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Mood Stability during Acute Stimulator Challenge in Parkinson's Disease Patients Under Long-Term Treatment with Subthalamic Deep Brain Stimulation

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Abstract: Acute and chronic behavioral effects of subthalamic stimulation (STN-DBS) for Parkinson's disease (PD) are reported in the literature. As the technique is relatively new, few systematic studies on the behavioral effects in long-term treated patients are available. To further study the putative effects of STN-DBS on mood and emotional processing, 15 consecutive PD patients under STN-DBS for at least 1 year, were tested ON and OFF stimulation while *on* or *off* medication, with instruments sensitive to short-term changes in mood and in emotional discrimination. After acute changes in experimental conditions, mood core dimensions (depression, elation, anxiety) and emotion discrimination processing remained remarkably stable, in the face of significant motor changes. Acute stimulator challenge in long-term STN-DBS–treated PD patients does not appear to provoke clinically relevant mood effects. © 2007 Movement Disorder Society

Key words: Parkinson's disease; deep brain stimulation; mood; stimulator challenge

Subthalamic deep brain stimulation (STN-DBS), a relatively new functional neurosurgical intervention for refractory Parkinson's disease (PD), provides impressive improvement in motor function.[1] Nevertheless, nonmotor effects of the procedure have been reported, including mood alterations that have been on occasions clinically significant (e.g., depression, mania, suicides).[2–5] This finding suggests that associative and limbic frontostriatal circuits can be affected by STN-DBS. Impairment in emotional processing was more recently reported as a possible consequence of DBS.[6,7] In contrast, beneficial acute mood effects and enhanced emotional processing were also reported in previous studies, when PD patients where compared with the stimulator acutely turned on or off.[8,9] Because no clear picture has yet emerged from the literature, and given there are few systematic reports on behavioral effects of the procedure in long-term treated patients, we report on the effects of an acute stimulator challenge in PD patients treated with STN-DBS for at least 1 year, a period of time uncontaminated by recovery from surgery or frequent adaptations of stimulation parameters and medication.

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PATIENTS AND METHODS

A total of 15 consecutive patients with advanced PD (9M/6F; mean age, 63.1 ± 9.3 years; duration of illness, 12.0 ± 6.0 years) were included. They were all still treated with levodopa and had bilateral STN-DBS implanted 15 ± 8.9 months in average before the experiment. The electrodes were implanted under stereotaxic

guidance using ventriculography, magnetic resonance imaging (MRI), and microelectrode recordings; postoperative MRI confirmed placement within the STN. Medication and stimulation parameters (mean voltage: right, 2.51 ± 0.66 V; left, 2.67 ± 0.70 V; pulse width, 96 ± 12.4 μsec; frequency, 185 ± 0 Hz for both sides) were stable for at least 3 months before inclusion. None of the patients included had dementia as defined by the International Classification of Diseases at any point before or after surgery.

Experimental Design

PD patients came to the center after an overnight 18-hour withdrawal from all anti-PD medication. They were tested ON and OFF DBS and before and after a challenge with a supraoptimal dose of L-dopa within 1 testing day. The order of the conditions are as follows: (1) *off*-Med/ON-DBS, (2) *off*-Med/OFF-DBS, (3) *on*-Med/OFF-DBS, and (4) *on*-Med/ON-DBS. There was no blinding as to the experimental conditions. The dose of L-dopa was chosen individually to induce an optimal motor response (mean dose, 250 mg; range, 200-300 mg). All study subjects were examined in each condition by the same neurologist (M.P.) and the same psychiatrist (A.B.). To optimize the stability of the patient's response, and limit fatigue, a waiting period (on average 45 min) was respected after each change in condition. Motor symptoms were assessed using the Unified Parkinson's Disease Rating Scale Motor subscale (UPDRS-III) and timed tests as defined in the CAPSIT protocol.[10]

