy (Chang *et al*, 2013), (3) subcaudate tractotomy, and (4) limbic leucotomy (essentially a combination of (2) and (3)). Limbic leucotomy probably had the best outcome (Coenen and Honey, 2009a). These lesion surgeries were performed until the mid of the 1990s at different centers and are still in place at certain very experienced institutions (Hurwitz *et al*, 2012) although most centers for good or bad reasons today have converted to the reversible, adjustable, and more benign DBS technology. Only recently the role of the reward system even in the in these historical and lesional surgical approaches were positively evaluated in a tractography study. The efficacy of all these approaches is at least in part based on their modulating action on the reward system (Schoene-Bake *et al*, 2010).

It was not until after 1950 that technical development made it possible to chronically stimulate human brains through implanted electrodes (Hariz *et al*, 2010; Miocinovic *et al*, 2013). Several scientists were independently exploring the potential of brain stimulation for psychiatric diseases, see Hariz *et al* (2010) for a detailed review of historical DBS research and Miocinovic *et al* (2013) for a discussion on mechanisms of DBS. Heath and colleagues described the concept of electrical self-stimulation in the human (Bishop *et al*, 1963; Heath, 1954). Patients and subjects stimulated at the 'septal area' (close to nucleus accumbens and thus in the rewards system) described this stimulation as 'pleasant' or 'euphoric' (see eg Bishop *et al*, 1963). This manipulation of emotions was suggested by the authors as treatment for intractable psychiatric disorders (Hariz *et al*, 2010). However, the lack of scientific rationale and the denial of scientific and ethical standards of their time left the Tulane University's research later being judged as highly dubious (Baumeister, 2000).

The dream of unlimited control over brain processes using electric currents was expressed by Delgado (1971), who believed autonomic and somatic functions, behavior and emotional and mental reactions could be manipulated by electrical stimulation of specific brain areas. This enthusiasm is still shared by some of today's researchers who believe that the possibility to manipulate human brain function 'might well shape history as powerfully as the development of metallurgy in the Iron Age, mechanization in the Industrial Revolution or genetics in the second half of the twentieth century' (Farah *et al*, 2004). This might reflect a culture in which we conceptualize our minds and bodies as machines whose dysfunctions can be fixed or substituted with technology—in most cases even without knowing about the mechanisms that are causing the symptoms. In spite of these dreams, a variety of available treatment options and novel avenues of interventions in research (Holtzheimer *et al*, 2012a; Schlaepfer *et al*, 2010), a third of patients suffering from depression can be classified as treatment-resistant (Rush *et al*, 2006), with very little hope

of recovery, highly stigmatized and unbearably low QoL. For these patients, deep brain stimulation (DBS) is currently under investigation.

## DEPRESSION NEUROBIOLOGY

Traditional treatment perspectives conceptualize depression as a general brain dysfunction by targeting hypothesized monoaminergic synaptic dysfunction (Crupi *et al*, 2011). More complete and appropriate treatments are thought to arise from correlating disease symptoms with dysfunctions of specific brain networks mediating mood and reward responses (Berton and Nestler, 2006; Krishnan and Nestler, 2008). This conceptualization leads to novel and testable hypotheses about targeted neuromodulatory interventions. Long-term data on DBS for depression have been recently reported on targeting the subgenual cingulate Cortex (Cg<sub>25</sub>) target (Coenen *et al*, 2011; Lozano *et al*, 2008; Mayberg *et al*, 2005; Puigdemont *et al*, 2011), the anterior limb of the internal capsule (ALIC) (Malone *et al*, 2009) and the nucleus accumbens septi (NAcc) (Bewernick *et al*, 2012; Bewernick *et al*, 2010). These studies, although limited in their generalizability due to small sample sizes ( $n < 20$ ) and missing sham control, have led to a new enthusiasm regarding significant antidepressant results. In a merely serendipitous fashion, the use of diffusion tensor magnetic resonance imaging (DTI) tractography allowed the explanation of psychotropic side effects of DBS to the subthalamic nucleus in Parkinson's disease (Coenen *et al*, 2009b). These novel studies that combined DBS with tractographic anatomy consequently led to a necessary and novel description of human reward system anatomy (Coenen *et al*, 2012). This whole line of research moved the reward system as a key network for stereotactic interventions into the focus of scientists' attention (Coenen *et al*, 2011) (Schoene-Bake *et al*, 2010). Only recently studies on optogenetic neuromodulation and fast cycling voltammetry (Howe *et al*, 2013; Russo and Nestler, 2013) confirm this previously addressed role of the reward system and now helps to better appreciate its role in depression genesis and interventional approaches.

## DBS TARGETS AND HYPOTHESES

### Subgenual Cingulate White Matter (Brodmann Area Cg25)

In an elegant model, the rostral cingulate cortex has been implicated to have a dominant role in regulating a corticolimbic network (Mayberg, 1997). It has been demonstrated that depression is associated with increased activity in the subgenual cingulate cortex (covering Cg25, Cg24, BA10) and remission was associated with a reduction of hypermetabolism in this region (Fily *et al*, 2011). Dysfunctional connections from the cingulate cortex to the dorsal (including the dorsolateral prefrontal cortex (PFC), inferior parietal cortex, and striatum) and ventral parts (hypothalamic-pituitary-adrenal axis, insula, subgenual cingulate, and brainstem) of the emotion regulation circuit in depression are involved in depression (Riva-Posse *et al*, 2013). It was hypothesized that DBS to the cingulate cortex would lead to antidepressant effects by modulating the

depression network through a reduction of Cg25 activity (Mayberg, 1997).

### Anterior Limb of The Capsula Interna

The cortico-striato-thalamo-cortical network has an important role in obsessive-compulsive disorder (OCD) (Bourne *et al*, 2012). Observations from lesion studies (Lippitz *et al*, 1999; Lipsman *et al*, 2007; Nuttin *et al*, 1999) and antidepressant effects that were seen in OCD patients who were stimulated in the ALIC/the ventral striatum (Greenberg *et al*, 2008), lead to a study in which this structure was stimulated in TRD (Malone *et al*, 2009).

### Targets in the Reward System: NAcc and MFB

Predictions about anticipated future rewarding events are encoded in dopamine concentrations in the ventral striatum. We now learn that the amount of dopamine itself encodes the distance from the reward (Howe *et al*, 2013). The reward system itself is obviously more concerned with the reward anticipation than with the consummatory phase of reward. Recent data suggest dysfunctions of structures implicated in the human reward system in mood disorders, particularly in the ventral tegmental area (VTA), the nucleus accumbens (NAcc) and the pathways associated with them (medial forebrain bundle (MFB)) (Russo and Nestler, 2013). These facts now and in retrospect render these structures as promising targets for neuromodulatory interventions with putative anti-anhedonic and motivational effects after tractographic research had earlier already anticipated these clinical effects (Coenen *et al*, 2011).

