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REVIEW

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Effect of subthalamic stimulation on mood state in Parkinson's disease: evaluation of previous facts and problems

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Abstract In an attempt to clarify the effect of deep brain stimulation (DBS) to the subthalamic nucleus (STN) on mood state, previous evidence and problems were evaluated through a systematic literature search. Twenty three articles reported the effect of STN DBS on mood state in Parkinson's disease (PD), and antidepressant, depressant, and mania-induced effects were reported in 16.7–76%, 2–33.3%, and 4.2–8.1% of the patients treated with STN DBS, respectively. Most articles reported larger subgroups showing antidepressant effects than those showing depressant effects. The average depression scale score of all subjects was improved or unchanged after STN DBS. Although there was a limitation due to the varied results, it was suggested that, in general, STN DBS had an antidepressant effect in PD. However, the studies reporting severe depressant symptoms, such as suicidal attempts, after STN DBS indicated the importance of careful attention to mood state as well as to motor symptoms after STN DBS. It may be crucial to reduce the variation in the results by, for example, the use of standardized protocols and the precise verification of the stimulated region in further investigations to address this issue.

Keywords Deep brain stimulation · Subthalamic nucleus · Mood state

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Introduction

Recently, the usefulness of surgical treatments for Parkinson's disease (PD) has become widely accepted based on accumulating evidence, as shown in the announcement from the American Academy of Neurology that "surgery for PD is rapidly becoming an important therapeutic consideration in the management of medication-resistant disease..." [19]. The surgical treatments for PD have been developing mainly in the field of lesion and stimulation therapy, and because of reversibility and adjustability of the effect, deep brain stimulation (DBS) is becoming more mainstream among current surgical treatments for PD. Among the major targets for DBS, such as the subthalamic nucleus (STN), internal globus pallidus (GPi), and ventral intermediate nucleus of the thalamus, many institutes are currently selecting the STN as a stimulation target because of the effects not only on rigidity and tremor, but also on bradykinesia and postural instability [24, 29, 33, 37, 40].

Although there are still many arguments regarding how STN DBS improves the physical symptoms of PD, inhibition of hyperactive neurons in the STN by high-frequency stimulation and following modulation of the neural circuit between cortex, striatum, and thalamus, known as the cortico–striato–thalamo-cortical loop (CSTC loop), is thought to be involved in the working mechanism [13, 32]. It had been believed that the major type of information conveyed by the CSTC loop was motor information, but recent anatomical studies revealed that information from the frontal lobe and the limbic system is transmitted by the CSTC loop as well as motor information [1, 43]. On the basis

of this anatomical knowledge, the possible effect of STN DBS on information other than motor information passing through the STN has been a focus of recent research. In fact, positron emission tomography (PET) and functional magnetic resonance imaging (MRI) studies reported changes in neuronal activity in the frontal lobe and the limbic system during STN DBS [51–53] and clinical studies reported changes in the frontal lobe function after STN DBS [10, 30, 35, 36, 47–49, 56, 57], suggesting that STN DBS has an influence on high-order brain function as well as motor function.

It is well known that depression is one of the most frequent impairments of high-order brain function observed in PD patients. A recent clinical study reported that almost 60% of variability in health-related quality of life was due to depression, whereas only 17% was due to physical symptom severity, and depression was indicated to be an important factor in the treatment of PD [16]. However, despite the clinical importance of depression, there have been limited studies focusing on the effect of STN DBS on mood state. Furthermore, the reported symptoms varied from depression to mania in the limited previous articles, and there seems to be confusion regarding the effect of STN DBS on mood state [5, 6]. Given the fact that STN DBS is becoming an established therapeutic option for medication-resistant physical symptoms of PD, and that the number of PD patients to be treated with STN DBS is predicted to increase, it is thought crucial to comprehend the effect of STN DBS on mood state for the better treatment of PD patients. In the present paper, the authors review the articles that reported on the effect of STN DBS on mood state to clarify what is known thus far, and attempt to identify problems to solve in future studies.

