

Long-Term Effects of Nucleus Accumbens Deep Brain Stimulation in Treatment-Resistant Depression: Evidence for Sustained Efficacy

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Deep brain stimulation (DBS) to the nucleus accumbens (NAcc-DBS) was associated with antidepressant, anxiolytic, and procognitive effects in a small sample of patients suffering from treatment-resistant depression (TRD), followed over 1 year. Results of long-term follow-up of up to 4 years of NAcc-DBS are described in a group of 11 patients. Clinical effects, quality of life (QoL), cognition, and safety are reported. Eleven patients were stimulated with DBS bilateral to the NAcc. Main outcome measures were clinical effect (Hamilton Depression Rating Scale, Montgomery-Asperg Rating Scale of Depression, and Hamilton Anxiety Scale) QoL (SF-36), cognition and safety at baseline, 12 months ($n = 11$), 24 months ($n = 10$), and last follow-up (maximum 4 years, $n = 5$). Analyses were performed in an intent-to-treat method with last observation carried forward, thus 11 patients contributed to each point in time. In all, 5 of 11 patients (45%) were classified as responders after 12 months and remained sustained responders without worsening of symptoms until last follow-up after 4 years. Both ratings of depression and anxiety were significantly reduced in the sample as a whole from first month of NAcc-DBS on. All patients improved in QoL measures. One non-responder committed suicide. No severe adverse events related to parameter change were reported. First-time, preliminary long-term data on NAcc-DBS have demonstrated a stable antidepressant and anxiolytic effect and an amelioration of QoL in this small sample of patients suffering from TRD. None of the responders of first year relapsed during the observational period (up to 4 years).

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INTRODUCTION

A large number of depressive patients cannot be helped with evidence-based treatment steps (eg, pharmacotherapy, psychotherapy, and electroconvulsive therapy). Up to 40% of patients responding to antidepressant therapy suffer from clinically relevant residual symptoms despite optimized treatment (Fava and Davidson, 1996). These patients suffer from debilitating, life-threatening symptoms, face a reduced quality of life (QoL), and are a burden for society (Murray and Lopez, 1996; Pincus and Pettit, 2001). For these patients, suffering from so-called treatment-resistant depression (TRD), deep brain stimulation (DBS) is currently under research as a possible treatment option.

DBS aims to modulate dysfunctional neuronal networks involved in depression (Krishnan and Nestler, 2010). Three major brain regions have been selected in a hypothesis-driven way for major depression: nucleus accumbens (NAcc) (Bewernick *et al*, 2010; Schlaepfer and Lieb, 2005), subgenual cingulate cortex (Cg₂₅) (Lozano *et al*, 2008; Mayberg *et al*, 2005) and the anterior limb of the capsula interna (ALIC) (Malone *et al*, 2009). Although the precise mechanism of action is not known yet, significant antidepressant effects have been shown in a 1-year follow-up period in 50–60% of the about 45 treated patients (Bewernick *et al*, 2010; Lozano *et al*, 2008; Malone *et al*, 2009). A normalization of brain metabolism in the target region and in brain areas belonging to neuronal network modulated by DBS has been demonstrated (Bewernick *et al*, 2010; Lozano *et al*, 2008). Neuropsychological assessment showed a normalization of previously sub-average performance in several cognitive domains in a 1-year follow-up (Grubert *et al*, 2011; McNeely *et al*, 2008).

Despite encouraging antidepressant effects of all targets, long-term outcome beyond 1 year has only been described

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recently in 14 patients stimulated at Cg₂₅ with 45% response after 2 years, 60% response after 3 years, and 55% response at last follow-up visit (up to 6 years) (Kennedy *et al*, 2011) and in a sample of 17 patients targeting the ALIC (Malone, 2010). Response rates were 53% after 12 months and 71% at last follow-up (ranging from 14 to 67 months) (Malone, 2010). The response criterion was a minimum of 50% reduction in Hamilton Depression Rating Scale (HDRS) or Montgomery-Asperg Rating Scale of Depression (MADRS) in all studies.

In this study, long-term effects of DBS to the NAcc are described in a group of 11 patients suffering from TRD. Clinical effects, QoL, cognition, and safety over a 2-year follow-up period, in five patients up to 4 years, are reported.

Contrary to the high relapse rates after treatment-as-usual (TAU) (eg, pharmacotherapy, psychotherapy) (Rush *et al*, 2006), but in line with stable antidepressant, anti-anhedonic, and anxiolytic effects of NAcc-DBS during first year, we hypothesized, that clinical effects as well as an increase in QoL would be stable during long-term follow-up (from 12 to 48 months).

PATIENTS AND METHODS

Patients

The study has been approved by the institutional review boards of the Universities of Bonn and Cologne. Eleven patients between 32 and 65 years of age received NAcc-DBS (see Table 1 for demographic data) Selection criteria were a minimum score on the 28-item HDRS (HDRS28) of 21, a

score in Global Assessment of Function below 45. Further inclusion criteria were at least four episodes of major depressive disorder (MDD) or chronic episode over 2 years; >5 years after 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 ECT (>6 bilateral treatments); an adequate trial of individual psychotherapy (>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. Patients met diagnostic criteria for MDD, unipolar type, and were in a current episode. All patients to be included in the study suffered from severely TRD (Sackeim, 2001).