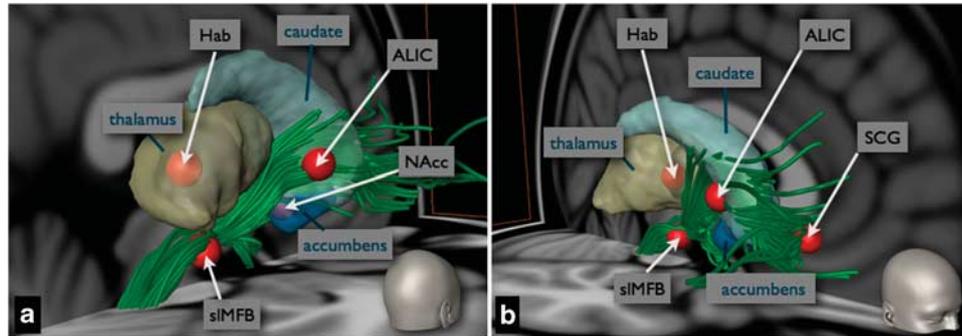
*Nucleus Accumbens septi.* NAcc is another structure that has been identified as a key center of the depression network (Berton and Nestler, 2006). Specifically, the NAcc is thought to act as the motivation gateway between systems involved in emotion and motor control (Schlaepfer *et al*, 2008). Anhedonia, which has been correlated with NAcc dysfunction (Pizzagalli *et al*, 2009; Pizzagalli *et al*, 2008; Tremblay *et al*, 2005) is a core symptoms in depression (Argyropoulos and Nutt, 1997; Rush and Weissenburger, 1994). Converging evidence from animal, pharmacological, and neuroimaging studies point toward NAcc dysfunction in depression and DBS of the NAcc leads to increases of all monoaminergic neurotransmitters in the PFC (van Dijk *et al*, 2012); this led to the hypothesis that DBS to the NAcc would lead to antidepressant effects by modulating the depression network (Schlaepfer *et al*, 2008).

*Supero-lateral branch of the medial forebrain bundle.* The supero-lateral branch of the medial forebrain bundle (slMFB) has also been proposed as a target (Coenen *et al*, 2011). Early lesional interventions have been found to exert their effect by influencing two major pathways (Schoene-Bake *et al*, 2010). These two affect-regulating fiber systems, the slMFB and the anterior thalamic radiation (ATR), are concerned with maintenance of emotional homeostasis. The slMFB is linked to reward-seeking and appetitive motivation (reward-seeking) in general, whereas the ATR is probably more involved in negative feelings (eg sadness, separation-distress, and psychic pain) (Coenen *et al*, 2012).

Compared with neurological indications, higher stimulation intensities have been used in DBS for depression; the generated large electric fields thus stimulate structures beyond the intended target sites. Electric field simulation and probabilistic fiber tracking has demonstrated that the slMFB is anatomically and functionally connected with other DBS targets (Cg25, ALIC, and NAcc) (Coenen *et al*, 2012; Coenen *et al*, 2011). This led to the hypothesis that most likely these targets are clinically effective because of a stimulation in a network that to a larger proportion is realized through the MFB a structure that had previously been identified to be involved in lesion surgery for depression (Schoene-Bake *et al*, 2010). A study using optogenetic neuromodulation together with DBS has recently shown that activation and modulation of afferent fiber tracts are a plausible mechanism of action in DBS (Gradinaru *et al*, 2009). Thus, modulation and not inactivation of the MFB would be postulated as the antidepressant mechanism of action (Coenen *et al*, 2012; Coenen *et al*, 2011). The VTA is an important relay station in the reward circuitry that serves a central role in motivation and reward processing (Lammel *et al*, 2014). This region projects via the MFB to the nucleus accumbens and via a separate pathway to the PFC. Very recently, two papers were published on optogenetic stimulation of the VTA. It was demonstrated that optogenetic recruitment of dopamine neurons potentially alters the neural encoding of depression-related behaviors in the downstream nucleus accumbens (Lammel *et al*, 2013; Tye *et al*, 2012). A second paper of different group demonstrated that optogenetic inhibition of the VTA-NAcc projection rapidly induced resilience, whereas inhibition of the VTA-mPFC projection promoted susceptibility in mice (Chaudhury *et al*, 2013). These results are insofar significant as it is likely that DBS to the MFB recruits the descending glutamatergic (and by that excitatory) projection (Russo and Nestler, 2013) from the PFC to the VTA (Schlaepfer *et al*, 2013). It needs to be considered that there are at least two distinct dopaminergic neuronal populations involved in the mechanisms of the VTA: (1) a population of tonic dopaminergic neurons that probably is related to reward promotion and (2) a population of phasic dopaminergic neurons which upon interference (or inhibition) result in increased resilience (Russo and Nestler, 2013). These distinct functions need to be further explored in future research but certainly have a role in the antidepressant effects of DBS to the MFB.

### EFFICACY AND SAFETY

For three targets (Cg25, ALIC, and NAcc), acute and long-term antidepressant effects have been published (Bewernick *et al*, 2012; Bewernick *et al*, 2010; Holtzheimer *et al*, 2012c; Kennedy *et al*, 2011; Lozano *et al*, 2008; Malone *et al*, 2009; Puigdemont *et al*, 2011). In two studies, patients have been followed for up to 6 years (Bewernick *et al*, 2012; Kennedy *et al*, 2011). Sample sizes of these studies are small (<30) and sham control is not included in all studies (Blumberger *et al*, 2013). Thus, efficacy data are still on a pilot level (see Figure 1, Table 1; overview of published studies (Aouizerate *et al*, 2004; Bewernick *et al*, 2012; Bewernick *et al*, 2010; Dougherty *et al*, 2012; Grubert *et al*, 2011; Holtzheimer *et al*,



**Figure 1** DBS targets in depression. Experimental targets (red spheres) for deep brain stimulation in major depression: (a) view from posterolateral right, (b) view from anterolateral right. Note how the medial forebrain bundle (green fiber structure) interconnects the majority of target sites (ALIC, NAcc, SCG, sIMFB) as a key structure. Legend: ALIC, anterior limb of internal capsule; Hab, habenula; caudate, caudate nucleus; NAcc, nucleus accumbens (anatomically: accumbens); SCG, subgenual cingulate gyrus; sIMFB, superolateral branch of the medial forebrain bundle.

**Table 1** DBS Targets for Major Depression

Target	Hypothesis	Hypothesis based on
Anterior Gyral Cinguli (Brodmann area Cg25)	Inactivation of Cg25 leads to recovery	Functional neuroimaging findings
Anterior limb of capsula interna	Inactivation of dysfunctional connections	Clinically effective neurosurgical interventions for OCD and depression
Medial forebrain bundle	Activation of this key structure of the human reward system leads to acute and longer term anti-anhedonic effects	Structural and functional neuroimaging. Animal studies
Nucleus accumbens	Modulation of the nucleus accumbens, which is a central structure in the reward system, leads to improvement of anhedonia	Clinical experience. Neurobiology of reward system
Habenula	Inhibition of the lateral Habenula leads to up regulation of serotonergic, noradrenergic, dopaminergic system and down regulation of HPA axis	Functional neuroimaging findings. Animal studies
Thalamus	Dysfunctional connection between thalamic system and orbitofrontal in depression. Disruption of over activation of frontal cortex with DBS	Functional neuroimaging findings. Animal studies

2012c; Jiménez *et al*, 2005; Kennedy *et al*, 2011; Lozano *et al*, 2012; Lozano *et al*, 2008; Malone *et al*, 2009; Mayberg *et al*, 2005; McNeely *et al*, 2008; Puigdemont *et al*, 2011; Sartorius *et al*, 2010; Schlaepfer *et al*, 2013; Schlaepfer *et al*, 2008)). A recent multicenter study on ALIC (Dougherty *et al*, 2012) has demonstrated the need for larger samples and raised a discussion on study design (see below).

