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Acute antidepressant effects of deep brain stimulation – Review and data from slMFB-stimulation

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ABSTRACT

Background: Acute effects of deep brain stimulation (DBS) have not been assessed systematically lacking valid instruments. In this study, a clinical tool for the assessment of acute antidepressant effects was developed and the predictive value of acute effects for long-term outcome was evaluated.
Methods: Acute effects were assessed with the depression acute effects scale (DACS), a questionnaire developed by our group: core items from depression rating scales were rated on a 10 point Likert scale by seven patients before and after test stimulation. The sum score of intra-operative changes in DACS was correlated with the reduction in MADRS score at three months to evaluate the association between acute and long-term effects.
Results: An acute amelioration in symptoms of depression was reported during intra-operative test stimulation. There was no significant correlation between intra-operative acute effects and long-term antidepressant response.
Conclusions: Acute changes in symptoms of depression can be measured with DACS. To assess the predictive value of acute effects for long-term outcome a larger sample is needed. The systematic assessment of acute antidepressant effects can help to optimize stimulation parameters in DBS studies. The predictive value of key symptoms of depression for the response to a treatment and for individually shaped treatment relies on assessment tools for acute effects in depression. Because of the high interest of this topic, we provide a comprehensive review of the literature on acute effects of DBS for depression.

Introduction

Depression is an episodic disorder and lifetime treatment concepts are evolving [1]. The time course of antidepressant response (e.g. early response versus late response) and its putative predictive value for long-term response might be helpful for the optimization of therapeutic strategies [2]. Knowing the predictive value of the treatment course or of singular symptoms, would allow a more individually shaped therapy.

An antidepressant response within hours is termed "acute response" if a response occurs within the first four weeks of treatment, it is coined "early response", after four weeks [3], "late response" in line with traditional designs of pharmacological studies [4]. Between 12 weeks up to 12 months, "long-term response" takes place, and afterwards "chronic response" (see Fig. 1).

In search of neurobiological, neuropsychological and clinical predictors of response [5], the onset of treatment effect has been explored as a factor [4,6,7]. It is a commonplace that there is a considerable variability in the onset of the treatment effect between patients. Researchers are pointing to the fact that an "early response" [3] might predict long-term response [2,4,8]. From the perspectives of clinicians and patients, it would be highly desirable to detect an early antidepressant response, because pharmacological treatment could be adapted more quickly. Methods to detect a response as early as possible will clearly influence the design of future studies.

An acute response, within hours, has been described in studies on sleep deprivation [9–11], transcranial magnetic stimulation (TMS) [6,12] or intravenous ketamine application [13–16]. Response to electroconvulsive therapy (ECT) is usually seen within the first week of a treatment course, this is considerably earlier than in pharmacological treatment [17]. It might be worthwhile to systematically assess the relationship of early response with long-term outcome.

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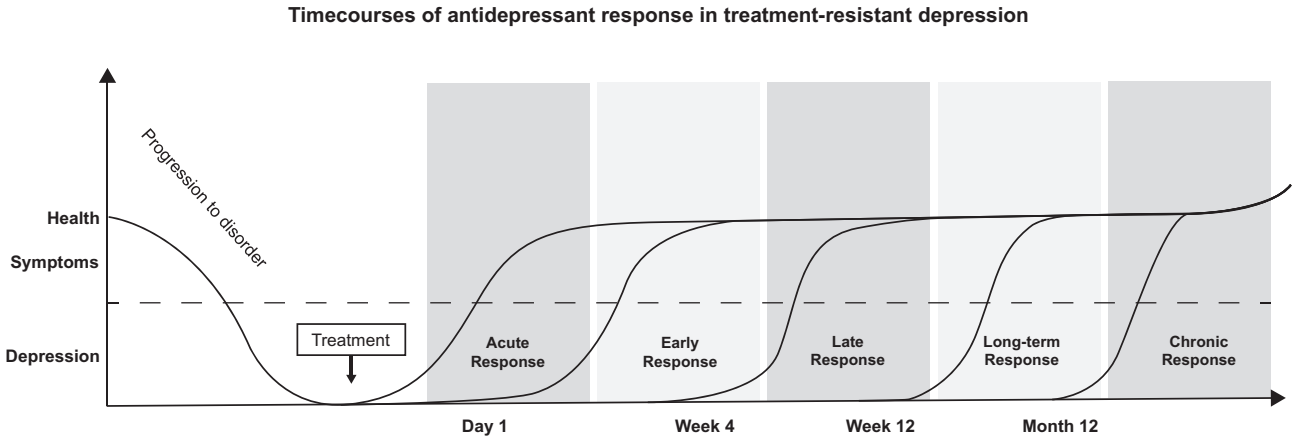

Fig. 1. (draft). Time courses of antidepressant response in treatment-resistant depression. Note. Patients in DBS studies on treatment-resistant depression have many years in severe depression or several depressive episodes. Time courses of antidepressant response vary between different DBS targets. DBS to the slMFB was actually associated with the fastest response.