Materials and methods

A systematic literature search was performed through the databases of PubMed, Cochrane Database of Systemic Review, Ovid Medline, Psycho INFO, and EMBase by using the following key words: deep brain stimulation, DBS, electrical, brain, Parkinson, subthalamic nucleus, STN, mood, depression, depressant, antidepressant, mania, and hypomania. Articles in a non-English language were excluded.

Results

The effect of STN DBS on mood state in PD was reported in 14 cohort studies and nine case studies from 1999 to 2004 (Tables 1 and 2). No case control study was reported. In all studies, the main aim of STN DBS was to improve fluctuating motor symptoms caused by on–off and wearing off phenomena after long-term medication and/or medication-induced dyskinesia, and the change in mood state was evaluated as a secondary objective. The cases which were unresponsive to L-dopa and/or with on-going neuropsychiatric symptoms as defined on Axis I in the "Diagnostic and statistical manual of mental disorders, fourth edition" (DSM-IV) were excluded.

The effect of STN DBS was evaluated less than 1 year from the start of STN stimulation in most studies, whereas a couple of studies followed up for 3–5 years [14, 25]. Depression scales used in the studies were as follows: the Beck Depression Inventory (BDI) in six studies, the Geriatric Depression Inventory (GDI) in two studies, the Hamilton Depression Rating Scale (HDRS) in two studies, and the Zung Self-Rating Depression Scale (Zung SDS) in one study. As for mania scales, one study used the Young Mania Rating Scale (YMRS) and the other used the Bech–Ragaelsen Mania Scale (BRAMS). Three other studies used the Unified Parkinson's Disease Rating Scale (UPDRS), three used the DSM-IV, one used the Mini International Psychiatric Inventory (MINI), and one used a Visual Analogue Mood Scale (VAMS). Two case studies only described the clinical pictures of the reported symptoms and did not use any scales [6, 26]. All but one study [41] reported that STD DBS affected mood states in PD.

Antidepressant effect

Four studies reported antidepressant effects [9, 15, 44, 50] and the other five studies reported both antidepressant and depressant effects observed after STN DBS [3, 10, 14, 42, 49]. All of these nine studies reported a significant improvement in motor symptoms. Mood state was evaluated with L-dopa intake (ON) in three studies, without L-dopa (OFF) in three studies, and in both ON and OFF phases in three separate studies (Table 1). Seven studies in the literature have documented changes in the daily dose of L-dopa and/or L-dopa agonists and all reported a significant decrease following STN DBS [3, 9, 10, 15, 44, 49, 50].

In the evaluation of individual depression scales, the cases of which depression scale scores were improved after STN DBS by more than one standard deviation (SD) were reported to be observed at a frequency of 16.7–76%, which was more frequent than those showing a decline in the scale scores by more than one SD [3, 10, 14, 49]. In the subgroup whose GDI scale scores had improved after STN DBS, Saint-Cyr et al. reported that the average scores were significantly reduced from pre-operative 11.8, which corresponds to a mild depressed state, to 9, which corresponds to a normal state, and indicated that there was a subgroup where STN DBS could achieve a clinically significant antidepressant effect [49]. Seven studies investigated the change in the average score of all tested subjects and all of them reported that the average was improved significantly after STN DBS [3, 9, 10, 14, 15, 44, 50].

Some articles attempted to detect the significant factors correlated with the antidepressant effect observed after STN DBS. A study by Ardouin et al. evaluated BDI scores in subgroups in ON and OFF phases before and after STN DBS to elucidate the possible antidepressant effect of L-dopa observed before and after STN DBS [3, 4]. A signif-

