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Deep brain stimulation to the medial forebrain bundle for depression- long-term outcomes and a novel data analysis strategy

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ABSTRACT

Background: Deep brain stimulation (DBS) of the supero-lateral branch of the medial forebrain bundle (slMFB) in treatment-resistant depression (TRD) is associated with acute antidepressant effects.
Objective: Long-term clinical effects including changes in quality of life, side effects and cognition as well as long-term data covering four years are assessed.
Methods: Eight TRD patients were treated with DBS bilateral to the slMFB. Primary outcome measure was a 50% reduction in Montgomery-Åsberg Depression Rating Scale (MADRS) (response) and remission (MADRS <10) at 12 months compared to baseline. Secondary measures were anxiety, general functioning, quality of life, safety and cognition assessed for 4 years. Data is reported as conventional endpoint-analysis and as area under the curve (AUC) timeline analysis.
Results: Six of eight patients (75%) were responders at 12 months, four patients reached remission. Long-term results revealed a stable effect up to four years. Antidepressant efficacy was also reflected in the global assessment of functioning. Main side effect was strabismus at higher stimulation currents. No change in cognition was identified. AUC analysis revealed a significant reduction in depression for 7/8 patients in most months.
Conclusions: Long-term results of slMFB-DBS suggest acute and sustained antidepressant effect; timeline analysis may be an alternative method reflecting patient's overall gain throughout the study. Being able to induce a rapid and robust antidepressant effect even in a small, sample of TRD patients without significant psychiatric comorbidity, render the slMFB an attractive target for future studies.

1. Introduction

About 30% of patients suffering from major depressive disorder (MDD) fail to respond to established pharmacological, psychotherapeutic or somatic treatments [1] and are then classified as having a treatment-resistant depression (TRD). Deep brain stimulation (DBS) at different brain targets is currently under research as a possible treatment option for TRD. In small pilot studies, antidepressant effects of DBS at the subgenual cingulate gyrus (Cg_{25}) [2–4], the anterior limb of the capsula interna (ALIC) [5,6] and the nucleus accumbens (Nacc) [7,8] are described. A significant response, defined as a reduction of symptoms over 50%, was reached in about 50% of the patients after 12 months of DBS treatment [6,9–13]. First larger clinical trials including a placebo phase stimulating ALIC [14] or Cg_{25} [15] failed to prove efficacy underlining the importance of a careful analysis of pilot studies to optimize the study design in randomized-controlled studies (for a detailed comment see Ref. [16]). Recently, DBS at the supero-lateral branch of the medial forebrain bundle (slMFB) was presented as a new DBS target. A more rapid antidepressant response in seven patients of the present sample with a response rate of 85% after three months DBS was obtained in an interim analysis [17] (for a detailed description of mode of action see Refs. [18–20]). Long-term data on this target are lacking.

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Traditionally, data in depression studies on patients that are not resistant to treatment is reported at predefined study end points, mostly six to twelve weeks, due to the assumed latency of clinical response to pharmacotherapy [21]. In the TRD population, different ways of data analysis are suggested [22,23]. Patients suffering from TRD cannot be cured –in the sense of a stable absence of symptoms-within short intervals and response to any treatment approach varies during the process of the study. Assessing at fixed, somewhat arbitrarily chosen end points might be misleading [23] and cannot convey all information about the impact of the treatment [24]. From the patient's as well as from the clinician's perspective, the benefit from a treatment is the degree of improvement over time. Therefore, we have analyzed our 12 months data both in the conventional way as well as in a timeline analysis. Timeline analyses are standard in other fields such as endocrinology [25], cardiology [26] and diabetes research [27]. A symptom reduction of 50% from baseline is conventionally used as response criterion. We propose a larger differentiation of this arbitrarily chosen criterion for the population of TRD (see Refs. [10,28], for a detailed discussion of the response criterion, [29]).

In this study, antidepressant effects of DBS to the slMFB for up to four years are described. Anxiety, social functioning, quality of life, safety and cognition are reported at fixed time points and with timeline data analysis.