Deep brain stimulation is currently under research for the treatment of severe, otherwise treatment-resistant depression and bipolar disorder [18–23] at several brain target sites. DBS to the supero-lateral branch of the medial forebrain bundle (slMFB) has been under research by our group leading to rapid and chronic antidepressant effects [24,25] effects. DBS studies with small sample sizes, describe acute antidepressant effects in single patients within minutes during test stimulation in the operating room or shortly after surgery without stimulation [18,19,26].

Acute antidepressant effects of DBS-immediately after the onset of stimulation- include more spontaneous initiation of adequate conversation, mood improvement, increased alertness and relaxation, an increase in motivation, higher level of activity and experiencing of calmness. Acute negative reactions are tension, dizziness and increased level of anxiety [18,19,26]. Only a subset of patients experienced acute effects [27,28] and preliminary data put into question whether acute effects are predictive of a long-term outcome [18,22,29]. It has been described that initial acute effects during surgery decrease after reinitiating the stimulation [19]. Patients who experience acute effects have high expectations regarding the efficacy of DBS and often feel disappointed when symptoms of depression reoccur. In this case, it is difficult to explain to patients that the lack of acute effects after parameter change might not be predictive of long-term outcomes. So far, acute effects in DBS research are described as anecdotes and have not been assessed systematically.

The mode of action of antidepressant therapies is far from being understood completely. Obviously, different therapeutic interventions induce an antidepressant effect by recruiting different neural pathways. Long-term effects seem to be associated with changes in widespread neuronal networks [17]. A modulation of glutamatergic neurotransmission has been proposed to contribute to the acute antidepressant response to sleep deprivation and after ketamine infusion [6]. In addition, clock genes have been implicated in the acute effect after sleep deprivation [6]. DBS seems to provide a more precise point of action to a depression network, but widespread changes of brain metabolism in brain areas distant of the stimulation site are also reported [18,20]. It is unclear, whether acute and long-term antidepressant effects are mediated by the same mechanism of action.

Changes in symptoms of depression within weeks (early and late response) are reported most often in widely accepted rating scales such as the Hamilton depression rating scale (HRSD) [30] or the Montgomery Åsberg Depression Rating Scale (MADRS) [31]. The most frequently used self-rating instrument is the Beck Depression Inventory (BDI) [32]. For the research field of antidepressant acute effects (within hours), valid instruments are lacking. Studies mostly use rating scales that have not been developed to measure this short period of time (e.g. HRSD, MADRS, and BDI). Mood state questionnaires e.g. the profile of mood states, [33] adjective lists (e.g. PANAS [34]) are another option to measure acute changes in mood, however, they are not specific for depression and lack normative data for depressed population or measure only one dimension of depression (e.g. anhedonia, SHAPS) [35]. The POMS for example requires assessing 65 adjectives such as “tense”, “friendly” in five grades from “not at all” to “extreme” which are then grouped to six scales.

Technically, visual analogue scales ((VAS) e.g. [36,37]) and Likert scales seem to be valid and easy methods to quantify acute mood changes. Visual analogue scales are widely used in depression research, but major differences in the selection of dimensions between studies and the lack of normative data do not allow comparison between studies. Interview-based Likert-scales are often favored tools to obtain intensity ratings when the patient is unable to fill in a questionnaire (e.g. during surgery, during MRI experiments). The average internal consistency reliability across all areas is approximately 0.66, while the average test–retest reliability is 0.82 independently of the number of scale points [38]. Parker and Roy [39] have developed a six item self-report measure for assessing antidepressant response on a daily (short-term) basis. A six-factor structure has led to the constructs of “depression”, “irritability”, “brooding”, “poor concentration”, “insomnia” and “anxiety”. Scores of these factors were associated with overall depression severity as assessed by the HRSD. This demonstrates that short questionnaires can be in principle a useful tool assessing antidepressant efficacy.

