# Nucleus Accumbens Deep Brain Stimulation Decreases Ratings of Depression and Anxiety in Treatment-Resistant Depression

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**Background:** While most patients with depression respond to combinations of pharmacotherapy, psychotherapy, and electroconvulsive therapy (ECT), there are patients requiring other treatments. Deep brain stimulation (DBS) allows modulation of brain regions that are dysfunctional in depression. Since anhedonia is a feature of depression and there is evidence of dysfunction of the reward system, DBS to the nucleus accumbens (NAcc) might be promising.

**Methods:** Ten patients suffering from very resistant forms of depression (treatment-resistant depression [TRD]), not responding to pharmacotherapy, psychotherapy, or ECT, were implanted with bilateral DBS electrodes in the NAcc. The mean (±SD) length of the current episode was 10.8 (±7.5) years; the number of past treatment courses was 20.8 (±8.4); and the mean Hamilton Depression Rating Scale (HDRS) was 32.5 (±5.3).

**Results:** Twelve months following initiation of DBS treatment, five patients reached 50% reduction of the HDRS (responders, HDRS = 15.4 [±2.8]). The number of hedonic activities increased significantly. Interestingly, ratings of anxiety (Hamilton Anxiety Scale) were reduced in the whole group but more pronounced in the responders. The [18F]-2-fluoro-2-deoxy-D-glucose positron emission tomography data revealed that NAcc-DBS decreased metabolism in the subgenual cingulate and in prefrontal regions including orbital prefrontal cortex. A volume of interest analysis comparing responders and nonresponders identified metabolic decreases in the amygdala.

**Conclusions:** We demonstrate antidepressant and antianhedonic effects of DBS to NAcc in patients suffering from TRD. In contrast to other DBS depression studies, there was also an antianxiety effect. These effects are correlated with localized metabolic changes.

**Key Words:** Deep brain stimulation, functional neuroimaging, major depression, neuromodulation, nucleus accumbens, treatment resistance

Major depression is the most common serious brain disorder with a lifetime prevalence of up to 17% (1). Available evidence-based treatments lead to symptomatic improvement in most patients; however, up to 40% of patients responding to antidepressant therapy suffer from clinically relevant residual symptoms despite optimized treatment (2). The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, which analyzed outcome following several standardized treatment steps, reported that 33% of patients did not respond despite four evidence-based treatment steps (3). A substantial proportion of patients are inadequately treated and some of these will go on to suffer from chronic, debilitating, and life-threatening symptoms; for those patients, other therapeutic options must be considered. Different neuromodulatory approaches beyond electroconvulsive therapy (ECT) are therefore being researched and have been demonstrated to show some promise in treatment-resistant depression (TRD) (4,5).

While the exact mechanisms mediating disordered processing of affective stimuli in major depression are unknown, recent models describe dysfunction in widely distributed forebrain networks, significantly modulated by monoamine projections from brainstem nuclei (dopamine from the ventral tegmental area, serotonin from the raphe nuclei, and noradrenaline from the locus coeruleus [6,7]).

Deep brain stimulation (DBS) is an approach affording to modulate various sites within this network. Recently, antidepressant effects of DBS have been demonstrated in two long-term studies in TRD patients (8,9). In this study, long-term effects of DBS in a subcomponent of the striatum, namely the nucleus accumbens (NAcc), are described in a group of 10 patients. In line with current models of depression, we aimed to ameliorate depression by modulating a brain area related to a specific symptom cluster. The NAcc was selected because of its central role in reward circuitry (10,11) and its dysfunction regarding rewarding stimuli in patients with major depression (12,13). Acute antidepressant and antianhedonic effects of 1 week of NAcc-DBS have been demonstrated previously (10). In line with our previous results (10), we hypothesized that NAcc-DBS would improve anhedonia and have significant antidepressant effects.

