

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.

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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 (Cg₂₅) [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 Cg₂₅ [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 sIMFB 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 sIMFB 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 (HDRS₂₄) [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	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 ≥ 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.

The **primary outcome measure** was the response on the Montgomery-Åsberg Depression Rating Scale (MADRS) [35] after 12 months of DBS stimulation (study endpoint). A 50% reduction of depressive symptom severity in MADRS was classified as a “clear response”, a 25% reduction as “partial response” and a 75% reduction as “strong response”, while a MADRS score below 10 was classified as remission according to conventions in depression studies [24]. We used different rating scales for the inclusion and the treatment outcome in order to prevent a rating bias from inclusion for the evaluation of therapeutic effect.

Secondary outcome measures included the 28-item Hamilton Depression Rating Scale (HDRS₂₈) [32], Beck Depression Inventory (BDI) [36], Hamilton anxiety scale (HAMA) [37], the short-form of health survey questionnaire (SF-36) [38], evaluating a patient's subjective change in quality of life, and global assessment of functioning (GAF) [33]. The list of positive activities consists of a list of 280 pleasant activities [39]. Before inclusion, the score of the modified antidepressant treatment history form (ATHF) [34] was computed. A score of “3” is the threshold for considering a trial adequate and the patient resistant to that treatment. Safety of the treatment method was documented in a standardized way to the Food and Drug Administration definitions [40]. The Compendium of Neuropsychological Tests [41] was used to assess the level of performance in the following cognitive domains: learning and memory, language, attention, visual perception, and executive function.

2.3. Surgical and stimulation procedure

Bilateral DBS electrodes were implanted using deterministic diffusion tensor imaging (DTI) [42,43]. For more details see supplementary material.

2.4. Data analysis

Baseline scores of outcome measures are reported as monthly scores from baseline up to 12 months of DBS (primary study endpoint). As the study had been extended up to four years, MADRS score was analyzed up to 4 years with visits every three months.

All scales were analyzed with ANOVA for repeated measures and the factor time. Post-hoc paired comparisons were calculated for each time point compared to baseline in an intention to treat analysis. Missing values were interpolated. The level of significance was set at 5%.

Changes in cognitive performance between baseline and one year were analyzed via paired *t* tests for dependent samples for each neuropsychological test.

To analyze the proportion of depression (measured with MADRS) in relation to time, area under the curve (AUC) was calculated individually using the trapezoid method, e.g. an approximation of an area under a set of adjoining straight line segments [44]. Baseline AUC was compared with mean AUC during 12 months DBS with ANOVA. For long-term effects, mean AUC per year were compared to mean baseline for the measure MADRS.

3. Results

3.1. Demographic and clinical characteristics

Eight patients between 30 and 55 years of age with a current depressive episode of 7.1 ± 4.48 years were included in this study (see Table 1 for demographic and clinical details). All patients were diagnosed having severe TRD with an ATHF score of 3 in the current episode. A score of “3” is the threshold for considering a trial adequate and the patient resistant to that treatment. Before DBS implantation, patients were treated with 18.8 ± 7.03 antidepressant

medications, had received ECT and psychotherapy without response.

3.2. Outcome variables

3.2.1. Response at primary study endpoint (month 12)

After 12 months of DBS, six of eight patients (75%) were classified as clear responders (>50% reduction in MADRS, $n = 3$) or strong responders (>75% reduction in MADRS, $n = 3$), for the whole sample MADRS 30 ± 7.39 at baseline and 10.5 ± 10.39 at one year. Four of these responders met the remission criterion (MADRS ≤ 10). Two patients were non-responders at month 12, one of them had reached response criterion (50%) for four months, the other patient had never achieved response (see Table 2). Cognition remained unchanged (see Table 1 supplementary material).

3.2.2. Response during the course of study (each month)

MADRS Scores were significantly reduced for each month compared to baseline regarding group mean (ANOVA for repeated measures and the factor time including post hoc tests) (see Fig. 1 and Table 2).

In order to assess the course of depression through the entire follow-up, AUC analysis was performed with MADRS (see supplementary material, Tables 2 and 3). Comparing MADRS baseline AUC (29.7, SD 7) with mean AUC during 12 months of DBS (11 SD 8) revealed a significant difference in depression in the ANOVA group analysis ($F_{18} = ; df = 12$) as well as for the comparison of each month vs. baseline. Furthermore, improvements in the HDRS, BDI and HAMA and SF-36 mental health were measured between baseline and the monthly visits (Table 2). Significant decreases in depression and anxiety ratings at each month compared to baseline values were demonstrated (Table 2). Quality of life (SF-36, subscore mental health) and positive activities were improved only on a descriptive level, physical health remained at baseline level. Level of functioning (GAF mean) changed from 41 (serious impairment) to 73 (no more than slight impairment).