Aims of the present study were, [1] to construct a tool for measuring acute effects during slMFB-DBS test stimulation in the surgery room and [2] to assess whether acute effects are predictive for long-term outcome. For this purpose, we compiled a questionnaire based on Likert scales for a standardized measurement of acute effects in depression, which is also suitable for DBS and other studies where the patient is unable to write. For an external validation, results of the questionnaire were compared with the analysis of video recordings. Acute effects were then compared to the late response after three months.

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Material and methods

Depression acute-effects scale (DACS)

Core items from HDRS [30] and MADRS [31] were selected. Items were chosen regarding the potential of reflecting acute changes: depressed mood, sadness, anhedonia, drive, anxiety and rumination. Higher values reflect the negative dimension of each item (e.g. more depressive symptoms) to avoid patients‘ mistakes in answers.

The applicable constructs (“depressive mood”, “anxiety”, “brooding”) from the six items self-report scale of Parker and Roy [39], having demonstrated high factor loading, were included. The selected six items were rated on a 10-point Likert scale by 7 severely depressed patients undergoing deep brain stimulation surgery (see 25 for demographic details).

Before intra-operative test stimulation, patients were asked about their actual state (baseline). Test stimulation was performed for five minutes for each hemisphere after electrode placing. After test stimulation, patients were asked about their actual state (left side, right side intra-operative stimulation). Patient’s behavioral expression during baseline and test stimulation was recorded on video. Acute effects were analyzed as changes from baseline. Item wise as well as global acute effect analysis (sum of all items for both left and right stimulation in comparison to baseline) were performed. Hemisphere effects were also assessed.

Intraoperative video recording

Four independent raters blinded for the condition analyzed intraoperative video recordings of the patients. On an 11-point Likert scale, raters determined the patient’s emotional expression (maximum negative to maximum positive). One minute video recording was assessed for baseline (before stimulation), left side and right side stimulation (last minute of standardized five minutes test stimulation). Interrater reliability was assessed with Cronbach’s alpha and intra-class correlation (ICC).

DACS ratings were compared to video ratings with non-parametric correlation analysis (Spearman’s rho).

Prediction of acute effects for long-term effects

Acute effects (sum of intra-operative acute effect in DACS) were compared with reduction in MADRS_raw score at 3 months with correlation analysis (Spearman’s rho).

The level of significance was set at 5% for all analyses.

Results

Self-reported intra-operative stimulation effect (DACS)

All patients ($n = 7$) reported changes of depression symptoms (measured with DACS) during intra-operative test stimulation (see Fig. 2 comparing global acute stimulation effect vs. baseline for each patient and Table 1 comparing the effect on specific symptoms). Fig. 2 demonstrated, that every patient reported a reduction in depressive symptoms as mean intra-operative stimulation effect. Patient #5, who was the only non-responder at three months chronic stimulation, reported the smallest acute effect.

Fig. 3 demonstrates an example of baseline, left and right test stimulation in an item wise analysis in patient #6.

Fig. 4 demonstrates item wise acute effects (DACS) individually for all seven patients. Individual differences were seen between individual items and hemispheres, but global effect in all patients was a reduction of DACS score reflecting an acute reduction of depressive symptoms. Especially “rumination” and “anxiety” were reduced.

In addition to the DACS scores, patients also spontaneously developed ideas about what to do after discharge from hospital and had the impression to be able to enjoy pleasant things more.

Comparison of patient’s reports (DACS) with video-ratings

Interrater reliability of the four raters was good (Cronbach’s alpha 0.859, intra-class-correlation 0.843). There was no significant correlation between mean video-ratings and mean stimulation effect as assessed with DACS (Spearman’s rho 0.14, n.s.).

Prediction of patient’s reports (DACS) for long-term antidepressant response (MADRS)

There was no significant correlation between intra-operative acute effects (DACS) and long-term antidepressant response (reduction in MADRS_raw at 3 months), see Table 2.

