

Deep Brain Stimulation of the Subthalamic Nucleus Enhances Emotional Processing in Parkinson Disease

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Background: High-frequency electrical stimulation of the subthalamic nucleus is a new and highly effective therapy for complications of long-term levodopa therapy and motor symptoms in advanced Parkinson disease (PD). Clinical observations indicate additional influence on emotional behavior.

Methods: Electrical stimulation of deep brain nuclei with pulse rates above 100 Hz provokes a reversible, lesioning-like effect. Here, the effect of deep brain stimulation of the subthalamic nucleus on emotional, cognitive, and motor performance in patients with PD (n=12) was examined. The results were compared with the effects of a supratherapeutic dose of levodopa intended to transiently restore striatal dopamine deficiency. Patients were tested during medication off/stimulation off (STIM OFF), medication off/stimulation on (STIM ON), and during the best motor state after taking levodopa without deep brain stimulation (MED).

Results: More positive self-reported mood and an enhanced mood induction effect as well as improvement in emotional memory during STIM ON were observed, while during STIM OFF, patients revealed reduced emotional performance. Comparable effects were revealed by STIM ON and MED. Cognitive performance was not affected by the different conditions and treatments.

Conclusions: Deep brain stimulation of the subthalamic nucleus selectively enhanced affective processing and subjective well-being and seemed to be antidepressive. Levodopa and deep brain stimulation had similar effects on emotion. This finding may provide new clues about the neurobiologic bases of emotion and mood disorders, and it illustrates the important role of the basal ganglia and the dopaminergic system in emotional processing in addition to the well-known motor and cognitive functions.

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THE PATHOLOGIC hallmark of Parkinson disease (PD) is the degeneration of dopaminergic cells within the substantia nigra and the subsequent dopamine depletion of the striatum. Studies in monkeys with experimental parkinsonism induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine could demonstrate that the striatal dopamine deficiency leads to abnormally high firing rates and altered neuronal discharge patterns of neurons in the internal globus pallidus and subthalamic nucleus (STN).¹ It is assumed that the overactive internal globus pallidus, an output nucleus of the basal ganglia, causes akinesia and rigidity through excessive inhibition of thalamocortical and brainstem motor circuits. The internal globus pallidus is driven in this scheme by excitatory projections from a disinhibited STN.¹ Administration of dopamine agonists alleviates motor symptoms of parkinsonism in parallel with a reduction of neuronal firing rates in the internal globus pallidus and STN.²⁻⁴ Inactivation of the STN or internal globus pal-

lidus through lesioning or electrical high-frequency stimulation also reverses parkinsonian symptoms^{1,5-7} by restoring thalamocortical and brainstem motor activity downstream to the site of dopaminergic action.

These observations and the shortcoming of current medical regimes in preventing long-term adverse effects, such as motor fluctuations and dyskinesias, have led to a resurgence of interest in surgical procedures for treating advanced PD. Permanent bilateral electrical high-frequency stimulation of the STN is one therapeutic option, leading to an average of 50% to 60% improvement in motor function.⁸⁻¹² Furthermore, deep brain stimulation (DBS) of the STN reduces medication requirements and diminishes motor fluctuations and dyskinesias. While impressive improvement in motor disability may result, several reports mention possible psychiatric adverse effects,¹³⁻¹⁶ such as transient apathy, depression, or anxiety. Inadvertent stimulation within the adjacent substantia nigra pars reticulata in a patient with PD, with electrodes implanted too deeply for STN stimu-

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lation, was associated with reversible symptoms of severe depression.¹⁷ In contrast, affective disinhibition with induction of involuntary laughter by stimulation within the STN was also reported.¹⁸

The basal ganglia maintain dense interconnections with wide areas of the frontal cortex in the form of anatomically segregated parallel circuits.¹⁹ The properties of basal ganglia neurons within these loops closely resemble the properties of the cortical projection neurons, eg, in their relationship to cognitive function in the prefrontal cortex or to parameters of movement in the premotor cortex. The STN has connections to the globus pallidus and substantia nigra pars reticulata, which contain distinct clusters of neurons projecting to the orbitofrontal cortex, the anterior cingulate cortex, and the temporal pole.¹⁹ These regions are implicated in emotional processing. On the other hand, the amygdala, heavily involved in emotion regulation, has substantial projections to ventral and caudal parts of the striatum, the putamen, and the ventral pallidum.²⁰ Hence, a connectivity between the STN and the limbic system can certainly be inferred and may explain some of the neuropsychiatric effects of subthalamic DBS.

