The World Journal of Biological Psychiatry, 2011; 12: 516–527

ORIGINAL INVESTIGATION

Neuropsychological safety of nucleus accumbens deep brain stimulation for major depression: Effects of 12-month stimulation

CHRISTIANE GRUBERT[1,5], RENÉ HURLEMANN[1], BETTINA H BEWERNICK[1], SARAH KAYSER[1], BARBARA HADRYSIEWICZ[1,6], NIKOLAI AXMACHER[3], VOLKER STURM[4] & THOMAS E SCHLAEPFER[1,2]

[1]*Department of Psychiatry and Psychotherapy, University Hospital, Bonn, Germany,* [2]*Departments of Psychiatry and Mental Health, The Johns Hopkins University, Baltimore, MD, USA,* [3]*Department of Epileptology, University Hospital, Bonn, Germany,* [4]*Department of Functional Neurosurgery University Hospital, Cologne, Germany,* [5]*Centre for Psychiatry Reichenau, and* [6]*Department of Psychology, University of Cologne, Germany*

Abstract

Objectives. Deep brain stimulation (DBS) to the nucleus accumbens (NAcc-DBS) has antidepressant effects in patients suffering from treatment-resistant depression (TRD). However, limited information exists regarding the impact of NAcc-DBS on cognitive functioning. The aim of this study was to examine whether NAcc-DBS in patients with TRD has any cognitive effects. *Methods*. A comprehensive neuropsychological battery was administered to 10 patients with TRD before onset of bilateral NAcc-DBS and after 1 year of DBS stimulation. Neuropsychological testing covered the domains of attention, learning and memory, executive functions, visual perception, and language. Performance was analyzed at baseline and after 1 year of continuous DBS. *Results.* No evidence was found for cognitive decline following NAcc-DBS comparing test results after 1 year of NAcc-DBS with baseline. However, significantly improved cognitive performance on tests of attention, learning and memory, executive functions and visual perception was found. In addition, there was a general trend towards cognitive enhancement from below average to average performance. These procognitive effects were independent of the antidepressant effects of NAcc-DBS or changes in NAcc-DBS parameters. *Conclusions*. These results not only support cognitive safety of NAcc-DBS but also stress its beneficial role in augmenting cognitive performance in patients with TRD.

Key words: *Major depressive disorder, neuropsychological tests, PET, deep brain stimulation, nucleus accumbens*

Introduction

Major depression is a chronic and life-threatening disorder affecting up to 20% of the population worldwide (Berton and Nestler 2006). Only 50% of patients with major depression show full remission in response to current pharmacological and psychological therapies (Fava 2003); thus treatment-resistant major depression (TRD) is a frequent clinical phenomenon. Network models of depression assuming depression to be associated with dysfunctions of distributed forebrain circuits have recently been posited (Krishnan and Nestler 2008). Hypothesis-guided deep brain stimulation (DBS) has been investigated systematically for its putative effects on those network dysfunctions and related clinical symptoms; first studies have demonstrated efficacy in small patient populations (Lozano et al. 2008; Schlaepfer et al. 2008b; Malone et al. 2009; Bewernick et al. 2010). Specifically, we have shown that DBS to the Nucleus Accumbens (NAcc-DBS) has antidepressant, anti-anhedonic and anti-anxiety effects in patients with TRD (Schlaepfer and Lieb 2005; Schlaepfer et al. 2008b; Bewernick et al. 2010).

DBS treatment is more localized than other brain stimulation therapies such as electroconvulsive therapy (ECT), magnetic seizure therapy (MST) or vagus nerve stimulation (VNS) (Schlaepfer et al. 2008a) yielding antidepressant effects (Schlaepfer et al. 2010). Thus, regarding cognitive deterioration, DBS might have advantages over seizure-evoking

This study is registered at ClinicalTrials.gov as *Deep Brain Stimulation for Treatment-Refractory Major Depression* (http://clinicaltrials.gov/ct2/show/NCT00122031).

Correspondence: Thomas E. Schlaepfer, MD, Department of Psychiatry, University Hospital, Sigmund-Freud-Strasse 25, 53105 Bonn, Germany. Tel: +49 228 287 14715. Fax: +49 228 287 15025. E-mail: schlaepf@jhmi.edu.

(Received 14 September 2010; accepted 29 March 2011)

ISSN 1562-2975 print/ISSN 1814-1412 online © 2011 Informa Healthcare
DOI: 10.3109/15622975.2011.583940

treatments (Lisanby et al. 2000; Sackeim 2000; Lisanby et al. 2003; Kosel et al. 2007; Prudic 2008). Already in 1997, it has been put forward that brain stimulation therapies might improve depression at the cost of further cognitive decline in patients already suffering from cognitive disturbances (Paradiso et al. 1997). The phenomenon of pseudodementia is defined as reversible cognitive impairment occurring in major depression, necessitating antidepressant treatments without cognitive side effects (Bulbena and Berrios 1986; Saez-Fonseca et al. 2007). Impairments in several cognitive domains, including attention, learning and memory, and executive functions have been found in depressed patients (Austin et al. 2001; Porter et al. 2003; Paelecke-Habermann et al. 2005; Krishnan and Nestler 2008). Further studies found evidence for structural and functional abnormalities believed to mediate cognitive symptoms of depression in the prefrontal cortex and hippocampus (Krishnan and Nestler 2008). Moreover, post-mortem and neuroimaging studies converge on suggesting structural and functional deficits in several subcortical regions including thalamus, amygdala, striatum, hypothalamus, and brainstem (Brody et al. 2001; Drevets 2001; Drevets et al. 2001; Nestler and Carlezon 2006). Thus, cognitive disturbances are frequent in patients suffering from depression, stressing the importance of treatments with cognitive safety.

Limited information exists regarding the influence of DBS on cognitive functioning in patients with TRD. Previous studies of DBS in TRD have not revealed any evidence for DBS-associated cognitive decline. For instance, McNeely et al. (2008) found no adverse neuropsychological events in six patients with TRD treated with DBS of Cg25, the subgenual cingulate region (SGR; Brodmann area 25). Some areas of cognition even showed slight improvement following DBS of Cg25, whereas transient motor slowing occurred as well. There are conflicting results regarding neuropsychological impairment, particularly in other studies of DBS in patients with Parkinson's disease (Zahodne et al. 2009) as well as with obsessive compulsive disorder (Greenberg et al. 2006) and Tourette-syndrome (Kuhn et al. 2007). This might be due to a lack of differentiation both in neuropsychological tests used and the target regions stimulated.

Cognitive changes should be comprehensively tested for, as they can occur in a number of specific neuropsychological areas, e.g., planning vs. executive function. Furthermore, individual characteristics of the stimulated target region must also be taken into account when considering potential cognitive changes (Nestler and Carlezon 2006). For instance, (McNeely et al. 2008) cognitive functions tended to increase from below average at baseline to average after 12 months of stimulation of Cg25. Interestingly, changes in cognitive functions did not correlate with improvements in mood as might have been expected, considering that deficits in concentration and memory belong to symptoms of depression (Austin et al. 2001). Similarly, Malone et al. (2009) did not detect any effects in 10 patients with TRD and DBS of the ventral capsule/ventral striatum.