2. Materials and methods

2.1. Patients

Three-month follow-up data of seven patients have recently been published [30]. One further patient has been included in this study because we had a raise in funding, he received the same protocol; so eight patients received slMFB DBS for 48 months. All patients suffered at baseline from severe treatment-resistant depression according to DSM-IV [SCID-I & II] [31]. One bipolar patient was included in this study (last manic episode occurred 23 years ago). Three raters analyzed clinical records. Inclusion criteria were a minimum score of 21 on the 24-item Hamilton Depression Rating Scale ($HDRS_{24}$) [32] and a score below 45 in the global assessment of functioning (GAF) [33] ((see 30 for inclusion criteria)). Common screening failures were comorbid psychiatric disorders, severe personality disorders or surgical contradictions. Drug treatment was kept constant for at least six weeks before and after surgery. The ATHF score [34] for the current depressive episode was 3 defining a treatment-resistance for the current antidepressant treatments for all patients. A score of "3" is the threshold for considering a trial adequate and the patient resistant to that treatment [34] (see Table 1).

The Institutional Review Board (IRB) of the University of Bonn approved this study; the study protocol has been registered @ http://Clinicaltrials.gov with the identifier NCT01095263. Adherence to inclusion criteria as stated in the protocol was reviewed by an external psychiatrist who is experienced in TRD. Informed consent was obtained from all patients.

2.2. Assessment and study protocol

Psychiatric assessments were conducted weekly for the first 12 weeks after treatment onset [30], then every four weeks up to 12 months (primary study endpoint). After 12 months, patients were assessed at minimum once in three months up to four years (endpoint of study extension).

Table 1
Demographic characteristics.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Mean	SD
Age at implant (years)	32	39	41	55	48	30	53	37	41.9	8.70
Sex	Female	Female	Male	Male	Female	Male	Male	Male	3 Female, 5 Male	
Duration of education (years)	13	13	16	9	13	13	13	10	12,5	2.14
Diagnosis	MDD	MDD	MDD	MDD	MDD	MDD	BD	MDD	7 MDD, 1 BD	
Working status	Parttime 75%	Unable to work	Retired due to MDD	Retired due to MDD	Retired due to MD D	Unable to work	Retired due to BD	Retired due to MDD	87.5% Retired	
Years in current episode	4	17	6	10	2	5	9	4	7,1	4.48
Number of previous episodes(lifetime)	2	2	1	1	2	2	6	2	2,3	1.58
Age at onset (years)	27	22	35	45	40	23	18	28	29,8	9.41
Time since diagnosis of affective disorder (Yyears)	5	16	6	10	8	7	35	8	11,9	9.93
Lengths of previous hospitalizations (months)	12	11	38	5	13	8	10	13	13,8	10.17
Number of antidepressive pharmaceuticals at implant	3	7	8	0	0	1	9	1	3,6	3.78
Number of medications in current episode	18	30	26	17	19	20	12	8	18,8	7.03
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Mean	SD
Number of medications (lifetime)	18	30	26	17	19	20	23	13	20,8	5.39
Total of ATHF score (current episode)	55	83	82	56	62	63	54	65	65,0	11.51
ATHF score (current episode)	3	3	3	3	3	3	3	3	3,0	0
Number of treatment trials (lifetime) with ATHF $\geq$ 3	10	17	20	13	13	14	11	6	13,0	4.28
Past ECT/MST	16, 12 unilat.	6	51, 43 unilat.	8 unilat.	13, 6 unilat.	5 unilat.	12 unilat.	38, 24 unilat.	14,5 (bilateral 8.25)	13.05 (bilateral 4.19)
Psychotherapy (hours)	60	117	>60	35	>50	65	>100	>80	70.875	26.87
Psychotherapy at baseline	yes	yes	no	yes	no	yes	no	no	50%	
Suicide attempts	0	3	2	0	0	0	2	0	0.9	1.17

Note. Mean, Standard division (SD). 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. MDD, major depression disorder; BP, bipolar disorder; ECT, electroconvulsive therapy; MST, magnetic seizure therapy.