Table 1 Summary of cohort studies reporting the effect of STN DBS on mood state

Author (year)	Number	Assessment time points	L-dopa	Scale used	Antidepressant effect	Depressant effect	Mania or hypomania	Note
Antidepressant effect								
Burchiel (1999)	9 (4 STN) (5 Gpi)	Base 3, 6, 12 months	ON	BDI	+			Total BDI ave.* was reduced (p<0.05)
Pillon (2000)	63	Base 3, 6, 12 months	ON & OFF	BDI	+			BDI ave.** was reduced (p<0.0005)
Funkiewiez (2003)	50	Base 3–48 months (average 12 months)	OFF	BDI	+			Total BDI ave. was reduced (p<0.01)
Schneider (2003)	12	ND	ON & OFF	HDRS	+			Total HDRS ave. was reduced
Anti- and depressant effects								
Ardouni (1999)	62 (49 STN) (13 Gpi)	Base 3–6 months	ON & OFF	BDI	+ (21%)**	+ (4%)**		BDI ave.*** was reduced (p<0.0001)
Saint-Cyr (2000)	11	Base 3–6 months	ON	GDI	+ (30%)	+ (10%)		
Daniele (2003)	20	Base 3, 6, 12, 18 months	ON	Zung SDS	+ (76% @ 3 months), (58% @ 6 months), (65% @ 12 months)	+ (12% @ 3 months), (17% @ 6 months), (6% @ 12 months)		Total Zung SDS ave. was reduced (p<0.05)
Okun (2003)	5	ND	OFF	VAMS	+	+		8/40 items of VAMS were improved 2/40 items of VAMS were worsened
Funkiewiez (2004)	60	Base 1, 3 years	OFF	BDI	+ (16.7% @ 3 years)	+ (6.7% @ 3 years)		Total BDI ave. was reduced (p<0.001)
Depressant effect								
Houeto (2002)	24	ND	ND	MINI		+ (16.7%)		12/24 had previous depression history 4/12 re-developed depression after DBS
Thobois (2002)	18	Base 6, 12 months	ND	UPDRS- I		+ (33.3%)		Total UPDRS-I ave. was not changed
Berney (2002)	24	Base 3–6 months	ON	HDRS		+ (25%)		Total HDRS ave. was not change d 3 cases were suicidal
Depressant and mania-inducing effects								
Krack (2003)	49	Base 1, 3, 5 years	ND	BDI		+ (2.0% @ <3 months), (16.7% @ >3 months)	+ (8.1% @ <3 months)	Total BDI ave. was not changed
Herzog (2003)	48	Base 6, 12, 24 months	OFF	UPDRS		+ (10.4%)	+ (4.2%)	

Pluses and number in parentheses in each column indicate the direction of the reported effect and the percentage of subjects that showed the reported effects, respectively. Asterisks indicate the additional information to the notes as follows: *average of 4 STN and 5 GPi **number of the subgroup was not described; and ***average of 57 subjects out of 49 STN and 13 GPi. Each abbreviation means as follows: *ON and OFF* mood state was assessed with and without L-dopa intake, respectively; *Ave*. average; and *ND* not described

icant reduction in the BDI average scores was observed after STN DBS, which was of the same level in both ON and OFF subgroups; however, the BDI average scores of the ON subgroup were lower than those of the OFF subgroup both before and after STN DBS. These results may indicate an additional antidepressant effect of L-dopa in the

Table 2 Summary of case reports indicating the effects of STN DBS on mood state

Author (year)	Number	Assessment time points	L-dopa	Scale used	Antidepressant effect	Depressant effect	Mania or hypomania	Note
Depressant effect								
Bejjani (1999)	1	3 weeks	ON & OFF	ND		+ ?		SN was stimulated?
Doshi (2002)	3	−1 year	ND	UPDRS		+		Mood was changed instantaneously. One case was suicidal
Mania-inducing effect								
Kumar (1999)	2	ND	ND	DSM-IV			+	Induced laughter
Krack (2001)	2	ND	ND	ND			+	Induced mirthful laughter
Romito (2002)	2	3, 6, 12 months	OFF	DSM-IV			+	Transient mania with hypersexuality
Kulisevsky (2002)	3	Base 5 days	ON	YMRS			+ ?	SN was stimulated?
Herzog (2003)	1	Base −7 weeks	ON	BRMAS			+	Mania lasted for 49 days
Depressant and mania-inducing effect								
Bejjani (1999)	6	ND	ND	DSM-IV		+	+	4 depressant and 2 eupholic cases
No effect								
Morrison (2000)	3	Base 1 month	ND	GDI				GDI was not changed

Pluses and number in parentheses in each column indicate the direction of the reported effect. Each abbreviation means as follows: *ON and OFF* mood state was assessed with and without L-dopa intake and *ND* not described

