

Rapid Effects of Deep Brain Stimulation for Treatment-Resistant Major Depression

Thomas E. Schlaepfer, Bettina H. Bewernick, Sarah Kayser, Burkhard Mädler, and Volker A. Coenen

Background: Treatment-resistant major depressive disorder is a prevalent and debilitating condition. Deep brain stimulation to different targets has been proposed as a putative treatment.

Methods: In this pilot study, we assessed safety and efficacy of deep brain stimulation to the supero-lateral branch of the medial forebrain bundle in seven patients with highly refractory depression. Primary outcome criterion was severity of treatment-resistant major depressive disorder as assessed with the Montgomery-Åsberg Depression Rating Scale. General psychopathologic parameters, social functioning, and tolerance were assessed with standardized scales, the Global Assessment of Functioning scale, quality of life (Short-Form Health Survey Questionnaire), and neuropsychological tests.

Results: All patients showed strikingly similar intraoperative effects of increased appetitive motivation. Six 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 onset of stimulation. At last observation (12–33 weeks), six patients were responders; among them, four were classified as remitters. Social functioning (Global Assessment of Functioning) improved in the sample as a whole from serious to mild impairment. Mean stimulation current was 2.86 mA; all side effects (strabismus at higher stimulation current, one small intracranial bleeding during surgery, infection at the implanted pulse generator site) could be resolved at short term.

Conclusions: These preliminary findings suggest that bilateral stimulation of the supero-lateral branch of the medial forebrain bundle may significantly reduce symptoms in treatment-resistant major depressive disorder. Onset of antidepressant efficacy was rapid (days), and a higher proportion of the population responded at lower stimulation intensities than observed in previous studies.

Key Words: Affective disorders, deep brain stimulation, diffusion tensor imaging, medial forebrain bundle, rapid antidepressant effects, treatment-resistant major depression

Major depressive disorder (MDD) is a highly prevalent, seriously disabling condition of worldwide bearing (1). Most patients with MDD respond to combinations of psychotherapy, pharmacotherapy, and electroconvulsive therapy; however, there are patients who profit little if anything even after many years of treatment. Between 10% and 30% of depressed patients taking an antidepressant are partially or totally resistant to treatments (2).

For about a decade, different modalities of targeted neuromodulation—among them most prominently deep brain stimulation (DBS)—are being actively researched as putative treatment options for these very treatment-resistant forms of depression (3). Recently, promising results on the use of DBS in small series of patients with treatment resistant depression have

been reported for three different stimulation targets: the subgenual cingulate gyrus (4), the anterior limb of the capsula interna (5), and the nucleus accumbens (NAcc) (6). Given the fact that patients included in DBS studies had hitherto been treated unsuccessfully for many years with conventional approaches renders these findings remarkable. Very recent studies show a stable long-term response (7). This gives hope to a substantial percentage of patients with treatment-resistant depression. However, only in 50% to 60% of the patients a significant response (decrease of depression severity of >50%) was achieved.

In recent years, research on major depression focused more on the role for the brain's reward regions in motivated behavior, depression, and antidepressant treatment (8). Converging evidence has identified the NAcc and its dopaminergic inputs from the ventral tegmental area (VTA) of the midbrain as one of the important anatomical substrates for drug reward as well as for natural rewards (9). This reward pathway evolved to promote activities that are essential to the survival of the species and consists of core structures—the NAcc, the VTA, the ventromedial and lateral nuclei of the hypothalamus, and the amygdala—that are interconnected through the medial forebrain bundle (MFB) (10). The VTA is one of the regions of the brain that receives various inputs from other brain regions and is one of the crucial areas for information processing related to motivated behavior. It uses dopaminergic neurotransmission, and evolution has preserved the VTA to be remarkably intact, as there is general similarity between the VTA nuclei of mammals ranging from rodents to humans (11). It has been speculated that the reward system might be partly dysfunctional in major depression (12,13).

In this study, we assessed the hypothesis that DBS to the human reward system in closer proximity to the VTA is efficacious in decreasing ratings of depression by bilaterally stimulating the supero-lateral branch of the medial forebrain bundle (sIMFB), a structure with proven convergence onto the prefrontal cortex

From the Department of Psychiatry and Psychotherapy (TES, BHB, SK), University Hospital Bonn, Germany; the Department of Psychiatry and Behavioral Sciences (TES), The Johns Hopkins University, Baltimore, Maryland; Stereotaxy and Functional Neurosurgery/Department of Neurosurgery (BM, VAC), University Hospital Bonn, Germany; and the Department of Stereotactic and Functional Neurosurgery (BM, VAC), University Hospital Freiburg, Germany.

Authors TES and VAC contributed equally to this work.

Address correspondence to Volker A. Coenen, M.D., Department of Stereotactic and Functional Neurosurgery, University Hospital Freiburg, Breisacher Straße 64, 79106 Freiburg, Germany; E-mail: volker.coenen@uniklinik-freiburg.de.

Received Aug 8, 2012; revised Dec 22, 2012; accepted Jan 30, 2013.

(14) and close functional connection (14,15) to previously suggested DBS target sites for depression (4–6).

Methods and Materials

The Institutional Review Board of the University of Bonn approved of this study; the protocol is registered at ClinicalTrials.gov with the identifier NCT01095263. All patients gave written informed consent, and their individual inclusion criteria were reviewed by a psychiatrist not related to our group.

Patients

Patients were referred from our outpatient department or from other hospitals, or they received information from contributions in press coverage. Ten percent of patients seen in our specialized DBS consultation were screening failures. Clinical standardized assessment tools (Structured Clinical Interview for DSM-IV [SCID-I and SCID-II]) were used for diagnosis, and all available clinical records (e.g., medical reports, referral letter, discharge letter) were analyzed to determine treatment resistance and patient history. Seven patients with treatment-resistant major depressive disorder were enrolled in the study.