Surgery/Target

Bilateral DBS electrodes were implanted as described previously (Schlaepfer *et al*, 2008) using a Leksell-stereotactic frame. Standard Medtronic model 3387 leads were used. This lead has four contacts over a length of 10.5 mm, each spaced 1.5 mm apart: (1) the shell and (2) the core regions of the NAcc, and (3) the ventral and (4) the medial internal capsule. The lowest contact was targeted at 7.5, 1.5, and 4 mm from the upper front edge of the anterior commissure, corresponding to MNI coordinates $\pm 7.5, 5.5, \text{ and } 4$

Table 1 Demographic and Clinical Characteristics

Variable	Mean	SD	Responders		Non-responders	
			Mean	SD	Mean	SD
Age at implant (years)	48.36	11.08	45.6	12.9	50.6	9.8
Sex (% female)	33		60		16.6	
Duration of education (years)	14.30	2.36	14.25	2.5	14.3	2.5
Retirement because of depression (% retired)	90.00		80		100	
Length of current episode (years)	9.26	7.64	5.98	3.5	12	9.3
Number of previous episodes (lifetime) ^a	1.29		1.75	0.9	0.6	0.5
Age at onset (years)	32.55	12.41	34.8	14.4	30.6	11.4
Time since diagnosis of affective disorder (years)	17.45	9.91	12.6	4.7	21.5	11.6
Lengths of previous hospitalizations (months)	20.18	11.24	18.4	10.2	21.6	12.7
Number of antidepressive pharmaceuticals at implant	4.36	1.21	3.8	1	4.8	1.1
Number of past medical treatment courses	22.18	7.73	19	5.5	24.8	8.7
Number of medications included in formula	13.82	5.34	12	4	15.3	6.1
Mean total of ATHF score ^b	40.27	15.24	38.6	14.3	41.6	17.1
Mean ATHF score and SD	3.18	0.40	3.4	0.5	3	0
Average number of treatment trials with ATHF ≥ 3	7.91	3.36	7.6	3.3	8.1	3.6
Past ECT/MST	21.09	8.48	22.2	8.7	20.1	8.9
Psychotherapy (h)	263.64	263.88	185.2	143.8	329	333.8
Suicide attempts (% of patients preoperative)	27		20		33.3	

^aFifty percent of patients did not have separate episodes.

^bModified antidepressant treatment history form (ATHF). A score of '3' is the threshold for considering a trial adequate and the patient resistant to the treatment. Mean and SD, if applicable, are reported.

9.0. Targets and trajectories were defined using stereotactic 3 Tesla MR imaging. Electrode positioning was verified after surgery as described in Huff *et al* (2010). Electrode type and location differed from the ALIC target only dorsally (Malone *et al*, 2009), because the electrodes used in this study had a smaller spacing of 10.5 mm and the electrodes used in the ALIC study had a wider space covering a larger brain area (Malone *et al*, 2009). Thus, the two most ventral ALIC contacts cover approximately the same brain area as the four contacts used in this study.

Assessment and Study Protocol

Psychiatric assessments were performed on a weekly basis during the first and second month after stimulation onset and up to half a year on a 2-weekly basis. From month 7 up to 2 years, patients were tracked on a monthly basis, then up to 4 years on a 3-monthly basis.

Primary outcome measure was antidepressant response (50% reduction of depressive symptom severity as assessed by the 28-item HDRS₂₈ (Endicott *et al*, 1981; Hamilton, 1967; Rosenthal and Klerman, 1966) or remission (HDRS-score of <10)). Patients were classified as responders and non-responders with regard to their response to NAcc-DBS 12 months post-surgery. Secondary outcome measures included MADRS (Montgomery and Åsberg, 1979) and Hamilton Anxiety Scale (HAMA) (Hamilton, 1976).

The Hautzinger list of positive activities is a list of 280 pleasant activities (Hautzinger, 2000; Lewinsohn and Graf, 1973). This score is used as a tool to assess progress in cognitive behavioral therapy. Lacking meaningful standardized measures of anhedonia, we used this list to assess changes in anhedonia and level of activity. Social functioning was measured with the Short-Form Health Survey Questionnaire (SF-36) (Ware and Sherbourne, 1992). The SF-36 assesses QoL in eight subscales that can be summarized into a score in 'physical health dimension' and 'mental health dimension'. Additionally, information about safety of the treatment method (see Table 4 for adverse events) was recorded.

Neuropsychological assessment with standardized tests was administered to the patients before implantation and once a year during follow-up. Thirteen cognitive tests were analyzed comparing baseline and last follow-up covering learning and memory (verbal and visual-spatial as well as working memory), attention, language, visual perception, and executive functions. Standard neuropsychological tests are clustered according to the Compendium of Neuropsychological Tests and described in detail elsewhere (Spreeen, 1991). See Grubert *et al* (2011) for a detailed description of neuropsychological tests applied. Some verbal test could not be performed on all patients for language reasons (see Table 3 for number of patients included in the analysis).

Stimulation Parameters and Additional Treatments

Stimulation was applied with permanent pulse-train square wave stimulation starting with the parameters amplitude 2 V, pulse width 90 μ s, frequency 130 Hz, and the electrode setting electrodes 1 and 2 negative against case. After an intra-operative trial, stimulation was switched off for 1 week to allow consolidation of the tissue surrounding the electrode

tips (eg, changes in resistance) and to control for microlesional effects (Cersosimo *et al*, 2009; Granziera *et al*, 2008). One week post-operatively, this DBS setting was resumed and the voltage was successively increased from 2 to 4 V.