Moreover, factors need to be taken into account, which might contribute to differences in cognitive tests. Studies assessing cognitive effects of DBS of the subthalamic nucleus (STN-DBS) in patients with Parkinson's disease resulted in heterogeneous findings (Parsons et al. 2006a; Zahodne et al. 2009). Advancing age (Morrison et al. 2000; Trepanier et al. 2000; Alegret et al. 2001) and stimulation parameters (Woods et al. 2003) have been identified as factors increasing the risk of postoperative cognitive deterioration, which is at odds with findings of improved cognitive functions as a result of higher stimulation parameters (Francel et al. 2004; Schoenberg et al. 2008). Interestingly, DBS of the hypothalamus with higher stimulation parameters was observed to produce more vivid autobiographical memory as well as to augment verbal learning and memory (Hamani et al. 2008). Another factor potentially contributing to performance on neuropsychological tests is the patients' gender. Sex differences in cognitive functions are frequently discussed (Hyde 1988). Therefore several factors have been found to be associated with cognitive performance and its changes that need to be taken into account.

We report here on the long-term outcome of NAcc-DBS on the neuropsychological profile of 10 patients with TRD. The ventral striatum (including the NAcc), where the stimulation electrode is placed, is ideally located to modulate cognitive processes orchestrated by other brain regions (Schlaepfer et al. 2008b). Specifically, the NAcc receives rich projections from cortical and subcortical regions such as orbital and medial prefrontal cortices, hippocampus, and amygdala (Nauta and Domesick 1984; Nestler and Carlezon 2006; Cohen et al. 2009). The NAcc, in turn, indirectly projects to Cg25, medial prefrontal cortex, amygdala, thalamus, and hypothalamus (Jones and Mogenson 1980; Mogenson et al. 1983; Kelley and Stinus 1984; Cohen et al. 2009). Thus, the NAcc is interconnected with multiple regions centrally involved in cognitive functions. The hippocampus, for instance, is crucial for spatial learning and declarative (explicit) memory (Squire 2004), whereas attention, working memory, and executive functions particularly engage prefrontal regions (Nestler and Carlezon 2006; Wittchen 2006).

The aim of the present study was to explore whether NAcc-DBS in patients with TRD changes

cognitive performance, in particular whether it impairs cognitive functions. In addition, we strived to investigate potential associations between changes in cognitive performance and potential influencing variables including decreases in depressive symptom load and stimulation parameters.

Methods and materials

Informed consent

The institutional review boards of both the Universities of Bonn and Cologne approved the study. Further details have been published previously (Schlaepfer et al. 2008b; Bewernick et al. 2010).

Participants

Ten patients between 32 and 65 years of age were treated with NAcc-DBS (see Table I for demographic data). All patients met criteria for major depressive disorder (MDD), unipolar type, and were in a current episode as diagnosed with the Structured Clinical Interview for DSM-IV-TR (SCID). The minimum 28-item Hamilton Depression Rating Scale ($HDRS_{28}$; Hamilton 1967) score was 21. In all cases, the illness had not responded to standard antidepressant treatments including pharmacotherapy, psychotherapy, and ECT. Last ECT treatment was at least 1 year before baseline assessment. Average time between last ECT and DBS baseline assessment was 40.3 months, ranging from 12 to 108 months. Patients were diagnosed as treatment-resistant according to the Antidepressant Treatment History Form (ATHF) (Sackeim 2001). Further inclusion and exclusion criteria have been published previously (Schlaepfer et al. 2008b; Bewernick et al. 2010). Mean (±SD) length of the current episode amounted to 10.8 (±7.5) years, the number of past medical treatment courses was 20.8 (±8.4), the mean $HDRS_{28}$ was 32.5 (±5.3) (for details see Table I).

Table I. Demographic and clinical characteristics.

Variable	Mean	SD
Age at implant (years)	48.6	11.65
Sex (% female)	40%	
Duration of education (years)	14.4	2.5
Percentage retired due to depression	90%	
Length of current episode (years)	10.79	7.51
Number of previous episodes (lifetime)	1.6*	0.89
Age at onset (years)	31.7	13.23
Time since diagnosis of affective disorder (years)	19.0	9.08
Lengths of previous hospitalizations (months)	19.5	12.39
Number of antidepressant pharmaceuticals at implant	4.3	1.34
Number of past medical treatment courses	20.8	8.35
Number of medications included in formula	14.1	5.63
Mean total of ATHF** score	41.7	15.33
Mean ATHF score and SD	3.2	0.42
Average number of treatment trials with ATHF ≥3	8.3	3.27
Past ECT/MST sessions received	20.8	8.63
Psychotherapy (hours)	316.4	265.25
Number of serious life events (lifetime)	17.6	6.13
Comorbid physical illnesses (%)	30%	
Suicide attempts (% preoperative)	30%	
Social support (% with support)	70%	

*Five patients did not have separate episodes.
**Modified Antidepressant Treatment History Form (ATHF) according to Sackeim (2001).
A score of "3" is the threshold for considering a trial adequate and the patient resistant to that treatment (Sackeim 2001).

Target and surgery

Electrode placement was individually planned using MRIs, as described elsewhere (Sturm et al. 2003). The target structure was the posteroventromedial part of the NAcc. Electrodes were implanted bilaterally in the ventral striatum. Each electrode has four contacts: (1) the shell and (2) the core regions of the NAcc, and (3) the ventral and (4) the medial internal capsule (Schlaepfer et al. 2008b). Electrodes were connected to an implanted neurostimulator. DBS electrode insertion was performed stereotactically; standard Medtronic model 3387 leads were used. This lead has four electrodes over a length of 10.5 mm, each spaced 1.5 mm apart. Intraoperative X-ray was used in order to verify the correct position of both electrodes (Schlaepfer et al. 2008b).

DBS treatment parameters

Initially, stimulation was applied with permanent pulse-train stimulation from 2 to 4 V in steps of 1 V. Pulse width (90 μs), frequency (130 Hz) and electrode settings (contacts 1 and 2 negative against case) were kept constant. Those parameters were chosen because of the experience with neurostimulation for neurological disorders (Deuschl and Bain 2002; Deuschl et al. 2006). Stimulation parameters were kept constant for 4 weeks in order to determine not only acute effects but also changes over longer periods of time, and then adjusted if necessary (e.g., no improvement in $HDRS_{28}$). Bilateral and symmetric changes were performed in the following sequence: amplitude, pulse width, selection of poles and frequency. Parameters ranged from 1.5 to 10.0 V, 100–150 Hz and 60–210 μs. Within the first 6 months after implantation, the two lowest of the four

contact sites of each electrode were set negative against the case (the lowest contact placed in the shell of the NAcc, the other in its core). After approximately half a year a frequent parameter setting was all four contacts negative against the case (case positive, contacts 0, 1, 2, 3 negative for both electrodes).

Psychopharmacotherapy and psychotherapy were kept constant where possible, at least throughout the first 6 months and for most patients during the whole year.

Assessment and study protocol

Neuropsychological assessment with standardized tests was administered to 10 patients before implantation and at 1 year of stimulation. Thirteen cognitive tests were analyzed comparing baseline and 12 months data covering cognitive functions such as learning and memory (verbal and visual-spatial as well as working memory), attention, language, visual perception, and executive functions. Standard neuropsychological tests were clustered according to the Compendium of Neuropsychological Tests and described in detail elsewhere (Spreen 1991).