Patients were eligible for inclusion if they were between 20 and 70 years of age and had received a primary diagnosis of MDD, determined according to the criteria of the DSM-IV (assessed with SCID-I) (16). Selection criteria were a minimum score on the 24 item Hamilton Depression Rating Scale (HDRS₂₄) of 21 and a score in Global Assessment of Function (GAF) below 45. Further inclusion criteria were at least four episodes of MDD or chronic episodes over 2 years; more than 5 years after the first episode of MDD; failure to respond to adequate trials of primary antidepressants from at least three different classes; adequate trials of augmentation/combination of a primary antidepressant using at least two different augmenting/combination agents; an adequate trial of electroconvulsive therapy (more than six bilateral treatments); an adequate trial of individual psychotherapy (more than 20 sessions); and no psychiatric co-morbidity and drug-free or on stable drug regimen at least 6 weeks before study entry. Exclusion criteria were current or past nonaffective psychotic disorder; any current clinically significant neurological disorder or medical illness affecting brain function, or severe personality disorder (assessed with SCID-II). All patients to be included in the study had severe treatment-resistant depression (17) (for demographic details, see Table 1).

One bipolar patient was included because the last episode of mania occurred 23 years ago, and the severity of depression qualified him for the study. In addition, actual studies with bipolar patients did not reveal differences in efficacy compared with unipolar depression (18).

Assessment and Study Protocol

Seven patients were observed for 12 weeks. Four patients were tracked longer (up to 33 weeks). Psychiatric assessments were performed on a weekly basis by a psychologist independent from the programmer. The primary outcome measure was antidepressant response on the Montgomery-Åsberg Depression Rating Scale (MADRS) (19), 50% reduction of depressive symptom severity recorded as response, and a MADRS score of <10 as remission. Secondary outcome measures included the 28 item HDRS₂₈ (20), Hamilton Anxiety Scale (HAM-A) (21), the GAF (22), and the Short-Form Health Survey Questionnaire (SF-36) (23). This instrument assesses quality of life; it is a self-rating questionnaire

and measures with eight subscales the patient's subjective change in quality of life. The subscales can be summarized into a score in "physical health dimension" and "mental health dimension."

At baseline, the score of the Modified Antidepressant Treatment History Form according to Sackeim (17) was calculated for each patient, indicating treatment resistance at the current episode and lifetime. A score of 3 is the threshold for considering a trial adequate and the patient resistant to that treatment.

Additionally, information about safety of the treatment method (see Table 2 for adverse events) was recorded in a standardized document with a priori definitions of adverse events and serious adverse events by the responsible psychologist (according to Food and Drug Administration definitions).

Cognitive effects were assessed with a standardized neuropsychological test battery clustered according to the Compendium of Neuropsychological Tests and described in detail elsewhere (24). See Grubert *et al.* (25) for a detailed description of neuropsychological tests applied. Patients were required not to change medication 6 weeks before and after surgery.

Imaging and Planning Procedure

Individual Diffusion Tensor Imaging-Guided Intervention. Because the MFB is a structure that cannot be identified with conventional MRI, we individually mapped the structure by means of deterministic diffusion tensor imaging with the use of an area lateral of the ventral tegmental area as seed region, which allowed displaying the projections of the sMFB through the NAcc to the prefrontal cortex (26,27) (Supplemental 1 and Figure 1).

Tracking results were transferred into the stereotactic planning software (FrameLink, Medtronic, Minneapolis, Minnesota). The target point was defined on the basis of the patient individual diffusion tensor imaging studies of the MFB in the center of its supero-lateral branch at its origin lateral and superior to the VTA (15). A trajectory with a precoronal entry point was planned bilaterally avoiding sulci, vessels, and cerebrospinal fluid spaces (Figure 1).

Surgical Procedure and Electrode Positions

Stereotactic implantations of bilateral quadripolar DBS electrodes (model 3389, Medtronic) were performed by means of a burr hole-mounted navigated frame (NexFrame, Medtronic), with the patient awake and predominantly under local anesthesia by use of mild analgesedation with Remifentanyl (Ultiva, B. Braun Melsungen AG, Germany) during burr hole placement.

Intraoperative test stimulation was performed at the target point (continuous 5 minutes of macrostimulation, 130 Hz, 60 μ sec, 2–3 mA, monopolar stimulation via the macro-tip of the MME electrode) to test for acute psychotropic effects and to qualify the side effects spectrum (oculomotor effects). During the testing phase, with the patient awake and responsive, the spatial center of the later verified DBS electrode implantation site was tested on its trajectory (between tentative contacts 1 and 2). Stimulation was performed with the macro-tip of the FHC electrode in a monopolar setting at 2.0 mA. This electrode was later exchanged for the DBS electrode that was not further tested intraoperatively. The most important effects were the onset of "appetitive motivation," change of the head position in space to make visual and social contact with the testing psychologist, and increased vigilance. Side effects of unilateral stimulation were predominantly an increase of the heart rate (typical increase of