Stimulation parameters were kept constant approximately for 4 weeks in order to retrieve sufficient observations of first acute and sub-acute effects (eg, 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 in order to optimize the individual response. The sequence and priority of changes was: amplitude, pulse width, selection of poles, (all possible monopolar and bipolar combinations), and frequency in the range 1.5–10.0 V, 100–150 Hz, and 60–210 μ s. Stimulation was always bilateral and symmetric. The individual optimum DBS setting was kept constant in each patient at least one month before and during the final follow-up.

Additional pharmacological treatment was kept constant at least 6 weeks before and after surgery. During follow-up, especially in non-responders, changes in pharmacological regime were allowed. Patients undergoing psychotherapy entering the study were allowed to continue the treatment.

Statistical Analysis

To evaluate clinical response, all rating scales were analyzed with ANOVA for repeated measures and the factor time. *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 ($n = 1$, 12 months) or patients in follow-up under 24 months ($n = 1$, 13 months) were analyzed in the last observation carried forward manner. Missing values were interpolated. Last follow-up was up to 4 years (five patients completed year 4). All analyses were performed as intent-to-treat analysis in order to avoid overestimation of clinical effect. Significance of change in cognitive performance between baseline and last observation (up to 36 months) was analyzed via paired *t*-tests for each neuropsychological test as recommended by Okun *et al* (2007) in order to evaluate whether surgery and stimulation lead to deterioration from baseline.

RESULTS

Demographic and Clinical Characteristics

All patients were diagnosed as severely treatment resistant with a mean length of current major depressive episode of 9.2 years (SD 7.6), and had 7.9 medical treatment courses in average with an antidepressant treatment resistance score (ATHF 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 (see Table 1 for demographic information). Responders and non-responders were compared concerning severity of depression at baseline (HDRS₂₈, MADRS) and clinical characteristics. No difference could be detected regarding baseline depression severity ((responders/non-responders HDRS₂₈ score: 34.5

(SD 5.2)/30.2 (SD 5.3); responders/non-responders MADRS score: 33.6 (SD 1.6)/31.2 (SD 4.6)) or demographic differences. Only the number of women in each group differed: three women were classified as responders (*vs* two men) and one woman was classified as non-responder (*vs* five men).

Clinical Outcomes

All measures are reported at baseline (mean baseline score over up to five visits in the last 3 months before surgery), $n = 11$, and at several time points up to 4 years after stimulation onset ($n = 11$).

Primary outcome (HDRS₂₈). Patients were classified as responders (50% reduction in HDRS) and non-responders (<50% reduction in HDRS) with regard to their response to NAcc-DBS 12 months post-surgery (Table 2, Figure 1a). Five patients (45.5%) reached the response criterion at this point; six patients (54.5%) were classified as non-responders. During the second year, response status remained stable in all patients. None of the non-responders reached response status for >2 consecutive months. One patient was in stable remission ($\text{HDRS}_{28} \leq 10$).

The mean total HDRS₂₈ score was significantly improved under stimulation at all-time points. Improvements were seen after first month of stimulation in the sample as a whole (HDRS₂₈-score: 32.2 (SD 5.5) at baseline, 23.2 (SD 5.6) after 1 month) and remained stable throughout the follow-up period (HDRS₂₈-score: 20.2 (SD 7.5) after 1 year, 19.5 (SD 9) after 2 years, 22.1 (SD 13.4) last follow-up). Responders and non-responders descriptively differed in HDRS score after first month of stimulation and differences were more pronounced during follow-up period. In the second year, group differences were even more pronounced. Stability of anti-depressive effect in each patient is demonstrated in Figure 2. Responders at 12 months remained responders at 24 months and last follow-up, non-responders kept their status respectively.

Secondary outcome variables (MADRS, HAMA, positive activities, QoL, cognition). MADRS was used to capture changes in additional depressive symptoms (eg, cognitive functioning, level of activity, interest, and negative thinking). Group effects were similar to those measured with the HDRS₂₈ (MADRS group mean at baseline: 32.3 (SD 3.7); group mean after 1 year: 20.2 (SD 7.3) after 2 years: 19.1 (SD 8.5) last follow-up: 21.6 (SD 10.7)) (Table 2, Figure 1b).

Improvement in depression was accompanied by a reduction in anxiety as measured by the HAMA (Table 2, Figure 1c). Compared with baseline, the sample as a whole showed a significant reduction in anxiety symptoms (HAMA at baseline: 23.3 (SD 5.7), after 1 year: 14.3 (SD 5.8), after 2 years 13.9 (SD 4.9), last follow-up: 14.7 (SD 8.8)). From first month of stimulation, the group mean was below 19, which is the cut-off for anxiety disorders in pharmacological studies (Hamilton, 1976). Similar to results in depression scales, responders had a more pronounced reduction in anxiety compared with non-responders.