Because DBS mimics lesioning of the target area,²¹ patients with PD with implanted DBS electrodes offer a unique opportunity to investigate the contribution of the basal ganglia to higher-order behavior in humans by reversible, experimental inactivation. This study aimed at investigating the effects of bilateral STN stimulation on emotional processing, cognition, and motor functions of patients with advanced PD. The stimulation effects were furthermore compared with those of a suprathreshold dose of levodopa as a challenge test for the dopaminergic system. We hypothesized that STN stimulation should influence, besides motor functioning, emotional processing more than cognition. Medication and stimulation, however, should not differentiate in their effects.

METHODS

SUBJECTS

Twelve patients with advanced PD (9 women, 3 men; age, mean \pm SD, 62.1 \pm 6.1 years; duration of illness, 17.0 \pm 6.3 years) gave informed consent to participate. The study protocol had been approved by the institutional review board of the Heinrich-Heine-University Medical School (Düsseldorf, Germany) in compliance with the Declaration of Helsinki. The mean \pm SD age at illness onset was 44.9 \pm 3.9 years, and patients had received medication for 14.4 \pm 6.5 years. They had undergone bilateral surgical implantation of stimulating electrodes into the STN for the treatment of severe motor fluctuations and/or dyskinesias a mean \pm SD of 9.3 \pm 6.9 months (range, 3-24 months) prior to the experiment and were in a stable therapeutic condition. The diagnosis of a psychiatric disorder (*DSM-IV*) represented an exclusion criterion for surgery as well as for the study. Hence, study patients exhibited no clinically relevant psychiatric symptoms. Patients were clinically assessed before and at regular intervals after surgery according to modified protocol of the core assessment program for intracerebral transplantation, as described elsewhere.⁸ Part of this assessment is a standardized motor examination using the Unified Parkinson's Disease Rating Scale (UPDRS) after overnight withdrawal of all antiparkinsonian drugs (MED OFF) and after administration of a suprathreshold dose of le-

vodopa during the best motor "on" state (MED ON). Both states mark the range of motor symptoms that a patient with advanced PD may exhibit during levodopa-induced motor fluctuations. The clinical efficacy of bilateral STN stimulation in our patients was reflected by an average (mean \pm SD, 70.5% \pm 22.0%) reduction of the UPDRS score in the MED OFF condition compared with the presurgical examination (UPDRS score before surgery, mean \pm SD, 51.33 \pm 15.32; after surgery, 15.36 \pm 9.88). This motor benefit allowed a reduced average (mean \pm SD) levodopa equivalent daily dose²² from 817 \pm 224 mg before to 330 \pm 207 mg after surgery.

PROCEDURES

Following overnight withdrawal from medication, patients were tested during medication off/stimulation off (STIM OFF), a medication off/stimulation on (STIM ON) condition, and as a control for similar effects of stimulation and medication, MED (mean \pm SD levodopa dose, 152.1 \pm 40.5 mg). Levodopa dose was chosen according to the individual amount necessary to induce an optimal motor response during preoperative clinical testing. The order of conditions was randomized except for MED, which always followed last. During the experimental sessions in the mornings, the stimulator was set to the starting condition according to the randomization protocol. Patients were not informed about the state of stimulation. The first experimental session was initiated after an instruction (15-30 minutes). Following neurologic examination, and taking into account the "best" medication and stimulation response based on prior clinical testing of patients, the next experimental session began after changing the status of stimulation. Usually, a waiting period of 15 to 45 minutes was necessary to achieve a stable treatment response after each change. The average time between conditions was therefore about 2 hours, since the application of all tests, including psychopathologic ratings, took about 1.30 hours per condition. Each investigation was performed within one testing session on the same day. For the conditions, standardized parallel test versions were used for emotion discrimination, emotional memory, the Benton test, and the verbal fluency task. The mood induction and the motor tests did not require parallel test versions.