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**Table 1.** Demographic and Clinical Characteristics

| Variable | Mean (SD) |
|---|---|
| Age at Implant (Years) | 48.6 (11.7) |
| Sex (% Female) | 40 |
| Length of Current Episode (Years) | 10.8 (7.6) |
| Number of Previous Episodes (Lifetime) | 1.6 (.9)[a] |
| Age at Onset (Years) | 31.7 (13.2) |
| Duration of Education (Years) | 14.4 (2.5) |
| Retirement from Work Preoperatively (%) | 100 |
| Time Since Diagnosis of Affective Disorder (Years) | 19.0 (9.1) |
| Lengths of Previous Hospitalizations (Months) | 19.5 (12.4) |
| Number of Antidepressant Drugs at Implant (Augmentation Therapies, Sleep Aids, Etc., Included) | 4.3 (1.3) |
| Number of Past Medical Treatment Courses | 20.8 (8.4) |
| Number of Medications Included in ATHF Score[b] | 14.1 (5.6) |
| Mean Total of ATHF Score | 41.7 (15.3) |
| Mean ATHF Score per Treatment (Lifetime) | 3.2 (.4) |
| Mean Number of Treatment Trials with ATHF ≥3 | 8.3 (3.2) |
| Past ECT Treatments (Lifetime) | 20.8 (8.6) |
| Received ECT (%) | 100 |
| Psychotherapy (Hours) | 316.4 (265.2) |
| Number of Stressful Life Events as Assessed with Clinical Interview (Lifetime) | 17.6 (6.1) |
| Comorbid Physical Illnesses (%) | 30 |
| Suicide Attempts (% Preoperative) | 30 |
| Social Support (% with Support) | 70 |

ATHF, Antidepressant Treatment History Form; ECT, electroconvulsive therapy.

[a]Fifty percent of patients did not have separate episodes.

[b]Modified ATHF according to Sackeim (38) including new antidepressant medications. A score of "3" is the threshold for considering a trial adequate and the patient resistant to that treatment (38).

## Methods and Materials

### Patients

The study was approved by the Institutional Review Boards (IRBs) of the Universities of Bonn and Cologne. The protocol is registered at http://ClinicalTrials.gov with the identifier NCT00122031. Ten patients between 32 and 65 years of age received NAcc-DBS (see Table 1 for demographic data). All met diagnostic criteria for major depressive disorder (MDD), unipolar type, and were in a current episode as diagnosed with the Structured Clinical Interview for DSM-IV (Axis I Disorders [SCID-I] and Axis II Disorders [SCID-II]). All patients to be included in the study suffered from severe treatment-resistant depression.

Generally, patients with depression are judged as being able to give informed consent (14). Nonetheless, we required—without stipulation by the IRBs—in addition to the patient's own consent the agreement of the closest caregiver and requested a waiting period before signing the informed consent form of 2 weeks after the information meeting that took place 8 to 12 weeks before implantation. An external TRD expert psychiatrist with has no relation to our center evaluated all patient data with a right to veto study inclusion.

The minimum score on the 28-item Hamilton Depression Rating Scale ($HDRS_{28}$) was 21 and the Global Assessment of Function score was below 45. Further inclusion criteria were at least four episodes of MDD or chronic episode over 2 years; more than 5 years after first episode of MDD; failure to respond to adequate trials (>5 weeks at the maximum recommended or tolerated dose) of primary antidepressants from at least three different classes, adequate trials (more than 3 weeks at the usually recommended or maximum tolerated dose) of augmentation/combination of a primary antidepressant using at least two different augmenting/combination agents (lithium, T3, stimulants, neuroleptics, anticonvulsants, buspirone, or a second primary antidepressant); an adequate trial of ECT (more than six bilateral treatments); an adequate trial of individual psychotherapy (more than 20 sessions with an experienced psychotherapist); and no psychiatric comorbidity 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, other than motor tics or Gilles de la Tourette's syndrome; any clinically significant abnormality on preoperative magnetic resonance imaging (MRI) impacting on the implantation of electrodes (e.g., enlargement of ventricle); and any surgical contraindications to undergoing DBS, current or unstably remitted substance abuse (aside from nicotine), or severe personality disorder.

The patients' clinical records and level of functioning were carefully reviewed up to a period of 15 years (e.g., letter of discharge from hospital, reviews of treating psychiatrists, appointments with relatives) to evaluate severity and course of depression. All patients were recruited from their treating psychiatrist, responded to contributions in media, or were referred from the University Hospital outpatient clinic.

### Surgery/Target

Bilateral DBS electrodes were implanted as described previously (10) using a Leksell Stereotactic frame (Elekta, Stockholm, Sweden). Standard Medtronic model 3387 leads (Medtronic, Minneapolis, Minnesota) were used. This lead has four contacts over a length of 10.5 mm, each spaced 1.5 mm apart: 1) the shell region of the nucleus accumbens, 2) the core region of the nucleus accumbens, 3) the ventral internal capsule, and 4) the medial internal capsule. The lowest contact was targeted at 7.5 mm, 1.5 mm, and 4 mm from the upper front edge of the anterior commissure, corresponding to Montreal Neurological Institute (MNI) coordinates ± 7.5, 5.5, 9. Targets and trajectories were defined using stereotaxic 3 Tesla MRI. X-ray was used to verify the positioning of the electrodes after surgery.