The level of hedonic activities (as measured by the Hautzinger's list of positive activities) rose significantly in the sample as a whole from first month of stimulation. Descriptively, the number of activities further increased in the group of responders during the follow-up period (Table 2, Figure 1d) and not in the group of non-responders. Physical health dimension (as one dimension of the QoL scale SF-36) changed from 34.0 (SD 4.5) at baseline to 34.1 (SD 11.2) at last follow-up for the group as a whole, thus patient's physical health remained stable. On a descriptive level, responders had a better physical health at baseline and this difference was more pronounced at last follow-up. 'Mental health' (the second QoL dimension of the SF-36) improved significantly from 19.4 (SD 4.5) at baseline to 29.99 (SD 11.2) at last follow-up for the sample as a whole. Thus, the group as a whole moved about 1 SD from 'much below average' (-3 SD) to 'below average' (-2 SD). Descriptively, responders improved more than non-responders.

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. Only weak symptoms of hypomania (elevated mood, less hours of sleep) were observed in two patients after parameter change, which disappeared within 24 h and did not meet diagnostic criteria for hypomania.

Comprehensive neuropsychological assessment revealed no detrimental effects on cognitive function after 12 months in a paper by Grubert *et al* (2011) on 10 patients of our current sample. In the contrary, cognitive performance significantly improved in tests of attention, learning and memory, executive functions, and visual perception during first year of follow-up. In addition, there was a general trend toward cognitive improvement from below average to average performance (Grubert *et al*, 2011). These effects were independent of the antidepressant effects of NAcc-DBS or changes in NAcc-DBS parameters (see for details). Analysis of the assessment at last observation (24 to 36 months) confirmed no changes in cognition from baseline except for nonverbal fluency, which was significantly improved at last follow-up (see Table 3 for an overview on tests and statistical analysis).

Stimulation Parameters

Stimulation parameters varied between patients. Most patients were stimulated between 5 and 8 V, at 90 μs , 130 Hz, monopolar. Individual best settings were analyzed and parameters only changed (mostly raise in amplitude or change of contacts) when side effects occurred or when the antidepressant response was not satisfying. In three patients, wider pulse widths or higher frequencies led to an increase in tension and restlessness. Small differences could be found on average between responders and non-responders: non-responders experienced parameter changes more frequently and later during follow-up (responders had only minor parameter adjustment after 13 months, whereas non-responders had parameter changes on average at 17 months). Responders were stimulated little less than non-responders (responders: 6.8 V/90 PW/130 rate, non-responders: 7.1 V/100 PW/135.5 rate on average). After

Table 2 Psychopathological Measures at Multiple Time Points During DBS Treatment

	Baseline	1 Month	3 Months	6 Months	9 Months	12 Months	15 Months	18 Months	21 Months	24 Months	Last observation
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
	p-Value main effect	p-Value	p-Value	p-Value	p-Value	p-Value	p-Value	p-Value	p-Value	p-Value	p-Value
<i>HDRS_28</i>											
Group	32.2 (5.5)	23.2 (5.6)	23.4 (5.1)	20.9 (4.6)	23.3 (5.5)	20.2 (7.5)	21.3 (7.1)	21 (8.9)	21.5 (8.1)	19.5 (9)	22.1 (13.4)
F = 4.1	$p < 0.001$	$p < 0.005$	$p < 0.001$	$p = 0.001$	$p < 0.005$	$p < 0.005$	$p < 0.005$	$p < 0.005$	$p < 0.01$	$p < 0.01$	$p < 0.05$
df = 10											
<i>MADRS</i>											
Group	32.3 (3.7)	24.2 (4.8)	23.4 (4.7)	20.9 (5.6)	22.8 (6.8)	20.2 (7.3)	21.2 (7.8)	21.1 (8.5)	21.7 (9.3)	19.1 (8.5)	21.6 (10.7)
F = 5.1	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.005$	$p = 0.001$	$p < 0.005$	$p < 0.005$	$p < 0.05$	$p < 0.005$	$p < 0.05$
df = 10											
<i>HAMA</i>											
Group	23.3 (5.7)	17.9 (7.3)	17.6 (5.9)	15.4 (3.9)	17.4 (3)	14.3 (5.8)	15.7 (9)	16 (10.4)	13.7 (6.4)	13.9 (4.9)	14.7 (8.8)
F = 2.7	$p < 0.005$	$p < 0.01$	$p < 0.05$	$p < 0.005$	$p < 0.005$	$p < 0.005$	$p < 0.05$	$p < 0.05$	$p < 0.005$	$p = 0.001$	$p < 0.05$
df = 10											
<i>Activities</i>											
Group	28.5 (16)	43.9 (24.8)	39 (21.8)	41.6 (24.4)	43.2 (20.5)	45.7 (20.7)	45.5 (25.4)	46.4 (25.3)	48 (29.6)	51.9 (35.5)	57.9 (37.7)
F = 2.4	$p < 0.05$	$p < 0.05$	$p < 0.05$	$p = 0.100$	$p < 0.05$	$p < 0.05$	$p = 0.052$	$p < 0.05$	$p = 0.075$	$p = 0.083$	$p < 0.05$
df = 10											
<i>SF 36</i>											
<i>Mental health</i>											
Group	19.4 (4.9)	23.3 (6.3)		19.5 (3.4)		20.5 (6.5)		19.9 (3.8)		24.3 (11.4)	29.9 (11.2)
F = 4.9	$p < 0.001$	$p < 0.05$		$p = 0.953$		$p = 0.551$		$p = 0.749$		$p = 0.172$	$p < 0.05$
df = 6											
<i>Physical health</i>											
Group	34.0 (4.5)	35.4 (7.9)		38.0 (5.9)		35.7 (4.6)		34.8 (3.9)		37.6 (8.5)	34.1 (13.3)
F = 0.7	$p = 0.651$	$p = 0.42$		$p = 0.40$		$p = 0.267$		$p = 0.565$		$p = 0.182$	$p = 0.980$
df = 6											

Abbreviations: Activities, number of positive activities after Hautzinger; HAMA, Hamilton Anxiety Scale; HDRS_28, Hamilton-28-Items Depression Rating Scale; MADRS, Montgomery-Asberg Depression Rating Scale; SF-36, Health Survey Questionnaire.