Discussion

Measuring acute effects

We detected acute changes in symptoms during DBS test stimulation with the Depression Acute Effects Scale (DACS). Lacking other standardized measures of acute antidepressant effects, the DACS was compared to ratings of the patients’ emotional facial expression, which have been assessed with videotapes. Although the acute effects seen on the videos were rated as similar by all blinded raters (high interrater correlation), the relationship between ratings of facial expressions on videotapes and DACS was not strong enough to show statistical significance. This is probably due to the small sample size and needs to be replicated with larger samples and limits current information about the validity of the scale. Another reason could be the difference in the quality of the videos (the orientation of the face was not always directly to the camera) and the lack of changes in the patients’ emotional expressions. It is well known that patients suffering from depression show a reduction in emotional expressivity [40] and being in the surgery room might lead to flattened emotional facial expressions. In a follow-up study, the depression acute effects scale (DACS) is used together with an optimized video system and different antidepressant treatments in order to validate the DACS on a larger sample.

Intra-operative acute effects

Subjective reports of acute effects have been assessed systematically during DBS surgery for depression. As much as patient’s symptoms of depression differ, as much acute effects reported by the patients varied. In sum (mean operation stimulation effect), patients reported an amelioration of depression during test stimulation. As patients reported changes in all items of the DACS, the selection of items seems helpful for the assessment of individual acute effects. Further studies are needed to assess psychometric properties of the questionnaire (e.g. value of each item for the acute effect). In DBS for neurological diseases (e.g. Parkinson’s disease, essential tremor), the onset of the response varies for different symptoms. DBS changes tremor instantaneously, rigor is improved within minutes and bradykinesia is changed after several minutes. Such a clear temporal pattern of response is improbable

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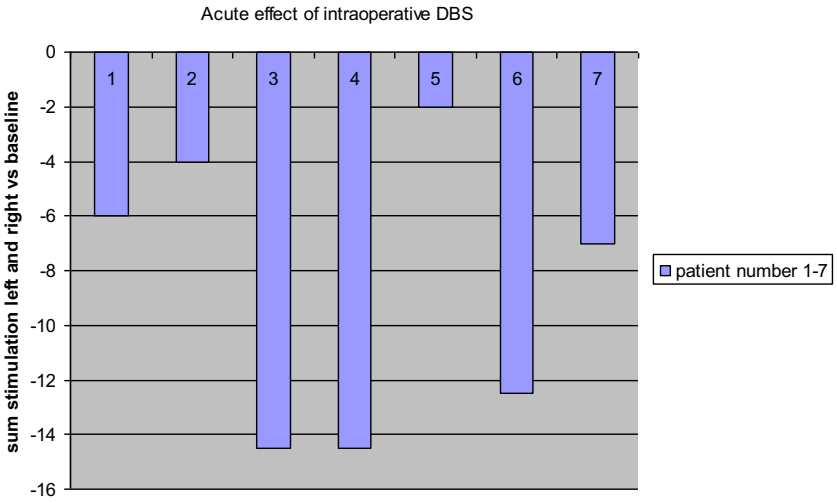

Fig. 2. Acute effect of intraoperative test. *Note:* Sum effect of DBS (sum effect left and right normalized to baseline) during intraoperative test stimulation as reported by the patients (DACS).

Table 1
Effect of Stimulation (right and left) compared to baseline (DACS).

Items	Pat. 01	Pat. 02	Pat. 03	Pat. 04	Pat. 05	Pat. 06	Pat. 07
Depressed Mood	−1	−3	2	−4	−1	−3	−2
Sadness	0	−2	−4	−2	0	−7	0
Anhedonia	−16	−2	0	0	0	−1	0
Drive	3	−2	0	4	0	−2	−2
Anxiety	0	4	−7	−12	−2	−4	−10
Rumination	2	−3	−20	−15	−1	−8	0
Total effect (sum of all items vs. Baseline)	−6	−4	−14,5	−16,5	−2	−12,5	−7

Note: negative values reflect reduction of depressive symptom.