General cognitive functions were measured by the Mini-Mental State Examination (MMSE) (Folstein 1990). *Attention* was assessed using the d2 attention-burden test (*d2 Aufmerksamkeits-Belastungstest*) analyzing total performance (Brickenkamp 1962). *Learning and memory* tests covering verbal and visual spatial learning and memory as well as working memory were applied. Specifically, the Verbal Learning and Memory Test (VLMT) (Helmstaedter 2001) served as a measure of declarative verbal memory. Total learning over five trials (1–5) was analyzed as well as delayed free recall and recognition (measured 30 min after the learning phase). The Rey Visual Design Learning Test (RVDLT; Rey 1964) was used to measure visual spatial learning and memory. Similar to the VLMT, total learning over five trials (1–5), delayed free recall and recognition were analyzed. Working memory was tested by application of Wechsler Memory Scale including digit and visual memory span (Haerting 2000), calculating total back- and forward. *Language* was assessed by HAWIE lexis tests (*Wortschatztest*) and HAWIE finding similarities (*Gemeinsamkeiten finden*) (Tewes 1991). *Executive functions* were evaluated by the Trail Making Tests (TMT) A and B, the Five-Point Test, and the Stroop test. The TMT consists of two subtests, with time for completion analyzed separately (Reitan 1959). The Five-Point Test examines the capacity for nonverbal fluid and divergent thinking as well as creativity (Regard 1982). Patients are asked to create as many different forms as possible by linking at least two out of five points. The Stroop Color and Word Test consists of three separate trials; the "word" trial requires the subject to rapidly name color words, the "color" trial requires naming of colored rows, and the "color-word" trial requires naming the color in which a word is written while ignoring the actual name of the word (Baeumler 1985). The interference condition analyzed here examines cognitive inhibition of conflicting information. *Visual perception* was measured by the Hooper Visual Organization Test (VOT (Hooper 1958)) examining the ability for visual integration of objects. Patients' task lies in the identification of 30 objects represented in line drawings as puzzle pieces.

Neuropsychological assessment with these tests was administered to patients before implantation (baseline) and at 1, 6 and 12 months of stimulation, analysis was performed comparing performance at baseline and 12 months of stimulation.

Statistical analyses

SPSS statistical software, edition 17.0 for Windows (2008) was used. Significance of change between baseline and 1 year was analyzed via paired *t*-tests for each neuropsychological test as recommended (Okun et al. 2007) in order to evaluate whether surgery and stimulation lead to deterioration from baseline. Stepwise regression analyses were calculated to examine the influence of possible contributing variables on cognitive changes. The influence of several predictor variables on the dependent variable *change score* (score at baseline minus score at 1 year) for each test was investigated. The following predictor variables were included: *reduction of depressive symptoms* (responder and non-responder (50% reduction criterion) in 28-item Hamilton rating scale for depression (also included as continuous variable in calculations)), *stimulation parameters* (median split of average stimulation per day for each patient within the first year of stimulation (multiplication of voltage, frequency and pulse width)), *age* and *gender*. In order to assess the patients' performance relative to a healthy population, *z* scores were calculated based on comparison with published age-corrected normative data. Performance resulting in a *z* score below one standard deviation was interpreted as below average, *z* scores of above one standard deviation as above average. Analyses of Variance (ANOVA) for repeated measures were calculated comparing *z* scores at baseline and 1 year for different clusters of cognitive functions. Different tests measuring the same cognitive function according to the Compendium of Neuropsychological Tests (Spreen 1991) were included in these analyses (see Table II). For all explorative analyses level of significance *P* was set at 0.05. The number of patients analyzed for each test is presented in Table II.

Table II. Scores on neuropsychological tests and significance of change according to different tests.

	Baseline		1 year		Change		*t*-test		Baseline	1 year	Change			
	Mean	SD	Mean	SD	Mean	SD	*t* value	*P*	*z* value	*z* value	Mean	*F* value	*P* value	η^2
General cognitive functions														
MMSE ($n = 10$)	28.40	1.78	29.20	1.14	–0.80	2.20	–1.15	0.28						
Attention												$F_{(1;6)} = 16.84$	$P < .01$	0.737
D2 total minus errors ($n = 7$)	264.29	81.70	308.43	80.50	–44.14	17.70	–6.60	0.001	–2.19	–1.53	+0.66			
Learning and memory												$F_{(1;8)} = 8.97$	$P < .05$	0.529
Verbal learning and memory														
VLMT total learning ($n = 9$)	39.78	12.95	46.00	10.00	–6.22	16.38	–1.14	0.29	–0.76	–0.28	+0.48			
VLMT recall ($n = 9$)	7.22	2.64	9.56	2.30	–2.33	2.83	–2.48	0.038	–1.12	–0.44	+0.68			
VLMT recognition ($n = 9$)	11.89	2.15	13.00	2.24	–1.11	2.15	–1.56	0.16	–0.6	0.08	+0.68			
Visual spatial learning and memory														
RVDLT total learning ($n = 9$)	24.33	8.05	32.00	8.28	–7.67	6.84	–3.36	0.010	–1.8	–0.88	+0.92			
RVDLT recall ($n = 9$)	4.89	1.76	6.67	2.06	–1.78	2.05	–2.60	0.031						
RVDLT recognition ($n = 7$)	12.71	1.25	12.14	1.46	0.57	1.99	0.76	0.48	–0.89	–1.13	–0.24			
Working memory														
Wechsler digit span ($n = 10$)	12.30	1.95	12.40	3.53	–0.10	2.60	–0.12	0.91	–0.63	–0.64	–0.01			
Wechsler visual memory span ($n = 10$)	12.50	3.10	13.20	3.43	–0.70	3.02	–0.73	0.48	–0.92	–0.83	+0.09			
Language												$F_{(1;7)} = 2.47$	$P = .16$	
HAWIE lexis test ($n = 8$)	18.50	4.50	19.50	4.00	–1.00	3.82	–0.74	0.48	–0.03	0.25	+0.28			
HAWIE finding similarities ($n = 8$)	22.25	5.12	25.63	2.50	–3.38	6.02	–1.59	0.16	0	0.66	+0.66			
Executive function												$F_{(1;7)} = 11.67$	$P = .01$	0.625
Five–Point Test ($n = 9$)	16.89	8.95	24.56	9.03	–7.67	7.5	–3.07	0.015	–1.17	–0.24	+0.93			
STROOP interference (in sec; $n = 8$)	167.63	124.89	106.63	31.99	61.00	104.53	1.65	0.14	–0.71	–0.03	+0.68			
TMT A (in s; $n = 10$)	54.70	29.87	47.2	19.85	7.50	23.53	1.01	0.34	–1.23	–0.84	+0.39			
TMT B (in s; $n = 10$)	147.90	86.10	112.80	63.99	35.10	73.11	1.52	0.16	–1.26	–0.47	+0.79			
Visual perception												$F_{(1;8)} = 5.45$	$P < .05$	0.405
VOT ($n = 9$)	18.00	4.50	20.22	3.77	–2.22	2.64	–2.53	0.035	–1.58	–1.16	+0.42			

Mean, Standard deviation (SD), two-tailed paired *t* tests with scores at baseline and at 12 months within each test as dependent variable; z scores at baseline and 1 year comparing our data to published normative data; ANOVAs for repeated measures with the factor time (12 months in comparison to baseline) separate for cognitive functions; MMSE, Mini-Mental-Status Examination; VLMT, Verbal Learning and Memory Test; RVDLT, Rey Visual Design Learning Test; HAWIE, Hamburg Wechsler Intelligence Test for Adults; TMT, Trail Making Test; VOT, Hooper Visual Organization Test.