In addition, individual data on MADRS, HDRS, BDI, SF-36 and GAF are presented in the supplementary materials for each quarter of a year during long-term follow-up.

Most common adverse events were oculomotor effects (blurred vision, and double vision) that could be stopped by parameter changes, especially by adjusting the stimulation amplitude (see Table 3). The oculomotor side-effects limited the raise in amplitude at the lowest contact. Some patients adjusted to a small strabism after several hours when the amplitude was raised at the lowest contact, but most patients' stimulation settings were optimized without transient strabism. One patient (# 5) suffered from a small intracranial bleeding during surgery (serious adverse event) that resolved after seven hours without complications (see Table 3 for adverse events during the 12 months) and another surgery was scheduled for the patient. No negative effect on cognition was assessed, no hypomania was detected.

Two patients stopped DBS treatment: Patient #5: stim off in month 18, in agreement with the PI, DBS was stopped, because the patient had not shown a response to the treatment. After discontinuation of DBS, the MADRS score dropped (MADRS:26 at DBS stop; MADRS 32 post treatment 2 years later), but did not exceed baseline level. Patient #7 was explanted in month 27 according to the patient's wish, without giving a reasonable explanation for his decision and against advice, because he was a stable remitter at this time (MADRS score 3), surprisingly he remained remitter after one year post treatment; , see online supplementary material: study flow chart, Fig. 1) but included in the statistical analysis as carried-forward.

Table 2
Clinical data per month of study.

		Inclusion	month 1	month 2	month 3	month 4	month 5	month 6	month 7	month 8	month 9	month 10	month 11	month 12
		mean (SD)	mean (SD)	mean (SD)	mean (SD)	mean (SD)	mean (SD)	mean (SD)	mean (SD)	mean (SD)	mean (SD)	mean (SD)	mean (SD)	mean (SD)
		main effect (p value)	p value											
MADRS	group	30 (7.39)	11.75 (8.71)	11.63 (10.64)	11 (9)	14.38 (9.16)	13.5 (8.19)	11.38 (7.95)	11.5 (9.29)	10.63 (10.77)	11.25 (9.53)	11.25 (9.27)	10.63 (9.41)	10.5 (10.39)
	F = 13.4 df = 12	p < 0.001	p=0.001	p=0.001	p=0.001	p < 0.005	p < 0.005	p=0.001	p < 0.005	p < 0.005	p=0.001	p=0.001	p=0.001	p < 0.005
HDRS28	group	28.13 (4.67)	11.88 (6.88)	13.5 (8.72)	13.88 (7.92)	14.5 (8.57)	12.88 (7.59)	12.25 (7.36)	11.38 (8.77)	11.25 (8.84)	11.63 (8.48)	11.63 (8.26)	10.5 (8.98)	10.25 (8.14)
	F = 13.4 df = 12	p < 0.001	p < 0.001	p < 0.005	p=0.001	p=0.005	p < 0.005	p=0.001						
BDI	group	28.13 (11.83)	19.88 (12.05)	17 (9.87)	18.88 (9.19)	20.5 (8.11)	20.38 (9.78)	18.25 (9.77)	17.13 (10.4)	16.5 (10.31)	16.5 (9.61)	17.38 (10.2)	18.25 (10.55)	17.63 (10.88)
	F = 3.4 df = 12	p < 0.05	p < 0.05	p < 0.005	p < 0.05									
HAMA	group	15.3 (6.7)	4.5 (2.88)	5.63 (3.16)	6.38 (2.13)	9.25 (2.82)	6.5 (2.98)	6.13 (4.22)	6.25 (5.39)	5.38 (5.13)	6.38 (3.25)	5.63 (3.5)	4.75 (3.38)	6 (3.89)
	F = 6 df = 12	p < 0.005	p < 0.005	p < 0.005	p < 0.001	p < 0.05	p < 0.05	p < 0.05	p < 0.05	p=0.005	p=0.005	p < 0.05	p < 0.01	p < 0.05
SF-36 Mental Health	group	19.25 (8.18)	26.72 (9.63)	29.36 (10.44)	28.38 (12.03)	25.21 (6.36)	26.19 (9.21)	26.35 (9.71)	30.54 (11.47)	26.75 (10.63)	26.16 (9.53)	28.93 (11.57)	29.06 (11.88)	28.09 (12.04)
	F = 1.4 df = 12	p = 0.261	p < 0.05	p < 0.005	p < 0.05	p=0.005	p=0.73	p < 0.05	p < 0.005	p = 0.097	p = 0.142	p=0.005	p=0.01	p < 0.05
SF-36 Physical Health	group	44.54 (9.26)	47.37 (8.76)	45.99 (6.16)	47.75 (7.45)	47.21 (10.43)	47.78 (7.89)	49 (7.41)	49.19 (9.1)	46.92 (10.91)	48.34 (7.83)	49.19 (7.54)	45.57 (14.01)	47.46 (9.23)
	F = 0.43 df = 12	p = 0.699	p = 0.271	p = 0.431	p = 0.119	p = 0.349	p = 0.246	p=0.1	p = 0.067	p = 0.691	p = 0.393	p = 0.147	p = 0.677	p = 0.084
Positive Activities	group	53.4 (28.63)	56.57 (29.02)	63.57 (42.08)	59 (23.97)	62.43 (31.43)	75.14 (37.29)	69.29 (33.49)	73 (36.13)	70.14 (40.09)	71.43 (39.63)	72.71 (32.3)	73 (35.6)	79.14 (41.45)
	F = 2.352 df = 12	p=0.1	p=0.5	p = 0.154	p = 0.383	p = 0.382	p=0.052	p < 0.05	p = 0.124	p=0.08	p = 0.415	p = 0.081	p=0.054	p < 0.05
GAF	group	4.13 (0.99)	6.5 (1.07)	6.63 (1.06)	6.63 (1.19)	6 (0.53)	6.63 (1.19)	6.75 (1.04)	7 (1.2)	7 (1.2)	6.63 (0.92)	6.88 (1.25)	7 (1.07)	7.25 (1.28)
	F = 10 df = 12	p < 0.001	p < 0.005	p=0.001	p=0.001	p=0.001	p=0.001	p < 0.005	p=0.001	p=0.001	p < 0.005	p < 0.005	p=0.001	p=0.001

