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