Mean, SD, ANOVAs for repeated measures with the factor time and *post-hoc* contrasts for each time point in comparison with baseline.

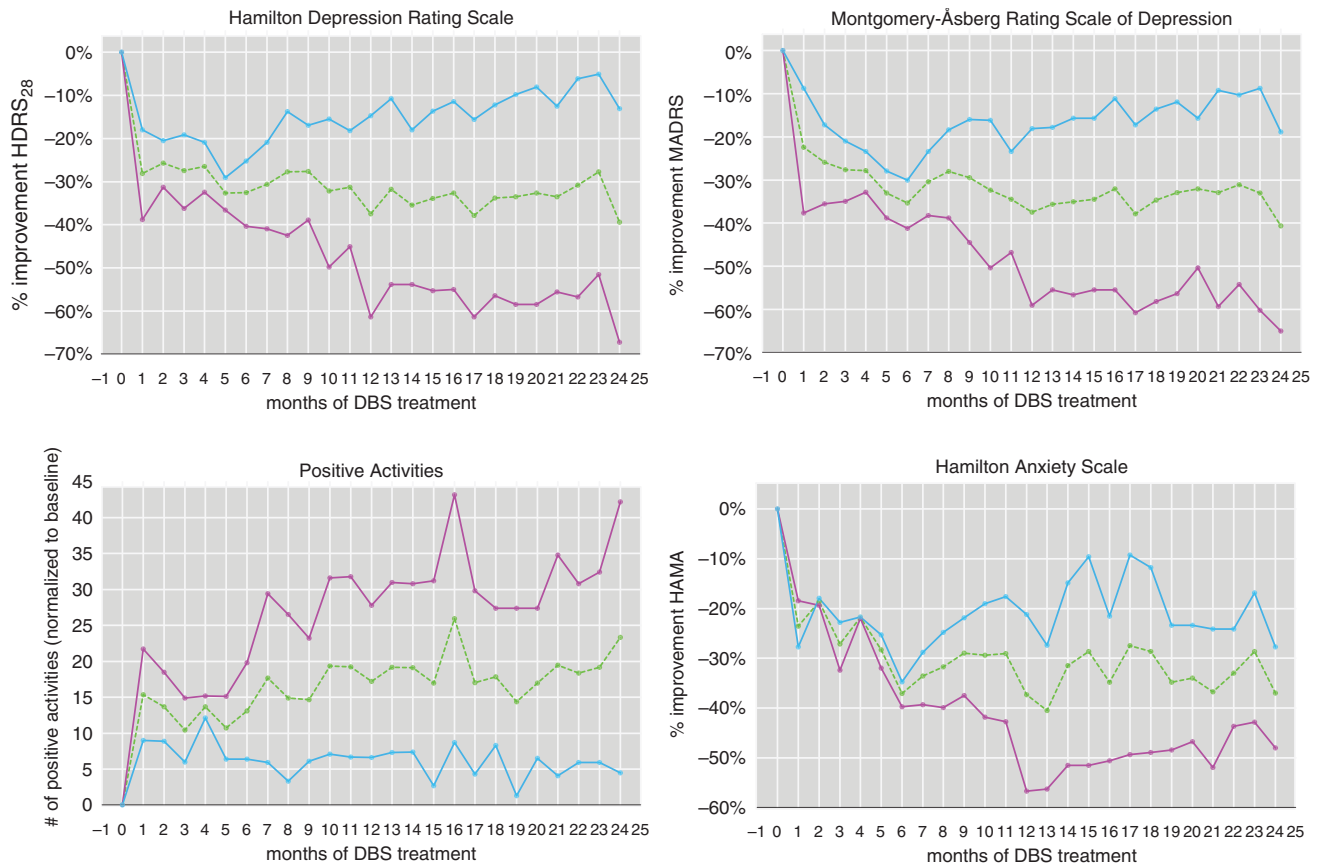


Figure 1 Clinical outcomes over time. Hamilton depression rating over time (top left); Montgomery-Asperg rating over time (top right); positive activities over time (bottom left); Hamilton anxiety rating over time (bottom right). In red responders (>50% reduction from baseline), in blue non-responders (<50% reduction from baseline), in green group mean scores. For the activities, panel red refers to patients who responded >50% in the HDRS score. At each time point, 11 patients contributed, as data were analyzed in an intent-to-treat method with last observation carried forward.