Results

Means, standard deviations, and results of two-tailed paired *t* tests over raw data as well as *z* scores are presented in Table II. Results of ANOVA for repeated measures calculated over *z* scores including tests measuring the same cognitive function are also presented in Table II as well as in Figure 1. Overall, paired *t*-tests revealed significant changes over time in the direction of improvement in the following cognitive domains: attention (d2), learning and memory (verbal: VLMT delayed free recall; visual spatial: RVDLT learning and delayed free recall), executive functions (Five-Point Test), and visual perception (VOT).

General cognitive functions

MMSE measuring general cognitive functions did not show any sign of impairment in our patients at baseline and 1 year. Paired *t*-tests did not reveal a significant difference between MMSE total at baseline compared to 1 year within our patients (Table II).

Attention

Attention measured by the d2 significantly changed over time (Table II). Patients showed improved scores at 1 year compared to baseline. ANOVA for repeated measures over *z* scores revealed significant differences within the cognitive function attention (Table II). Performance improved over time but remained below average compared to normative data (Figure 1).

Learning and memory

For verbal learning and memory, significant changes were found in the VLMT condition long duration free recall. At 1 year patients recalled more words compared to baseline, improving from below average to average. VLMT total learning and recognition scores improved over time but change was not significant. The *z* scores were average at both time points for total learning and recognition, improving over time (Table II). Within visual spatial learning and memory measured by the RVDLT we also found significant changes. Patients improved between baseline and 1 year in the subtests total learning and delayed free recall. Within the subtest recognition results remained constant. Compared to normative data, performance in recognition decreased slightly from close to below average to below average, and in total learning patients were below average at baseline but improved to average over time. No norms were available for the condition RVDLT recall. Across the sample, verbal and visual spatial learning and memory improved over time (see Table II). Working memory measured by Wechsler digit and visual memory span (WMS) did not change significantly over time and remained average (Table II).

Within learning and memory, ANOVA for repeated measures over *z* scores revealed a significant main effect directing to improvement (Table II). RVDLT recognition was excluded in ANOVA since the sample size was < 8 (in contrast to the other tests included), as well as RVDLT recall because of the lack of available norms. Performance in learning and

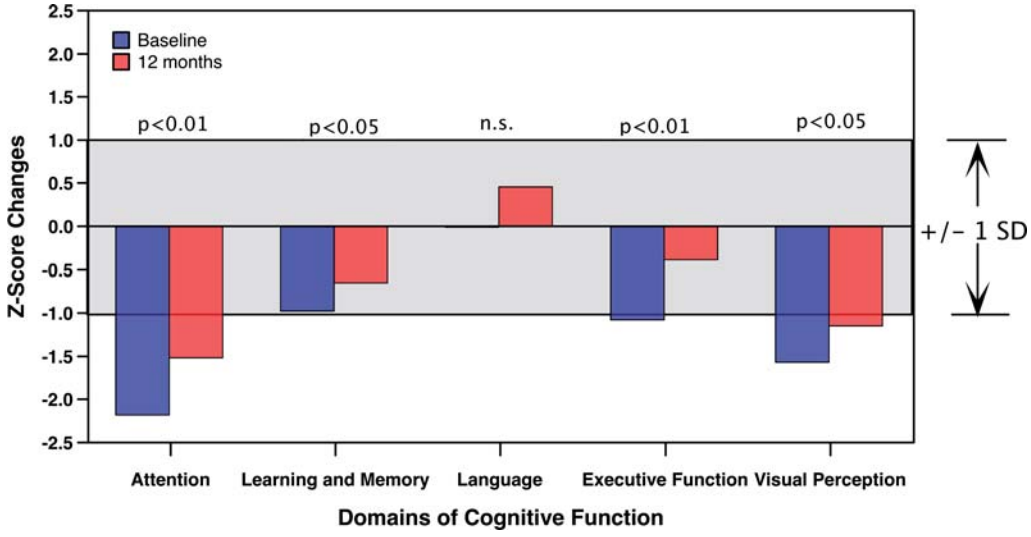

Figure 1. Domains of cognitive function. The graph shows results of ANOVAs for repeated measures (12 months compared to baseline) over z-transformed scores separate for different areas of cognitive functions according to the Compendium of Neuropsychological Tests (Spreen 1991). Neuropsychological tests used are: attention (d2); learning and memory (VLMT (Verbal Learning and Memory Test), RVDLT (Rey Visual Design Learning Test), Wechsler digit and visual memory span); language (HAWIE lexis test and finding similarities); executive function (Five-Point Test, STROOP, Trail Making Test A and B); visual perception (VOT (Hooper Visual Organisation Test)).

memory improved within the average level compared to normative data (Figure 1).

Language

Language measured by HAWIE subtests "lexis test" and "finding similarities" did not change significantly over time (Table II). Within language tests ANOVA for repeated measures over *z* scores did not reveal a significant main effect (Table II). As presented in Figure 1, scores in language tests improved within the average level.

Executive function

Trail Making Tests (TMT) A and B did not show significant differences between baseline and 1 year. However, at a descriptive level, patients showed an improved performance from below average at baseline to average at 1 year within both tests (Table II). Nonverbal fluency according to the Five-Point Test did change significantly over time. Patients showed an improvement from below average to average within the Five-Point Test at 1 year compared to baseline (Table II). Stroop interference did not change significantly over time. However, at a descriptive level again, patients performed better after 1 year of treatment compared to baseline, remaining on an average level.

ANOVA for repeated measures over *z* scores within tests measuring executive function revealed a significant main effect (Table II). Performance improved over time as indicated by the *z* scores. Compared to normative data patients showed scores below average at baseline improving to average at 1 year.

Visual perception

Paired *t*-tests revealed a significant effect within the VOT in our patients. Patients showed improved scores within visual perception measured by the VOT at 1 year compared to baseline but remained below average (Table II). ANOVA for repeated measures over *z* scores did reveal a significant main effect (Table II). Performance improved within the average level compared to normative data (Figure 1).

Stepwise regression analyses

In order to identify factors contributing to performance changes in neuropsychological tests we conducted stepwise regression analyses. The influence of the predictor variables *reduction of depressive symptoms, stimulation parameters, age* and *gender* on the dependant variable *change score* (score at baseline minus score at 1 year) was investigated for each test. With the exception of stimulation parameter, no significant predictor variable for the change score in each neuropsychological test was found. However, stimulation parameter only became significant in the Five-Point Test measuring nonverbal fluency. Stepwise linear regression analyses revealed negative partial regression weights for stimulation parameter (median split) predicting nonverbal fluency ($R^2 = 0.59$; $\beta = -0.80$; $t = -3.54$; $P = 0.009$). Fifty-nine percent of variance was explained through the predictor stimulation parameter. The negative beta weight shows that a higher stimulation parameter is associated with lower change scores and thus with better scores in nonverbal fluency. Therefore, a relatively high stimulation was associated with better performance in nonverbal fluency. Average change scores and standard deviations depending on stimulation parameter in the Five-Point Test are presented in Figure 2. The predictor variable *reduction of depressive symptoms* according to $HDRS_{28}$ became significant neither as a dichotomous variable (responder vs. non-responder) nor as a continuous variable. All in all, positive neuropsychological effects were independent of a reduction of depressive symptoms and stimulation parameters, as well as age and gender.