PSYCHOPATHOLOGIC ASSESSMENT

Expert ratings were based on established psychiatric rating scales and a clinical interview using a 2-way communicating system to blind the psychiatrist to the treatment conditions. The psychiatrist and patient were located in different, adjacent rooms, where they had no visual contact. During the interview, they could communicate with an intercom. Ratings had to rely on this acoustic information. Depressive symptoms were measured using the 21-item version of the Hamilton Depression Scale (HAMD²³). The Brief Psychiatric Rating Scale (BPRS²⁴) and the Well-Being Scale (BF-S²⁵) were used to evaluate psychosocial functioning and general psychopathologic symptoms.

TASKS

Mood Induction

For happy and sad mood induction, 40 slides of facial expressions were presented (happy or sad).²⁶ The patients were asked to adjust their own emotional state according to the perceived facial expressions. Sex differentiation using the same stimulus material served as a cognitive control condition. Subjects had to determine the sex of the actor on each slide. Immediately following each condition, subjects were asked to rate their emotional

Positive and Negative Affective Scores (PANAS) During the Mood Induction Conditions, the Deep Brain Stimulation Conditions, and the Medication Condition*

Mood Induction Condition	PANAS	STIM ON	STIM OFF	MED
Happiness	Positive	26.83 (7.90)	23.67 (8.30)	24.42 (9.05)
	Negative	13.08 (4.76)	13.58 (5.09)	13.25 (3.67)
Sadness	Positive	22.83 (8.91)	22.50 (9.40)	21.67 (8.70)
	Negative	15.67 (5.94)	15.08 (7.48)	15.08 (6.23)
Sex differentiation (cognitive control task)	Positive	25.67 (8.27)	23.00 (9.33)	22.92 (9.41)
	Negative	12.92 (5.11)	13.58 (4.98)	13.08 (3.65)

Abbreviations: MED, best motor state after taking levodopa; STIM ON, medication off/stimulation on; STIM OFF, medication and stimulation off.
*Data are given as mean (SD).

state on standardized rating scales (Positive and Negative Affect Schedule²⁷; Emotional Self Rating²⁶). Conditions were administered in counterbalanced order, with the control condition amid the 2 emotional conditions to minimize carry-over effects.

Emotional Memory

This task is similar to a subtest in the Wechsler Memory Scale.²⁸ German emotional and neutral stories were used and have been evaluated previously.²⁹ Subjects were read a short story (about 100 words) that was neutral or emotional (the order was randomized). Immediately thereafter, subjects were required to recall the story. A second free recall of the same story (delayed recall) was obtained after the performance of other tasks that had to be completed during the actual condition (15-minute delay).

Emotion Discrimination

The PENN Facial Discrimination Test^{26,30} was used to assess performance in emotion and age discrimination. This test contains 10 happy, 10 sad, and 20 neutral facial expressions, representing an emotional task with more cognitive loads.

Cognition

The verbal fluency test, in the version by Mayes and Daum,³¹ and the Benton Test (recognition version)³² were applied. The verbal fluency test contains 3 categories: word production with a certain letter, word production with a certain category, and alternating 2 categories (cognitive flexibility). Patients were instructed to produce corresponding words during 1 minute. The Benton test includes the recognition of graphic figures of increasing complexity from 6 various alternatives, after each has been presented to the subject for 10 seconds.

Motor

A finger-tapping task and a walking test were used. We counted the number of taps between 2 squares painted on a cardboard with a center to center distance of 30 cm using the right index finger during 1 minute. For the walking test, subjects had to walk a distance of 16 m. The time required and the number of steps taken were noted.