Note. ANOVA for repeated measures (factor time) with simple contrasts versus baseline. For the main effect Greenhouse-Geisser corrected values were used.

During the observation period of one year, three patients received changes to their medication (see Table 3).

3.3. Stimulation parameters

See supplementary material.

4. Discussion

4.1. Antidepressant efficacy - conventional analysis

Long-term antidepressant effects following bilateral supero-lateral branch of the medial forebrain bundle (slMFB)-DBS in patients suffering from severe TRD have been demonstrated in this study. 75% of the patients responded to the slMFB-DBS at twelve months. There was a significant reduction in depression score in each month compared to the baseline in all depression scales (see Ref. [45] for a meta-analysis of the correlation of different measures of depression in long-term studies). The antidepressant effect developed in line with an augmentation of quality of life and social functioning. No serious side effects related to the DBS stimulation were observed; the frequently occurring strabismus could be counteracted by stimulation parameter change. There was no hypomania or impulsivity as signs of overstimulation. Cognition remained unchanged after 12 months compared to baseline. The speed of response [30] and the proportion of responders is at least comparable to the antidepressant effect reported in most other DBS targets (Cg25, ALIC, NAcc), referring to a percentage of responders

between 21% and 62.5% at 12 months [2–10,12,13,46,47]. This study demonstrated a large statistical effect (with a high statistical power) over a long follow-up period in small, highly selected samples without comorbidity, which is typical for pilot DBS studies. These results could probably render slMFB an attractive target for further research on DBS in treatment-resistant depression and lead to larger placebo-controlled trials. In a first independent replication, an antidepressant effect has been demonstrated in an interim analysis in three out of four patients after one week and in two out of three patients after 26 weeks [48].

Although patients responded in most months clinically to DBS, depression severity ratings of less than 50% reduction from baseline severity occurred: one patient suffered from an acute worsening of depression after he had suddenly stopped the antidepressant medication in the second month following DB stimulation [30], another patient, who had met the response criteria in month three suffered from a considerably worsening of symptoms twice (in the fourth and seventh months) due to family matters. However, in months 10 and 11 this patient again met the response criterion. A third patient suffered from an aggravation of depression at month 10 due to work matters. These results also put into question taking a fixed time point analysis and the actual response criterion of 50% as meaningful markers for efficacy (see below).