Discussion

The primary aim of this study was to longitudinally assess cognitive functioning in 10 patients with TRD and NAcc-DBS over a 12-month period. Most

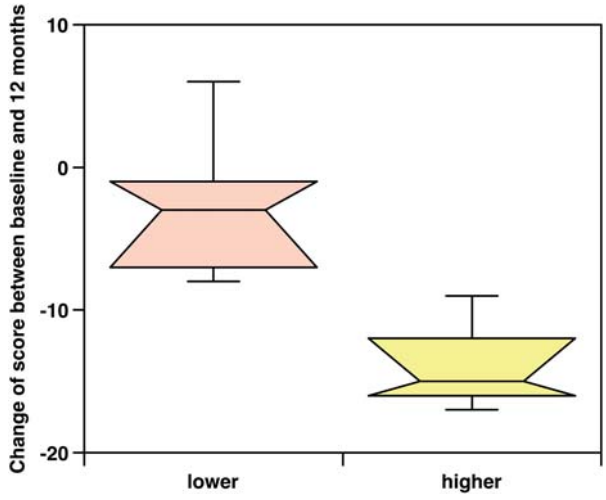

Figure 2. Change score in the Five-Point Test depending on stimulation parameters. Shown are average change scores (baseline minus 12 months) and standard deviations depending on stimulation parameter (higher vs. lower) in the Five-Point Test; with a more negative change score representing higher improvement in the test.

importantly, we found no evidence for significant deterioration in any cognitive test after 1 year of NAcc-DBS compared to baseline, suggesting that there is no acute or chronic cognitive decline following NAcc-DBS. Our results are thus in line with previous reports of absent deleterious effects of DBS of Cg25 or the striatum in TRD patients (McNeely et al. 2008). Ensuring high ethical standards also by examining potential negative side effects from early on with explorative statistical analyses is of great importance to us (Kuhn et al. 2009; Schlaepfer and Bewernick 2009; Schlaepfer and Fins 2010; Synofzyk and Schlaepfer 2010).

Strikingly, our patients even exhibited substantial cognitive improvement after 12 months of NAcc-DBS, an effect, which encompassed the domains of attention, learning and memory, executive functions, and visual perception. Within executive functions, performance improved from below average to average, whereas all other cognitive functions improved within the average or below-average level. We found a general trend towards improvement in cognitive functions from below average to average levels, which resembles the reversal of baseline deficits documented by McNeely et al. (2008) in patients with TRD and Cg25-DBS. The observed change is clinically significant according to the criteria defined by Jacobson (1984). Therefore, in contrast to other brain stimulation treatments such as ECT, which were found to be associated with cognitive deterioration (Lisanby et al. 2000, 2003; Prudic 2008; Sackeim 2000), NAcc-DBS not only resulted in no evidence for cognitive deterioration, but even in an improvement of cognitive functions in our sample. This is remarkable because stepwise regression analyses did not reveal reductions of depression ratings to significantly influence these positive cognitive effects (in analogy to McNeely et al. 2008). Thus, NAcc-DBS appears to affect cognition independent of general symptomatic improvement. This suggests that NAcc-DBS may trigger a cognition-enhancing process independent of its antidepressant effects. Our findings thus lend further support to the idea that cognitive deficits in MDD represent a separate group of symptoms of cortical-subcortical network dysfunctions and are not merely secondary to low mood (Marvel and Paradiso 2004). We therefore speculate that cognitive deficits in MDD might be directly susceptible to NAcc-DBS.

Stimulation parameter was the only variable that predicted test outcome. Specifically, higher stimulation parameters were associated with better performance on a test of executive functions. In contrast to previous studies of patients with Parkinson's disease and STN-DBS (Woods et al. 2003), stimulation parameter was not predictive of cognitive deterioration. Consistent with our findings, Francel et al. (2004) reported higher stimulation parameters to be correlated with better results in problem-solving abilities of patients with Parkinson's disease and STN-DBS. However, further research is needed to further examine this effect. Borders of stimulation intensity are taken very seriously and highest amplitude used is 10 V. "Higher stimulation intensity" in these analyses needs to be understood as higher referring to median split. In contrast to other studies, however, we found no influence of age or gender on neuropsychological changes (Morrison et al. 2000; Trepanier et al. 2000; Alegret et al. 2001; Francel et al. 2004). This result is in line with recent gender research underscoring similar cognitive performance across sexes. Thus, positive neuropsychological effects in our study were independent of a reduction of depressive symptoms and stimulation parameters, as well as age and gender.

The neurobiological mechanisms underlying the putative procognitive effects of NAcc-DBS remain to be elucidated. As stated before, the NAcc is both directly and indirectly connected to multiple brain regions centrally involved in cognitive functioning. Previously published analyses of PET data of seven patients demonstrated the following areas of significant metabolic change: decreases in prefrontal subregions (including the orbital prefrontal cortex, OFC), subgenual cingulate region (SGC), posterior cingulate cortex, thalamus, and caudate nucleus, and an isolated increase in the precentral gyrus (Bewernick et al. 2010). Distributed changes in metabolic activity across cortical and subcortical areas support the idea that NAcc-DBS triggers neuronal activity changes that might be associated with cognitive improvement (Bewernick et al. 2010). Specifically, areas of significant metabolic change encompassed decreases across a widely distributed cortical and subcortical network, a dysfunction of which is thought to be central to the pathophysiology of MDD (Bewernick et al. 2010). Our PET data obtained from seven patients are thus in accordance with our formerly described hypothesis that NAcc-DBS might lead to a decrease of disease-related hypermetabolism by lowering abnormal over-activity in these regions (Schlaepfer et al. 2008b; Bewernick et al. 2010). In contrast to earlier findings (Mayberg et al. 2005; McNeely et al. 2008) there might be decreases in activity instead of increases that are associated with positive cognitive changes. This might in part be due to different targets stimulated. These findings strongly support the idea (Rauch et al. 2006) that cortical-thalamic-striatal-cortical circuitry is modulated by DBS. We note that areas of significant metabolic change in our patient sample are related to several cognitive functions that appear

to benefit from NAcc-DBS: Learning and memory has been found to engage posterior cingulate cortex and caudate nucleus (Graybiel 2005), whereas the OFC is involved in executive functions (Bechara et al. 1994; Kringelbach 2005). In addition, there is evidence for an influence of caudate nucleus (Abdullaev et al. 1998) and precentral gyrus (Hirsch et al. 2001) on language. Attention has been reported to engage the SGC (Liotti and Mayberg 2001; Rolls et al. 2003; Hamani et al. 2008), precentral gyrus (Hirsch et al. 2001), caudate nucleus (Abdullaev et al. 1998), and thalamus (Steriade and Llinas 1988). These widespread cognitive-enhancing effects of NAcc-DBS are compatible with current concepts that specific sets of brain areas are transiently bound together as functional units to enable cognitive functions (Hirsch et al. 2001).