### Acute Effects

During surgery, intraoperative test stimulation is used to determine possible side effects and to assess acute clinical effects (Table 2). After surgery, at the initiation of chronic stimulation, repeated sessions within several weeks are required to determine best stimulation parameters (titration phase).

Immediate clinical effects, during intraoperative test stimulation or at the initiation of chronic stimulation occur within a few minutes. These effects include more spontaneous engagement in conversation, positive change in mood, increased alertness, relaxation, increased motivation, higher activity level, and a sense of calmness (Bewernick *et al*, 2010; Holtzheimer *et al*, 2012c; Mayberg *et al*, 2005), but also tension, dizziness, and anxiety. Only some patients

experience acute effects, which do not seem predictive for long-term effects (Bewernick *et al*, 2010; Puigdemont *et al*, 2011). Possibly, an initial acute stimulation effect during surgery diminishes after re-initiation of stimulation (Holtzheimer *et al*, 2012c). In a recent pilot study of sIMFB stimulation, all seven patients showed similar acute effects during intraoperative testing (eg, increased alertness, orientation reaction, spontaneous and appropriate engagement in conversation, eye contact), typically dominantly on one (but inter-individual distinct) side of intraoperative testing (Schlaepfer *et al*, 2013).

### Longer-Term Clinical Effects

Long-term clinical effects are long-lasting changes that occur after 1–6 months of chronic DBS. Antidepressant response has been demonstrated in six small studies at three different targets (Cg25, ALIC, NAcc). (Bewernick *et al*, 2010; Kennedy *et al*, 2011; Lozano *et al*, 2012; Lozano *et al*, 2008; Malone *et al*, 2009; Puigdemont *et al*, 2011). Amelioration of other clinical measures (eg QoL, anxiety, general psychopathological burden) has been associated with antidepressant effects for these targets. When comparing outcomes of DBS studies, different ways of analyzing results has an

**Table 2** DBS Studies in Major Depression

Target/hypothesis	Reference	n	Study design	Mean stimulation parameters	Effect at 12 m % responders at 12 months	Effect at 2 years % responders at 2 and more years	Neurophysiology/ Cognition	Side effects
Subgenual Cingulate (Cg 24/25): Inactivation of Cg25 leads to recovery based on functional neuroimaging findings	Kennedy <i>et al</i> , 2011; Lozano <i>et al</i> , 2008; Mayberg <i>et al</i> , 2005; McNeely <i>et al</i> , 2008	20	Uncontrolled study; multisite study. Systematic parameter search, blinding phase, up to 6 years follow-up	Bilateral, monopolar stimulation, mean parameters 124.7 Hz, 70.6 $\mu$ s, 4.3 V	55% Responders	2 Years: 45% responders; 3 years: 60% responders	Normalization of brain metabolism in Cg25 using $^{15}$ O-water and $^{18}$ F-fluorodeoxyglucose-PET. Neuropsychological assessment no worsening of cognitive functions	Three wound infection and hardware removal; six hospitalizations for psychiatric reasons; two committed suicides; two suicide attempts
	Puigdemont <i>et al</i> , 2011	8	Uncontrolled study; 12 months observation	4.2 V, 135 Hz, 90 $\mu$ s, bipolar stimulation	62.5% Responders		Neuropsychological performance at the time of clinical stabilization unaffected by DBS	Two cephalgia; three pain in the neck; one suicide attempt; two relapses of depression requiring hospitalization. Additional ECT in one patient
	Holtzheimer <i>et al</i> , 2012c	10 MDD; 7 bipolar	Single blind sham phase (4 weeks, n = 3)	130 Hz, 90 $\mu$ s, 5–8 mA	43% Responders	2 Years: 70% responders	Neuropsychological assessment: improved or stable cognitive functions	Two infection; two anxiety; one worsening depression; one suicidal ideation; two suicide attempts; one system dislodged; one extension break; one erosion; three headache; two hand numbness; one arm weakness; one gait disorder; four nausea; one chest pain; one anemia
	Lozano <i>et al</i> , 2012	21 MDD	Multisite study; 12 months observation	Mean parameters at 12 months: 128.1 Hz, 93.9 $\mu$ s, 5.2 mA, 1.5 (right), 1.4 (left) active contacts	29% Responders			Three skin erosion; two extension break; one chest pain; one pneumonia infection; one suicide attempt; one suicide; 15 gastrointestinal; 12 musculoskeletal; nine skin; six headache; four pain; four psychiatric (agitation, reaction to amplitude increase); three dizziness; two polyuria; one weight gain; one buzzing in ears; one insomnia
Anterior limb of capsula interna (ALIC): Clinically effective neurosurgical interventions for OCD and depression	Malone, 2011; Malone <i>et al</i> , 2009	17	Up to 5.5 years	6.7 V, 113.0 $\mu$ s, 127.0 Hz	53% Responders		Neuropsychological assessment no worsening of cognitive functions	Stimulation effects: paraesthesia, anxiety, mood changes, and autonomic effects (reversible by parameter change); one I lead fracture; two suicidal ideation; two syncope; two mood elevation (hypomania); two depression worsening

**Table 2 (Continued)**

Target/hypothesis	Reference	n	Study design	Mean stimulation parameters	Effect at 12 m % responders at 12 months	Effect at 2 years % responders at 2 and more years	Neurophysiology/ Cognition	Side effects
	Dougherty <i>et al</i> , 2012	30 MDD	Randomized sham-controlled trial; multisite study (Medtronic pivotal trial)	Not reported	21 % Responders			Infection, worsening of depression, suicidal ideation; two suicide attempts
Nucleus accumbens septi: Modulation of the nucleus accumbens, which is a central structure in the reward system, leads to improvement of anhedonia, based on clinical experience and neurobiology of reward system	Bewernick <i>et al</i> , 2010; Bewernick <i>et al</i> , 2012; Grubert <i>et al</i> , 2011; Schlaepfer <i>et al</i> , 2008	13 MDD	Up to 4 years observation, 5–8 V, 90 $\mu$ s, 130 Hz, blinding phase, systematic monopolar parameter search		45% Responders	2 Years: 45% responders	Normalization of brain metabolism in N. Accumbens and Cg25 Normalization or no change in neuropsychological measures	Stimulation effects: paraesthesia, anxiety, mood changes, and autonomic effects (reversible by parameter change); paraesthesia, vision/eye movement, transient mood elevation, erythema, anxiety; one seizure; one lead dislodgement; one suicide attempt; one committed suicide; one syncope
Supero-lateral branch of the medial forebrain bundle (slMFB): The slMFB is linked to reward-seeking and appetitive motivation; electric field stimulation and probabilistic fiber tracking suggest an involvement of the slMFB in DBS of the current DBS targets (Cg25, ALIC; NAcc); excitatory modulation of the MFB was proposed to have antidepressant effects (Coenen <i>et al</i> , 2011)	Schlaepfer <i>et al</i> , 2013	6 MDD; 1 bipolar	Uncontrolled study	2–3 V, 60 $\mu$ s, 130 Hz, bipolar	85% Responders at 3 months (response within days of stimulation)		No changes	Haemorrhage in one patient (the only non-responder) (Coenen <i>et al</i> , 2013). Oculomotor dysfunction (resolved with parameter adjustment)
Lower stem of thalamus: Dysfunctional connection between thalamic system and orbitofrontal cortex in depression, disruption of overactivation of frontal cortex with DBS. Based on functional neuroimaging	Jiménez <i>et al</i> , 2005	1 MDD	Case report; 24 months follow-up, 2 months blinding phase; Comorbid; Personality disorder and bulimia nervosa	2.5 V, 130 Hz, 450 $\mu$ s	Remission of depression, Relapse during blinding off phase		Improvement in verbal and nonverbal memory and abstraction tests. Decrease in learning-to-learn capabilities (WCST)	
N. Caudatus/ N. Accumbens: Inactivation of dysfunctional connections based on neurosurgical interventions for OCD and depression	Aouizerate <i>et al</i> , 2004	1 MDD and OCD	Case report; 6 months observation	4 V, 130 Hz, 120 $\mu$ s	Remission of depression at 6 months (HDRS < 7)			
Habenula: Overactivation of lateral habenula during depression, based on functional neuroimaging findings and animal studies	Sartorius and Henn, 2007; Sartorius <i>et al</i> , 2010	1 MDD	Case report; 60 weeks, no blinding phase	5 to 10.5 V, 165 Hz, 60 ms pulse width	No acute effects, Stimulation I (5 V): Relapse: Stimulation II (increased to 10.5): full and stable remission (HAMD <sub>21-3</sub> ), Stimulation III (after relapse due to stimulation stop because of bike accident); Patient reached remission (HAMD <sub>21-0</sub> ) after 12 weeks of high-voltage DBS		FDG-PET: a localized metabolic increase at the stimulation sites, no metabolic change in lateral habenula. Normal cognitive functioning verified by neuropsychological test battery	