### Assessment and Study Protocol

Psychiatric assessments and parameter adjustment were performed on a weekly basis during the first and second month following stimulation onset and up to half a year on a 2-week basis. From month 7 up to 2 years, patients were tracked on a monthly basis. To capture potential effects of operation, patients were assessed daily in the week following surgery when no stimulation occurred.

Primary outcome measure was antidepressant response (50% reduction of depressive symptom severity as assessed by the $HDRS_{28}$) (15-17) or remission ($HDRS_{28}$ score of less than 10). Patients were classified as responders and nonresponders with regard to their response to NAcc-DBS 12 months post-surgery. Secondary outcome measures included Montgomery Åsberg Depression Rating Scale (MADRS) (18), Hamilton Anxiety Scale (HAMA) (19), Beck Depression Inventory (BDI) (20), the Inventory for Depressive Symptomatology-Self-Rated (IDSSR) (21), the 90-Item Symptom Checklist (SCL-90) (22), and the list of positive activities modified according to Hautzinger (23,24). Additionally, preliminary information about the

**Table 2.** Adverse Events

| Adverse Event | Classification | | |
|---|---|---|---|
| *N* | Related to Surgical Procedure | Related to Parameter Change | Unrelated to DBS |
| Erythema | | 4 | |
| Anxiety Increase | | 3 | |
| Sweating | | 3 | |
| Disequilibrium | | 2 | |
| Hypomania | | 2 | |
| Paresthesia | | 2 | |
| Agitation | | 2 | |
| Headache | | 1 | |
| Lead Dislodgment | | 1 | |
| Psychotic Symptoms | | 1 | |
| Muscle Cramps | | 1 | |
| Vision/Oculomotor | | 1 | |
| Dysphagia | 3 | 1 | |
| Swollen Eye | 6 | | |
| Pain | 3 | | |
| Suicide Attempt | | | 1 |
| Suicide | | | 1 |
| Dyskinesia | | | 1 |
| Syncope | | | 1 |
| Gastritis | | | 4 |
| Leg Fracture | | | 2 |
| Herniated Disk | | | 1 |
| Breast Cancer | | | 1 |

DBS, deep brain stimulation.

safety of the treatment method (see Table 2 for adverse events) was recorded.

Neuropsychological assessment (general intellectual ability, language, processing speed, executive function, learning, and memory) was performed at baseline, following the blinding phase, and subsequently every 6 months to assess cognitive changes. At the same time points, [18F]-2-fluoro-2-deoxy-D-glucose positron emission tomography ([18F]FDG-PET) studies were conducted to quantify changes in brain metabolic activity with chronic DBS. Psychotherapy and drug therapy were kept constant during the study.

### Stimulation Parameters

Stimulation was applied with permanent pulse-train square-wave stimulation starting with the parameters amplitude 2 V, pulse width 90 μsec, frequency 130 Hz, and the electrode setting electrodes 1 and 2 negative against case. Following an intraoperative trial, stimulation was switched off to allow consolidation of the lesions. One week postoperatively, this DBS setting was resumed and the voltage was successively increased from 2 V to 4 V.

Stimulation parameters were kept constant for approximately four weeks to retrieve sufficient observations of first acute and subacute effects (e.g., improvement in clinical impression as assessed by HDRS). Next, only when side effects occurred or when the antidepressant response was not satisfying, DBS parameters were varied to optimize the individual response. The sequence and priority of changes were amplitude, pulse width, selection of poles (all possible unipolar and bipolar combinations of the two lowest contacts), and frequency in the range 1.5 V to 10.0 V, 100 Hz to 150 Hz, and 60 μsec to 210 μsec. Stimulation was always bilateral and symmetrical. The handling of stimulation parameters followed the extensive experience with neurostimulation for neurological disorders (25). The so obtained individual optimum DBS setting was kept constant in patient at one month both before the final follow-up and the PET study.

Details on the PET acquisition and analyses are presented in Supplement 1.