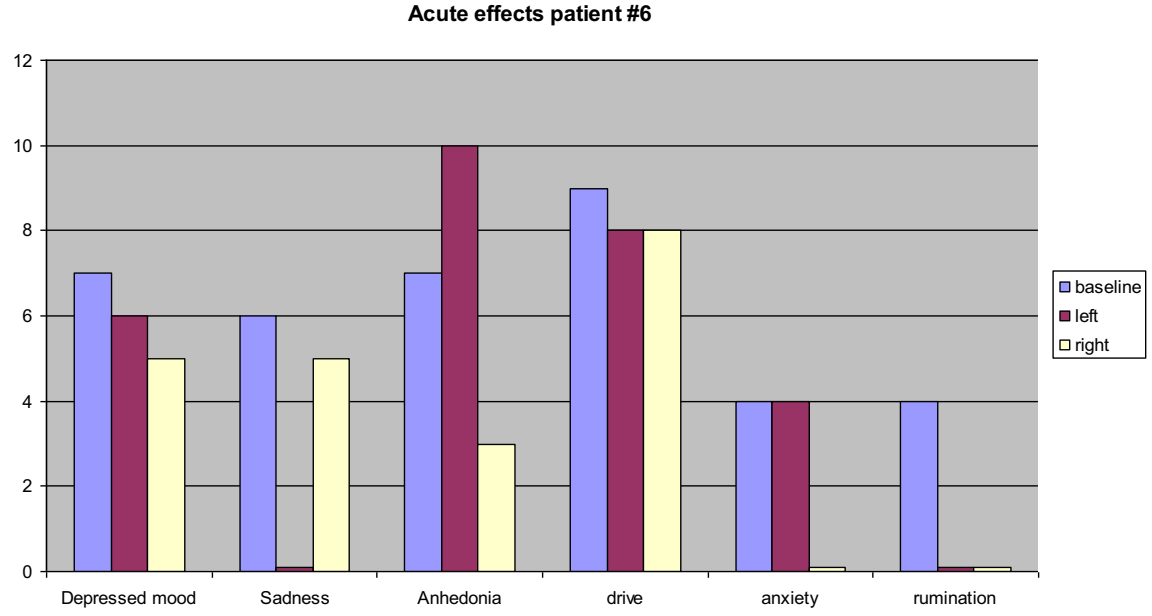

Fig. 3. Acute effects Patient #6. *Note:* Acute effects of DBS during surgery showing baseline, left and right stimulation for an individual patient for each item of the DACS (Depression acute-effects scale) Higher values reflect the negative dimension of each item.

in DBS for depression because symptoms of depression are much more variable over time than motor symptoms. Nonetheless, all patients reported a reduction in rumination and anxiety, an interesting finding in respect to the mode of action below.

Mode of action of acute effects in slMFB-DBS

Unexpectedly, all patients included in the study reported acute effects already during intra-operative test stimulation. This is

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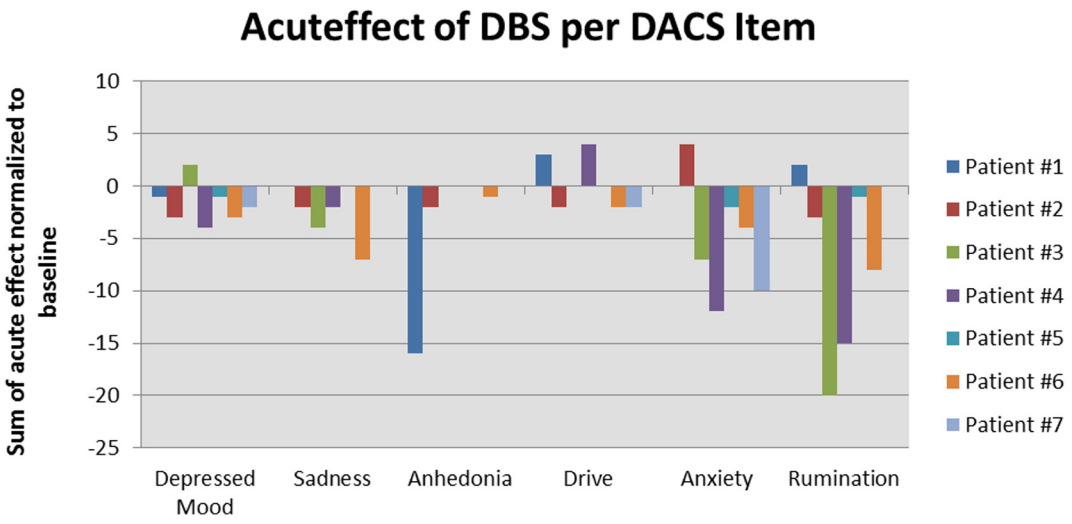

Fig. 4. Acute effect of DBS per Item. *Note:* Sum of acute effect of left and right stimulation in individual patients, normalized to baseline score.

Table 2
Correlation of intraoperative acute effect (DACS) with long-term effect (reduction in MADRS).