Overview of published reports of DBS for treatment-resistant major depressive disorder (TR-MDD).

impact on efficacy because most dropouts are non-responders. Therefore, intent-to-treat analysis (of all patients including dropouts up to the final endpoint, mostly in a carried forward manner) seems to be a more adequate, conservative method to reflect efficacy (see, for example, Bewernick *et al*, 2012; Puigdemont *et al*, 2011). Nonetheless, other groups present data analyzed as ‘per protocol/as treated’ (Holtzheimer *et al*, 2012c; Kennedy *et al*, 2011). In this way, dropouts and non-responders are not reflected in the data after their dropout, this leads to an artificially inflated efficacy. In addition, it is questionable whether a newly introduced time point ‘last observation’ is of scientific value, as it mostly reflects scores of patients that are treated for a short time and others treated long-term (up to many years) (see, for example, Malone, 2011). Response is uniformly described as a reduction of 50% or more reduction of the rating scale (Hamilton rating scale or depression or Montgomery Åsberg rating scale for depression) from baseline.

Response rates are similar for Cg25, ALIC, and NAcc (Bewernick *et al*, 2010; Lozano *et al*, 2008; Malone *et al*, 2009; Puigdemont *et al*, 2011). Twenty patients stimulated at Cg25 had a response rate of 55% after 1 year, 45% after 2 years, 60% after 3 years, and 55% response at the last follow-up visit (up to 6 years) in an intent-to-treat analysis (Kennedy *et al*, 2011). Similarly, a study with eight patients stimulating Cg24/25, reported response rates of 87% after 6 months and 62.5% after 12 months ( $n=8$ ) (Puigdemont *et al*, 2011). In a mixed sample with 10 MDD patients and 7 patients suffering from bipolar disorder (Holtzheimer *et al*, 2012c), response rates for the patients still followed in the study ( $n=12$  after 2 years) were 36% after 1 year ( $n=14$ ), and 92% after 2 years ( $n=12$ ) in a per protocol analysis. In a multicenter open-label trial targeting subgenual cingulate ( $n=21$ ), 48% of patients responded after 6 months, and 29% after 12 months (Lozano *et al*, 2012). Seventeen patients were studied targeting the ALIC. Response rates were 53% after 12 months ( $n=17$ ) and 71% at last follow-up (ranging from 14 to 67 months) (Malone *et al*, 2009).

Eleven patients were stimulated at the NAcc, 50% responded significantly during the first 6 months and remained stable during follow-up (up to 4 years), in an intent-to-treat analysis (Bewernick *et al*, 2012). Young, female patients with previous response to ECT and periods in remission after first onset of depression appear to benefit from DBS (Bewernick *et al*, 2010; Puigdemont *et al*, 2011) although small sample sizes limit the possibility to identify predictors of response. In addition, NAcc-DBS specifically influenced the symptoms of anhedonia and anxiety (Bewernick *et al*, 2010). Only recently, a hypothesis concerning exact electrode position has been assessed. In one study targeting Cg<sub>25</sub>, electrode position had an influence on antidepressant outcome (Puigdemont *et al*, 2011); among responders most patients had electrodes placed in Cg<sub>24</sub>. Another study did not find a relationship between electrode location and clinical effect (Lozano *et al*, 2008).

Pivotal study results in which DBS was not superior to sham stimulation, have been published from a randomized, sham-controlled, study of ALIC-DBS in 30 patients (Dougherty *et al*, 2012) contrasting results obtained at the same target (Malone *et al*, 2009). The percentage of patients

responding to sham and active stimulation was similar (14.3% responding to sham, 20% to active stimulation) and the mean reduction in MADRS was larger in the sham stimulation group (−24.6%) compared with the real stimulation group (−19.6%). This study demonstrates how important design aspects in DBS studies are, here especially the amount of time used to identify optimum stimulation parameters and the point at which a sham condition was introduced in the study protocol (after stable antidepressant effects have been established or as staggered onset design, see below) are debatable.

A recent pilot study on DBS to the sLMFB yielded interesting results: all patients showed strikingly similar intra-operative effects of increased appetitive motivation. Six of seven patients attained the response criterion; response was rapid—mean Montgomery-Åsberg Depression Rating Scale of the whole sample was reduced by >50% at day 7 after stimulation onset. At last observation (12–33 weeks), six patients were responders; among them, four were classified as remitters (Schlaepfer *et al*, 2013). In the only non-responder a hemorrhage occurred, and a tractographic *post hoc* analysis revealed that a significant amount of sLMFB fibers that connect to the frontal lobe were missing due to the bleeding (Coenen *et al*, 2013). In the whole group, social functioning (Global Assessment of Functioning) improved from serious to mild impairment. Mean stimulation current was 2.86 mA. Currently a sham-controlled study with a staggered stimulation onset design is underway in order to further establish efficacy and safety at our center.