### Statistical Analysis

To evaluate clinical response, all rating scales were analyzed with analysis of variance for repeated measures and the factor time (baseline, 1, 2, 6, 9, and 12 months). Post hoc paired comparisons were calculated for each time point compared with baseline. Level of significance was set at 5% for all analyses. Data from early terminators ($n = 1$) or patients in follow-up under 12 months ($n = 2$) were analyzed in a last observation carried forward manner. Missing values were interpolated, averaging the two preceding and following values.

## Results

### Demographic and Clinical Characteristics

The patients' demographic and clinical characteristics are shown in Table 1. All patients were diagnosed as severely treatment-resistant with a mean length of current major depressive episode of 10.8 years and had 8.3 medical treatment courses on average with an Antidepressant Treatment History Form score above 3 defining an adequate treatment dose and length, including augmentation and combination therapy. At time of implantation, the mean number of antidepressant medications was 4,3. All patients had received ECT and psychotherapy without response. Fifty percent of patients had never reached remission status since first diagnosis and all were retired from work due to depression. In comparison with other brain stimulation studies with therapy-resistant depressive patients (8,9), our subjects were at least as treatment-resistant.

### Clinical Outcomes

All measures are reported at baseline (mean baseline score over up to five visits in the last 3 months before surgery) and at several time points up to 1 year after commencing stimulation.

**Primary Outcomes ($HDRS_{28}$).** The primary measure of effectiveness was a reduction of 50% in the $HDRS_{28}$ (i.e., responders). Patients were classified as responders and nonresponders with regard to their response to NAcc-DBS 12 months postsurgery (Figure 1). Fifty percent of patients reached the response criterion at this point. For a one-month period, three patients were classified as in remission ($HDRS_{28} \leq 10$).

The mean total $HDRS_{28}$ score was significantly improved under stimulation at all time points. Improvements were seen after 1 month of stimulation in the whole sample ($HDRS_{28}$ score: 32.5 at baseline, 23.8 after 1 month) and remained stable throughout the follow-up period ($HDRS_{28}$ score: 20.8 after 1 year). Responders and nonresponders descriptively differed in HDRS score from first month of stimulation and differences were more pronounced during follow-up period.

**Secondary Outcomes (MADRS, IDSSR, HAMA, Positive Activities, SCL-90).** As a further outcome measure, MADRS was also used to capture changes in additional depressive symptoms (e.g., cognitive functioning, level of activity, interest, and negative thinking) (Figure 1). Group effects were similar to those measured with the $HDRS_{28}$ (MADRS group mean at baseline: 30.6; group mean after 1 year: 20.3). Likewise, depression self-rating score (IDSSR) showed a significant reduction in depression in all months as judged by the patients.

Improvement in depression was accompanied by a reduction in anxiety as assessed by the HAMA (Figure 1). Compared with