STATISTICAL ANALYSES

Statistical analysis was based on a priori hypotheses and included *t* tests and analyses of variance (ANOVAs). The level of

significance was set at $\alpha = .05$. Because of our hypotheses, Bonferroni corrections were not applied. Performing corrections for multiple comparisons would be unnecessarily conservative on type I errors since this is a pilot study and the sample size is relatively small (the number of recruitable patients is currently still restricted). Our hypothesis of enhanced emotion processing during STIM ON compared with STIM OFF was derived from our clinical observations of improved mood and more stable affective states in patients following surgery. Furthermore, we hypothesized that STIM ON would be equal to the medication control condition. Hence, statistical comparisons were performed between STIM ON and STIM OFF states. Comparable analyses were performed between STIM ON and MED.

The dependent measure for the subjective ratings was derived from the Positive and Negative Affect Schedule scores. These scores were introduced into the ANOVA. The mood induction effect was quantified from ratings of positive and negative scores according to the procedure described earlier.²⁶ Here, $MI = MI_{\text{Happy}} - MI_{\text{Sad}}$, where MI is the mood induction effect, MI_{Happy} is the difference between positive and negative scores for the happy mood induction condition, and MI_{Sad} is the same difference for the sad condition. Two 3-way ANOVAs with the repeated-measures factors condition (STIM ON, STIM OFF, and MED), task (happiness and sadness), and scale (positive and negative score) were conducted.

Two 3-way ANOVAs with the repeated-measures factor condition (STIM ON, STIM OFF, and MED), task (happiness and sadness) and scale (positive and negative score) were conducted. The number of correctly recalled predefined elements of each story, the percentage of correct identifications, and the number of words generated for each category (for the categorical shifting, we calculated correct pairs) served as dependent variables. Separate *t* tests were used for the number of correctly recognized figures (Benton), the number of taps (tapping test), the steps for the distance divided by seconds (walking test), and global psychopathologic test scores.

RESULTS

MOOD INDUCTION

Successful mood induction was indicated by a significant interaction between task and scale ($F_{1,11} = 5.19$, $P = .04$). Differential effects were indicated by an interaction among condition, task, and scale ($F_{1,11} = 4.81$, $P = .05$) (**Table**). The mood induction effect was significant only during STIM ON ($t_{11} = 3.31$, $P = .007$) (not dur-

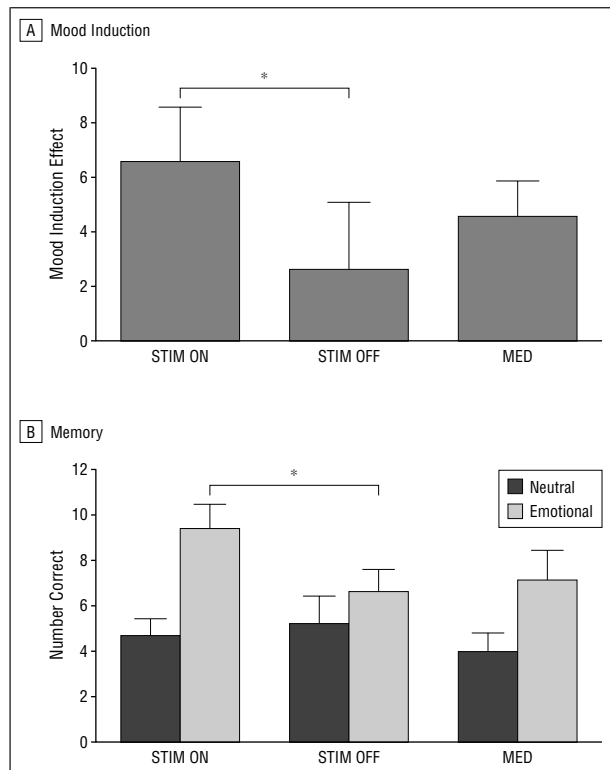


Figure 1. Successful mood induction (significant interaction between condition, task, and scale) occurred during STIM ON (medication off/stimulation on) but not during STIM OFF (medication off/stimulation off). No differences between STIM ON and MED (best motor state after taking levodopa without deep brain stimulation) (A, $n=12$) were found. Mood induction effect (MI) = $MI_{\text{Happy}} - MI_{\text{Sad}}$. Memory advantage for emotional material was similarly better during STIM ON than during STIM OFF (B, $n=12$). Here, emotional material was retained and recalled more easily than neutral material during STIM ON and similarly during MED. The asterisk indicates significant effects/differences.

ing STIM OFF [$t_{11}=1.10$, $P=.30$]). As expected, no differences were found between STIM ON and MED ($F_{1,11}=1.31$, $P=.27$). A significant interaction was found only between task and scale ($F_{1,11}=15.36$, $P=.002$). Hence, the findings indicate that DBS of the STN facilitates emotional experience (**Figure 1A**) and implies effects equal to those of levodopa.