ON subgroup, as well as an antidepressant effect of STN DBS itself in both subgroups. Since physical symptoms are known to affect mood state as well as L-dopa [22], Saint-Cyr et al. investigated the relationship between the improvement in motor symptoms and mood state achieved after STN DBS. They failed to find any significant relationship between these two factors, which did not support the hypothesis that motor improvement by STN DBS improved mood state secondarily [49]. Daniele et al. reported that the Zung SDS scores were improved significantly after DBS surgery, regardless of the stimulation state (i.e., either ON or OFF), and indicated the presence of factors, other than stimulation itself, which had contributed to the antidepressant effect observed after STN DBS. They reported a significant improvement in motor symptoms, quality of life (QOL), activity of daily living (ADL), and mood state after STN DBS; however, no factors significantly correlated with the antidepressant effect were reported [10]. No other articles reported any significant factors correlated with the antidepressant effect observed after STN DBS.

Although no statistical analysis was performed due to the limited sample size, Okun et al. reported that stimulation to the optimal place for motor improvement induced the improvement of eight out of 40 VAMS items measured, whereas the stimulation to a couple of millimeters ventral or dorsal to the optimal place resulted in the improvement of 2/40 and 6/40 VAMS items, respectively. These results were thought to suggest that the precise locus of stimulation is important for the induction of the antidepressant effect by STN DBS [42].

Depressant effect

The depressant effect of STN DBS, as well as improvements in motor symptoms, were reported in 13 articles [3, 5, 6, 8, 10, 12, 14, 20, 23, 25, 42, 49, 55], of which, eight studies consistently reported a decrease in L-dopa daily dose following STN DBS [3, 8, 10, 12, 23, 25, 49, 55]. Mood state was evaluated in the ON phase in three studies, in the OFF phase in three studies, and in both phases in two other studies. Five articles provided no information regarding medication (Table 1).

The cases in which depression scale scores were worsened by more than one SD after STN DBS were reported at a frequency of 2–33.3%, which was less frequent than those showing an improvement of the scores [3, 10, 14, 49]. In the study of Berney et al., the HDRS average scores of the subgroup showing a depressant effect significantly declined after STN DBS [8]. However, none of the five studies that evaluated the change in the scale scores' average of all tested subjects reported any significant decline in the average [3, 8, 10, 14, 25]. Although the depressive state after STN DBS was transient in most studies [6], some studies reported suicidal attempts after STN DBS [8, 12], and it was indicated that attention to mood state was crucial in certain groups following STN DBS.

Due to the lack of case control studies, the influence of the natural course of PD, during which patients frequently develop depression, on the results was not clear. However, the influence of PD's natural course was thought to be

negligible in the cases that showed a depressive state two days after the stimulation parameters were changed, which improved instantaneously after re-adjustment of the stimulation to the original settings [12], and in those whose VAMS scores worsened 5 min after STN DBS started [42]. Other than the influence of the natural course of PD, several studies attempted to detect the factors that correlate significantly with the depressant effect observed after STN DBS. Four studies evaluated the correlation between previous depression history and depressant effect after STN DBS, and three of them indicated a significant correlation [12, 23, 55], whereas the remaining study did not uncover any correlation [8]. No other significant factors predicting the depressant effect of STN DBS have been reported. For instance, Berney et al. investigated the difference in age, gender, improvement of motor symptoms, and L-dopa dose between depressed and not-depressed subgroups, and failed to detect any significant differences [8]. Although no statistical correlation was found, Houet et al. reported that older patients performed worse on a social adjustment scale following STN DBS, which may affect mood state, and indicated the importance of careful assessment of the socio-familial situation [23].

Like the results mentioned in the previous section for antidepressant effects, Okun et al. reported that stimulation applied slightly ventrally or dorsally to the optimal place for motor improvement caused depression more frequently than stimulation applied to the optimal place [42]. Bejjani et al. introduced a case where the tip of the electrode was placed near the substantia nigra (SN) after passing through the STN, and reported that depressive mood change was observed a few seconds after STN DBS had started [6]. These reports seem to indicate that slight movements of the stimulation electrode could be associated with depressant effects observed after STN DBS.