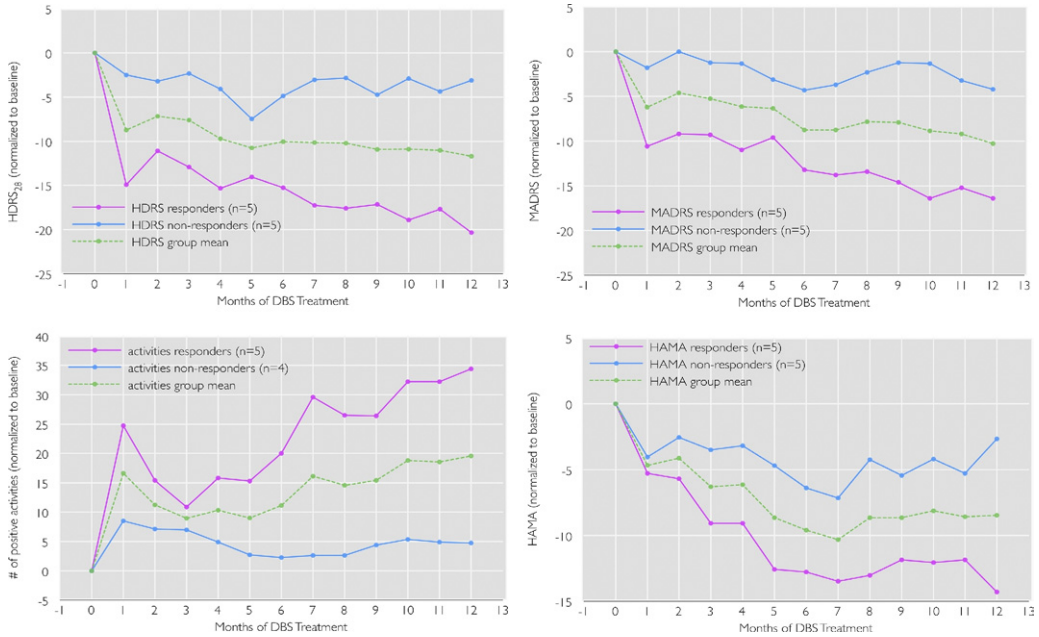


**Figure 1.** Outcomes over time. Hamilton Depression Rating Scale over time (top left); Montgomery Åsberg Depression Rating Scale over time (top right); positive activities over time (bottom left); and Hamilton Anxiety Scale over time (bottom right).

baseline, the whole sample showed a significant reduction in anxiety symptoms (HAMA at baseline: 23.3, after 1 year: 14.9). From the first month of stimulation onwards, the group mean was below 19, which is the cutoff for anxiety disorders in pharmacological studies (19). As seen in depression scales, descriptive data showed that responders had a more pronounced reduction in anxiety compared to nonresponders.

The Hautzinger list of positive activities is a list of 280 pleasant activities (23,24). This score is used as a tool to assess progress in cognitive behavioral therapy. Lacking meaningful standardized measures of anhedonia, we employed this list to assess changes in anhedonia and level of activity. The level of activities rose in the whole sample from first month of simulation and further increased in the group of responders during the follow-up period (Figure 1). A significant increase in the level of activities was observed in the first month (46.3) and after 12 months (50.1) in comparison with baseline (28.8) for the whole sample. Nonresponders did not show an increase following a third month of stimulation. Patients also showed a significant reduction in general psychopathological symptoms as measured with SCL-90 in the first month (98.6) and after 6 months (103.6) and 12 months of treatment (98.1) compared with baseline (125.9).

In addition to observed long-term changes, acute effects occurred frequently after parameter change. Patients had acute improvements of depression, anxiety, and anhedonia lasting up to 2 weeks. These acute effects were not predictive for long-term outcome. Contrasting with other studies (9), no hypomania was observed after surgery or parameter change in any of the patients at any point in time. Comprehensive neuropsychological testing revealed no detrimental effects on cognitive function.

### Stimulation Parameters

Stimulation parameters varied between patients. Individual best settings were analyzed and parameters only changed (mostly a rise in amplitude or addition of poles) when side effects occurred or when the antidepressant response was not satisfying. In some patients, wider pulse widths or higher frequencies led to an increase of tension and restlessness.

### PET Imaging: Metabolic Effects of NAcc-DBS

Positron emission tomography-computed tomography overlays in MNI normalized space confirmed the accurate position of the inserted DBS electrode at the targeted MNI coordinates in each patient. SPM5 (Wellcome Department of Imaging Neuroscience, London, United Kingdom; www.fil.ion.ucl.ac.uk/spm5.html) analysis demonstrated distributed changes in metabolic activity across cortical and subcortical areas as an effect of NAcc-DBS. Areas of significant metabolic change encompass decreases in prefrontal subregions (including the orbital prefron-

**Table 3.** PET Imaging

| Region | x[a] | y | z | Size | *t* |
|---|---|---|---|---|---|
| Metabolic Decreases | | | | | |
| Ventral superior frontal sulcus | 26 | 62 | 16 | 1478 | 6.00 |
| Orbital prefrontal cortex[b] | −28 | 46 | −12 | 3003 | 5.31 |
| Thalamus | −2 | −12 | 10 | 178 | 3.63 |
| Dorsal medial frontal gyrus | 48 | 20 | 48 | 79 | 3.17 |
| Caudate nucleus | −14 | 12 | 8 | 57 | 3.04 |
| Cerebellum | −44 | −52 | −50 | 104 | 2.98 |
| Subgenual cingulate cortex | 2 | 24 | −14 | 48 | 2.47 |
| Cerebellum | −2 | −24 | 34 | 47 | 2.42 |
| Posterior cingulate cortex | 50 | −58 | −44 | 44 | 2.30 |
| Dorsal superior frontal sulcus | 24 | 54 | 34 | 59 | 2.18 |
| Metabolic Increases | | | | | |
| Precentral gyrus | 48 | −38 | 30 | 42 | 2.81 |

Listed are coodinates, cluster sizes, and *t* values of significant voxels ($p = .05$, $k = 40$) as provided by SPM5 resulting from a paired *t* test comparing preoperative and 6-month postoperative [18F]FDG-PETs of $n = 7$ patients.

