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

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**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 (slMFB), a structure with proven convergence onto the prefrontal cortex

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(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 resistancy 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 ($HDRS_{24}$) 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 $HDRS_{28}$ (20), Hamilton Anxiety Scale (HAMA) (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 resistancy 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 slMFB 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 analgosedation with Remifentanil (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 μsec, 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 (occulomotor 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 slMFB 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.
[a]Associated with stimulation/parameter change.
[b]Surgery–related.
[c]Device malfunction.
[d]Not 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 ± .4 mA; right. 2.88 ± .38 mA). The nonresponder (patient 5, Figure 3C) is stimulated at left, 4.9 mA; right, 4.7 mA. Pulse width was 60 μsec; 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 division, 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

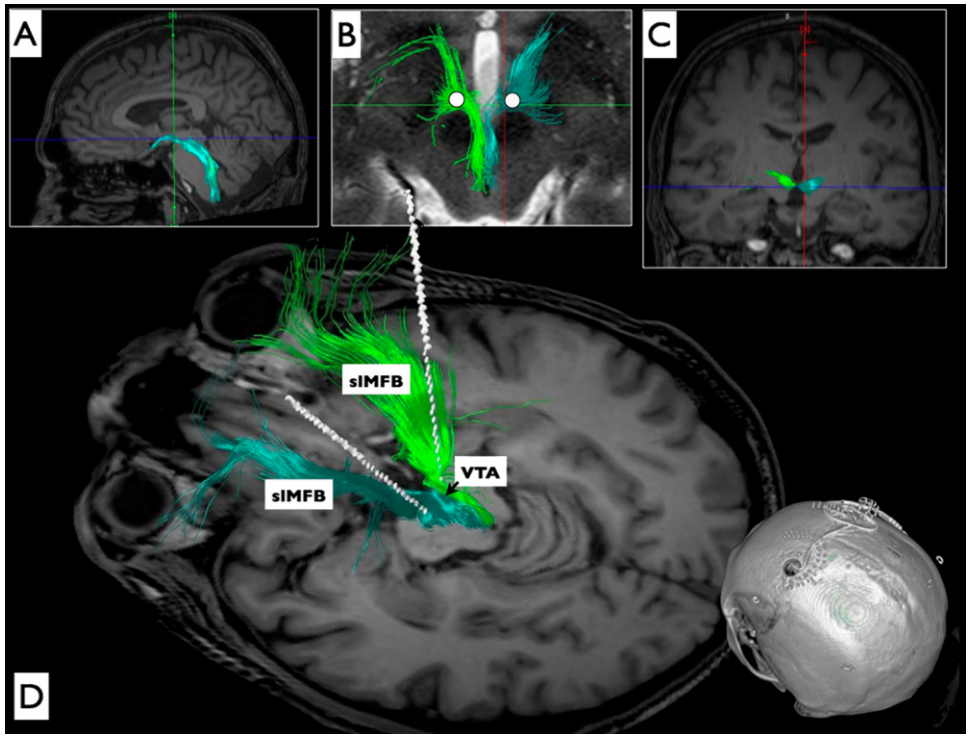


**Figure 1.** Diffusion tensor imaging–based patient individual planning of bilateral supero-lateral medial forebrain bundle (slMFB) deep brain stimulation (DBS). Data from patient 3 shown. **(A–C)** Projection of the slMFB (dark green, left side) onto sagittal **(A)**, axial **(B)**, and coronal **(C)** 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.

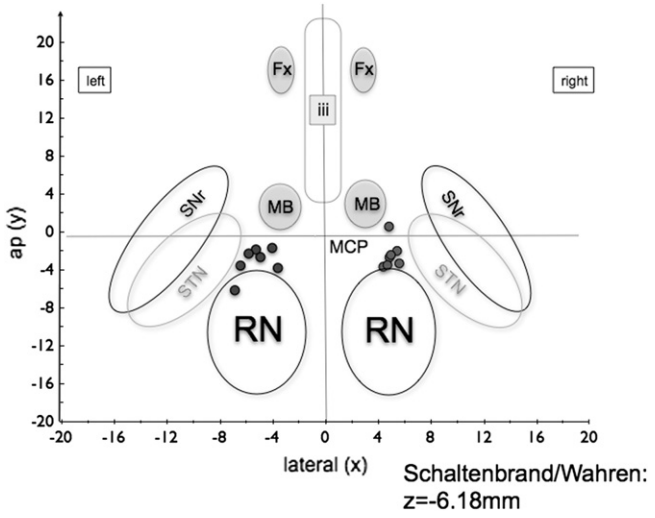


**Figure 2.** Effective electrode contact positions as projected onto an idealized axial slice adapted from Schaltenbrand/Wahren, *Atlas for Stereotaxy of the Human Brain* (28). Fx, fornix; iii, third ventricle; MB, mammillary body; MCP, mid-commissural point; RN, red nucleus; SNr, substantia nigra; 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 $HDRS_{24}$ 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 Cipralex to Escitalopram in week 12).