	Pat. 01	Pat. 02	Pat. 03	Pat. 04	Pat. 05	Pat. 06	Pat. 07
Total acute effect (DACS reduction of depressive symptoms)	−6	−4	−14,5	−16,5	−2	−12,5	−7
Reduction in MADRS_raw at 3 months	−26	−23	−13	−5	−1	−2	−20

Note: Correlation (Spearman's rho −0.33, n.s.).

especially interesting regarding the fact that in other DBS studies for depression, acute effects have only occurred in a few patients [18,19,26]. The acute and stable antidepressant response [25] after DBS to the superolateral branch of the medial forebrain bundle (slMFB), lead to a new hypothesis on the processing of affective stimuli. The neurophysiological basis of acute effects and the predictive potential of these effects are debated [23,41–44]. The slMFB is proposed as a speed access to brain circuits involved in depression [41,44]. The acute antidepressant effect could be mediated by modulating the slMFB connecting the VTA with other targeted structures of the reward system (NAcc, anterior limb of the capsula interna, Cg_{25}). A modulation of dopaminergic transmission of the VTA and connected structures as the NAcc and the PFC is probable [42,44].

By stimulating close to the origin of the slMFB, a larger population of fibers is possibly recruited at lower stimulation intensities compared to the other stimulation sites [42,44]. This might lead to an acceleration of the antidepressant effect.

Opposing system theory

It has been proposed that two opposing systems are involved in establishing an emotional response. The slMFB is thought to be part of the "seeking system" which is engaged in appetitive motivation. The seeking system, engaged in appetitive motivational behavior, modulates ones motivation to search for a positive experience and has a lower activity in depression [42]. The acute effects seen in the present study (orientation reaction, increased visual exploration of the surroundings and engagement in verbal interaction, reduced anhedonia and augmentation of drive) can be attributed to a modulation of the "seeking system". This reaction was seen in all patients.

In addition to the appetitive motivation, anxiety, depressive mood, sadness and rumination were reduced in some patients. These symptoms reflect over-activity of the "panic system", anatomically probably realized as the anterior thalamic radiation system [42]. The observed fast amelioration of these symptoms of the panic system underline the theory of a close and fast reacting relationship between "seeking" and "panic system".

We thus explain the described acute effects with a normalization of the opposing systems. Most probable, the dysfunctional reduced activity of the seeking system is normalized by slMFB. No patient reported a reinforcing or hedonic effect per se with DBS, as it has been observed in electrical stimulation of the reward system [45]. This might be due to the low stimulation intensity (about 2.5 mA). Due to side effects of the oculomotor system occurring at higher stimulation intensities, we could not test this hypothesis by augmenting stimulation intensities.

Acute effects and long-term outcome

In this study, the predictive value of acute effects on long-term outcome was not proven, probably due to the small sample size and lacking a substantial proportion of non-responders. Interestingly, the only non-responder showed also the smallest acute effect. In other studies on antidepressant effects, the relationship between acute effects and long-term outcome is even less clear [4,6,7]. Future studies are needed to address the relationship between intra-operative acute effects and long-term as well as chronic outcome. At the time, when DBS will be available to a larger number of patients, the DACS scale could be helpful to assess the predictive value of individual key symptoms of depression for the antidepressant outcome. This would allow individualizing DBS as a therapy option for a carefully selected subgroup of patients (e.g. for patients with predominantly anhedonia symptoms or with a reduction in incentive drive). Individual stimulation settings or brain targets might be found in respect to key symptoms, as it is discussed in Parkinson's disease currently [46,47].

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Conclusions

We reported on the systematic assessment of acute effects of DBS in patients suffering from depression with a new questionnaire. DBS to the slMFB revealed a strong acute amelioration of symptoms in all patients during test stimulation in the operating room. The acute changes in depression symptoms can possibly be attributed to a modulation of the "seeking system" which is a germane part of the emotional regulating system in the brain. The slMFB-DBS might be interpreted as a speed access to the system processing affective stimuli [41,44].

Furthermore, with the depression acute effects scale (DACS), the influence of stimulation parameters (e.g. electrode selection and stimulation site) on acute antidepressant response could be assessed. This might help to find the right parameters during titration phase and during parameter optimization phase. The DACS could also be applied assessing effects of sleep deprivation, ECT, TMS and ketamine. Thus, allowing a better comparison of acute effects between studies. In larger samples, the DACS could possibly be used to assess the predictive value of an acute treatment effect on individual symptoms of depression in order to optimize the selection of patients for a respective treatment by individualizing therapies.

Acknowledgements and conflicts of interest

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