### Putative Mode of Action of sLMFB DBS

It is a little outside the scope of this review but the current interest in reward system DBS warrants a brief discussion on the topic: the mode of action of sLMFB DBS at this moment remains unclear. There is circumstantial evidence, however, that allows for a plausible hypothesis and we have previously speculated about this (Schlaepfer *et al*, 2013). The sLMFB contains short axons of unmyelinated dopaminergic neurons that cannot be directly recruited with DBS at short pulse widths (60  $\mu$ s) (Ikemoto, 2010). The mode of action must be different and not through a direct activation. Glutamatergic fibers that descend from the PFC into the VTA have an activating effect. Very likely these heavily myelinated fibers are activated by the short pulse width (60  $\mu$ s) used for sLMFB DBS (Russo and Nestler, 2013). Most likely the DA neurons in the VTA are activated by these glutamatergic projections. Recently studies by Gale *et al*, in a primate model show that a chronic stimulation of the MFB in the zona incerta at high frequencies induces a DA release in the striatum (Gale *et al*, 2013). Also there is evidence from the OCD literature that DBS leads to a DA release (Figeo *et al*, 2013). Obviously at least two DA-neuron populations are present in the VTA, tonic, and phasic neurons. Optogenetics teaches us that silencing highly active phasic population increases resilience in mice. At the same time, activating the tonic DA neurons reduces susceptibility. We speculate that the tonic DA output from the VTA is increased and leads to increased free synaptic Dopamine in NAcc and the PFC. This is likely to increase appetitive motivation and might modulate reward

expectancy. Uncovering the true effect of sMFB DBS is a very important next step and is the focus of our current research in animal models and human imaging studies.

### Sham Stimulation Effects

Only few data on sham-controlled DBS in depression have been published hitherto (Bewernick *et al*, 2010; Holtzheimer *et al*, 2012c; Lozano *et al*, 2008) but small sample sizes do not allow the estimation of a sham effect. Significant sham effects in this group of very treatment-resistant patients seem improbable as likelihood of placebo response decreases with treatment resistance (Schatzberg and Kraemer, 2000). On the other hand, it has been shown in studies of DBS for Parkinson's disorder that expectation and placebo effects account for clinically pertinent aspects of improvement with this procedure (Mercado *et al*, 2006). This together with the recent finding of high-sham response rates in ALIC-DBS for depression (Dougherty *et al*, 2012) really speaks for the need of large sham-controlled studies before DBS can be recommended clinically. Sham condition is difficult to maintain as have a hard time tolerating off phases leading to massive worsening of symptoms with increased risk for suicidal ideation. This problem could be partly addressed with staggered onset design protocols (Goodman *et al*, 2010), with a clear-cut rescue criterion for sham stimulation phases and weekly visits.

### Cognition

Safety regarding cognitive effects has been documented for DBS to Cg25 (McNeely *et al*, 2008) and to NAcc (Grubert *et al*, 2011) and ALIC (Malone *et al*, 2009). Cognitive improvement in the domain of attention, memory, executive function, and visual perception has been demonstrated in patients treated with NAcc-DBS. This amelioration was not explained by the improvement in depression severity and could thus be shown independent of response status. There was a general trend toward cognitive normalization from below average, to average performance (Grubert *et al*, 2011). Until now, there is no evidence for cognitive enhancement effects above normal functioning at the evaluated target sites.

### Adverse Effects

Side effects are related to the surgical procedure, to a malfunctioning of the DBS device or to the stimulation (see Table 1 for details). Wound infection after surgery or battery exchange, lead migration and device-related infections are important surgical complications in DBS studies. Lead migration (2.5% of patients), erosion, and infection (4.5–8.9% of patients) have been reported (Doshi, 2011; Fily *et al*, 2011). So far, there is only one report of hemorrhage in DBS studies for depression (Schlaepfer *et al*, 2013), but statistically, DBS surgery has a substantial of 0.9% to cause hemorrhage (Zrinzo *et al*, 2012). Side effects due to stimulation (eg erythema, increase in anxiety, agitation, and elevation of mood) are in most cases transient and occur within minutes to hours after new parameters have been programmed. The exact mechanism how side effects are induced is not fully understood, in some cases (eg

oculomotor side effects), a modulation of neighboring neuronal tissue to the target region can explain the effect. If side effects persist and are judged to be troublesome, a change in stimulation settings is required. Careful assessment of patients is needed after parameters have been changed, especially if psychiatric side effects are possible.

The aggravation of symptoms due to battery depletion, unattended stimulation stop or during the blinding phase has been described (Bewernick *et al*, 2012; Holtzheimer *et al*, 2012b; Lozano *et al*, 2008). In spite of regular careful visits, suicides and suicide attempts have been reported (Bewernick *et al*, 2010; Holtzheimer *et al*, 2012b; Kennedy *et al*, 2011; Lozano *et al*, 2012). TRD is associated with a 15% risk of suicide (Isometsa *et al*, 1994; Wulsin *et al*, 1999). This risk is 4–5 times higher in severe depression compared with moderate or mild depression (Holtzheimer *et al*, 2012b). Thus, careful patient tracking is needed during follow-up; especially before optimal stimulation parameters have been established, after parameter change and during sham stimulation.

### DISCUSSION

After a decade of DBS against depression, we are still away from effectively influencing dysfunctional emotional states. However, first studies have found encouraging antidepressant effects.

### What Might be Truly Relevant Outcome Measures?

*Traditional clinical rating scales.* Depression studies commonly use depression scales (MADRS or HDRS); similar to pharmacotherapy studies, a 50% reduction in the measured depression score is judged as a significant response. This reduction reflects a major change in symptom load and in the patient's QoL. It has been discussed, whether a reduction of cut-off for response to 40% is reasonable in DBS studies (Lozano *et al*, 2012), because many patients varied between 40% and 50% response during follow-up in this study. This already means for therapy-resistant patients a major change in QoL. Nonetheless, we believe that to maintain comparability with other therapies the conservative 50% criterion should be applied for efficacy evaluation. The commonly used depression rating scales however are not very sensitive in patients suffering from severe depression due to floor effects. Thus, new DBS-specific clinical measures are needed. Recently, a new putative measure, the Illness Density Index has been proposed, which might reflect DBS effects more adequately (Kelley *et al*, 2012).

*Quality of life.* In DBS studies for the treatment of neurological diseases, QoL has now been brought into focus, because a change in motor symptoms (eg in Parkinson's disease), was not necessarily associated with an amelioration in QoL (Daniels *et al*, 2011). How important are QoL issues in DBS depression research? QoL scales measure dimensions beyond symptom improvement, eg abilities to interact socially, to enjoy leisure activities, to work effectively, and to manage everyday life. Treatment for MDD has

been shown to improve QoL in the acute treatment phase, but QoL remains low compared with healthy controls even when symptoms are in remission following treatment (Ishak *et al*, 2011a; Ishak *et al*, 2011b; Kennedy *et al*, 2001). Changes of QoL seem to have different timelines as compared with symptom change (Kennedy *et al*, 2001). QoL is strongly related to the symptoms of depression (Daniels *et al*, 2011), but few studies exist exploring QoL in chronic, therapy-resistant depression (Miller *et al*, 1998). DBS studies assess changes in QoL using the medical outcomes study short-form SF-36 (Ware *et al*, 1998). Improvement in QoL in DBS depression studies have been reported for Cg25 (Kennedy *et al*, 2011) and NAcc (Bewernick *et al*, 2012), but the patients remained below average of healthy persons. Today, it is unclear, whether QoL changes in relation to response status. Thus, a QoL measure adds important information beyond symptom rating scales, especially when efficacy is not clear according to symptom rating scales.