## Discussion

In this article, we report on effects of DBS to the slMFB 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

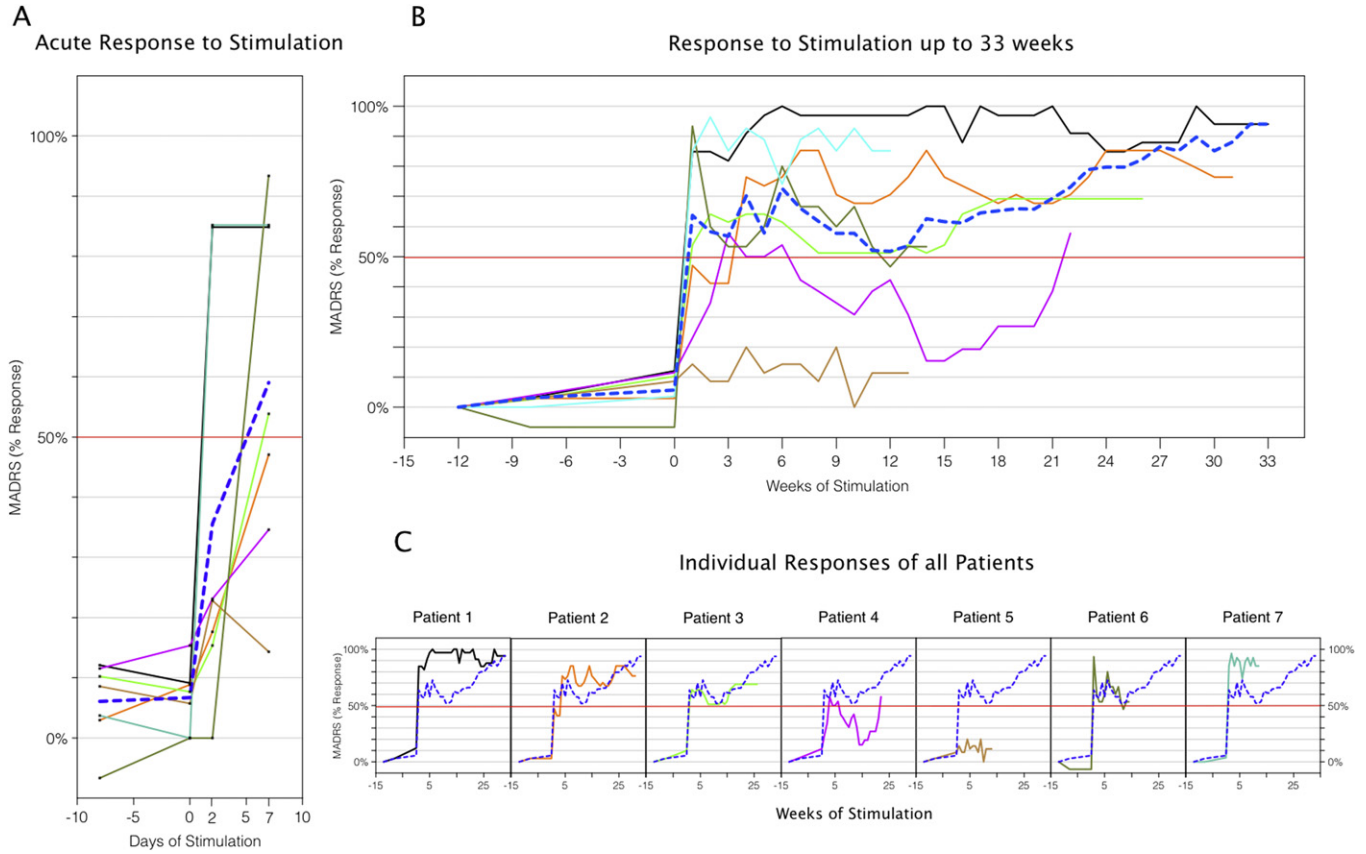


**Figure 3.** **(A)** Acute response to stimulation. Time course of antidepressant response (percent reduction in Montgomery-Åsberg Depression Rating Scale [MADRS] score) 1 week before to 1 week after stimulation onset. **(B)** Response to stimulation up to week 33. Time course of antidepressant response (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 slMFB 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 slMFB (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 slMFB 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 slMFB 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 slMFB 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 slMFB-DBS exerts its antidepressant effect in combination with other treatments or if it would be effective alone.

The putative mode of action of slMFB 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 | *n* | Mean | SD | Mean Change | SD Change | *t* Value | *df* | *p* 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, $cg_{25}$). The slMFB consists of short axons of unmyelinated dopaminergic neurons that are not prone to direct recruitment with DBS at short pulse widths (60 μsec) 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 slMFB (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, slMFB 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 slMFB 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 slMFB-DBS might be a safe, highly efficacious alternative method for treatment-resistant depression, associated with a rapid onset of action.

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