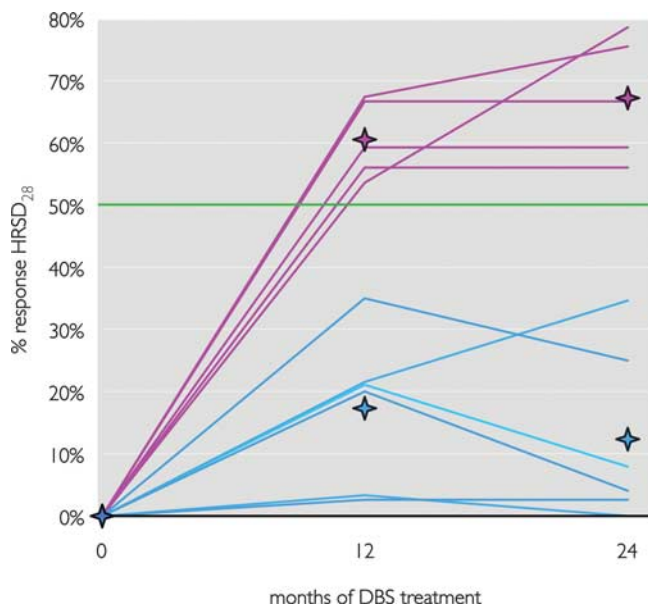


Figure 2 Stability of clinical effect. Individual response over time. Red lines are responders (>50% reduction from baseline), $n=5$, in blue non-responders (<50% reduction from baseline), $n=6$, at time points 12 and 24 months. Diamonds represent corresponding group mean values.

approximately 6 months, most patients had all four contacts activated negative against the case.

Adverse Events and Dropouts

Adverse events were either related to the surgical procedure (eg, swollen eye, dysphagia, pain), directly to parameter change (eg, erythema, subjective transient increase in anxiety or tension, sweating, within minutes to few hours) (see Table 4) or unrelated to the DBS treatment (eg, gastritis, leg fracture, herniated disc). Most importantly, all side effects related to the DBS treatment were transient or could be stopped immediately by means of parameter change, so that patients did not suffer any permanent adverse effects.

One patient attempted suicide and one patient committed suicide during 12 months follow-up. These patients were non-responders to DBS.

One patient had the device explanted after 2 years because of breast cancer and associated infection after chemotherapy. Two patients have been followed under 24 months; five patients have been tracked for 4 years. In order to prevent overestimation of clinical effect, all patients ($n=11$) contributed in an intent-to-treat analysis to all points in time.

Table 3 Neuropsychological Assessment of Cognitive Changes at Baseline and at Last Observation

Cognitive domain/test	Mean	N	SD	Paired samples t-test		T-value	df	p-Value
				Mean change	SD change			
<i>Verbal learning and memory</i>								
VLMT total learning								
Baseline	40.3	10	12.28	-1.20	15.67	-0.24	9.00	0.81
Last observation	41.50	10	14.88					
VLMT delayed recall								
Baseline	7.40	10	2.76	-0.40	4.17	-0.30	9.00	0.77
Last observation	7.80	10	3.43					
VLMT recognition								
Baseline	12.10	10	2.13	-0.50	1.96	-0.81	9.00	0.44
Last observation	12.60	10	2.17					
<i>General cognitive functions</i>								
MMSE								
Baseline	28.73	11	1.68	0.09	2.02	0.15	10.00	0.88
Last observation	28.64	11	1.43					
<i>Language</i>								
HAWIE lexis test								
Baseline	18.78	9	4.32	-0.11	3.10	-0.11	8.00	0.92
Last observation	18.89	9	3.55					
HAWIE finding similarities								
Baseline	22.67	9	5.00	-1.22	3.19	-1.15	8.00	0.28
Last observation	23.89	9	4.04					
<i>Working memory</i>								
Wechsler digit span								
Baseline	13.09	11	2.95	-0.18	2.79	-0.22	10.00	0.83
Last observation	13.27	11	4.76					
Wechsler visual memory span								
Baseline	13.45	11	3.50	1.18	3.25	1.21	10.00	0.26
Last observation	12.27	11	5.62					
<i>Executive function</i>								
TMT A (s)								
Baseline	52.73	11	29.12	-3.91	14.23	-0.91	10.00	0.38
Last observation	56.64	11	32.87					
TMT B (s)								
Baseline	134.64	11	87.49	-30.82	49.90	-2.05	10.00	0.07
Last observation	165.45	11	113.31					
STROOP interference (s)								
Baseline	302.57	7	70.23	-7.43	29.07	-0.68	6.00	0.52
Last observation	310.00	7	76.16					
Five-point test								
Baseline	20.20	10	10.84	-5.80	5.45	-3.36	9.00	0.01
Last observation	26.00	10	10.75					
<i>Visual spatial learning and memory</i>								
RVDLT total learning								
Baseline	27.20	10	9.05	-5.50	10.50	-1.66	9.00	0.13
Last observation	32.70	10	14.62					

Table 3 Continued

Cognitive domain/test	Mean	N	SD	Paired samples t-test		T-value	df	p-Value
				Mean change	SD change			
RVDLT delayed recall								
Baseline	6.10	10	2.92	-0.50	2.22	-0.71	9.00	0.50
Last observation	6.60	10	3.34					
RVDLT recognition								
Baseline	24.89	9	2.03	1.00	2.92	1.03	8.00	0.33
Last observation	23.89	9	4.01					
Visual perception								
VOT								
Baseline	18.00	8	4.99	-1.75	2.62	-1.89	7.00	0.10
Last observation	19.75	8	5.00					
Attention								
D2 total minus errors								
Baseline	280.44	9	124.47	-5.44	51.57	-0.32	8.00	0.76
Last observation	285.89	9	97.84					

Abbreviations: HAWIE, Hamburg Wechsler Intelligence Test for adults; MMSE, Mini-Mental Status Examination; RVDLT, Rey Visual Design Learning Test; TMT, Trail Making Test; VLMT, Verbal Learning and Memory Test; VOT, Hooper Visual Organization Test.