Table 1. Demographic and Clinical Characteristics of Patients

Variable	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Mean	SD
Age at Implant (Years)	32	39	41	55	48	30	53	42.6	9.8
Sex	Female	Female	Male	Male	Female	Male	Male	3 Female/ 4male	
Duration of Education (Years)	13	13	16	9	13	13	13	12.9	2.0
Diagnosis	MDD	MDD	MDD	MDD	MDD	MDD	BD		
Working Status	Parttime 75%	Unable to work	Retired due to MDD	Retired due to MDD	Retired due to MDD	Unable to work	Retired due to MDD	85% Retired	
Length of Current Episode (Years)	4	17	6	10	2	5	9	7.6	5.0
Number of Previous Episodes (Lifetime)	2	2	1	1	2	2	6	2.3	1.7
Age at Onset (Years)	27	22	35	45	40	23	18	30.0	10.1
Time Since Diagnosis of Affective Disorder (Years)	5	16	6	10	8	7	35	12.4	10.6
Lengths of Previous Hospitalizations (Months)	12	11	38	5	13	8	10	13.9	11.0
Number of Antidepressive Pharmaceuticals at Implant	3	7	8	0	0	1	9	4.0	3.9
Number of Medications in Current Episode	18	30	26	17	19	20	12	20.3	6.0
Number of Medications (Lifetime)	18	30	26	17	19	20	23	21.9	4.7
Total ATHF Score (Current Episode)	55	83	82	56	62	63	54	65.0	12.4
Mean ATHF Score (Current Episode)	3	3	3	3	3	3	3	3.0	.0
Number of Treatment Trials With ATHF ≥ 3	10	17	20	13	13	14	11	14.0	3.5
Past ECT/MST	16 (12 unilateral)	6	51 (43 unilateral)	8 (unilateral)	13 (6 unilateral)	5 unilateral	12 unilateral	14.3 (unilateral)	14.3
Psychotherapy (Hours)	60	117	>60	35	>50	65	>100	>69	
Suicide Attempts	0	3	2	0	0	0	2	1.0	1.3
MADRS at Inclusion	33	34	39	26	35	15	27	29.9	8.0
MADRS at 1-Week DBS Stimulation	5	18	18	17	30	1	4	13.3	10.4
MADRS at 12 Weeks	2	8	12	13	31	7	4	11.0	9.7
HDRS ₂₄ at Inclusion	22	25	25	23	23	21	22	23.0	1.5
HDRS ₂₈ at 1 Week	3	22	16	15	26	5	0	12.428	9.947
HDRS ₂₈ at 12 Weeks	2	14	21	17	25	18	6	14.714	8.159
HAMA at Inclusion	15	17	31	11	11	11	12	15.428	7.253
HAMA at 1 Week	3	11	15	8	9	1	0	6.7142	5.559
HAMA at 12 Weeks	3	5	8	10	6	7	5	6.2857	2.288
SF-36 Mental Health at Inclusion	30.28	7.06	16.36	12.38	18.14	22.6	30.39	23.750	11.463
SF-36 Mental Health at 12 Weeks	53.31	26.32	16.68	17.37	21.01	24.75	35.86	27.9	12.946
SF-36 Physical Health at Inclusion	46.68	61.78	29.8	39.22	43.38	50.85	41.44	46.269	8.855
SF-36 Physical Health at 12 Weeks	54.93	62.5	40.57	41.75	42.65	45.53	46.69	47.802	7.451
GAF at Inclusion	5	4	2	5	4	5	4	4.142	1.069
GAF at 12 Weeks	9	7	6	6	5	6	7	6.571	1.272

Modified Antidepressant Treatment History Form (ATHF) according to Sackeim (17). A score of 3 is the threshold for considering a trial adequate and the patient resistant to that treatment (Sackeim). All medications including antipsychotics, anticonvulsants, and sleep medication if used for the treatment of depression are counted.

BD, bipolar disorder; ECT, electroconvulsive therapy; GAF, global assessment of functioning; HAMA, Hamilton Anxiety Scale; HDRS_{24/28}, Hamilton Rating Scale for Depression, 24 or 28 items; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; MST, magnetic seizure therapy; SF-36, short for health survey (36 item version).

10 beats/min) and induced double vision caused by oculomotor nerve fiber co-activation. The latter—if double vision occurred at currents lower than 2 mA—was used to guide a change of the electrode position, accordingly.

After definite electrode placement, DBS electrodes were externalized for electrophysiological evaluation. After 2 days, internal pulse generators (ACTIVA PC, Medtronic) were implanted subclavicularly or abdominally under general anesthesia (Figures 1 and 2).

Postoperative electrode positions were analyzed with respect to the sIMFB as described before, with the use of postoperative helical computed tomography and fusion to the MRI planning

data (27). With respect to the MCP (midcommissural point) system, the coordinates for the center position of the effectively stimulated contacts were laterality $x = 5.1 \pm .9$ mm (lateral left or right, respectively), anterior-posterior $y = -2.8 \pm 1.6$ mm (posterior to MCP), and vertical $z = -6.2 \pm 1.1$ mm (inferior to MCP) (Figure 2) (28).

Stimulation Parameters and Additional Treatments

Stimulation was initiated 1 week after surgery in a bipolar setting bilaterally with contacts 1 anodal and contacts 2 and 3 (being the two most superficial contacts) grouped cathodally. Constant voltage stimulation was initiated (2–3 V) with a typical

Table 2. Adverse Events and Serious Adverse Events in Seven Patients

	Patients	Number of Events
Serious Adverse Events		
Intracranial bleeding ^b	1	1
Adverse Events		
Increased sweating ^a	2	2
Headache ^b	4	7
Vision/eye movement disorder ^a	7	23
Aconuresis ^b	1	1
Infection at IPG ^b	2	2
Contact malfunction ^c	1	1
Partial hemiparesis ^b	1	1
Dysarthria ^b	1	1
Hypertension ^b	1	1
Dizziness ^a	3	4
Circulation problems (low blood pressure) ^d	1	2

IPG, implantable pulse generator.

^aAssociated with stimulation/parameter change.

^bSurgery-related.

^cDevice malfunction.

^dNot related to the study.

target current of 2–2.5 mA (as measured with therapeutic current readings), depending on oculomotor side effects. Stimulation was performed at constant voltage to observe changes in impedance over time. Although a target current was defined, stimulation was performed at constant voltage. Amplitude of stimulation was

augmented to maximize clinical effects (antidepressant response as measured in MADRS) if necessary.

At the time of evaluation, mean current for responders was 2.4–3.5 mA (left), 2.3–3.1 mA (right) (mean: left, $2.85 \pm .4$ mA; right, $2.88 \pm .38$ mA). The nonresponder (patient 5, Figure 3C) is stimulated at left, 4.9 mA; right, 4.7 mA. Pulse width was 60 μ sec; frequency was 130 Hz in all patients.

Pharmacological treatment was kept constant (medication and dose) for at least 6 weeks before and after surgery. During follow-up, changes in pharmacological regime were allowed. In two patients, medication change occurred after week 6 (one patient deliberately stopped all medications in week 8 and consequently had a worsening of symptoms that was successfully counteracted by re-initiation of medication. In the second case, the treating psychiatrist decided to change the medication from citalopram to escitalopram in week 12; this was inconsequential with regard to depression ratings. Patients undergoing psychotherapy entering the study continued the treatment.