4.2. Limitations and placebo effects

Limitations of the study were the absence of a control group and the lack of a placebo phase. We did not implement a control group

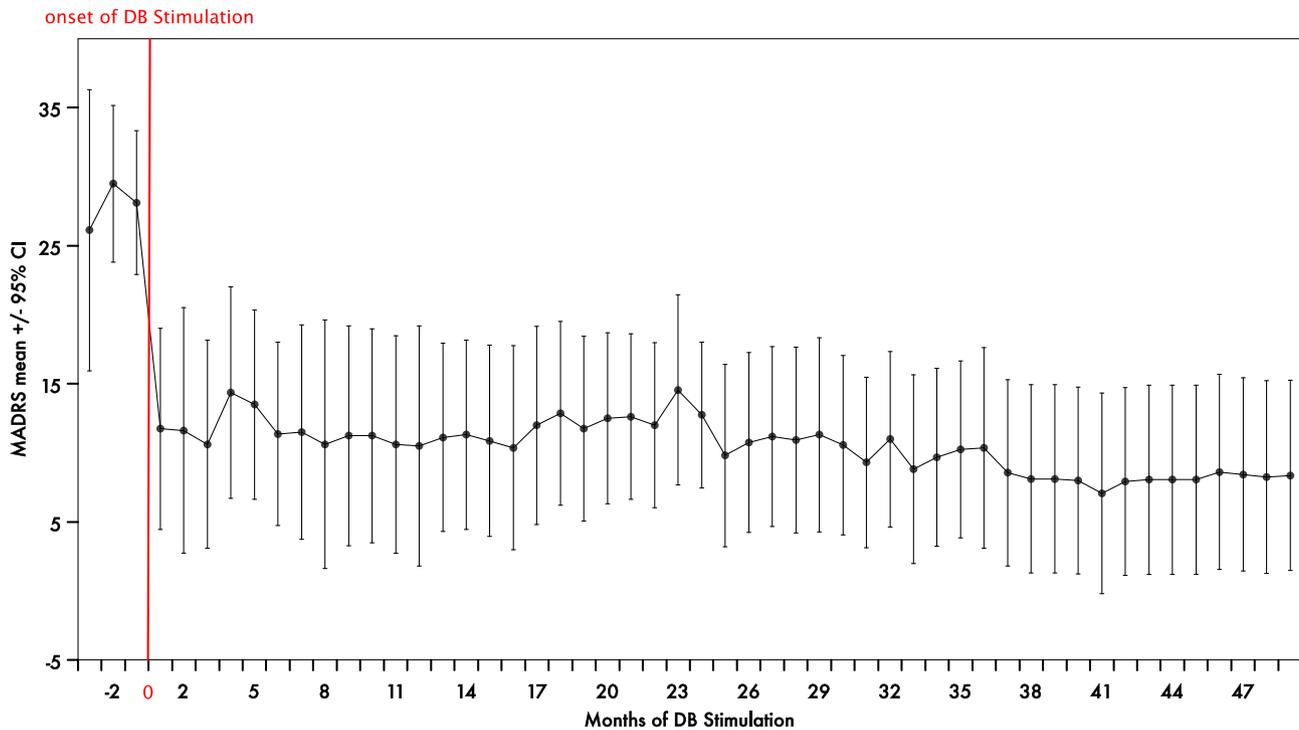


Fig. 1. Clinical outcome (MADRS group mean and contingency interval (95% CI) over time.

Table 3
Adverse events and medication change.

	Patients	Number of Events
Serious Adverse Events		
Intracranial bleeding	1	1
Adverse Events		
Aconuresis ^{d)}	1	1
Blurred vision ^{a)}	5	21
Circulation problems (low blood pressure) ^{a)}	1	5
Contact malfunction ^{c)}	1	1
Dizziness ^{a)}	4	8
Dysarthria ^{b)}	1	1
Dyskinesia ^{a)}	1	4
Headache ^{d)}	6	11
Hypertension ^{b)}	1	1
Hypothyroidism ^{d)}	1	3
Increased sweating ^{a)}	2	1
Infection at IPG ^{b)}	2	2
Intraocular pressure ^{a)}	2	5
Internal unrest ^{a)}	1	4
Partial hemiparesis ^{b)}	1	1
Scalp itching ^{d)}	1	1
Vision/eye movement disorder ^{a)}	8	59
Medication change		
Medication change	2	2
Medication stop	1	1

Note. a) associated with stimulation/parameter change; b) Surgery related, successfully treated with antibiotics; c) device malfunction; d) not related to the study. Adverse events and serious adverse events up to primary study endpoint (12 months).