Mean, number of patients in analysis, SD, two-tailed paired *t*-tests with scores at baseline and at last observation (24 to 36 months) within each test as dependent variable. Percentile rank (PR) at baseline and last follow-up comparing our data with published normative data.

DISCUSSION

This study demonstrated sustained antidepressant effects over 2 years of NAcc-DBS in 11 patients suffering from severe TRD. Some patients were followed up to 4 years (last observation).

Effect of NAcc-DBS on TRD

Response rates. About 45% of patients responded significantly (reduction in HDRS $\geq 50\%$ in all studies) during the first 6 months of NAcc-DBS and reached the response threshold after 12 months of stimulation at the latest (for a detailed description of response during first year of follow-up see Bewernick *et al* (2010)). This response rate was similar to studies on other stimulation targets after 24 months, namely Cg₂₅ (Kennedy *et al*, 2011; Lozano *et al*, 2008) and ventral striatum (Malone, 2010; Malone *et al*, 2009) (Cg₂₅: response rate 45% after 24 months, 55% at last follow-up; ventral striatum: response rate 53.3%) and 12 months (ventral striatum: response rate 53 after 12 months, 71% at last follow-up, ranging from 14 to 67 months).

Comparing time courses of response in DBS studies with courses in TAU studies using pharmacotherapy, psychotherapy, or ECT, DBS-induced changes seem to require more time than effects induced by conventional treatment methods; first antidepressant effects could be observed after first months, however, the establishment of stable amelioration required up to 6 months, which might be at least partly explained by the need to adapt stimulation parameters for treatment optimization.

Typical 24 months response rates in TAU studies for TRD (mostly pharmacotherapy) are around 19% (Dunner *et al*, 2006). Response rates of DBS in the present small sample as well as in other studies on Cg₂₅ (Kennedy *et al*, 2011) and ALIC seem to be substantially higher, keeping in mind that the selected patients were per inclusion criteria non-responders to conventional treatments.

Stability of antidepressant effect. After about 8–12 months of treatment, patient's response status never changed, thus response remained stable during second year and up to 4 years. Responders had a sustained reduction in depressive and anxiety. Clinically equally important, the significant anti-anhedonic effect measured as number of positive activities remained also stable in responders during follow-up. This stabilization in psychopathological measures was also reflected in social functioning. QoL (mental health) changed from 'far below average' to 'slightly below average', whereas the patient's physical health score did not change. It has to be kept in mind that the main burden on the patient is depression itself causing reduced QoL. Nonetheless, patients started to work part-time, took care of their personal matters, resumed new hobbies, one patient developed the desire to have a child, and so on. In this small group of patients, these anecdotal changes were more convincing than any QoL measure could possibly point out.

It has to be kept in mind that no conventional treatment method (pharmacotherapy, psychotherapy, and ECT) lead to significant amelioration of any of these patients before and the majority of patients had not been in remission since

Table 4 Adverse Events

Adverse events	Related to surgical procedure	Related to parameter change	Unrelated to DBS
Seizure	1		
lead dislodgment	1		
Dysphagia	3		
Pain	4		
Swollen eye	6		
Psychotic symptoms		1	
Muscle cramps		1	
Vision/eye movement disorder		1	
Headache		1	
Paresthesia		2	
Transient mood elevation		2	
Agitation		3	
Disequilibrium		3	
Erythema		4	
Transient increase in anxiety (subjective)		4	
Increased sweating		4	
Suicide attempt			1
Suicide			1
Dyskinesia			1
Syncope			1
Herniated disc			1
Aneurysm in groin			1
Reduced pulmonary function			1
Cataract surgery			1
Breast cancer			1
Leg fracture			2
Aconuresis			2
Gastritis			5

Number of patients experiencing adverse events related to the surgical procedure, to parameter changer or judged to be unrelated to DBS.

first diagnosis. This long-term antidepressant effect is especially remarkable as in conventional antidepressant treatment approaches relapse is the rule. Relapse rates are up to 90% for third episode patients (Rush *et al*, 2006). The more treatment steps a patient requires, the higher will be the relapse rate (Rush *et al*, 2006). In the present sample, all patients had by definition numerous treatment steps and several or decades lasting episodes. After conventional treatments, most patients relapse within the first 6 months (Kellner *et al*, 2006; Rush *et al*, 2006). Studies on treatment as usual, assessing long-term effect beyond 1 year are rare in depression research. In this study, none of the responders suffered an aggravation in depression in 2 to 4 years.

Thus, DBS seems to be a promising therapy option for TRD so far, offering persistent antidepressant effects over many years.

