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Factors associated with neuropsychiatric side effects after STN-DBS in Parkinson's disease

Karsten Witt[a,*], Christine Daniels[b], Jens Volkmann[c]

[a] Department of Neurology, Christian- Albrechts- University, Kiel, Germany
[b] Department of Psychiatry, University Hospital of Würzburg, Germany
[c] Department of Neurology, University Hospital of Würzburg, Germany

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SUMMARY

Neurostimulation of the subthalamic nucleus is an established treatment for advanced Parkinson's disease, and it might be the second milestone in treatment of Parkinson's disease after the introduction of L-dopa and dopamine agonists. However there are cognitive and psychiatric adverse effects have attracted increasing attention. In this context the subthalamic nucleus (STN) and the stimulation of the STN has been highlighted. The STN is part of the basal ganglia that are considered as part of distributed cortico-subcortical networks, which are involved in the selection, facilitation and inhibition of movements, emotions, behaviors and thoughts. Within this conception of the basal ganglia as a global "Go-/No-go-system" the STN is viewed as a central regulator. Those behavioral or cognitive effects of STN high frequency stimulation which can be modulated by changes in stimulation are therefore likely reflecting the intrinsic role of the STN in non-motor domains. However, there is insufficient knowledge about which proportion of neuropsychiatric effects directly relates to such a modulation of the intrinsic basal ganglia state or which individual susceptibility factors may contribute to their clinical presentation. In this review the role of the preoperative factors and also the relevance of the intraoperative and postoperative management is analyzed.

1. Introduction

Over the last ten to twenty years surgical therapies have established a firm place in the treatment of movement disorders and might be perhaps the second most important therapeutic advances in Parkinson's disease (PD) after the introduction of L-dopa and dopamine agonists. Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is considered an evidence-based, routine therapy for patients with severe tremor or motor complications of long-term L-dopa therapy. In two large clinical trials subthalamic neurostimulation was found to be superior in treating the motor complications of advanced Parkinson's therapy compared to best medical management alone [1,2]. STN-DBS was associated with a marked improvement in quality of life measures, whereas medication was just able to maintain the given level of daily functioning in these severely disabled patients. This improvement in quality of life after STN-DBS has only been recorded over a short period of time, so there is a need for studies conducted over a longer time frame, since the time course of improvement of quality of life over a range of years remains unclear.

There are multiple targets available for treating PD patients by DBS and every target has an individual risk for changes in the motor and the non-motor domains. Chronic stimulation of the nucleus ventralis-intermedius (VIM) of the thalamus and the globus pallidus internus (GPi) are relatively safe in terms of cognitive and behavioral side effects. Postoperatively the stimulation parameter can be rapidly increased usually within a few days without the need to reduce the antiparkinsonian medication dramatically. Stimulation parameters seldom interfere with the antiparkinsonian medication indicating also the need of a higher antiparkinson medication after electrode implantation. After STN-DBS increasing stimulation parameters significantly interfere with the antiparkinson medication, which means that the risk for behavioral changes is higher compared to Gpi stimulation. On the other hand long-term side effects of the medication such as psychosis and hyperkinesias can be controlled in a more effective way after STN-DBS. Therefore, in this brief review the neuropsychiatric side effects of STN-DBS are discussed in more detail.

2. Neuropsychiatric changes after STN-DBS

A wide spectrum of abnormal behaviors had been reported after STN-DBS and most of them were reported in a case report form [3]. So only a hand full of studies systematically assessed the effects

* Corresponding author. Karsten Witt, MD, PhD. Department of Neurology, Universitätsklinikum Schleswig-Holstein, Campus Kiel, Arnold-Heller-Strasse 3, Haus 41, 24105 Kiel, Germany.
Tel.: +49 431 597 8509; fax: +49 431 597 8506.
E-mail address: k.witt@neurologie.uni-kiel.de (K. Witt).