[18F]FDG, [18F]-2-fluoro-2-deoxy-D-glucose; FWE, family-wise error; PET, positron emission tomography.

[a]Negative x coordinates indicate the left hemisphere.

[b]$p = .038$ on cluster level after family-wise error (FWE) correction.

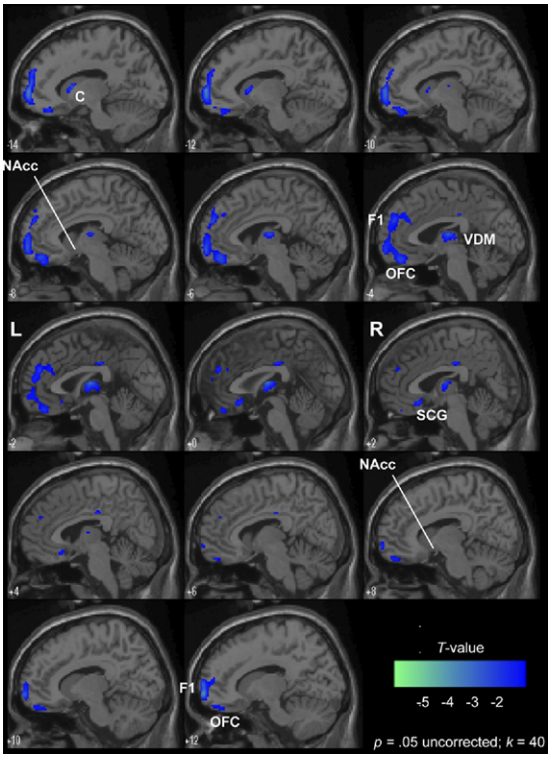


**Figure 2.** [18F]FDG-PET analysis. Shown is a series of sagittal sections illustrating the SPM5 results of a voxel-wise paired *t* test comparing [18F]FDG-PET images obtained from seven patients before and 6 months after the onset of deep brain stimulation to the nucleus accumbens. Blue regions denote cortical and subcortical areas of decreased metabolism ($p = .05$ uncorrected, voxel extent threshold k = 40). L and R indicate the first plain left and right from the midplain, respectively. CN, caudate nucleus; F1, superior frontal gyrus; [18F]FDG, [18F]-2-fluoro-2-deoxy-D-glucose; NAcc, nucleus accumbens; OFC, orbital prefrontal cortex; PET, positron emission tomography; SGC, subgenual cingulate; VDM, ventro-dorso-medial thalamus.

tal cortex [OFC]), subgenual cingulate region (SGC), posterior cingulate cortex, thalamus, and caudate nucleus and an isolated increase in the precentral gyrus (Table 3, Figures 2 and 3).

### Adverse Effects

Adverse effects were either related to the surgical procedure (e.g., swollen eye, dysphagia, pain), to parameter change (e.g., erythema, subjective transient increase in anxiety or tension, sweating) (Table 2), or unrelated to the DBS treatment (e.g., gastritis, leg fracture). Most importantly, all side effects related to the DBS treatment were transient and could be stopped immediately by means of parameter change, so that patients did not suffer any permanent adverse effects.

One patient attempted and another patient committed suicide during the follow-up period. These serious adverse events are judged unrelated to the DBS treatment, as the suicide attempt was related to noncompliance of the patient (unpredictable, sudden omission of all medications and refusal to attend study visits to adjust stimulation parameters) and this patient is now classified as responder with stable stimulation parameters. The suicide took place during a personal crisis caused by critical life events (separation from partner, conflicts with close relatives) that was not counteracted by their psychiatrist. At the time, the patient was unable to attend study visits for a stimulation parameter change. Both events were not related to parameter changes. Both patients also had attempted suicide previous to entering the study.

## Discussion

This study demonstrated antidepressant effects of NAcc-DBS in a group of patients suffering from severe treatment-resistant depression; half of them responded significantly. Prior to inclusion, their depression was unrelenting and they had experienced up to 42 different drug treatment attempts. The rate of response was the same as in prior studies on different stimulation targets (Brodman area cg25 [8] and ventral striatum [9]). This is important since the patient population included in this study was at least as treatment-resistant as those studied previously. In contrast to previous data, we were able to demonstrate an antianxiety effect. Clinically probably most important, a significant increase in positive activities and thus an antianhedonic effect was observed in responders.