Statistical Analysis

Clinical data (MADRS, HDRS, HAMA, GAF, SF-36) were analyzed with descriptive methods (mean, standard deviation, frequency). Because of small sample size of these pilot data, inferential statistics are not applicable. Neuropsychological data were analyzed with a *t* test for dependent samples, comparing baseline and 3-month outcome. Data were analyzed by B.H.B. and T.E.S.

Baseline scores in primary and secondary measures of efficacy (MADRS, HDRS, HAMA, GAF, SF-36) are reported as changes after 1 week, 1 month, and 2 and 3 months of stimulation. As usually

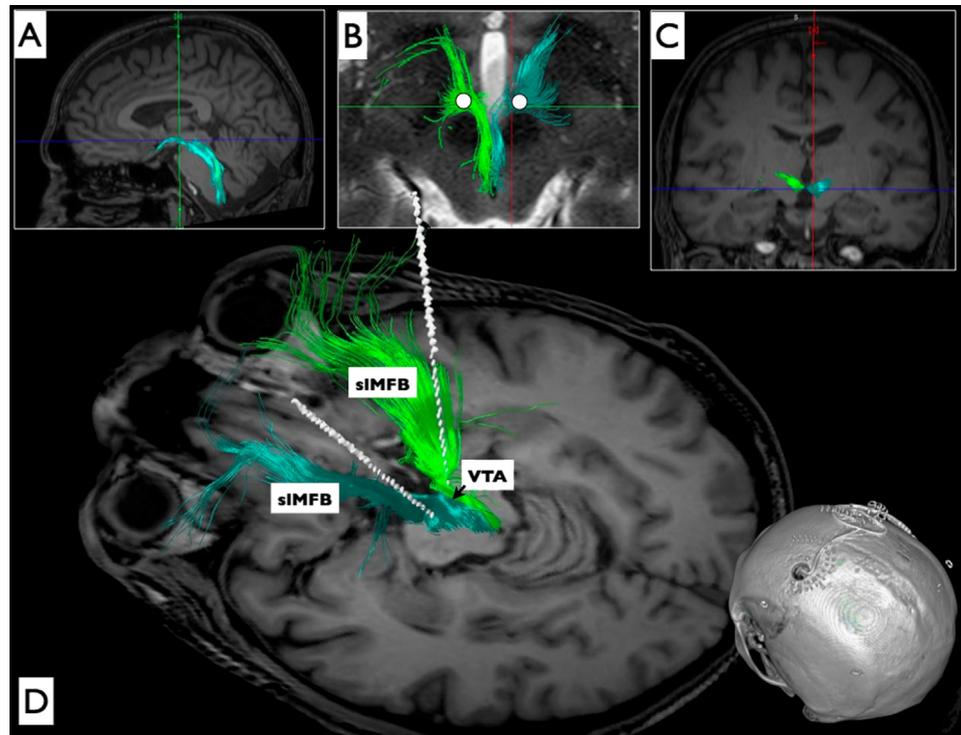


Figure 1. Diffusion tensor imaging–based patient individual planning of bilateral supero-lateral medial forebrain bundle (sIMFB) deep brain stimulation (DBS). Data from patient 3 shown. (A–C) Projection of the sIMFB (dark green, left side) onto sagittal (A), axial (B), and coronal (C) sections. Note bilateral DBS electrode positions in B (white circles). (D) Three-dimensional rendering as seen from posterior and superior left includes final DBS electrode positions (white rods). VTA, ventral tegmental area.

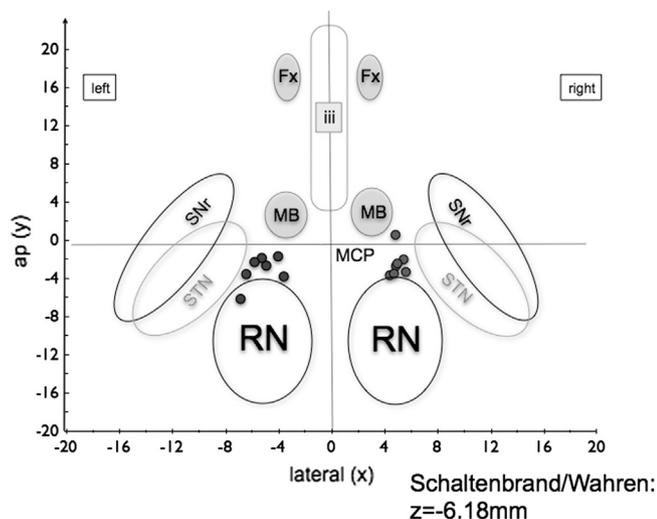


Figure 2. Effective electrode contact positions as projected onto an idealized axial slice adapted from Schaltenbrand/Wahren, *Atlas for Stereotaxy of the Human Brain* (28). Fx, fornix; iii, third ventricle; MB, mammillary body; MCP, mid-commissural point; RN, red nucleus; SNr, substantia nigra; STN, subthalamic nucleus.

applied in pharmacological and DBS studies in treatment resistant depression, a minimum reduction of 50% of depressive symptoms—assessed by the MADRS (19)—was classified as response, a MADRS score of <10 was classified as remission. Safety information is presented in Table 2.

Results

Demographic and Clinical Characteristics

All seven patients were diagnosed as severely treatment-resistant, with a mean length of current major depressive episode of 7.6 years (SD 5), and had 14 medical treatment courses on average (SD 3.5) with an antidepressant treatment resistance score (Modified Antidepressant Treatment History Form score) above 3 defining an adequate treatment dose and length, including augmentation and combination therapy. At the time of implantation, the mean number of antidepressant medications was 4 (SD 3.9). All patients had received electroconvulsive therapy and psychotherapy without response. Mean HDRS₂₄ was 23 at baseline (SD 1.5), indicating severe depression (Table 1).

Clinical Outcomes

During intraoperative test stimulation, all patients showed strikingly similar signs of appetitive motivation (e.g., orientation reaction, initialization of eye contact, engaging in conversation with the psychologist) and mood improvement. No indication of hypomania or anxiety was observed. Immediately after the onset of chronic stimulation 7 days after surgery, six patients reported acute changes in mood, anxiety, and drive. Figure 3A shows acute response of stimulation 2 and 7 days after initialization of chronic DBS stimulation. Decreases of depression severity ratings are shown as percent reduction compared with baseline (Figure 3B).