For the first patient zopiclone was stopped at week 24 and quetiapine was stopped at week 38, because of improvement in depression. For the second patient zopiclone was stopped at week 12, mianserine at week 25, and agomelatine was reduced from 50 to 25 mg at week 46, again because of improvement of depression symptoms. One patient was not compliant to medication and stopped all medications in month two.

missing adequate other treatment options because patients were non-responders to all conventional treatments according to the inclusion criteria. In addition, a meaningful placebo phase can be

planned only after a careful analysis of pilot data (see discussion below).

Placebo effects are very unlikely for the following reasons: First, this group of patients had never had a treatment effect before although many therapeutic approaches including ECT have been attempted. Second, in the patient group of severe, recurrent depression and patients with long depressive episodes, placebo effects are very unlikely [49,50]. Third, during long-term follow-up, in one patient, unforeseen and unknown battery depletion occurred. Within a week, this patient had a relapse with most of the symptoms known from baseline. Only after three months, this patient regained response status. Fourth, to our knowledge, there are no studies reporting a stable placebo response over a period of four years. Nonetheless, placebo effects were discussed as one possible explanation of the lack of group differences in the recent RCT [14]. The authors point out many other explanations (choice of endpoints, insufficient stimulation parameters optimization phase, lack of assessment of individually stimulated fiber pathways, etc), thus, placebo effects would be a too shortsighted explanation of the results.

Before larger RCTs are performed and lacking a direct comparison of targets (same surgeon, same enrollment criteria, randomized to two or 3 surgical target options), comparisons about the efficacy of the targets currently under research seem premature.

4.3. Antidepressant efficacy- a new perspective on response

DBS studies include severely ill, treatment-resistant patients. Since remission (e.g. a patient not fulfilling ICD-10 criteria for major depression anymore or a HAMD_17 score below 7) is not often achievable in these patients, a symptom reduction of 50% is arbitrarily chosen as response criterion for this group of treatment-resistant patients [10,24]. Furthermore, relapse (defined as a new depressive episode within six months after remission) [21] is often used in DBS studies in the sense of “losing the 50% response status”.

This nomenclature is misleading and the response-criterion is arbitrary and may need revision. In addition, predefined study end points after several weeks as known from pharmacological studies may not grasp the antidepressant impact of long-term chronic DBS in this group of patients [21]. We therefore propose meaningful ways of data analysis and a differentiation of the 50% response criteria for DBS-TRD studies.

4.4. Timeline analysis- a different approach to efficacy assessment in DBS-TRD studies

In order to reflect the antidepressant effect over time, we suggest an area under the curve (AUC) analysis [23,46]. This conveys information about the antidepressant effect throughout the entire time of treatment and corresponds to the patient's perspective, evaluating the subjective profit from a study not at a given end point, but each day throughout the course of the study. Here, a significant antidepressant effect in 7/8 patients for most months in the study could be revealed by AUC analysis and a significant antidepressant effect comparing mean baseline AUC with mean stimulation was observed on the group level for each month of the study. Only one patient, clinically a clear non-responder, did not have a relevant reduction in AUC throughout the study (patient #5). Long-term AUC data showed a significant reduction of depression up to four years in this study.

4.5. Differentiation of the response criterion in DBS-TRD studies

A symptom reduction of 50% is an arbitrary cut-off and does not reflect the benefit from a therapy for a treatment-resistant patient [10,24,28]. Other DBS researchers also suggested a weaker criterion for this population of TRD patients taking into account that many patients respond between 40% and 50% [10]. We propose more differentiation of response such as “partial response” (25%), clear response (50%) and strong response (75%) for several reasons: For patients suffering from treatment-resistant forms of a disease, a smaller effect than a 50% reduction of symptoms, might nonetheless be associated with a substantial gain in quality of life. Additionally, stopping a treatment at partial response only or switching to another experimental treatment method is associated with the risk of losing even the small benefit of partial response. In this study, one patient (patient #4) did not achieve response of 50% at month 12. According to the endpoint analysis this patient was classified as “non-responder”, but reached the response criterion in four months during the first year. The patient also had a meaningful reduction of symptoms (partial response) in several other months and did not wish to terminate treatment after the end of this study. In this case, a careful risk-benefit analysis was performed and treatment continued. A stronger differentiation of the response criterion also allows the identification of different types of responders.

