Neuropsychopharmacology (2014), 1–12

www.neuropsychopharmacology.org

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 attenuation, 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.
Neuropsychopharmacology advance online publication, 5 March 2014; doi:10.1038/npp.2014.28

Keywords: major depression; deep brain stimulation; reward system; neuromodulation; nucleus accumbens; medial forebrain bundle

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).

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Received 9 September 2013; revised 21 January 2014; accepted 21 January 2014; accepted article preview online 11 February 2014

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

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_{25}) 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 lead 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 (Brodman 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 lead 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*,

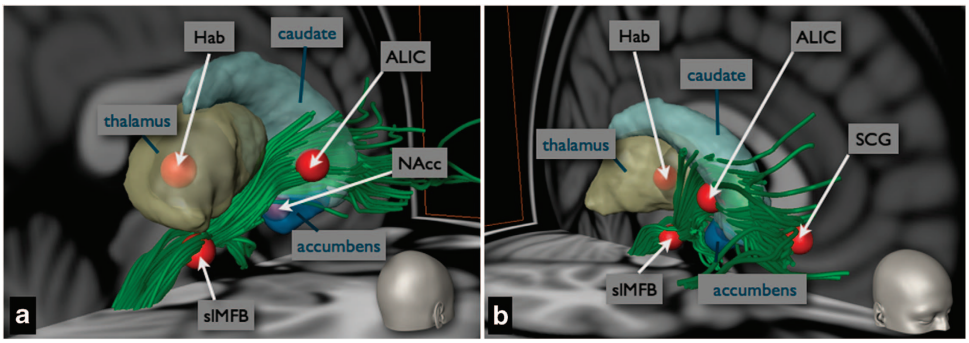

Figure 1 DBS targets in depression. Experimental targets (red spheres) for deep brain stimulation in major depression: (a) view from posterolateral right, (b) view from anterolateral right. Note how the medial forebrain bundle (green fiber structure) interconnects the majority of target sites (ALIC, NAcc, SCG, slMFB) 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; slMFB, superolateral branch of the medial forebrain bundle.

Table 1 DBS Targets for Major Depression

Target	Hypothesis	Hypothesis based on
Anterior Gyrus Cinguli (Brodman 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 slMFB 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 *et al*, 2011; Lozano *et al*, 2008; Mayberg *et al*, 2005; McNeely *et al*, 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 μs, 4.3 V	55% Responders	2 Years: 45% responders; 3 years: 60% responders	Normalization of brain metabolism in Cg25 using ^{15}0-water and ^{18}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 *et al*, 2011	8	Uncontrolled study; 12 months observation	4.2 V, 135 Hz, 90 μs, 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 *et al*, 2012c	10 MDD; 7 bipolar	Single blind sham phase (4 weeks, $n = 3$)	130 Hz, 90 μs, 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 *et al*, 2012	21 MDD	Multisite study; 12 months observation	Mean parameters at 12 months: 128.1 Hz, 93.9 μs, 5.2 mA, 1.5 (right), 1.4 (left) active contacts	29% Responders			Three skin erosion; two extension break; one chest pain; one pneumonia 1infection; one suicide attempt; one suicide; 15 gastrointestinal; 12 musculoskeletal; n ine 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 *et al*, 2009	17	Up to 5.5 years	6.7 V, 113.0 μs, 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 1 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 *et al*, 2012	30 MDD	Randomized sham-controlled trial; multisite study (Medtronid 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 *et al*, 2010; Bewernick *et al*, 2012; Grubert *et al*, 2011; Schlaepfer *et al*, 2008	13 MDD	Up to 4 years observation, blinding phase, systematic parameter search	5–8 V, 90 μs, 130 Hz, monopolar	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 *et al*, 2011)	Schlaepfer *et al*, 2013	6 MDD; 1 bipolar	Uncontrolled study	2–3 V, 60 μs, 130 Hz, bipolar	85% Responders at 3 months (response within days of stimulation)		No changes	Haemorrhage in one patient (the only non-responder) (Coenen *et al*, 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 *et al*, 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 μs	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 *et al*, 2004	1 MDD and OCD	Case report; 6 months observation	4 V, 130 Hz, 120 μs	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 *et al*, 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 (HAMD21_3), Stimulation III (after relapse due to stimulation stop because of bike accident): Patient reached remission ($HAMD_{21}$ _ 0) 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_{25}, electrode position had an influence on antidepressant outcome (Puigdemont *et al*, 2011); among responders most patients had electrodes placed in Cg24. 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 intraoperative 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 μs) (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 μs) 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 (Figee *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 physic 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 slMFB 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 lead 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.

FUNDING AND DISCLOSURE

SK reports no biomedical financial interests or potential conflicts of interest. None of the authors is employed organization that may gain or lose financially through this publication. None of the authors owns stocks or shares in companies that may gain or lose financially through this publication; receives consultation fees or other forms of remuneration from organizations that may gain or lose financially or owns patents or patent applications whose value may be affected by publication. No funding specifically for conducting this review has been obtained.

ACKNOWLEDGEMENTS

TES and VAC received partial funding for two investigator-initiated studies on DBS for major depression from Medtronic Inc. and the Hope for Depression Research Foundation (HDRF) and the Institute for Affective Neuroscience (ISAN). VAC is consultant for Medtronic Europe and occasionally received honoraria for talks. TS is chair of the project group, 'Deep Brain Stimulation in Psychiatry: Guidance for Responsible Research and Application', funded by the Volkswagen Foundation (Hanover, Germany). TS and BB are members of the working Group *Neuromodulation* of the German Research Foundation. RH was supported by a Starting Independent Researcher Grant (*NEMO—Neuromodulation of Emotion*) jointly provided by the Ministry of Innovation, Science, Research and Technology of the German State of North Rhine-Westphalia (MIWFT) and the University of Bonn.

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