A rapid reduction of depression ratings was observed in six of seven patients after 2 days of stimulation, and, after 1 week, four of seven patients had reached the response criterion (50% reduction in MADRS). Figure 3B shows response to stimulation

up to 33 weeks. After 6 weeks, five of seven patients were classified as responders and remained as responders (except patient 4). At last observation (12–33 weeks), six of seven patients were responders; among them, four were classified as remitters. Individual responses of all patients are shown together with the group mean in Figure 1C.

Secondary Outcome Variables (HDRS, HAMA, SF-36, GAF, Cognition)

The HDRS (28-item version) was used to capture changes in additional depressive symptoms, and patients showed similar responses as in MADRS (Table 1). Improvement in depression was accompanied by a reduction in anxiety as measured by the HAMA from a clinically significant level of anxiety (HAMA score >10) to a subclinical level of anxiety (HAMA <10) after 1 week. The mean group score in the GAF changed from baseline 42.8 “serious impairment” (SD 11) to 61 × 4 (SD 8.9) “mild impairment” after 4 weeks of stimulation and further improved to 65.7 (SD 1.2) after 12 weeks of stimulation. Physical health (as one dimension of the quality of life scale SF-36) remained stable throughout the study, but mental health (the second quality of life dimension of the SF-36) improved about 1 SD from “much below average” (–3 SD) to “below average” (–2 SD). No significant change in cognitive functioning has been found in the different domains (Table 3) (29–38).

The most prominent adverse events were blurred vision and strabismus, which occurred in all patients at higher amplitudes when specific electrode contacts were activated. Oculomotor problems were a limiting factor for parameter changes. Other adverse events related to stimulation were dizziness and increased sweating. One patient had a small intracranial bleeding during implantation of the first electrode (left) with transient hemiparesis and dysarthria, which resolved after 7 hours. In a second surgery, bilateral electrodes were implanted without complications (Table 2).

Patients were required not to change medication 6 weeks before and after surgery. In two patients, medication change occurred after week 6 (one patient stopped all medications in week 8, one patient changed from Ciprallex to Escitalopram in week 12).

Discussion

In this article, we report on effects of DBS to the sIMFB in an unblinded trial in seven patients with extreme forms of treatment-resistant major depression. This approach and the results obtained are noteworthy for several reasons; the target selection was hypothesis-based, individual deterministic diffusion tensor imaging was used to identify target sites in each patient, the onset of antidepressant response was unexpectedly rapid, and last, the short-term antidepressant effects were more robust than those reported in previous studies (4–6).

Hypothesis-Guided Target Site Selection

The symptom of anhedonia is a germane part of the depression syndrome. On the basis of three lines of reasoning, 1) the ventral striatum is heavily implicated in both normal and abnormal reward processes, 2) the NAcc acts as a “motivation gateway” between limbic systems involved in emotion and systems involved in motor control, and 3) the ventral striatum is uniquely located to modulate activity in other regions of the brain we previously demonstrated that DBS to the NAcc has