Limitations

Some limitations of our results need to be considered: Until now there is only a small sample size we can report on, although this is also the case for all other studies in this emerging field. Analyses were explorative striving to examine whether there are changes in cognitive performance. A larger sample size will be assessed to further inquire neuropsychological effects as well as possible contributing variables (such as stimulation parameters).

A further difficulty lies in creating the variable stimulation intensity in a way that is the best approach to real stimulation. Stimulation intensity as measured in our analyses is much more realistic than calculations including just amplitude as done in other DBS studies. Thus our complex variable is up to now the best available approach to stimulation intensity. Impedance might be an important factor for future analyses.

Theoretically, a withdrawal of pharmacological treatment would have been preferable. However, such a withdrawal was not feasible, but for most patients medications were held constant. In this context we note that (Paradiso et al. 1997) no effect of chronic medication on psychomotor and cognitive abilities was found. Furthermore, increasing evidence indicates that there is no sedative effect of antidepressant drugs on cognitive functions when patients have been on a chronic medication regimen (Amado 1995; Veldhuijzen et al. 2006).

Another limitation is that we did not include a control group, which raises the question whether the observed cognitive effects could be only due to learning along with repeated test administration. Practice effects could be a potential limitation because neuropsychological tests were applied at several time points within NAcc-DBS treatment. However, there are a few important aspects speaking against this: first, we did not find improvement in all neuropsychological tests, but instead only in certain domains. Benefits from practice should be seen to some degree in every test if repeated testing resulted necessarily in practice effects (Parsons et al. 2006b). Second, the majority of neuropsychological tests did not demonstrate significant practice effects when test-retest interval is of sufficient duration, meaning approximately six months (Dodrill and Troupin 1975; Sarazin 1993; Kaufman 1994; Dikmen et al. 1999; McCaffrey 2000). Thus, we assume that time frames between neuropsychological testing procedures in our study were long enough to render practice effects unlikely. Third, we used alternate forms of tests where available reducing the probability of practice effects (Benedict and Zgaljardic 1998; Dikmen et al. 1999; McCaffrey 2000). Importantly, those tests, which included alternate forms, overlapped with some of the tests (e.g., VLMT) in which cognitive improvement was demonstrated. We also chose tests constructed in a way to minimize practice effects (e.g., avoided measures where novelty is a substantial part of problem-solving tasks) (Dikmen et al. 1999). Furthermore, tests applied in our battery measuring functions such as language, working memory, motor skills, executive functions, and attention were found to have negligible practice effects (Dikmen et al. 1999; Wilson et al. 2000; Sackeim 2001; Sackeim et al. 2001).

Finally, certain participant characteristics have been found to be a factor potentially advancing the incidence of practice effects. According to Dikmen et al. (1999), younger participants (<39 years) and cognitively more able people (as indicated by better baseline performance) tend to benefit more from practice. Thus, in our sample consisting of relatively older patients (see Table I) who had baseline performance below average for most neuropsychological tests, we assume that practice effects did not have confounding effects. The possibility of a contribution of practice effects on improved performance in some neuropsychological tests cannot be ruled out, however, due to the stated reasons we assume that their influence is negligible. It therefore is unlikely that learning effects alone explain our findings.

Conclusion

NAcc-DBS did not lead to cognitive deterioration in 10 patients suffering from TRD. These results provide strong support for the cognitive safety of NAcc-DBS. Moreover, unchanged or even improved performance was found on the majority of neuropsychological tests.

Surprisingly, we found significant improvement in several cognitive domains including attention, learning and memory, visual perception and executive functions. Interestingly enough, significant procognitive effects occurred independently of a reduction of depressive symptoms and changes in stimulation parameters. Thus, NAcc-DBS might have an independent augmenting effect on cognition. The question is whether DBS-targeted neuromodulation to circuits processing cognitive functions could be beneficial in other neuropsychological disorders with marked cognitive dysfunction. Future research is needed to validate the effect in a larger sample size as well as to further investigate the underlying mechanism leading to such an improvement of cognitive functions following NAcc-DBS.

Acknowledgements

We thank patients and their relatives for participating in this study and for their motivation and unfaltering trust.

Statement of Interest

This investigator-initiated study was funded in part (deep brain stimulation device, battery exchange, medical costs, limited support for study nurse) by a Grant of Medtronic, Inc. to Drs Schlaepfer and Sturm. Dr Hurlemann is supported by a Starting Independent Researcher Grant provided by the Ministry of Innovation, Science, Research and Technology of the State of North Rhine-Westphalia (MIWFT). All other authors report no biomedical financial interests or potential conflicts of interest. The sponsor had no influence on design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. The corresponding author (TES) had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

Abdullaev YG, Bechtereva NP, Melnichuk KV. 1998. Neuronal activity of human caudate nucleus and prefrontal cortex in cognitive tasks. Behav Brain Res 97:159–177.

Alegret M, Junque C, Valldeoriola F, Vendrell P, Pilleri M, Rumia J, Tolosa E. 2001. Effects of bilateral subthalamic stimulation on cognitive function in Parkinson disease. Arch Neurol 58: 1223–1227.

Amado I. 1995. [Cognitive effects of chronic antidepressant treatment]. Encephale 21(Spec No 1):15–18.

Austin MP, Mitchell P, Goodwin GM. 2001. Cognitive deficits in depression: possible implications for functional neuropathology. Br J Psychiatry 178:200–206.

Baeumler G. 1985. Farbe-Wort-Interferenztest (FWIT) nach J.R. Stroop. Goettingen: Hogrefe.

Bechara A, Damasio AR, Damasio H, Anderson SW. 1994. Insensitivity to future consequences following damage to human prefrontal cortex. Cognition 50:7–15.

Benedict RH, Zgaljardic DJ. 1998. Practice effects during repeated administrations of memory tests with and without alternate forms. J Clin Exp Neuropsychol 20:339–352.

Berton O, Nestler E. 2006. New approaches to antidepressant drug discovery: beyond monoamines. Nat Rev Neurosci 7:137–151.

Bewernick BH, Hurlemann R, Matusch A, Kayser S, Grubert C, Hadrysiewicz B, et al. 2010. Nucleus accumbens deep brain stimulation decreases ratings of depression and anxiety in treatment-resistant depression. Biol Psychiatry 67:110–116.

Brickenkamp R. 1962. Test d2. Aufmerksamkeits-Belastungs-Test. Goettingen: Hogrefe.

Brody AL, Barsom MW, Bota RG, Saxena S. 2001. Prefrontal-subcortical and limbic circuit mediation of major depressive disorder. Semin Clin Neuropsychiatry 6:102–112.

Bulbena A, Berrios GE. 1986. Pseudodementia: facts and figures. Br J Psychiatry 148:87–94.

Cohen MX, Axmacher N, Lenartz D, Elger CE, Sturm V, Schlaepfer TE. 2009. Good vibrations: cross-frequency coupling in the human nucleus accumbens during reward processing. J Cogn Neurosci 21:875–889.

Deuschl G, Bain P. 2002. Deep brain stimulation for tremor [correction of trauma]: patient selection and evaluation. Mov Disord 17(Suppl 3):S102–111.

Deuschl G, Schade-Brittinger C, Krack P, Volkmann J, Schafer H, Botzel K, et al. 2006. A randomized trial of deep-brain stimulation for Parkinson's disease. New Engl J Med 355:896–908.