4.6. Course of the disease in TRD and assessments

Patients suffering from severe treatment-resistant depression have few fluctuations in the chronic course of the disease. Nonetheless, sudden changes in symptom severity can occur and are – in the contrary to mild depression – often unrelated to life events [51]. In the present study, patients classified as responders to DBS showed a tendency to more fluctuations with DBS and have a vulnerability to life events (e.g. a relapse after discontinuation of medication, worsening of symptoms due to family matters and business affairs). Thus, even though DBS did not lead to stable remission in all patients, the course of the illness was changed concerning severity and fluctuations [51]. In order to observe the

individual course of the illness under treatment as usual (TAU), it might be useful to follow patients several months before DBS initiation.

The impact of social support during recovery is critical for the long-term response to DBS [52]. To the patient and his social environment to adapt to the (sudden) antidepressant response, it is advisable to initiate psychotherapy [53] and include caregivers at baseline and throughout the study. This would allow assessing the interaction between social environment, pharmacological treatment and DBS.

DBS will likely be a lifetime treatment when extrapolating from the treatment of movement disorders. Today, long-term data on antidepressant effects are available only for 1–5 years at maximum [6,9–12]. It is well known that 20%–80% patients suffering from treatment-resistant depression suffer from relapse within five years after response to conventional treatments and in spite of maintenance treatments [1,13,24,54]. It is therefore necessary to evaluate long-term effects in order to assess the risk-benefit ratios for DBS.

4.7. Pilot studies and placebo controlled designs

The failure of two large placebo-controlled trials stimulating ALIC [14] and Cg25 [15], after positive results in small pilot studies has led to a large skepticism regarding the interpretation of results from uncontrolled pilot studies.

In the following, we argue in favor of open-label pilot studies when first-time evaluating new DBS targets, before placebo-controlled large trials are launched in a second step: as in other DBS studies, a neuroanatomical hypothesis is the starting point: here, the sIMFB has been evaluated first-time as a target for DBS. The selection of this target was based on a neuroanatomical and functional hypothesis using new fiber tracking techniques [43,55]: two opposing systems, the anterior thalamic radiation (ATR) and the superolateral branch of the medial forebrain bundle (sIMFB) were anatomically described and assumed to mediate negative (ATR) and positive (sIMFB) emotions [43,55], but this brain area had never been stimulated before. At this stage of research, small pilot studies are crucial for a general feasibility of DBS at a chosen target (e.g. possibility to surgically reach this target etc.). Pilot data also give many information that allows to plan larger studies more adequately, e.g. what are optimal stimulation parameters, are there predictors of response, is there a typical time course of response [56], what are expected side effects for the risk-benefit analysis, what scales allow best interpretation of response (e.g. discussion about quality of life in addition to depression rating scales in Ref. [57]), when and how long should a placebo phase be implemented in the design what is the expected effect size for the power analysis, what are relevant design characteristics in relation to an insertion effect or a placebo response. Furthermore, a highly selected small sample, followed by the same scientists prevents interrater or center effects (as discussed in 14) and minimizes confounding variables (psychiatric comorbidity etc.).

The “failure” of the two large trials [14,15] has demonstrated that these aspects need to be evaluated carefully to prevent study failures, patient discouragement and, not to forget, financial investment failures which can easily lead to a premature ending of a very promising therapeutic strategy.

5. Conclusions

The sIMFB appears to be a promising target for DBS in TRD. The strong antidepressant effect was sustained up to four years with few side effects and could be detected in a small sample. Traditionally, placebo-controlled comparison-group trials are the gold

standard in clinical studies. For TRD-DBS, a high-risk interventional treatment for chronically ill patients, study designs have to be carefully balanced with ethical criteria, especially in the light of the failure of the two large placebo-controlled trials stimulating ALIC [14] and Cg25 [15]. Possibly, an initial staggered onset phase could be a meaningful alternative to the traditional comparison-group design. In small DBS studies with patients suffering from treatment-resistant severe depression, conventional response criteria (remission, 50% symptom reduction, a single predefined study end point) might not reflect the gain from treatments regarding antidepressant effect over time. Timeline analysis (e.g. AUC) and a stronger differentiation of the response criterion may better interpret the treatment effect of DBS. To grasp the benefit for the patient in terms of a cost-benefit analysis, the individual course of the disease before DBS and long-term data (>5 years) are helpful. Currently, a sham-controlled study (n = 16) with a staggered onset design is under way which was designed on the basis of this pilot study as well as a replication by an independent group [48].

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.brs.2017.01.581>.

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