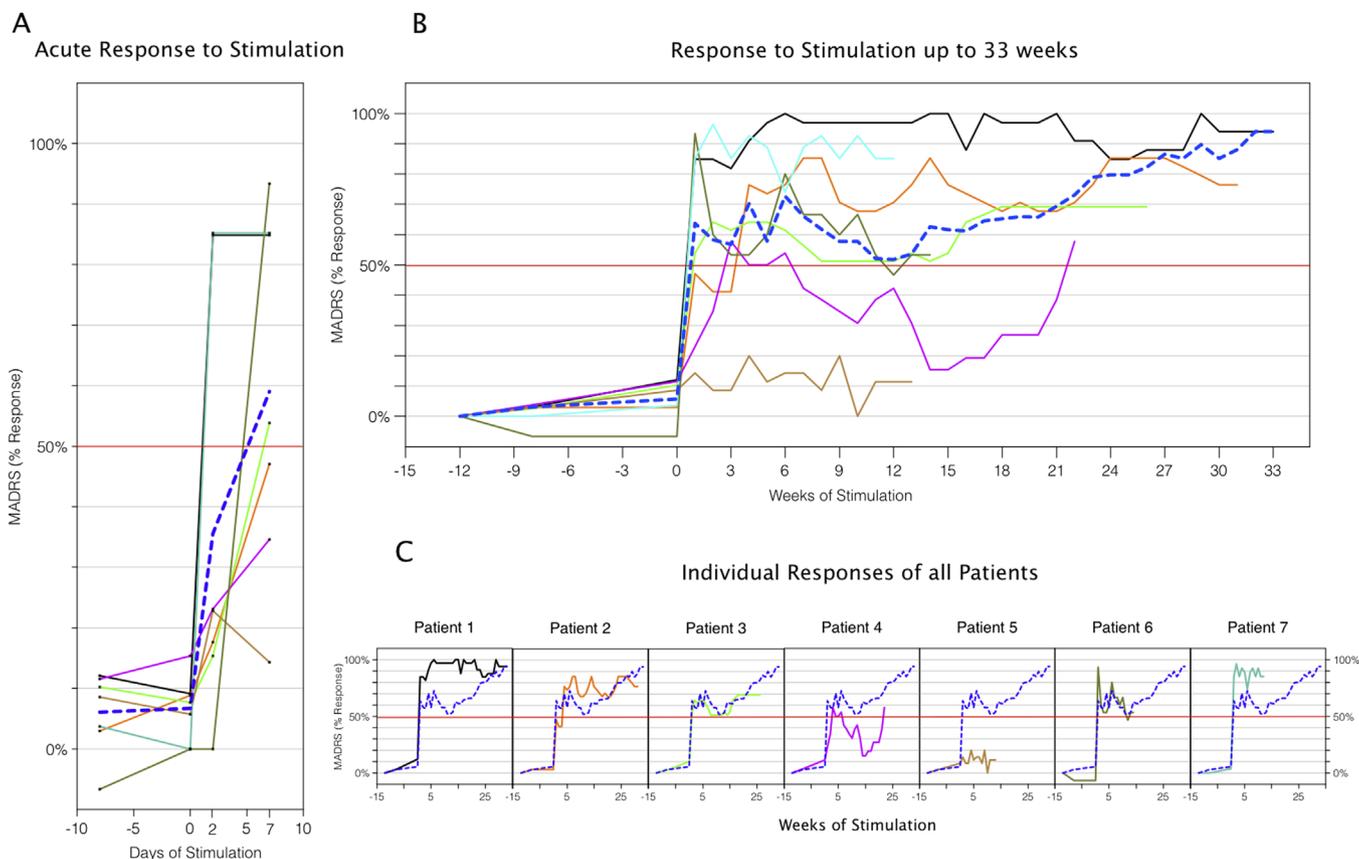


Figure 3. (A) Acute response to stimulation. Time course of antidepressant response (percent reduction in Montgomery-Åsberg Depression Rating Scale [MADRS] score) 1 week before to 1 week after stimulation onset. (B) Response to stimulation up to week 33. Time course of antidepressant response (percent reduction in MADRS score) from baseline (4 months before stimulation onset) to up to 33 weeks of stimulation. (C) Individual responses of all patients. Individual patient's contribution to the average (dotted line) is demonstrated. In contrast to (A), in (C), weeks of stimulation are plotted.

acute anti-anhedonic and longer-term antidepressant effects (6,39). We demonstrated the involvement of the sIMFB in DBS of the three current targets for the treatment of treatment-resistant major depressive disorder and therefore posited that a direct stimulation of the sIMFB (15) would result in stronger antidepressant effects (15). Indeed, our results appear to support this hypothesis because the effects were achieved with the use of a mean stimulation current of 2.86 mA, a current that is about one-third of the stimulation current used in previous studies.

Individual Diffusion Tensor Imaging–Guided Intervention

Because the sIMFB is a structure that cannot be identified with conventional MRI, we individually mapped the structure by means of deterministic diffusion tensor imaging (40) with the use of an area lateral of the VTA as seed region, which allowed displaying the projections of the sIMFB through the NAcc to the prefrontal cortex (26,27).

Rapid Onset of Antidepressant Response

Unexpectedly (given the experience of the development of the antidepressant effect seen in earlier DBS studies), response was rapid; mean MADRS was reduced by >50% at day 7 after onset of stimulation, and six of the patients had significant effects over only 2 days of stimulation (Figure 3A). Comparably instant effects in major depression have only been demonstrated in studies with the use of ketamine (41,42) or sleep deprivation.

However, the clinical effect of ketamine lasts up to 2 weeks only (43) and effects of sleep deprivation only until the next sleeping phase. In contrast, the effects of sIMFB DBS reported here appear to be enduring.

Antidepressant Efficacy

Six of the seven patients attained the response criterion; mean MADRS of the whole sample decreased from group mean at baseline of 29.9 (SD 8) to a group mean of 14.6 (SD 10.1) after 12 weeks of stimulation. At last observation (12–33 weeks), six of seven patients were responders; four were classified as remitters (MADRS <10). Baseline elevated levels of anxiety (HAMA) were reduced to subclinical level. Social functioning (GAF) improved in the sample as a whole from serious to mild impairment; this was also reflected in subjective patient reports, which described an augmentation in quality of life to a meaningful degree. The majority of patients were treated with antidepressants and psychotherapy during the study, and only one patient stopped medications, which was associated with a relapse in depression. One responder was not taking any medication. Thus, it remains open whether sIMFB-DBS exerts its antidepressant effect in combination with other treatments or if it would be effective alone.

The putative mode of action of sIMFB DBS must be elucidated and at this moment remains hypothetical. The density of the fiber tract at the stimulation site suggests a connection of the VTA to a

Table 3. Neuropsychological Assessment at Baseline and at 3-Month Follow-Up

Cognitive Domain	Test	<i>n</i>	Mean	SD	Mean Change	SD Change	<i>t</i> Value	<i>df</i>	<i>p</i> Value	Reference
Verbal Learning and Memory										
VLMT total learning	Baseline	7	45.43	12.41	−.43	7.21	−.16	6	.88	(29)
	3-Month follow-up	7	45.86	15.57						
VLMT delayed recall	Baseline	7	8.86	3.58	1.43	3.31	1.14	6	.30	(29)
	3-Month follow-up	7	7.43	5.32						
VLMT recognition	Baseline	7	11.71	2.14	−.29	3.30	−.23	6	.83	(29)
	3-Month follow-up	7	12.00	3.27						
General Cognitive Functions										
MMSE	Baseline	7	29.00	1.00	1.29	1.70	2.00	6	.09	(30)
	3-Month follow-up	7	27.71	2.06						
Language										
HAWIE lexis test	Baseline	7	18.29	6.73	3.58	6.65	1.42	6	.21	(31)
	3-Month follow-up	7	14.71	7.99						
HAWIE finding similarities	Baseline	7	25.57	4.12	1.00	3.32	.80	6	.46	(31)
	3-Month follow-up	7	24.57	5.80						
Working Memory										
Wechsler digit span	Baseline	7	15.71	3.50	.85	2.12	1.07	6	.32	(32)
	3-Month follow-up	7	14.86	3.08						
Wechsler vis. Mem. Span	Baseline	7	15.00	1.53	−1.71	2.69	−1.69	6	.14	(32)
	3-Month follow-up	7	16.71	2.36						
Executive Functions										
TMT A (sec)	Baseline	7	39.71	19.21	−.58	15.44	−.10	6	.93	(33)
	3-Month follow-up	7	40.29	8.54						
TMT B (sec)	Baseline	7	103.00	74.16	−14.71	51.12	−.76	6	.48	(33)
	3-Month follow-up	7	117.71	92.42						
STROOP int. (sec)	Baseline	6	170.33	27.93	−55.50	97.05	−1.40	5	.22	(34)
	3-Month follow-up	6	225.83	95.87						
Five-Point Test	Baseline	7	26.57	6.65	−3.43	8.62	−1.05	6	.33	(35)
	3-Month follow-up	7	30.00	8.45						
Visual Spatial Learning and Memory										
RVDLT total learning	Baseline	6	33.67	13.50	−1.66	10.33	−.40	5	.71	(36)
	3-Month follow-up	6	35.33	20.23						
RVDLT delayed recall	Baseline	6	7.33	3.67	.16	2.79	.15	5	.89	(36)
	3-Month follow-up	6	7.17	4.45						
RVDLT recognition	Baseline	6	19.83	4.40	1.00	11.24	.22	5	.84	(36)
	3-Month follow-up	6	18.83	10.89						
Visual Perception										
VOT	Baseline	7	24.42	3.55	−.50	2.38	−.56	6	.60	(37)
	3-Month follow-up	7	24.92	4.21						
Attention										
D2 total minus error	Baseline	6	328.17	89.30	36.67	36.69	2.45	5	.06	(38)
	3-Month follow-up	6	291.50	109.89						