### Effect of NAcc-DBS on TRD

Deep brain stimulation of the striatum led to antidepressant effects in TRD patients; although the effect varied between patients, substantial positive changes in clinical symptoms and social life (e.g., returning to work part-time, starting a new hobby, establishing a daily structure, making new acquaintances) were observed in all patients. No other conventional treatment methods ever led to significant amelioration in any of these

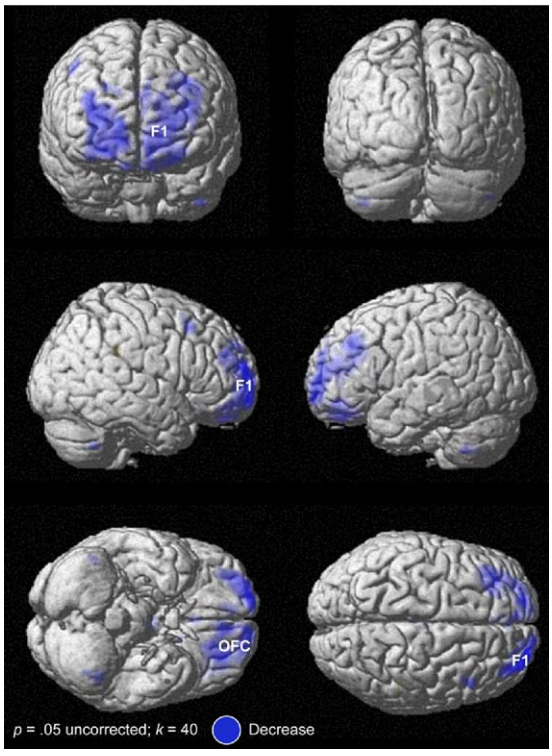


**Figure 3.** [18F]FDG-PET analysis, surface rendering. Shown is a surface rendering of the SPM5 results of a voxel-wise paired *t* test comparing [18F]FDG-PET images obtained from seven patients before and 6 months after the onset of deep brain stimulation to the nucleus accumbens. Blue regions denote cortical areas of decreased metabolism ($p = .05$ uncorrected, voxel extent threshold k = 40). F1, superior frontal gyrus; [18F]FDG, [18F]-2-fluoro-2-deoxy-D-glucose; OFC, orbital prefrontal cortex; PET, positron emission tomography.

patients before; half of the patients had never experienced any remission since first diagnosis.

No worsening of symptoms, recurrence of new symptoms, or cognitive impairments was observed. On the contrary, the general psychopathological burden (as assessed by SCL-90), as well as anxiety (as measured by HAMA), were decreased significantly. Besides clinical efficacy, tolerability and preliminary safety information were further aspects in this study. Overall, the safety of the intervention was comparable with DBS for neurological indications. All adverse effects related to stimulation could be counteracted by parameter adjustments; the absence of side effects led to high adherence. No patient exercised the option to remove the device.

### Putative Mechanism of Action

The advent of functional neuroimaging methods fosters new conceptualizations of the underlying neurobiology of depression and allows the development of testable hypotheses (26,27). Newer models of depression-based functional neuroimaging (28) and early results from DBS studies (10,29) and preclinical models (30,31) relate different symptom clusters to dysfunction in specific nodes in the depression network (6). While we have to be aware of the fact that these models are of limited heuristic value and reflect limitations in the ability of currently available research methods to understand systems-level dysfunction, they indeed provide the bases for hypothesis-guided approaches for neuromodulation treatments. An individual symptom-specific approach might be the future of psychiatric treatments; it is improbable that stimulation of one brain area will be optimal for all types of depression. Therefore, it is important to evaluate specific effects of DBS at different target sites both for clinical practice and for the understanding of mechanisms of depression.

Anhedonia is a core symptom in depression and other mental disorders (e.g., substance abuse, schizophrenia, and obsessive-compulsive disorder) (11). The nucleus accumbens is implicated in the processing of reward and pleasure (32); it has been demonstrated that the NAcc is dysfunctional in depression (12,13). One aim of the study was to improve depression by selectively influencing anhedonia. Our hypothesis was that modulation of the dysfunctional NAcc—as being part of the reward system—would improve this symptom. Anhedonia was indeed significantly reduced in all patients, as reflected by the number of pleasant activities the patients performed, confirming previously published findings on acute stimulation to the NAcc target (10). Thus, it seems possible to modulate specific symptoms of depression by targeting distinct brain areas with DBS.