EMOTIONAL MEMORY

In healthy subjects, emotional material is better recalled than neutral information.^{33,34} Comparing recalled neutral vs emotional material during STIM ON and STIM OFF states, we found a significant interaction between condition and valence ($F_{1,11}=6.63$, $P=.03$). This interaction was not significant for the comparison of STIM ON and MED ($F_{1,11}=1.96$, $P=.19$). Post hoc paired t tests were performed, decomposing the significant interaction. During STIM ON, more emotional than neutral elements were recalled ($t_{11}=7.39$, $P=.001$). This effect was reduced, resulting in a nonsignificant difference between recalled elements of emotional and neutral stories during STIM OFF ($t_{11}=1.51$, $P=.16$; **Figure 1B**). During STIM ON, more emotional items were recalled than during STIM OFF ($t_{11}=2.53$, $P=.03$). For delayed recall, the comparison of recalled neutral vs emotional elements during STIM ON

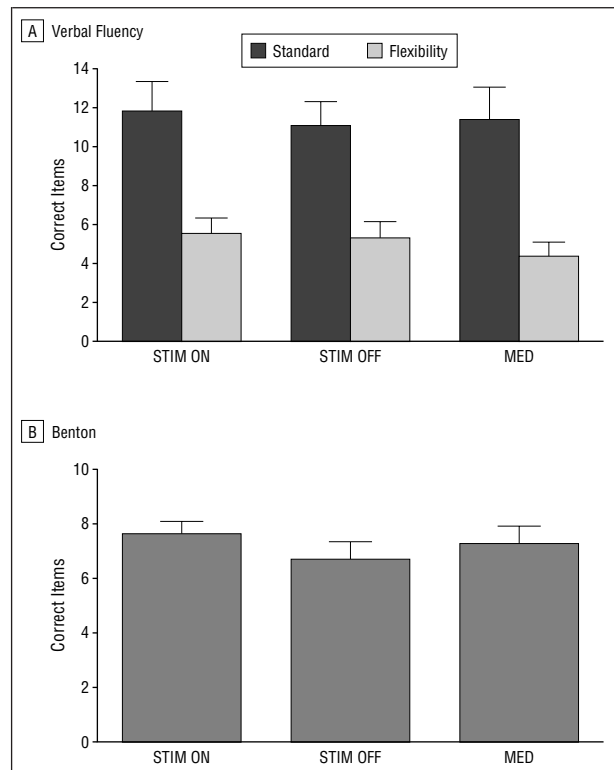


Figure 2. Performance of patients ($n=12$) on both tasks of verbal fluency (recall of words of a certain category [standard = correct items] and of 2 alternating categories [flexibility = pairs of correct items]) as well as on visual recognition (Benton test) under the different stimulation conditions. MED indicates best motor state after taking levodopa without deep brain stimulation; STIM OFF, medication off/stimulation off; and STIM ON, medication off/stimulation on.

and STIM OFF states yielded no significant interaction between condition and valence ($F_{1,11}=2.67$, $P=.13$). The same applied to the comparison of STIM ON and MED ($F_{1,11}=0.80$, $P=.39$).

Emotion Discrimination

There were no significant stimulation effects, as revealed in the results. The 2-way ANOVAs yielded no significant meaningful interactions ($F_{1,11}=1.40$, $P=.26$) (ON vs MED: $F_{1,11}=1.10$, $P=.32$).