Dikmen SS, Heaton RK, Grant I, Temkin NR. 1999. Test-retest reliability and practice effects of expanded Halstead-Reitan Neuropsychological Test Battery. J Int Neuropsychol Soc 5: 346–356.

Dodrill CB, Troupin AS. 1975. Effects of repeated administrations of a comprehensive neuropsychological battery among chronic epileptics. J Nerv Ment Dis 161:185–190.

Drevets WC. 2001. Neuroimaging and neuropathological studies of depression: implications for the cognitive-emotional features of mood disorders. Curr Opin Neurobiol 11:240–249.

Drevets WC, Gautier C, Price JC, Kupfer DJ, Kinahan PE, Grace AA, et al. 2001. Amphetamine-induced dopamine release in human ventral striatum correlates with euphoria. Biol Psychiatry 49:81–96.

Fava M. 2003. Diagnosis and definition of treatment-resistant depression. Biol Psychiatry 53:649–659.

Folstein MF, Folstein SE, McHugh PR. 1990. MMST. Mini-Mental-Status-Test. Weinheim: Beltz.

Francel P, Ryder K, Wetmore J, Stevens A, Bharucha K, Beatty WW, Scott J. 2004. Deep brain stimulation for Parkinson's disease: association between stimulation parameters and cognitive performance. Stereotact Funct Neurosurg 82:191–193.

Graybiel AM. 2005. The basal ganglia: learning new tricks and loving it. Curr Opin Neurobiol 15:638–644.

Greenberg BD, Malone DA, Friehs GM, Rezai AR, Kubu CS, Malloy PF, et al. 2006. Three-year outcomes in deep brain stimulation for highly resistant obsessive-compulsive disorder. Neuropsychopharmacology 31:2384–2393.

Haerting C, Markowitsch HJ, Neufeld H, Calabrese P, Deisinger K, Kessler J. 2000. WMS-R. Wechsler Gedächtnistest – Revidierte Fassung. [Deutsche Adaptation der revidierten Fassung der Wechsler Memory Scale]. Bern: Huber.

Hamani C, McAndrews MP, Cohn M, Oh M, Zumsteg D, Shapiro CM, et al. 2008. Memory enhancement induced by hypothalamic/fornix deep brain stimulation. Ann Neurol 63:119–123.

Hamilton M. 1967. Development of a rating scale for primary depressive illness. Br J Soc Clin Psychol 6:278–296.
Helmstaedter C, Lendt M, Lux S. 2001. VLMT. Verbaler Lern- und Merkfähigkeitstest. Goettingen: Beltz.
Hirsch J, Moreno DR, Kim KH. 2001. Interconnected large–scale systems for three fundamental cognitive tasks revealed by functional MRI. J Cogn Neurosci 13:389–405.
Hooper HE. 1958. The Hooper Visual Organization Test. Beverly Hills, CA: Western Psychological Services.
Hyde JSL. 1988. Gender differences in verbal ability: a meta-analysis. Washington, DC: National Science Foundation.
Jacobson NS, Follette WC, Revenstorf D. 1984. Psychotherapy outcome research: Methods for reporting variability and evaluating clinical significance. Behav Ther 15:336–352.
Jones DL, Mogenson GJ. 1980. Nucleus accumbens to globus pallidus GABA projection: electrophysiological and iontophoretic investigations. Brain Res 188:93–105.
Kaufman AS. 1994. Encyclopedia of human intelligence. In: Sternberg RJ, editor. Encyclopedia of human intelligence. Vol 2. New York: Macmillan Publishing Company. p 828–833.
Kelley AE, Stinus L. 1984. The distribution of the projection from the parataenial nucleus of the thalamus to the nucleus accumbens in the rat: an autoradiographic study. Exp Brain Res 54:499–512.
Kosel M, Sturm V, Frick C, Lenartz D, Zeidler D, Brodesser D, Schlaepfer TE. 2007. Mood improvement after deep brain stimulation of the internal globus pallidus for tardive dyskinesia in a patient suffering from major depression. J Psychiatr Res 41:801–803.
Kringelbach ML. 2005. The human orbitofrontal cortex: linking reward to hedonic experience. Nat Rev Neurosci 6:691–702.
Krishnan V, Nestler EJ. 2008. The molecular neurobiology of depression. Nature 455:894–902.
Kuhn J, Gaebel W, Klosterkoetter J, Woopen C. 2009. Deep brain stimulation as a new therapeutic approach in therapy-resistant mental disorders: ethical aspects of investigational treatment. Eur Arch Psychiatry Clin Neurosci 259(Suppl 2):S135–141.
Kuhn J, Lenartz D, Mai JK, Huff W, Lee SH, Koulousakis A, et al. 2007. Deep brain stimulation of the nucleus accumbens and the internal capsule in therapeutically refractory Tourette-syndrome. J Neurol 254:963–965.
Liotti M, Mayberg HS. 2001. The role of functional neuroimaging in the neuropsychology of depression. J Clin Exp Neuropsychol 23:121–136.
Lisanby SH, Maddox JH, Prudic J, Devanand DP, Sackeim HA. 2000. The effects of electroconvulsive therapy on memory of autobiographical and public events. Arch Gen Psychiatry 57: 581–590.
Lisanby SH, Moscrip T, Morales O, Luber B, Schroeder C, Sackeim HA. 2003. Neurophysiological characterization of magnetic seizure therapy (MST) in non-human primates. Suppl Clin Neurophysiol 56:81–99.
Lozano AM, Mayberg HS, Giacobbe P, Hamani C, Craddock RC, Kennedy SH. 2008. Subcallosal cingulate gyrus deep brain stimulation for treatment-resistant depression. Biol Psychiatry 64:461–467.
Malone DA Jr, Dougherty DD, Rezai AR, Carpenter LL, Friehs GM, Eskandar EN, et al. 2009. Deep brain stimulation of the ventral capsule/ventral striatum for treatment-resistant depression. Biol Psychiatry 65:267–275.
Marvel CL, Paradiso S. 2004. Cognitive and neurological impairment in mood disorders. Psychiatr Clin North Am 27:19–36, vii–viii.
Mayberg HS, Lozano AM, Voon V, McNeely HE, Seminowicz D, Hamani C, et al. 2005. Deep brain stimulation for treatment-resistant depression. Neuron 45:651–660.
McCaffrey RJ, Duff K, Westervelt HJ. 2000. Practitioner's guide to evaluating change with intellectual assessment instruments. New York: Kluwer Academic/Plenum Press.
McNeely HE, Mayberg HS, Lozano AM, Kennedy SH. 2008. Neuropsychological impact of Cg25 deep brain stimulation for treatment-resistant depression: preliminary results over 12 months. J Nerv Ment Dis 196:405–410.
Mogenson GJ, Swanson LW, Wu M. 1983. Neural projections from nucleus accumbens to globus pallidus, substantia innominata, and lateral preoptic-lateral hypothalamic area: an anatomical and electrophysiological investigation in the rat. J Neurosci 3:189–202.
Morrison CE, Borod JC, Brin MF, Raskin SA, Germano IM, Weisz DJ, Olanow CW. 2000. A program for neuropsychological investigation of deep brain stimulation (PNIDBS) in movement disorder patients: development, feasibility, and preliminary data. Neuropsychiatry Neuropsychol Behav Neurol 13:204–219.
Nauta WJ, Domesick VB. 1984. Afferent and efferent relationships of the basal ganglia. Ciba Found Symp 107:3–29.
Nestler EJ, Carlezon WA Jr. 2006. The mesolimbic dopamine reward circuit in depression. Biol Psychiatry 59:1151–1159.
Okun MS, Rodriguez RL, Mikos A, Miller K, Kellison I, Kirsch-Darrow L, et al. 2007. Deep brain stimulation and the role of the neuropsychologist. Clin Neuropsychol 21:162–189.
Paelecke-Habermann Y, Pohl J, Leplow B. 2005. Attention and executive functions in remitted major depression patients. J Affect Disord 89:125–135.
Paradiso S, Lamberty GJ, Garvey MJ, Robinson RG. 1997. Cognitive impairment in the euthymic phase of chronic unipolar depression. J Nerv Ment Dis 185:748–754.
Parsons TD, Rogers SA, Braaten AJ, Woods SP, Troster AI. 2006a. Cognitive sequelae of subthalamic nucleus deep brain stimulation in Parkinson's disease: a meta-analysis. Lancet Neurol 5:578–588.
Parsons TD, Tucker KA, Hall CD, Robertson WT, Eron JJ, Fried MW, Robertson KR. 2006b. Neurocognitive functioning and HAART in HIV and hepatitis C virus co-infection. AIDS 20:1591–1595.
Porter RJ, Gallagher P, Thompson JM, Young AH. 2003. Neurocognitive impairment in drug-free patients with major depressive disorder. Br J Psychiatry 182:214–220.
Prudic J. 2008. Strategies to minimize cognitive side effects with ECT: aspects of ECT technique. J ECT 24:46–51.
Rauch SL, Dougherty DD, Malone D, Rezai A, Friehs G, Fischman AJ, et al. 2006. A functional neuroimaging investigation of deep brain stimulation in patients with obsessive-compulsive disorder. J Neurosurg 104:558–565.
Regard M, Strauss, E., Knapp, P. 1982. Der Fuenf-Punkt Test. Zuerich: UniversitaetsSpital, Neurologische Klinik.
Reitan RM. 1959. Trail Making Test. Indianapolis, IN: Indiana University Medical Center.
Rey A. 1964. L'Examen Clinique en Psychologie. Paris: Presse Universitaire de France.
Rolls ET, Inoue K, Browning A. 2003. Activity of primate subgenual cingulate cortex neurons is related to sleep. J Neurophysiol 90:134–142.
Sackeim HA. 2000. Memory and ECT: from polarization to reconciliation. J ECT 16:87–96.
Sackeim HA. 2001. The definition and meaning of treatment-resistant depression. J Clin Psychiatry 62(Suppl 16):10–17.
Sackeim HA, Keilp JG, Rush AJ, George MS, Marangell LB, Dormer JS, et al. 2001. The effects of vagus nerve stimulation on cognitive performance in patients with treatment-resistant depression. Neuropsychiatry Neuropsychol Behav Neurol 14:53–62.