Experimental Measures

Because standard depression scales are not designed to be repeated over short periods of time, changes in mood across experimental conditions were assessed with the Profile of Mood State (POMS),[11] a sensitive scale designed to measure small moment to moment fluctuations in mood, where subjects have to rate a list of words, according to how much it corresponds to their current mood state (scale, 0–3). Ratings are grouped in six self-report bipolar subscales: composed–anxious, agreeable–hostile, elated–depressed, confident–unsure, energetic–tired, and clearheaded–confused. In addition, the Montgomery Asberg Depression Rating Scale (MADRS), a scale widely used to evaluate clinical depression, was rated at baseline to assess for mood state over the past 2 weeks. Emotion discrimination was assessed with a computerized task, consisting in the presentation of pairs of validated exemplars of facial expressions of five basic emotions (happiness, surprise, anger, disgust, and sadness). Each pair conveys the same or different emotions,[12] and subjects must decide whether it is the same emotion or a different one. A short trial before performance measurement was conducted to verify correct understanding of the task. Random order of presentation of emotional stimuli within the task was computer generated. To assess nonemotional face processing, a potential confounding factor in the emotion discrimination task, the Benton test for face recognition was performed in condition 1 and 2 (*off*-Med/ON-DBS, *off*-Med/OFF-DBS). The protocol was reviewed and approved by our Institutional Ethics Board. Data were analyzed by means of repeated-measures analysis of variance (ANOVA) with condition as a four-level within-subject factor; the level of significance was set at $\alpha = 0.05$.

RESULTS

Motor Status

Repeated-measures ANOVA showed a highly significant effect of condition on UPDRS Motor scores ($F = 23.28$; $df = 3$; $P < 0.0001$), indicating a clear impact of the different experimental conditions. Post hoc analysis revealed significant differences for each comparison with the *off*-Med/OFF-DBS condition, with a worsening of motor symptoms in the OFF DBS conditions and restoration in the ON DBS conditions (Table 1).

Mood

Overall, mood state remained unaffected by either discontinuation or reinstallation of stimulation, with no clinically remarkable changes. Repeated-measures ANOVA on each subscales of the POMS revealed no significant changes on the three main subscales assessing mood core dimensions (POMS-depression, -anxiety, and -hostility). There was a small but significant effect of condition for POMS-feeling unsafe ($F = 3.14$; $df = 3$; $P = 0.035$), -fatigue ($F = 4.99$; $df = 3$; $P = 0.005$), and -confusion ($F = 5.69$; $df = 3$; $P = 0.002$). Post hoc analysis showed that improvement of "feeling unsafe" was related to the restoration of medication. "Fatigue" worsened and improved with discontinuation and reinstallation of the stimulation respectively. Feeling of "mental confusion" improved after restoration of medication and further improved after restoration of stimulation (Table 1). For 3 patients, the baseline MADRS score was in the moderate depressive range (1 was treated with an antidepressant of the selective serotonin reuptake inhibitor type), whereas the remaining 12 were not clinically depressed (mean MADRS, 6.9 ± 7.6). The 3 depressed patients did not respond differently to the stimulator challenge than the rest of the patients, and

TABLE 1. *Motor, mood, and cognitive performance across testing conditions*

	off Med		*on* Med		Effect of condition
	ON DBS	OFF DBS	OFF DBS	ON DBS	
Motor					
UPDRS-III	29.0 ± 12.3*	40.6 ± 14.5	22.1 ± 13.3*	18.4 ± 13.8*	$P < 0.0001$
Mood (POMS)					
Anxiety	50.3 ± 9.3	47.1 ± 8.0	48.6 ± 8.9	47.1 ± 6.5	n.s.
Hostility	45.4 ± 8.1	47.5 ± 9.6	47.1 ± 8.2	45.9 ± 2.9	n.s.
Depression	46.8 ± 6.1	45.1 ± 6.1	46.6 ± 5.2	46.4 ± 5.0	n.s.
Feeling unsafe	47.3 ± 5.1	45.1 ± 8.1	48.0 ± 4.6**	50.0 ± 6.3	$P < 0.05$
Fatigue	48.1 ± 5.7*	44.9 ± 8.4	46.0 ± 3.6	51.8 ± 5.0*	$P < 0.01$
Confusion	47.8 ± 7.5	46.1 ± 8.7	49.4 ± 6.2*	52.1 ± 5.6**	$P < 0.01$
Cognition					
Emotion discrimination	76 ± 8	76 ± 8	75 ± 9	75 ± 8	n.s.
Face recognition (Benton test)	45.3 ± 4.5	46.6 ± 2.9			n.s.

Data presented as mean ± SD of motor, mood, and cognitive performance across testing conditions. Data are normalized scores, higher scores reflect better mood. Emotion discrimination scores are rate of correct responses (%). Benton face recognition scores are corrected for age and education (normal range, 41-54). Significant main effects of condition are present in the three domains. Significant contrasts with the *off*-Med/OFF-DBS condition in the post hoc analysis: *$P < 0.05$, **$P < 0.005$.