Cognition

The ANOVA for the verbal fluency task revealed no meaningful significant interaction between condition and task ($F_{2,20}=1.66$, $P=.23$) (**Figure 2A**). However, a main effect for task emerged ($F_{2,20}=24.53$, $P=.001$) due to higher word production in a certain category and higher word production with a certain letter, compared with the pairs counted during categorical shifting. The equivalent ANOVA for MED and STIM ON yielded only a comparable main effect for task ($F_{2,22}=43.48$, $P=.001$) and no significant interaction ($F_{2,22}=0.46$, $P=.56$). Also, no significant effects emerged for the number of items correctly recognized in the Benton test during STIM ON and STIM OFF ($t_{11}=1.20$, $P=.26$). Furthermore, no differences were found between STIM ON and MED ($t_{11}=0.53$, $P=.61$).

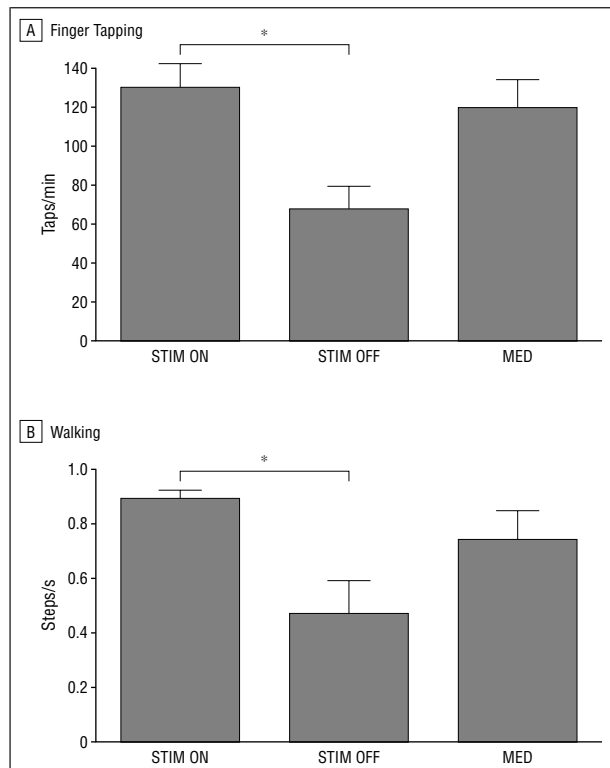


Figure 3. A strong beneficial effect of STIM ON (medication off/stimulation on) was found for motor functions ($n=12$): motor performances during finger tapping (A) as well as for the walking test (B) showed marked improvements during STIM ON compared with STIM OFF (medication off/stimulation off). Motor functions during STIM ON were comparable with MED (best motor state after taking levodopa without deep brain stimulation). The asterisk indicates significant effects/differences.

Motor

Results demonstrated a strong improvement in STIM ON, visible by the walking test (steps per second) ($t_{11}=3.61$, $P=.004$) as well as by finger tapping ($t_{11}=6.58$, $P<.001$) (**Figure 3**). In contrast, STIM ON and MED did not differ in their effects on walking ($t_{11}=1.53$, $P=.15$) or tapping ($t_{11}=1.19$, $P=.26$).

Psychopathology

Increased depressive symptoms (HAMD, $t_{11}=-5.59$, $P<.001$) and general psychiatric symptoms (BPRS, $t_{11}=-4.53$, $P<.001$) were measured during STIM OFF compared with STIM ON (**Figure 4**). The same applied to self ratings of well-being (Bf-S, $t_9=-4.13$, $P=.003$). As expected, MED and STIM ON did not differ in the psychopathologic ratings (HAMD: $t_{11}=-1.48$, $P=.17$; BPRS: $t_{11}=-1.12$, $P=.29$) or self ratings (Bf-S: $t_9=-1.58$, $P=.15$).