Mania-inducing or hypomania-inducing effect

Six case studies [5, 21, 26–28, 46] and two cohort studies [20, 25] reported manic and/or hypomanic states after STN DBS. Mood state was evaluated in the ON phase in two studies and in the OFF phase in two other studies. Four articles provided no information about medication (Table 1). A decrease in daily the L-dopa dose was consistently reported in four studies following STN DBS [21, 25, 27,46].

STN DBS was reported to cause states such as "laughter" [26, 28], an increase in mania scale scores [21, 27], and manic episodes, as defined by DSM-IV [5, 46]. Two studies reported that these symptoms were observed at a frequency of 4.2–8.1% [20, 25], and no studies reported permanent manic symptoms. All of the eight studies except for one reported the improvement of motor disabilities as well as mania or hypomania after STN DBS [20, 21, 25–28,46]; however, no studies reported any significant factors correlated with mania and hypomania after STN DBS. Kulisevsky et al. showed that manic states were induced by the stimulation to the ventral electrode and not by the dorsal electrode, suggesting the possibility that stimulation to SN might be associated with manic states observed after STN DBS [27].

Discussion

Although there have been several articles that have reviewed the effect of STN DBS on general frontal lobe function, the present article is, to our knowledge, the first review focusing on the effects of STN DBS on mood state [30, 35, 36, 47, 48, 56, 57]. Antidepressant, depressant, and mania/hypomania-inducing effects were reported in nine, thirteen, and eight studies, respectively, and there was a variation in the magnitude of the effects of STN DBS reported (Table 3). Although the variability of the results limits our ability to draw definitive conclusions regarding the effects of STN DBS on mood state, given that the reported frequency of antidepressant effects were higher than that of depressant effects, and that the total averages of the depression scale scores were improved or unchanged after STN DBS, STN DBS is thought to have an antidepressant effect in general. However, as some studies reported only the depressant effects of STN DBS and suicidal attempts observed after STN DBS, careful attention to mood state is necessary in certain subgroups after STN DBS, particularly in patients with a previous history of depression [12, 23, 55].

Possible reasons for the variation in the results are thought to be the limited sample sizes, which may have caused biased sampling, and the usage of different mood scales, which may have affected statistical analysis due to the various score ranges from scale to scale (i.e., different numerical evaluation for the same clinical change). Given the results of Ardouin et al., which indicated an additional antidepressant effect of L-dopa to the effect of STN DBS [3], it may be possible that differences in the usage of L-dopa at the assessment points from study to study contributed to the variation in the results as well (Tables 1 and 2). Additionally, since the evaluation was performed at various time periods between several days to 5 years from the start of STN DBS, and no case control studies have been reported,

Table 3 Summary of reported effects of STN DBS on mood state

	Antidepressant effect	Depressant effect	Mania or hypomania
Number of studies	9	13	8
% of the affected subjects	16.7~76%	2.0~33.3%	4.2~8.1%
Ave. of scale scores of the affected subjects	Improved significantly	Declined significantly	ND
Ave. of the scale scores of all subjects	Improved significantly	No change or improved significantly	ND

the possibility that the natural course of PD may have affected the results cannot be entirely excluded. It is possible that these factors may have contributed to the variation in the results and caused difficulties in differentiating the "true" effect of STN DBS on mood state from that of other factors known to affect mood state (i.e., changes in L-dopa dose, motor symptoms, QOL, and ADL after STN DBS). In order to reduce the possible biases that might have been caused by these factors, it is thought useful to evaluate the effect of STN DBS by using a common protocol and to compare the results between matched controls (i.e., waiting list patients) and the STN DBS subgroup. In particular, using common evaluation protocols is thought to be of importance, since it will make meta analysis more feasible and will eventually solve the sample size problem. An attempt to evaluate STN DBS effects using a common protocol started in the field of intracerebral transplantation in the early 1990s [31] and, as DBS became popular, a modified protocol called Core Assessment Program for Surgical Interventional Therapies in Parkinson's disease (CAPSIT-PD) was announced in 1999 [11]. Since CAPSIT-PD suggests a detailed protocol covering a broad field (i.e., candidate selection, time period and scale for neuropsychological tests, criteria for imaging follow-up and medication adjustment), it may be useful to apply a protocol such as CAPSIT-PD to future STN DBS studies to reduce the risk of errors which may be caused by the variation in the assessment methods.