Non-responders. More parameter settings were tried in the group of non-responders compared with the responders. Unfortunately, only short time or minimal long-term (from 5 to 45% response) antidepressant effects could be achieved in these patients. Increasing experience with NAcc-DBS allow more effective parameter search procedures and larger patient samples will make it possible to evaluate predictors of response. Although, antidepressant effects were small in the group of non-responders, only one patient even considered removing the DBS system but chose to remain stimulated. It is debatable, if non-responders to one target might be implanted to another target currently under research (eg, Cg₂₅, medial forebrain bundle, and habenula). Non-responders did not differ from responders in depression score at baseline or in demographic characteristics, but more men were classified as non-responders compared with women.

Cognition. It has been demonstrated at two target sites that DBS does not have negative effects on cognition (Grubert *et al*, 2011; McNeely *et al*, 2008). To the contrary, we demonstrated cognitive improvements in 10 patients treated with NAcc-DBS, which were not explained by the improvement in depression severity and could be shown independent of response status (Grubert *et al*, 2011). Analysis of last observation (24 to 36 months) compared with baseline performance have demonstrated no negative and in the domain of nonverbal fluency even an amelioration of function. Larger samples will further investigate possible procognitive effects in several cognitive domains.

Side effects and adverse events. Side effects occurred rarely directly after parameter change (minutes to few hours) and could be counteracted by small adjustments of stimulation settings. Adverse events were related to the surgery or not related to DBS as assessed by the investigator. One patient committed suicide and one patient attempted suicide during first year. It has to be taken into account that severe depression is associated with a 4–5 times elevated risk for suicide compared with moderate or mild depression (Hardy, 2009). Given the high risk of suicide (approximately 15% in TRD) (Isometsa *et al*, 1994; Wulsin *et al*, 1999) and compared with the suicide rate found in DBS to Cg₂₅ (10%) (Kennedy *et al*, 2011), in our sample, the one tragic suicide of a patient (suicide rate in our sample 9%) still remains below statistical expectation. Therefore, and because the suicide was judged not to be related to the stimulation (Bewernick *et al*, 2010), DBS as treatment option for TRD should not be abandoned because of risk of suicide, but close patient tracking is necessary as well as close collaboration with additional health care providers (local psychiatrist, psychotherapy, and professional social support).

Given robust antidepressant effects and minimal side effects, patients were very compliant to DBS-related duties (battery recharge, regular visits).

Parameters. It was important to carefully determine individual best parameters. This required frequent visits during first months. Acute effects at the beginning of treatment were not predictable for long-term outcome. Stable clinical effects after parameter change occurred within 2 to 4 weeks,

thus it is generally not indicated to change parameters more frequently. Depending on stimulation parameters, patients daily recharge the battery for up to 2 h ($n = 5$ patients) or need to have a battery replacement about once every 15 months ($n = 6$).

Limitations

All DBS studies so far are reporting on a relatively small number of patients, thus response ratios between 40 and 60% (Kennedy *et al*, 2011; Lozano *et al*, 2008; Malone *et al*, 2009; Mayberg *et al*, 2005) are limited in interpretation. Especially in long-term studies, dropouts, and patients who have not yet completed the whole observation period require special care in statistical analysis. Obviously, larger sample sizes are needed to convincingly ascertain clinical efficacy.

At study initiation, first patients entered a blinded sham stimulation phase. Owing to symptom aggravation and delayed recurrence as well as weaker antidepressant effect, the design was changed leaving out the sham condition. These problems have been reported also by Holtzheimer *et al* (2012) during a single-blind discontinuation phase in therapy-resistant depression and by Denys *et al* (2010) in patients suffering from obsessive-compulsive disorder. This is a strong limitation in respect to placebo effects. Although this study was not sham controlled, none of our patients was able to guess immediately whether the stimulator is on or off. Incidental interruption of stimulation (for reason of battery depletion or programming error), always led to an aggravation of symptoms after several days to weeks (for a discussion of placebo-effects in TRD, see Bewernick *et al*, 2010). In further studies it has to be planned thoroughly how a sham condition can be included in the design, possibly as a lead-in sham condition. A discontinuation criterion (eg, suicidal ideation, increase in depression score to 70% of baseline score) has to be determined prior.

Stimulation amplitudes were higher than in DBS for the treatment of neurological diseases. This applies to all targets under research so far (Cg₂₅, ALIC, and NAcc). This requires regular battery recharge (2 h per day) or battery exchange (every 8–15 months) and means an additional burden for the patient. As all targets are interconnected in the neuronal network for mood regulation (Krishnan and Nestler, 2010; Nestler and Carlezon, 2006), it is questionable, if the optimal target has been found. Actually, the medial forebrain bundle is under debate as a new target possibly reducing electric current (Coenen *et al*, 2011).

Conclusion/outlook

DBS to the NAcc has demonstrated sustained antidepressant effects over up to 4 years in a small sample. Anxiolytic effects and amelioration of social functioning were observed at this stimulation site. A favorable side-effect profile contributed to very good compliance and adherence. Nonetheless, surgical risk and the possible aggravation of depression or other psychiatric side-effects (especially suicidality) require a very experienced team of experts; neurosurgeons specialized in stereotactic surgery, psychiatrist experts in the treatment of depression, psychologist to assess severity of depression and cognitive effects. In addition, a central registry for DBS should guarantee that positive and negative

results as well as information from small feasibility and single case studies are brought to notice to the scientific community (Synofzik *et al*, 2011). Taken into account small sample size in all DBS studies in depression, larger studies have to be initiated before DBS can be seen as treatment option in less severe TRD.

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