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of STN-DBS on behavior. Most important there is a higher than expected frequency of suicide among patients undergoing STN-DBS for advanced PD. Suicide rates were 12- to 15-fold higher in surgically treated patients than the global suicide rate reported by the WHO [4]. Postoperative depression, being single, and a previous history of an impulse control disorder were found to be independent risk factors for suicide in these patients [4]. Even in the absence of these risk factors patients should be informed preoperatively about the suicide risk and suicide risk should be screened in every clinical visit.

Postoperative euphoria and/or hypomanic states have been described in up to 15% of patients whereas manic episodes have been less frequent, occurring in 0.9–1.7% of patients [3]. Hypomanic and manic states typically develop in close association with the initiation of STN-DBS and usually vanish in the fist 6 months. The close relationship between the initiation of the STN-DBS and hypomanic behavior favors the idea that mood changes can be triggered by the stimulation of the limbic part of the STN itself. The conversion of a hypomania to a manic psychosis is also often triggered by an unbalanced synergistic action of dopaminergic medication and neurostimulation early in the postoperative adjustment period. A careful management of the medication and the neurostimulation during a hospital stay is a precondition to avoid or to deescalate euphoric and/or hypomanic states.

Despite the fact that most studies using standardized diagnostic criteria to examine mood symptoms have reported that depression develops in 20–25% of patients with PD following STN-DBS, the two prospective randomized trails of STN-DBS incorporating a medically treatment control group found small beneficial effects on measures of depression in the surgically treated group after 6 months [2,5]. These changes were detectable using the Beck Depression Inventory, a clinical scale that also measures partly non-motor dysfunction in PD. Risk factors for a postoperative depression include rapid or excessive withdrawal of dopaminergic medication and a previous history of depression. After neurostimulation of the most ventral electrode contacts Okun et al. reported that their PD patients rated themselves as more confused, less energetic, less happy and sad [6]. So if symptoms of severe depression occur a more dorsal stimulation can be optimal for PD patients. Symptoms of apathy might also be misdiagnosed as signs and symptoms of depression. Apathy is defined as a syndrome that includes a lack of motivation, goal directed activity, cognition and emotional concomitance of goal-directed behaviors. Apathy was documented in up to 24.6% of patients in the third postoperative year. Apathy is predicted by preoperative non-motor fluctuations in everyday life and fluctuations during L-dopa challenge in motivation, mood and anxiety [7]. Testing the impact of a single L-dopa challenge and the acute effects of STN-DBS on symptoms of depression and hedonic tone, the results demonstrate that symptoms of depression improved after L-dopa and STN stimulation [8]. However, hedonic tone improved only with L-dopa. In conclusion, an excessive reduction in dopaminergic medication after surgery in a patient who suffers from non-motor fluctuation during the preoperative L-dopa test or in everyday life is a standard scenario for a patient to become apathetic. First of all it is recommended to screen for apathy using standardized scales such as the Aurodin-Behaviour-Scale, the Starkenstein-Apathy-Scale or the Neuropsychiatric Inventory part G (Apathy). Second, in the treatment of apathy a long-acting D2/D3 receptor agonist should be introduced and if symptoms of depression are the dominant symptoms once might start nortriptyline. It must kept in mind that depression scores are highly correlated with the quality of life in PD patients [9].

There are about forty studies investigating the effects of STN-DBS on cognition, however there are only a couple of studies including a randomized control group which is especially important to disentangle cognitive changes from the natural course of disease progression in PD. In a meta-analysis of 23 studies Parsons et al. reported a decline in executive functioning, verbal fluency and memory after STN-DBS [10]. In a randomized study we found no significant deterioration in scores of global cognition, but we detected a worsening after STN-DBS in verbal fluency scores and on Stroop Test scores, both sensitive for a dysexecutive syndrome [5]. An important finding was that patients who decline in executive test-scores improved in quality of life, so a slight decline in the cognitive domain after STN-DBS is not associated with a clinically relevant decline in activities of daily living that drive quality of life.