COMMENT

Deep brain stimulation of the STN was effective on 2 fronts simultaneously: it demonstrated enhanced emotional processing as well as impressive improvements in motor function. Similar to previous reports, the motor effect of STN-stimulation in the tapping and walking tasks was approximately equivalent to the best levodopa

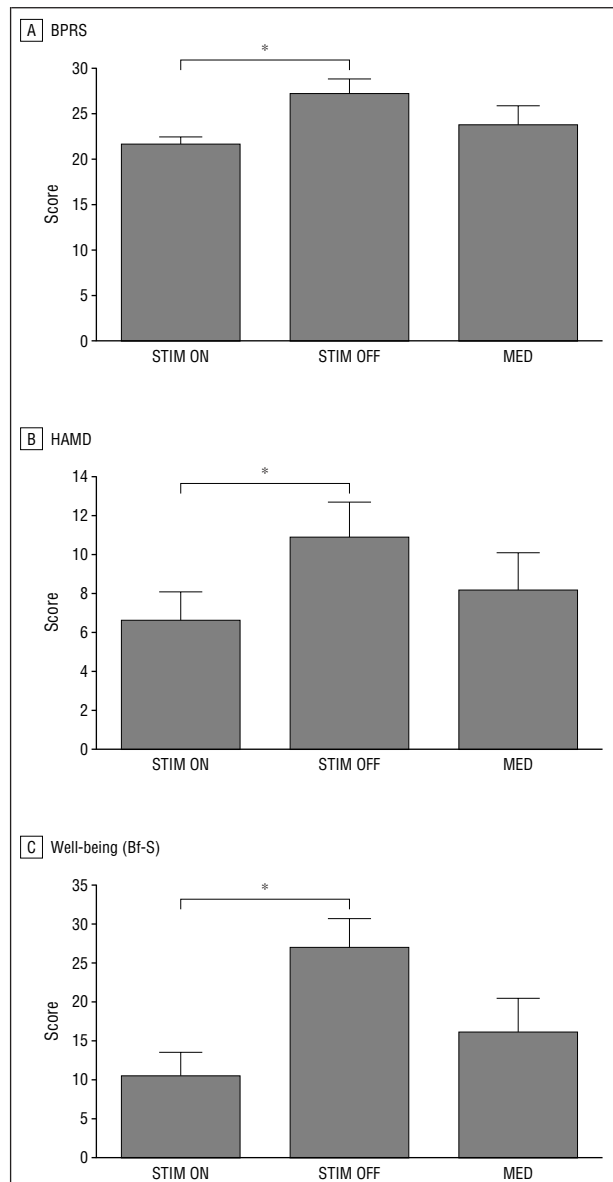


Figure 4. Psychiatric assessments (Brief Psychiatric Rating Scale [BPRS], Hamilton Depression Scale [HAMD]) and self-ratings ($n=12$) of symptoms (Well-being Scale [Bf-S]) indicate parallel variations between conditions, with a greater degree of psychopathologic symptoms, of depression, and of impairment in well-being during STIM OFF (medication off/stimulation off) compared with STIM ON (medication off/stimulation on) (BPRS, HAMD, and Bf-S). Again, STIM ON and MED (best motor state after taking levodopa without deep brain stimulation) produced no differential effects. The asterisk indicates significant effects/differences.

response.^{8-12,35} No adverse effects of DBS or levodopa on cognitive functions were observed. Our brief test battery, focusing on frontal executive functions, had been chosen according to preceding reports of subtle changes in verbal fluency after DBS of the STN without significant effects in other cognitive domains.³⁶ However, the negative finding in our study is corroborated by Jahanshani et al,³⁷ who subjected STN-stimulated PD patients to a more difficult version of the verbal fluency test that demanded increased cognitive loads on flexibility (categorical shifting); neither found significant stimulation effects. Our results support the general view, that DBS of the STN is relatively safe concerning cognitive

adverse effects,³⁸ but does not completely exclude subclinical abnormalities in more detailed cognitive testing.

In our study, STN stimulation appeared to have an antidepressive effect, similar to or even stronger than the previously described thymoleptic effect of levodopa during “motor off” periods.³⁹ This is surprising in the light of several reports describing increased apathy, depression, or anxiety as transient psychiatric adverse events after subthalamic DBS.^{15,16} These neuropsychiatric symptoms occurred mostly during the first postoperative weeks, when extensive reduction of dopaminergic medication took place. A withdrawal syndrome is therefore an obvious explanation, also because an increase in dopaminergic medication is most effective in alleviating these symptoms.¹⁵ We cannot exclude that in some patients with suboptimally placed electrodes in the subthalamic area, neuropsychiatric adverse events result from unintended costimulation of neighboring nuclei or fiber tracts. In this study, patients were selected because of their excellent motor response to subthalamic DBS as a physiologic verification of correct electrode placement. These electrodes are most often located in the dorsal border of the STN, adjacent to the zona incerta.⁴⁰ The mood-enhancing effect of subthalamic DBS was accompanied by intensified emotional experience, improved processing of emotionally laden information, and enhanced self-reported well-being. It is a well-known phenomenon that the emotional content of material enhances retention and facilitates learning.^{33-34,41} This effect is lost, however, after selective amygdala damage⁴² and can be blocked by β -adrenergic antagonists.⁴³ During the parkinsonian “off” state that our patients experienced in the STIM OFF condition, a similar blocking effect was observed.