## OUTLOOK

After a decade of DBS for TRD, studies have shown relevant antidepressant effects. Nonetheless, with DBS is still associated with substantial surgical and psychiatric risks (eg hemorrhage, suicide) as well as high costs. Experience from first preliminary studies has led to proposal of new target sites (Coenen *et al*, 2011; Mayberg *et al*, 2005) in a hypothesis-guided way. These new targets await rigorous scientific evaluation. Taken together, the data on DBS for major depression accumulated until today holds the promise that this intervention may lessen the suffering of those patients who hitherto have little or no hope to recover from treatment-resistant forms of the disease. This is remarkable. However, we have to remain modest and cognizant of the fact that DBS for neuropsychiatric disorders remains for now a ‘halfway technology’, a term created by Lewis Thomas to describe therapies that only ameliorate but not eliminate a disease condition (Olds and Milner, 1954). Thomas states that

“...It is characteristic of this kind of technology that it costs an enormous amount of money and requires a continuing expansion of hospital facilities. The only thing that can move medicine away from this level of technology is new information, and the only imaginable source of this information is research. The real high technology of medicine comes as the result of a genuine understanding of disease mechanisms.” (Thomas, 1971)

DBS certainly has the potential to be used as a powerful research tool, informing us about the underlying neurobiology of major depression and related psychiatric disorders. Already now it has contributed to a novel view of depression—moving away from a ‘synaptocentric’ view to a conceptualization of disordered brain networks, networks processing responses to affective stimuli (Krishnan and Nestler, 2008) including reward and reward anticipation (Russo and Nestler, 2013; Schlaepfer *et al*, 2013). It has become evident, that several psychiatric disorders might be correlated with network dysfunctions (Insel, 2010).

Research on DBS will most certainly lead to more effective treatments of depression, which might then in turn

altogether use different forms of neuromodulation (Famm *et al*, 2013). Only when we fully understand the real underpinnings of major depression, a stimulation method can become a ‘decisive technology’ in Thomas’s terms and might even as a translational research strategy contribute to a new understanding of mental disorders. We believe that such a development is possible and that then DBS and its progressions into more refined neuromodulation strategies will deliver on today’s promises one day.

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## REFERENCES

- Aouizerate B, Cuny E, Martin-Guehl C, Guehl D, Amieva H, Benazzouz A *et al* (2004). Deep brain stimulation of the ventral caudate nucleus in the treatment of obsessive-compulsive disorder and major depression. Case report. *J Neurosurg* **101**: 574–575.
- Argyropoulos SV, Nutt DJ (1997). Anhedonia and chronic mild stress model in depression. *Psychopharmacology (Berl)* **134**: 333–336.
- Baumeister AA (2000). The Tulane Electrical Brain Stimulation Program a historical case study in medical ethics. *J History Neurosci* **9**: 262–278.
- Berton O, Nestler EJ (2006). New approaches to antidepressant drug discovery: beyond monoamines. *Nat Rev Neurosci* **7**: 137–151.
- Bewernick B, Kayser S, Sturm V, Schlaepfer TE (2012). Long-term effects of nucleus accumbens deep brain stimulation in treatment-resistant depression: evidence for sustained efficacy. *Neuropsychopharmacology* **37**: 1975–1985.