VLMT, Verbal Learning and Memory Test; MMSE, Mini-Mental State Examination; HAWIE, Hamburg-Wechsler-Intelligenztest für Erwachsene; TMT, Trail Making Test; STROOP int., Stroop Color and Word Test; RVDLT, Rey Visual Design Learning Test; VOT, Hooper Visual Organization Test; Wechsler vis. Mem. Span; Wechsler Visual Memory Span.

whole network of the previously targeted structures of the reward system (NAcc, anterior limb of the capsula interna, cg₂₅). The sIMFB consists of short axons of unmyelinated dopaminergic neurons that are not prone to direct recruitment with DBS at short pulse widths (60 μ sec) used here (44). It was suggested earlier that the modulation of a network of forebrain structures via the MFB is merely realized by an activation of thoroughly myelinated fibers descending from the frontal lobe into the VTA. Upstream dysfunctional cortical input into the network might therefore be ameliorated by modulating cortical regions, whereas downstream dopaminergic VTA neurons could be recruited and activated indirectly. As a result, the VTA might exert its activating effects on forebrain structures and the prefrontal cortex by way of the DBS to the sIMFB (15,27,40).

It has been demonstrated that electrical stimulation of parts of the reward system can lead to acute reinforcing effects (45). In this study, however, sIMFB stimulation was not associated with a direct reinforcing, hedonic, or liking (46) effect per se. The only acute effect seen in all patients (including the one who did not respond) was a strikingly similar onset of behavior with increased appetitive motivation, visual exploration of the surroundings, and increased verbal interaction without any symptoms of hypomania or anxiety. It might be that at the low stimulation intensity used in this study (mean of 2.5 mA), we could elicit “wanting” (incentive salience) effects only, whereas higher currents at this very site could elicit the clearly discernible “liking” (hedonic impact) effects (47). Because higher currents amplified oculomotor side effects—because the sIMFB target site is in close proximity to the oculomotor nerve fibers in their passage

through the brain stem—in all patients (Table 2), we are unable to test this assumption.

Obvious limitations of this study are the small sample size and the lack of a sham-controlled design. The first criticism is somewhat stifled by the rapid and strong effects, following a strikingly similar development in six of the seven patients; the second must be addressed in future study designs, mainly in light of findings that DBS for Parkinson's disease is associated with an unexpectedly sizeable sham response. DBS is certainly a major invasive intervention, which at least in principle could be associated with sham effects even in treatment-resistant psychiatric disorders.

Taken together, we believe that the results from this study point to the possibility that sMFB-DBS might be a safe, highly efficacious alternative method for treatment-resistant depression, associated with a rapid onset of action.

This investigator-initiated study was supported in part (deep brain stimulation device, battery exchange, medical costs, limited personnel support) by a grant from Medtronic, Inc., to Drs. Schlaepfer and Coenen; Drs. Coenen and Schlaepfer acknowledge support from Hope for Depression Research Foundation and the Institute for Affective Neuroscience; the protocol is registered at ClinicalTrials.gov with the identifier NCT01095263. We thank patients and their relatives for participating in this study and for their motivation and unfaltering trust. All other authors report no biomedical financial interests or potential conflicts of interest. The sponsor had no influence on design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. The first author (TES) had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

ClinicalTrials.gov: Effects of Deep Brain Stimulation in Treatment Resistant Major Depression; <http://clinicaltrials.gov/show/NCT01095263>; NCT01095263.

Supplementary material cited in this article is available online at <http://dx.doi.org/10.1016/j.biopsych.2013.01.034>.