UPDRS-III, Unified Parkinson's Disease Rating Scale motor subscale; POMS, Profile of Mood State (subscales: anxiety, hostility, depression, feeling unsafe, fatigue, and confusion); n.s., not significant.

removing them from the analysis did not change the results.

Cognition

Face recognition (Benton) was in the normal range and did not change with DBS (Table 1). Performance on the emotion discrimination task did not change across experimental conditions; however, mean performance in our sample was significantly lower than the performance found in a previous study with the same discrimination task in medically treated PD patients at an earlier stage of the disease.[13]

DISCUSSION

In the present study conducted in PD patients under chronic long-term STN-DBS, acute stimulator challenge, *on* and *off* medication, led to the expected worsening and improvement, respectively, of the core motor symptoms. Of interest, mood core dimensions (i.e., depression, elation, or anxiety), remained remarkably stable. Subjective changes associated with acute changes in stimulation were limited to feelings of fatigue and of mental confusion, which were improved on stimulation.

There is little doubt that STN-DBS is on occasion associated with impressive behavioral effects[5]; however, in the present study conducted systematically in a consecutive series of patients treated for at least 1 year with STN-DBS, the stability of the main mood measures in the face of important motor changes was notable. One explanation for this finding could be that affective blunting occurs with advancing disease, yet, the rate of clinically depressed patients (3 of 15) is well in the range of other reports on this study population.

The inclusion of an emotion processing task was motivated by the possibility of direct effects of STN-DBS on such cognitive dimension raised by recent studies reporting either a worsening[6] or an improvement[9] in performances with STN-DBS. Aspects of emotional processing tested here (emotional faces discrimination) were unaffected by acute changes in stimulation or medication. Of interest, performance in this group of patients was significantly lower than the performance of a non-operated PD patients at an earlier stage of the disease assessed with the same task,[13] possibly reflecting a deterioration with disease progression[13]; one cannot exclude that lower performance reflects a deleterious effect of chronic STN-DBS, as recently suggested by others,[6,7] but this conclusion remains to be clarified.

Different behavioral effects of STN-DBS found in different study samples may be partly the consequence of positioning of the contact electrodes within the STN.[14] Direct evidence supporting this view, is provided by a recent functional MRI case study, demonstrating dissociated brain activation patterns through the stimulation of either an electrode contact eliciting motor improvement, or another one eliciting mood lowering in the same patient.[15] Furthermore, changes over time in functional circuits and neural plasticity with chronic DBS may mediate a change in some DBS effects over time. Reports of behavioral effects seen in the early postoperative period and fading with time,[2,3,15] somewhat support this view[16] and are in keeping with the present data suggest-

ing lack of important changes in mood in response to acute changes in stimulation in patients under long-term STN-DBS. Indeed, some behavioral effects may fade with chronic DBS and, therefore, acute behavioral effects may be more likely in the early postoperative period. Another study would be required to compare behavioral effects during acute stimulator challenge early versus late in the course of long-term chronic STN-DBS, within the same sample of patients. Nevertheless, this study suggests that acute changes in DBS stimulation does not worsen or improve mood importantly in patients under long-term STN-DBS. This finding is of interest because such challenge may be required to reevaluate the optimal stimulation parameters or assess disease progression in the long-term follow-up of patients.

A few factors could limit the validity of this observation. First, our sample size was small, therefore limiting our power. Second, there was no blinding per the testing condition. Blinding would have required important adaptations, for example, the use of a screen or video monitor or that of sham stimulation. These measures were thought still not to guarantee effective blinding because of the important motor effects and the previous experience of medication challenge or adaptation of stimulation parameters of these patients. We believe that these design limitations would most probably not have prevented the observation of clinically important mood changes, although we cannot exclude that smaller mood changes could have been missed. Moreover, small changes were picked up in this study and concerned fatigue and mental confusion, but not mood core dimensions. Third, the short period of observation could have limited our sensitivity. Some mood changes might need more time to become apparent following changes in stimulation parameters, as it is the case for some of the motor signs.[17] Ideally, one would have tested the different conditions on separate days and with a longer period of time within and between each condition, but this strategy was impractical as patients were recruited from a very large area. In conclusion, this systematic study conducted in PD patients treated with long-term STN-DBS, revealed little subjective and cognitive effects, and notable stability in mood core dimensions in the face of marked changes in motor status during acute stimulator challenge.

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