- Bewernick BH, Hurlmann R, Matusch A, Kayser S, Grubert C, Hadrysiewicz B *et al* (2010). Nucleus accumbens deep brain stimulation decreases ratings of depression and anxiety in treatment-resistant depression. *Biol Psychiatry* **67**: 110–116.
- Bishop MP, Elder ST, Heath RG (1963). Intracranial self-stimulation in man. *Science* **140**: 394–396.
- Blair-West GW, Cantor CH, Mellsop GW, Eyeson-Annan ML (1999). Lifetime suicide risk in major depression: sex and age determinants. *J Affect Disord* **55**: 171–178.
- Blumberger DM, Mulsant BH, Daskalakis ZJ (2013). What is the role of brain stimulation therapies in the treatment of depression? *Curr Psychiatry Rep* **15**: 368.
- Bourne SK, Eckhardt CA, Sheth SA, Eskandar EN (2012). Mechanisms of deep brain stimulation for obsessive compulsive disorder: effects upon cells and circuits. *Front Integr Neurosci* **6**: 29.
- Chang WS, Roh D, Kim CH, Chang JW (2013). Combined bilateral anterior cingulotomy and ventral capsule/ventral striatum deep brain stimulation for refractory obsessive-compulsive disorder with major depression: do combined procedures have a long-term benefit? *Restor Neurol Neurosci* **31**: 723–732.
- Chaudhury D, Walsh JJ, Friedman AK, Juarez B, Ku SM, Koo JW *et al* (2013). Rapid regulation of depression-related behaviours by control of midbrain dopamine neurons. *Nature* **493**: 532–536.
- Coenen V, Honey C (2009a). Ablative procedures for depression. In: Lozano A, Gildenberg PL, Tasker RR (eds). *Textbook of Stereotactic and Functional Neurosurgery*. Springer: Berlin, Heidelberg, pp 2943–2952.
- Coenen VA, Honey CR, Hurwitz T, Rahman AA, McMaster J, Burgel U *et al* (2009b). Medial forebrain bundle stimulation as a pathophysiological mechanism for hypomania in subthalamic nucleus deep brain stimulation for Parkinson's disease. *Neurosurgery* **64**: 1106–1114.
- Coenen VA, Mädler B, Schlaepfer TE (2013). Reply to: medial forebrain bundle stimulation-speed access to an old or entry into a new depression neurocircuit? *Biol Psychiatry* **74**: e45–e46.
- Coenen VA, Panksepp J, Hurwitz TA, Urbach H, Madler B (2012). 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* **24**: 223–236.
- Coenen VA, Schlaepfer TE, Maedler B, Panksepp J (2011). Cross-species affective functions of the medial forebrain bundle—implications for the treatment of affective pain and depression in humans. *Neurosci Biobehav Rev* **35**: 1971–1981.
- Crupi R, Marino A, Cuzzocrea S (2011). New therapeutic strategy for mood disorders. *Curr Med Chem* **18**: 4284–4298.
- Daniels C, Krack P, Volkmann J, Raethjen J, PINSKER MO, Kloss M *et al* (2011). Is improvement in the quality of life after subthalamic nucleus stimulation in Parkinson's disease predictable? *Mov Disord* **26**: 2516–2521.
- Delgado JMR (1971). *Physical Control of the Mind – Toward a Psychocivilized Society*. Harper Colophon books: New York.
- Doshi PK (2011). Long-term surgical and hardware-related complications of deep brain stimulation. *Stereotact Funct Neurosurg* **89**: 89–95.
- Dougherty D, Carpenter L, Bhati M, Howland R, O'Reardon J, Denko T *et al* (2012). A Randomized Sham-Controlled Trial of DBS of the VC/VS for Treatment-Resistant Depression. Society of Biological Psychiatry 67th Annual Scientific Convention. 071-Late Breaking Oral Session #2—Mixed Topics <http://goo.gl/PGTpo>.
- Famm K, Litt B, Tracey KJ, Boyden ES, Slaoui M (2013). Drug discovery: a jump-start for electroceuticals. *Nature* **496**: 159–161.
- Farah MJ, Illes J, Cook-Deegan R, Gardner H, Kandel E, King P *et al* (2004). Neurocognitive enhancement: what can we do and what should we do? *Nat Rev Neurosci* **5**: 421–425.
- Figee M, de Koning P, Klaassen S, Vulink N, Mantione M, van den Munckhof P *et al* (2013). Deep brain stimulation induces striatal dopamine release in obsessive-compulsive disorder. *Biol Psychiatry* **S0006-3223**: 00631–00638.
- Fily F, Haegelen C, Tattevin P, Buffet-Bataillon S, Revest M, Cady A *et al* (2011). Deep brain stimulation hardware-related infections: a report of 12 cases and review of the literature. *Clin Infect Dis* **52**: 1020–1023.
- Gale JT, Lee KH, Amirnovin R, Roberts DW, Williams ZM, Blaha CD *et al* (2013). Electrical stimulation-evoked dopamine release in the primate striatum. *Stereotact Funct Neurosurg* **91**: 355–363.
- Goodman WK, Foote KD, Greenberg BD, Ricciuti N, Bauer R, Ward H *et al* (2010). Deep brain stimulation for intractable obsessive compulsive disorder: pilot study using a blinded, staggered-onset design. *Biol Psychiatry* **67**: 535–542.
- Gradinaru V, Mogri M, Thompson KR, Henderson JM, Deisseroth K (2009). Optical deconstruction of parkinsonian neural circuitry. *Science* **324**: 354–359.
- Greenberg BD, Askland KD, Carpenter LL (2008). The evolution of deep brain stimulation for neuropsychiatric disorders. *Front Biosci* **13**: 4638–4648.
- Grubert C, Hurlmann R, Bewernick BH, Kayser S, Hadrysiewicz B, Axmacher N *et al* (2011). Neuropsychological safety of nucleus accumbens deep brain stimulation for major depression: effects of 12-month stimulation. *World J Biol Psychiatry* **12**: 516–527.
- Hariz MI, Blomstedt P, Zrinzo L (2010). Deep brain stimulation between 1947 and 1987: the untold story. *Neurosurg Focus* **29**: E1.
- Heath RG (1954). *Studies In Schizophrenia*. Harvard University Press: Cambridge, MA, pp 46–47.
- Holtzheimer PE 3rd, Kosel M, Schlaepfer T (2012a). Brain stimulation therapies for neuropsychiatric disease. *Handb Clin Neurol* **106**: 681–695.
- Holtzheimer PE, Kelley ME, Gross RE, Filkowski MM, Garlow SJ, Barrocas A *et al* (2012b). Subcallosal cingulate deep brain stimulation for treatment-resistant unipolar and bipolar depression. *Arch Gen Psychiatry* **69**: 150–158.
- Holtzheimer PE, Kelley ME, Gross RE, Filkowski MM, Garlow SJ, Barrocas A *et al* (2012c). Subcallosal cingulate deep brain stimulation for treatment-resistant unipolar and bipolar depression. *Arch Gen Psychiatry* **69**: 150–158.
- Howe MW, Tierney PL, Sandberg SG, Phillips PE, Graybiel AM (2013). Prolonged dopamine signalling in striatum signals proximity and value of distant rewards. *Nature* **500**: 575–579.
- Hurwitz TA, Honey CR, Allen J, Gosselin C, Hewko R, Martzke J *et al* (2012). Bilateral anterior capsulotomy for intractable depression. *J Neuropsychiatry Clin Neurosci* **24**: 176–182.
- Ikemoto S (2010). Brain reward circuitry beyond the mesolimbic dopamine system: a neurobiological theory. *Neurosci Biobehav Rev* **35**: 129–150.
- Insel TR (2010). Faulty circuits. *Scientific American* **302**: 44–51.
- Ishak WW, Greenberg JM, Balayan K, Kapitanski N, Jeffrey J, Fathy H *et al* (2011a). Quality of life: the ultimate outcome measure of interventions in major depressive disorder. *Harv Rev Psychiatry* **19**: 229–239.
- Ishak WW, Ha K, Kapitanski N, Bagot K, Fathy H, Swanson B *et al* (2011b). The impact of psychotherapy, pharmacotherapy, and their combination on quality of life in depression. *Harv Rev Psychiatry* **19**: 277–289.
- Isometsa ET, Henriksson MM, Aro HM, Heikkinen ME, Kuoppasalmi KI, Lonnqvist JK (1994). Suicide in major depression. *Am J Psychiatry* **151**: 530–536.
- Jiménez F, Velasco F, Salin-Pascual R, Hernández JA, Velasco M, Criales JL *et al* (2005). A patient with a resistant major depression disorder treated with deep brain stimulation in the inferior thalamic peduncle. *J Neurosurg* **57**: 585–593.