We believe that the currently used rating scales do not fully reflect antidepressant effects in very therapy-resistant patients; indeed, clinically significant treatment response was more obvious to the clinician than reflected by percent change in rating scales. These scales were developed to assess effects of pharmacotherapy in a wide spectrum of depressions; severe TRD might well be associated with a floor effect in these scales. New scales designed to capture changes in TRD patients and to not only detect individual symptoms but also changes in everyday life are needed. These changes in quality of life were more important to our patients and more obvious to us; predictive diagnostics taking individual symptom expression into account are missing.

Based on acute effects of NAcc DBS (10), we hypothesized that modulation of the NAcc through its anatomical and functional connections with other limbic and prefrontal regions would normalize disease-related hypermetabolism in these regions. This a priori hypothesis is supported by the present [18]FDG-PET data obtained from 7 of the 10 patients in this study. Deep brain stimulation to the nucleus accumbens decreased metabolism in the SGC and in prefrontal regions including the OFC, which is consistent with metabolic decreases observed in patients undergoing DBS to the SGC (8). We interpret our findings as evidence for a generalizable role of the SGC in mediating a clinical response to DBS, irrespective of whether DBS targets this area directly or indirectly via functional interactions with the NAcc. This assumption is underlined by a first tractography study examining the connectivity of two DBS targets in depression. This study demonstrated patterns of connectivity between NAcc and SGC in healthy subjects (33).

In contrast to our previous findings (10), we did not find any increase in NAcc metabolism; a possible explanation is that this hypermetabolism might reflect a short-lasting acute tissue reaction to the implantation. In addition, there is increasing evidence that neuromodulatory effects of DBS might not be mediated by activation or inactivation of targeted regions at all but by frequency-related electrophysiological gating mechanisms (34).

Interestingly, our volume of interest analysis comparing responders and nonresponders identified decrease in metabolism in the amygdala to be significantly different. Indeed, one of the most notable findings from functional neuroimaging studies of anxiety-disordered patients is an abnormal hyperresponsiveness of the amygdala to fear signals (35), and it might well be that a DBS-induced normalization of metabolism in the amygdala is correlated with the reduction in anxiety scores in the responders.

### Limitations

Patients varied in the time they were followed, between 12 months and 36 months, due to the recruitment process. Thus, long-term effects reflect only 12 months on group level but last follow-up is composed of different time points. In addition, we only report on a relatively small patient number; however, this is also the case for other published studies (8,9,30). As group size enlarges, we will be able to analyze mediator variables that distinguish between responders and nonresponders. Deep brain stimulation studies in TRD are unwieldy to organize from a patient support, ethical, and technical standpoint and should only be undertaken by highly trained teams in well-equipped centers.

Another problem is that this study—just as the other published ones—is not sham controlled; indeed, none of our patients was able to guess whether the stimulator was on or off. This would be ideal for a sham-controlled study and this study was originally planned in a sham-controlled design, but we abandoned the blinding phase after three patients for several reasons. First, patients did not tolerate off phases due to massive worsening of symptoms, so blinding had to be broken and stimulation reassumed. Second, when stimulation was discontinued accidentally (e.g., battery exhaustion) without the patient's and clinician's knowledge, depression worsened rapidly. This renders a mere placebo effect unlikely. Third, a possible placebo effect in this group of treatment-resistant patients seems improbable; it is known that the likelihood to have a placebo response decreases with treatment resistance (36). A study of vagus nerve stimulation in refractory MDD demonstrated that only 10% of patients responded to sham stimulation over a 10-week period; patients in this study were far less treatment-resistant than the ones described here (37).

### Conclusion/Outlook

In summary, DBS to the nucleus accumbens had clinically relevant antidepressant and antianhedonic effects in a patient

population that was at least as treatment-resistant as those reported on in other studies of DBS in major depression (8,9). The efficacy to adverse event ratio in this small group was favorable. Site-specific antianxiety effects also could be demonstrated.

By targeting one site in a network of brain regions implicated in processing of affective stimuli, it was possible to manipulate anhedonia in particular. Additional studies with larger sample sizes and rigid selection criteria are needed to analyze effects of stimulation to different targets on specific symptoms and clinical phenotypes of depression. In the future, symptom-based DBS therapy, adapted to the individual needs of the patients, could be a plausible treatment option for severe TRD.

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*Supplementary material cited in this article is available online.*

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