3. Risk factors for a cognitive decline after STN-DBS in PD

Analysing risk factors for a cognitive decline in a systematic way, risk factors can be separated into preoperative, periprocedural and postoperative risk factors. Before the electrode implantation every patient has a specific risk for a cognitive decline. We compared 60 STN-DBS patients with 63 PD patients of the best medical treatment group that served as a control group [11]. The STN-DBS group showed a significant decline only in the executive function domain 6 months after DBS, which was significantly correlated with age, L-dopa-equivalence dosage (LED) and axial subscore of the UPDRS in the off-medication state at baseline. Multiple regression analysis showed that these three factors explained, however, only about 23% of the variance. Patients with higher age, higher baseline LED, and/or higher axial subscore of the UPDRS at baseline have an increased risk for worsening of executive function after STN-DBS [11]. High scores of these factors might reflect an advanced stage of disease progression. As these baseline factors explained the variance of the change score executive function only to a minor proportion, other factors including the surgical procedure, the exact placement of the electrode or postsurgical management might be more relevant for a decline in executive functioning after STN-DBS.

Little attention had been paid to the impact of the trajectory of the electrodes on cognitive changes. Each trajectory might have its individual risk for a cognitive decline. The electrode enters the brain through the prefrontal cortex or even the dorsolateral prefrontal cortex that is involved in higher cognitive functioning. The trajectory might lesion small parts of the anterior limb of the internal capsule including fibers connecting the thalamus or the head of the caudate with the frontal lobes. Frequently the electrodes traverse the head of the caudate nucleus, a structure that supports executive functions. York et al. found preliminary evidence that cognitive and emotional changes observed in patients with PD 6 months after bilateral STN-DBS were related to the cortical entry point and the position of the simulating electrode in the subthalamic area [12].

Testing PD patients in an “on” and “off” stimulation setting the intrinsic impact of the STN neurostimulation on cognitive functions can be evaluated. A relatively consistent finding with stimulation turned “on” is impairment of response inhibition in conflict situations, as assessed by the Stroop test, go/no-go tasks or stop signal paradigms [13]. The increases in error rates observed in these tasks can be interpreted as premature responding. The STN is an important nucleus in the indirect pathway of the corticobasal ganglia-thalamocortical loops. The STN has a central regulatory role providing a global “no-go” signal [14]. Electric stimulation of the STN inhibits this global “no-go” signal and premature responses are activated.

4. Summary

Neuropsychiatric symptoms account for the majority of adverse effects that occur following DBS of the STN in patients with PD. Such symptoms are typically transient and mild if managed

Box 1. The most important questions for future research

- What is the impact of electrode trajectories on behavioral and cognitive side effects of STN-DBS?
- What is the impact of the exact electrode position on behavioral and especially on neuropsychological side effects of STN-DBS?
- STN-DBS impairs decision making in a conflicting situation. What is the relevance for daily living?
- What is the impact of STN-DBS on social cognition?

STN, Subthalamic nucleus; DBS, Deep brain simulation

appropriately. Patients suitable for surgery showed a substantial benefit in quality of life, that clearly outlasts adverse effects. However, there are still questions left to answer, as summarized in Box 1. The answers to these questions are important to improve patient selection as well as intraoperative and postoperative management of patients. Additionally the characterization of the STN function also improves our understanding of the way the corticobasal ganglia-thalamocortical loops are involved in motor, emotional and cognitive processes.

Conflict of interests

Karsten Witt is a member of the Advisory Board for UCB, and has received grants from German Research Council and Parkinson International Fonds. Jens Volkmann is a member of Advisory Boards for GlaxoSmithKline and Solvay, has received honoraria from GlaxoSmithKline, Solvay, Desitin and Medtronic, and has received grants from GlaxoSmithKline, Medtronic and UCB. Christine Daniels has no conflicts of interest to declare.

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