- Kelley ME, Franco AR, Mayberg HS, Holtzheimer PE (2012). The Illness Density Index (IDI): a longitudinal measure of treatment efficacy. *Clin Trials* 9: 596–604.
- Kennedy SH, Eisfeld BS, Cooke RG (2001). Quality of life: an important dimension in assessing the treatment of depression? *J Psychiatry Neurosci* 26 Suppl: S23–S28.
- Kennedy SH, Giacobbe P, Rizvi SJ, Placenza FM, Nishikawa Y, Mayberg HS *et al* (2011). Deep brain stimulation for treatment-resistant depression: follow-up after 3 to 6 years. *Am J Psychiatry* 168: 502–510.
- Krishnan V, Nestler EJ (2008). The molecular neurobiology of depression. *Nature* 455: 894–902.
- Lammel S, Lim BK, Malenka RC (2014). Reward and aversion in a heterogeneous midbrain dopamine system. *Neuropharmacology* 76 Pt B: 351–359.
- Lammel S, Tye KM, Warden MR (2013). Progress in understanding mood disorders: optogenetic dissection of neural circuits. *Genes Brain Behav* 13: 38–51.
- Lippitz BE, Mindus P, Meyerson BA, Kihlstrom L, Lindquist C (1999). Lesion topography and outcome after thermocapsulotomy or gamma knife capsulotomy for obsessive-compulsive disorder: relevance of the right hemisphere. *Neurosurgery* 44: 452–458.
- Lipsman N, Neimat JS, Lozano AM (2007). Deep brain stimulation for treatment-refractory obsessive-compulsive disorder: the search for a valid target. *Neurosurgery* 61: 1–11.
- Lisanby SH (2007). Electroconvulsive therapy for depression. *N Engl J Med* 357: 1939–1945.
- Lozano AM, Giacobbe P, Hamani C, Rizvi SJ, Kennedy SH, Koliakos TT *et al* (2012). A multicenter pilot study of subcallosal cingulate area deep brain stimulation for treatment-resistant depression. *J Neurosurg* 116: 315–322.
- Lozano AM, Lipsman N (2013). Probing and regulating dysfunctional circuits using deep brain stimulation. *Neuron* 77: 406–424.
- Lozano AM, Mayberg HS, Giacobbe P, Hamani C, Craddock RC, Kennedy SH (2008). Subcallosal cingulate gyrus deep brain stimulation for treatment-resistant depression. *Biol Psychiatry* 64: 461–467.
- Malone DA (2011). Use of deep brain stimulation in treatment-resistant depression. *Cleve Clin J Med* 77: 77.
- Malone DA Jr., Dougherty DD, Rezai AR, Carpenter LL, Friehs GM, Eskandar EN *et al* (2009). Deep brain stimulation of the ventral capsule/ventral striatum for treatment-resistant depression. *Biol Psychiatry* 65: 267–275.
- Mayberg HS (1997). Limbic-cortical dysregulation: a proposed model of depression. *J Neuropsychiatry Clin Neurosci* 9: 471–481.
- Mayberg HS, Lozano AM, Voon V, McNeely HE, Seminowicz D, Hamani C *et al* (2005). Deep brain stimulation for treatment-resistant depression. *Neuron* 45: 651–660.
- McNeely HE, Mayberg HS, Lozano AM, Kennedy SH (2008). Neuropsychological impact of Cg25 deep brain stimulation for treatment-resistant depression: preliminary results over 12 months. *J Nerv Ment Dis* 196: 405–410.
- Mercado R, Constantoyannis C, Mandat T, Kumar A, Schulzer M, Stoessl AJ *et al* (2006). Expectation and the placebo effect in Parkinson's disease patients with subthalamic nucleus deep brain stimulation. *Mov Disord* 21: 1457–1461.
- Meyer A, Beck E, Mc LT (1947). Prefrontal leucotomy; a neuro-anatomical report. *Brain* 70: 18–49.
- Miller IW, Keitner GI, Schatzberg AF, Klein DN, Thase ME, Rush AJ *et al* (1998). The treatment of chronic depression, part 3: psychosocial functioning before and after treatment with sertraline or imipramine. *J Clin Psychiatry* 59: 608–619.
- Miocinovic S, Somayajula S, Chitnis S, Vitek JL (2013). History, applications, and mechanisms of deep brain stimulation. *JAMA Neurol* 70: 163–171.
- Moniz E (1994). Prefrontal leucotomy in the treatment of mental disorders. 1937. *Am J Psychiatry* 151(Suppl 6): 236–239.
- Nuttin B, Cosyns P, Demeulemeester H, Gybels J, Meyerson B (1999). Electrical stimulation in anterior limbs of internal capsules in patients with obsessive-compulsive disorder. *Lancet* 354: 1526.
- Olds J, Milner P (1954). Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain. *J Comp Physiol Psychol* 47: 419–427.
- Papez JW (1995). A proposed mechanism of emotion. 1937. *J Neuropsychiatry Clin Neurosci* 7: 103–112.
- Pizzagalli DA, Holmes AJ, Dillon DG, Goetz EL, Birk JL, Bogdan R *et al* (2009). Reduced caudate and nucleus accumbens response to rewards in unmedicated individuals with major depressive disorder. *Am J Psychiatry* 166: 702–710.
- Pizzagalli DA, Iosifescu D, Hallett LA, Ratner KG, Fava M (2008). Reduced hedonic capacity in major depressive disorder: evidence from a probabilistic reward task. *J Psychiatr Res* 43: 76–87.
- Puigdemont D, Perez-Egea R, Portella MJ, Molet J, de Diego-Adelino J, Gironell A *et al* (2011). Deep brain stimulation of the subcallosal cingulate gyrus: further evidence in treatment-resistant major depression. *Int J Neuropsychopharmacol* 15: 121–133.
- Riva-Posse P, Holtzheimer PE, Garlow SJ, Mayberg HS (2013). Practical considerations in the development and refinement of subcallosal cingulate white matter deep brain stimulation for treatment-resistant depression. *World Neurosurg* 80: S27 e25–S27.
- Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D *et al* (2006). Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR\*D report. *Am J Psychiatry* 163: 1905–1917.
- Rush AJ, Weissenburger JE (1994). Melancholic symptom features and DSM-IV. *Am J Psychiatry* 151: 489–498.
- Russo SJ, Nestler EJ (2013). The brain reward circuitry in mood disorders. *Nat Rev Neurosci* 14: 609–625.
- Sartorius A, Henn FA (2007). Deep brain stimulation of the lateral habenula in treatment resistant major depression. *Med Hypotheses* 69: 1305–1308.
- Sartorius A, Kiening KL, Kirsch P, von Gall CC, Haberkorn U, Unterberg AW *et al* (2010). Remission of major depression under deep brain stimulation of the lateral habenula in a therapy-refractory patient. *Biol Psychiatry* 67: e9–e11.
- Schatzberg AF, Kraemer HC (2000). Use of placebo control groups in evaluating efficacy of treatment of unipolar major depression. *Biol Psychiatry* 47: 736–744.
- Schlaepfer TE, Bewernick BH, Kayser S, Madler B, Coenen VA (2013). Rapid effects of deep brain stimulation for treatment-resistant major depression. *Biol Psychiatry* 73: 1204–1212.
- Schlaepfer TE, Cohen MX, Frick C, Kosel M, Brodessa D, Axmacher N *et al* (2008). Deep brain stimulation to reward circuitry alleviates anhedonia in refractory major depression. *Neuropsychopharmacology* 33: 368–377.
- Schlaepfer TE, George MS, Mayberg H (2010). WFSBP Guidelines on brain stimulation treatments in psychiatry. *World J Biol Psychiatry* 11: 2–18.
- Schoene-Bake JC, Parpaley Y, Weber B, Panksepp J, Hurwitz TA, Coenen VA (2010). Tractographic analysis of historical lesion surgery for depression. *Neuropsychopharmacology* 35: 2553–2563.
- Shorter E, Healy D (2007). *Shock Therapy: A History of Electroconvulsive Treatment in Mental Illness*. University of Toronto Press: Toronto.
- Spiegel EA, Wycis HT, Marks M, Lee AJ (1947). Stereotaxic apparatus for operations on the human brain. *Science* 106: 349–350.
- Thomas L (1971). The technology of medicine. *N Engl J Med* 285: 1366–1368.

- Tremblay LK, Naranjo CA, Graham SJ, Herrmann N, Mayberg HS, Hevenor S *et al* (2005). Functional neuroanatomical substrates of altered reward processing in major depressive disorder revealed by a dopaminergic probe. *Arch Gen Psychiatry* **62**: 1228–1236.
- Tye KM, Mirzabekov JJ, Warden MR, Ferenczi EA, Tsai HC, Finkelstein J *et al* (2012). Dopamine neurons modulate neural encoding and expression of depression-related behaviour. *Nature* **493**: 537–541.
- van Dijk A, Klomp makers AA, Feenstra MG, Denys D (2012). Deep brain stimulation of the accumbens increases dopamine, serotonin and noradrenaline in the prefrontal cortex. *J Neurochem* **123**: 897–903.
- Ware JE Jr., Kosinski M, Gandek B, Aaronson NK, Apolone G, Bech P *et al* (1998). The factor structure of the SF-36 Health Survey in 10 countries: results from the IQOLA Project. International Quality of Life Assessment. *J Clin Epidemiol* **51**: 1159–1165.
- Whiteford HA, Degenhardt L, Rehm J, Baxter AJ, Ferrari AJ, Erskine HE *et al* (2013). Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. *Lancet* **382**: 1575–1586.
- Wulsin LR, Vaillant GE, Wells VE (1999). A systematic review of the mortality of depression. *Psychosom Med* **61**: 6–17.
- Zrinzo L, Foltynie T, Limousin P, Hariz MI (2012). Reducing hemorrhagic complications in functional neurosurgery: a large case series and systematic literature review. *J Neurosurg* **116**: 84–94.