- Kupfer DJ, Frank E, Phillips ML (2012): Major depressive disorder: New clinical, neurobiological, and treatment perspectives. *Lancet* 379: 1045–1055.
- 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.
- Schlaepfer TE, George MS, Mayberg H (2010): WFSBP Guidelines on Brain Stimulation Treatments in Psychiatry. *World J Biol Psychiatry* 11: 2–18.
- Lozano AM, Mayberg HS, Giacobbe P, Hamani C, Craddock RC, Kennedy SH, *et al.* (2008): Subcallosal cingulate gyrus deep brain stimulation for treatment-resistant depression. *Biol Psychiatry* 64: 461–467.
- Malone DA Jr, Dougherty DD, Rezai AR, Carpenter LL, Friehs GM, Escander EN, *et al.* (2009): Deep brain stimulation of the ventral capsule/ventral striatum for treatment-resistant depression. *Biol Psychiatry* 65:267–275.
- 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.
- Bewernick BH, 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.
- Schlaepfer TE, Lieb K (2005): Deep brain stimulation for treatment of refractory depression. *Lancet* 366:1420–1422.
- Nestler EJ, Carlezon WA Jr (2006): The mesolimbic dopamine reward circuit in depression. *Biol Psychiatry* 59:1151–1159.
- Zellner MR, Watt DF, Solms M, Panksepp J (2011): Affective neuroscientific and neuropsychanalytic approaches to two intractable psychiatric problems: Why depression feels so bad and what addicts really want. *Neurosci Biobehav Rev* 35:2000–2008.
- Oades RD, Halliday GM (1987): Ventral tegmental (A10) system: Neurobiology, 1: Anatomy and connectivity. *Brain Res* 434:117–165.
- Blood AJ, Iosifescu DV, Makris N, Perlis RH, Kennedy DN, Dougherty DD, *et al.* (2010): Microstructural abnormalities in subcortical reward circuitry of subjects with major depressive disorder. *PLoS One* 5: e13945.
- Martin-Soelch C (2009): Is depression associated with dysfunction of the central reward system? *Biochem Soc Trans* 37:313–317.
- Schoene-Bake JC, Parpaley Y, Weber B, Panksepp J, Hurwitz TA, Coenen VA, *et al.* (2010): Tractographic analysis of historical lesion surgery for depression. *Neuropsychopharmacology* 35:2553–2563.
- Coenen VA, Schlaepfer TE, Maedler B, Panksepp J, *et al.* (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.
- American Psychiatric Association. (1994): *Diagnostic and Statistical Manual of Mental Disorders (DSM IV)*. Washington, DC: American Psychiatric Association.
- Sackeim HA (2001): The definition and meaning of treatment-resistant depression. *J Clin Psychiatry* 62(Suppl 16):10–17.
- Holtzheimer PE, Kelley ME, Gross RE, Filkowski MM, Garlow SJ, Barrocas A, *et al.* (2012): Subcallosal cingulate deep brain stimulation for treatment-resistant unipolar and bipolar depression. *Arch Gen Psychiatry* 69:150–158.
- Montgomery S, Åsberg M (1979): A new depression scale designed to be sensitive to change. *Br J Psychiatry* 134:382–389.
- Hamilton M (1967): Development of a rating scale for primary depressive illness. *Br J Social Clin Psychol* 6:278–296.
- Hamilton M (1976): Hamilton anxiety scale. In: Guy W, editor. *ECDEU Assessment Manual for Psychopharmacology*. Rockville, MD: Rev Ed, 193–198.
- Jones SH, Thornicroft G, Coffey M, Dunn G, *et al.* (1995): A brief mental health outcome scale—reliability and validity of the Global Assessment of Functioning (GAF). *Br J Psychiatry* 166:654–659.
- Ware JE Jr, Sherbourne CD (1992): The MOS 36-item short-form health survey (SF-36), I: Conceptual framework and item selection. *Med Care* 30:473–483.
- Spreen O, Strauss E (1998): *A Compendium of Neuropsychological Tests, 1st ed.* Cambridge: Oxford University Press.
- 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.
- Coenen VA, Honey CR, Hurwitz T, Rahman AA, McMaster J, Bürgel U, *et al.* (2009): 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, Panksepp J, Hurwitz T, Urbach H, Mädler B, *et al.* (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 Neuro-psychiatry Clin Neurosci* 24:1–14.
- Schaltenbrand G, Wahren W (1977): *Atlas for Stereotaxy of the Human Brain*. Stuttgart: Thieme.
- Helmstaedter C, Lendt M, Lux S (2001): *Verbaler Lern- und Merkfähigkeitstest - VLMT*. Göttingen: Beltz Test GmbH.
- Folstein MF, Folstein SE, McHugh PR (1990): *MMST. Mini-Mental-Status-Test*. Weinheim: Beltz.
- Tewes U (1991): *HAWIE-R. Hamburg-Wechsler Intelligenztest für Erwachsene*. Bern: Huber.
- Haerting C, Markowitsch HJ, Neufeld H (2000): *WMS-R: Wechsler Gedächtnistest - Revidierte Fassung. [Deutsche Adaptation der revidierten Fassung der Wechsler Memory Scale]*. Bern: Huber.
- Reitan RM (1959): *Trail-Making Test A*. Indianapolis, Indiana: University Medical Center.

34. Baeumler G (1985): *Farbe-Wort-Interferenztest (FWIT) nach J.R. Stroop*. Goettingen: Hogrefe.
35. Regard M, Strauss E, Knapp P (1982): *Der Fuenf-Punkt Test*. Zuerich: UniversitaetsSpital, Neurologische Klinik.
36. Rey A (1964): *L'Examen Clinique en Psychologie*. Paris: Presses Universitaire de France.
37. Hooper HE (1958): *The Hooper Visual Organization Test*. Beverly Hills, California: Western Psychological Services.
38. Brickenkamp R (1962): *Test d2. Aufmerksamkeits-Belastungs-Test*. Goettingen, Hogrefe.
39. Schlaepfer TE, Cohen MX, Frick C, Kosel M, Brodesser D, Axmacher N, *et al.* (2008): Deep brain stimulation to reward circuitry alleviates anhedonia in refractory major depression. *Neuropsychopharmacology* 33:368–377.
40. Coenen VA, Schlaepfer TE, Allert N, Mädlar B (2012): Diffusion tensor imaging and neuromodulation: DTI as key technology for deep brain stimulation. *Int Rev Neurobiol* 107:207–234.
41. Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, Charney DS, *et al.* (2000): Antidepressant effects of ketamine in depressed patients. *Biol Psychiatry* 47:351–354.
42. Zarate CA Jr, Singh JB, Carlson PJ, Brutsche NE, Ameli R, Luckenbaugh DA, *et al.* (2006): A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Arch Gen Psychiatry* 63:856–864.
43. Murrrough JW (2012): Ketamine as a novel antidepressant: From synapse to behavior. *Clin Pharmacol Ther* 91:303–309.
44. Ikemoto S (2010): Brain reward circuitry beyond the mesolimbic dopamine system: A neurobiological theory. *Neurosci Biobehav Rev* 35:129–150.
45. Berridge KC (2003): Pleasures of the brain. *Brain Cogn* 52:106–128.
46. Smith KS, Berridge KC, Aldridge JW (2011): Disentangling pleasure from incentive salience and learning signals in brain reward circuitry. *Proc Natl Acad Sci U S A* 108:E255–E264.
47. Berridge KC, Robinson TE, Aldridge JW (2009): Dissecting components of reward: 'liking,' 'wanting,' and learning. *Curr Opin Pharmacol* 9: 65–73.