The emotion discrimination performance, in contrast, was not differentially affected by STN stimulation. Emotion discrimination is, rather, a cognitive demand that does not entail strong emotional participation. During mood induction and emotional memory, emotional processing can be characterized by behavioral consequences (memory advantage of emotional material and mood changes) that are not observed during emotion discrimination. Hence, this categorization task may involve brain networks other than those involved in the sole experience of emotion or emotional memory processes.⁴⁴ The recognition of different basic emotions may, however, rely on various neural substrates.^{45,46} Mood experience during mood induction may generally require more subcortical regions to participate.⁴⁷⁻⁴⁹

Impaired emotional processing in nondepressed PD patients compared with healthy subjects has been reported.⁵⁰ Smith et al⁵¹ described spontaneous facial expression to be selectively affected. Corroborating our results in emotion discrimination are the findings of Benke et al.⁵² Here, patients with normal cognitive function showed intact emotion discrimination and emotion recognition but impaired emotion expression, which is another indication that emotion discrimination may be more linked to cognitive processes than to emotion expression, experience, or memory. Correspondingly, those PD patients who demonstrated mental impairments performed poorly in all 3 tasks.

Funkiewiez et al⁵³ recently reported the acute effects of subthalamic stimulation on mood in comparison with a levodopa challenge in a group of 50 patients with PD. Using the Addiction Research Center Inventory (developed to reveal affective changes after abuse of narcotics), they found the response profile of levodopa exposure or STN-stimulation to closely resemble cocaine- or amphetamine-induced euphoria. Both drugs are known to act through increases in synaptic dopamine level and may, therefore, alter the functional state of the limbic basal ganglia loop.⁵⁴

Our findings support the hypothesis that STN stimulation may—in a similar manner to the influence on motor circuits—disinhibit nonmotor limbic circuits passing through the basal ganglia and projecting to the prefrontal cortex. An H₂O¹⁵ positron emission tomography study of patients with STN stimulation showed increases in regional cerebral blood flow not only in the supplementary and primary motor cortex but also in its limbic projection areas, such as the cingulate cortex.⁵⁵

Several limitations in our study design warrant cautious interpretation of the results. First, since the experimental procedure was time-consuming (approximately 6 hours per patient), medication effects could not be tested in randomized order. The long washout period would have required repeated testing on different days, which could not be realized in an outpatient setting. Second, the small sample size may have reduced the statistical power. Still, DBS is a new therapy, and the number of patients recruitable for such a study is small at this time. Third, blinding of patients to the stimulation state was impossible (in contrast with blinding of the psychiatrist) for the whole testing period since a worsening of motor function became apparent several minutes after switching off the stimulation. A couple of factors suggest, however, that the observed affective changes following levodopa or STN stimulation are unlikely to simply reflect a reaction to improved motor function: (1) patients were highly motivated and readily accepted a transient worsening of motor symptoms at the time they agreed to participate in the experiment; (2) within the short time periods in which the stimulation was turned off, a carry-over effect of prolonged stimulation prevented the full picture of off-period symptoms to develop.

Nevertheless, our results underscore the importance of the STN in the neurobiologic network of emotion processing and affect regulation. They also support the concept of a common pathophysiologic principle in neuropsychiatric and movement disorders.^{19,56,57} Middleton and Strick¹⁹ recently advanced the hypothesis that these disorders may share altered neuronal activity in different combinations of motor, cognitive, and limbic basal ganglia loops.

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