Considering the results of Okun et al., who stated that slight differences in the locus of stimulation were associated with different effects of STN DBS on mood state, inconsistency of the brain areas stimulated may be another significant factor contributing to the variation seen in previous studies [42]. The STN is a dense structure with a volume of approximately 158 mm^3, and contains many neural fibers connecting not only with the motor but also with the limbic area of the striatum [1, 17, 43]. Adjacent structures such as the SN, GPi, lateral hypothalamus, and ventral tegmentum area are connected with the limbic system and are known to be involved in the modulation of emotion [2, 39]. Taking into account that electrical stimulation spreads around the electrodes [7, 34] and may affect the activity of the surrounding structures (i.e., activation of axonal elements over 2.5 mm in radius of the electrode with therapeutic ~3 V stimulus [58]), one should consider that STN DBS delivers the electric field with a certain expansion to areas containing dense mood-related structures and, therefore, may alter the activity not only of motor-related but also mood-related neural networks [3, 26, 44]. The stimulating effect of the electric field generated by DBS is affected by stimulation intensity and distance from the stimulating electrodes [38]. Although no previous studies attempted to compare the stimulation parameters between subgroups that showed improvement and worsening of mood state after STN DBS, the stimulation parameters were similar in the studies that reported only antidepressant [9, 15, 44] versus only depressant effects after STN DBS [6, 8, 12, 23, 55] (average amplitude 2.7 V vs. 2.8 V, average frequency 142.5 Hz vs. 141.4 Hz, average pulse width 71.1 μs vs. 61.9 μs, ratio of the cases stimulated monopolarly 84.4% vs. 87.0%, in 122 cases that developed less vs. 46 cases that developed more depressive symptoms, respectively). Thus, it was not indicated that the difference in the stimulation intensity played a major role in the variation of previous results. On the other hand, only nine of the studies reviewed confirmed the location of the stimulating electrodes by post-operative MRI, and none of them, with the exception of two which reported the depressive and manic states induced by the stimulation via the electrodes ventral to the STN [6, 27], described the position of the stimulating electrodes with regards to the STN. Therefore, the possibility that DBS stimulated other structures close to the stimulating electrodes, which were placed near or off the boundaries of the STN, as well as the STN cannot be excluded in the reviewed studies.

For targeting of the STN, the following methods have been employed before and/or during stereotactic surgery: (1) indirect targeting based on the relative coordinates of the STN to anterior commissure (AC), posterior commissure (PC), AC–PC line and/or intercomissural point; (2) direct targeting of the STN on MRI images; and (3) physiological targeting by intra-operative microrecording and/or macrostimulation. Zonenshayn et al. reported that the average distance error of the STN coordinates between the anatomical (i.e., direct and indirect) and physiological targeting was on the order of magnitude of ~2.6 mm, and indicated the risk of electrode misplacement by the anatomical targeting, particularly by the direct targeting [59]. The risk of error associated with the anatomical targeting was indicated by the other studies, which reported that the STN, as defined in MRI and autopsy studies, was smaller and located more lateral and posterior than that shown in atlases [18, 45]. It is suggested that intra-operative recording allows precise identification of the boundaries of the STN and reduces the risk of electrode misplacement [54]. Given that a small deviation in the electrode position (~1 mm) can substantially alter the activation area [38], the precise targeting and careful identification of the stimulated region is considered to be crucial to elucidate the effect of STN DBS on mood state in future studies.

Conclusions

Deep brain stimulation (DBS) to the subthalamic nucleus (STN) was reported to have clinically significant effects on mood state in certain Parkinson's disease (PD) patient subgroups. In general, STN DBS has antidepressant effects. However, given that several studies reported severe depressant effects such as suicidal attempts after STN DBS, careful attention should be paid not only to motor symptoms but also to mood state after STN DBS. Further investigations, in particular, regarding the precise location of stimulation, are important to clarify the effects of STN DBS on mood state.

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