Saez-Fonseca JA, Lee L, Walker Z. 2007. Long-term outcome of depressive pseudodementia in the elderly. J Affect Disord 101: 123–129.

Sarazin FF, Morrison L, Foss N, Cameron DW. 1993. Practice effects on memory measures in repeated neurocognitive assessments: methodological issues.In: First National Conference on Human Retroviruses and Related Infections. Washington DC. 188 pp.

Schlaepfer TE, Bewernick B. 2009. Deep brain stimulation for psychiatric disorders-state of the art. Adv Tech Standards Neurosurg 34:37–57.

Schlaepfer TE, Fins J. 2010. Deep brain stimulation and the neuroethics of responsible publishing: when one is not enough. J Am Med Assoc 303:775–776.

Schlaepfer TE, Lieb K. 2005. Deep brain stimulation for treatment of refractory depression. Lancet 366:1420–1422.

Schlaepfer T, Frick C, Zobel A, Maier W, Heuse I, Bajbouj M, et al. 2008a. Vagus nerve stimulation for depression: efficacy and safety in a European study. Psychol Med 38:651–662.

Schlaepfer TE, Cohen MX, Frick C, Kosel M, Brodesser D, Axmacher N, et al. 2008b. Deep brain stimulation to reward circuitry alleviates anhedonia in refractory major depression. Neuropsychopharmacology 33:368–377.

Schlaepfer TE, George MS, Mayberg H. 2010. WFSBP Guidelines on Brain Stimulation Treatments in Psychiatry. World J Biol Psychiatry 11:2–18.

Schoenberg MR, Mash KM, Bharucha KJ, Francel PC, Scott JG. 2008. Deep brain stimulation parameters associated with neuropsychological changes in subthalamic nucleus stimulation for refractory Parkinson's disease. Stereotact Funct Neurosurg 86:337–344.

Spreen OS. 1991. A compendium of neuropsychological tests. New York: Oxford University Press.

Squire LR. 2004. Memory systems of the brain: a brief history and current perspective. Neurobiol Learn Mem 82:171–177.

Steriade M, Llinas RR. 1988. The functional states of the thalamus and the associated neuronal interplay. Physiol Rev 68:649–742.

Sturm V, Lenartz D, Koulousakis A, Treuer H, Herholz K, Klein JC, Klosterkotter J. 2003. The nucleus accumbens: a target for deep brain stimulation in obsessive-compulsive- and anxiety-disorders. J Chem Neuroanat 26:293–299.

Synofzyk M, Schlaepfer T. 2011. Electrodes in the brain – ethical criteria for research and treatment with deep brain stimulation for neuropsychiatric disorders. Brain Stimul 4:7–16.

Tewes U. 1991. HAWIE-R. Hamburg-Wechsler Intelligenztest fuer Erwachsene. Revision 1991. Bern: Huber.

Trepanier LL, Kumar R, Lozano AM, Lang AE, Saint-Cyr JA. 2000. Neuropsychological outcome of GPi pallidotomy and GPi or STN deep brain stimulation in Parkinson's disease. Brain Cogn 42:324–347.

Veldhuijzen DS, van Wijck AJ, Verster JC, Kenemans JL, Kalkman CJ, Olivier B, Volkerts ER. 2006. Acute and subchronic effects of amitriptyline 25mg on actual driving in chronic neuropathic pain patients. J Psychopharmacol 20:782–788.

Wilson BA, Watson PC, Baddeley AD, Emslie H, Evans JJ. 2000. Improvement or simply practice? The effects of twenty repeated assessments on people with and without brain injury. J Int Neuropsychol Soc 6:469–479.

Wittchen H-UH. 2006. Klinische Psychologie und Psychotherapie. Heidelberg: Springer Medizin Verlag.

Woods SP, Fields JA, Lyons KE, Pahwa R, Troster AI. 2003. Pulse width is associated with cognitive decline after thalamic stimulation for essential tremor. Parkinsonism Relat Disord 9:295–300.

Zahodne L, Okun M, Foote K, Fernandez H, Rodriguez R, Wu S, et al. 2009. Greater improvement in quality of life following unilateral deep brain stimulation surgery in the globus pallidus as compared to the subthalamic nucleus. J Neurol 256:1321–1329.