Deep Brain Stimulation of the Subthalamic Nucleus and Cognitive Functions in Parkinson's Disease

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Received December 7, 2007; Accepted December 28, 2007.

Key words: Deep brain stimulation – Executive functions – Logical memory – Parkinson's disease – Subthalamic nucleus

This study was supported by a grant from IGA MZ ČR No. 1A/8629-5 and from the Czech Ministry of Education, Research Program MSM0021620849.

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Abstract: Deep brain stimulation of the subthalamic nucleus (DBS/STN) is an effective treatment for motor symptoms in advanced Parkinson's disease (PD). However, it is less clear how DBS/STN affects cognitive functions. We investigated 19 PD patients (13 male, 6 female, mean age 57±6, mean PD duration 15±4 years) who received bilateral DBS/STN. Neuropsychological assessment was done before the surgery and at least 12 months after DBS implantation. The patients were examined in their optimal motor status. Global cognitive performance measured by Mattis Dementia Rating Scale was not significantly changed after DBS STN. The performance in Wechsler Memory Scale III decreased in the subtest Logical Memory, in delayed recall ($p<0.05$) and in recognition ($p<0.05$). In Stroop Test, the performance worsened in the second ($p<0.05$), and third condition ($p<0.01$) measuring interference and ability to suppress automatic reactions. In conclusion, patients treated by DBS/STN tend to worsen in executive functions and in logical memory.

Introduction

Deep brain stimulation of the subthalamic nucleus (DBS/STN) is an effective treatment for late motor complications in Parkinson's disease (PD) [1]. In comparison with unequivocal positive effects on the motor functions, the effect of DBS/STN on cognitive functions is not so clear. Most studies of DBS/STN influence on cognitive functions compare the patient's performance before and after DBS, in various time periods after the implantation of electrodes [2, 3]. To differentiate specific influence of the stimulation and the effect of the surgery on cognitive performance, some studies investigate, in addition, the difference in cognitive performance with the stimulator switched on and off [3, 4].

Some studies suggest that general cognitive performance measured by global scales for the assessment of dementia does not change after the implementation of DBS STN [5, 6]. However, when specific tests were used, focusing on partial cognitive deficits in PD, an aggravation in specific function domains was found in a number of studies, most often in verbal fluency [2, 5, 7].

The aim of our study was to verify the effects of DBS/STN on cognitive functions in a sample of patients in advanced stages of PD.

Material and Methods

We investigated 19 patients (13 men, 6 women) with PD in the advanced stage with disabling motor fluctuations and/or dyskinesias, who were included in the DBS/STN treatment program. The average age of patients was 57.4±(SD) 6 years, PN duration 14.9±4 years. All the patients fulfilled the CAPSIT-PD criteria for enrolment in the DBS/STN program. None of the patients suffered from any other serious disease. Magnetic resonance imaging of the brain did not show any significant structural changes. In all patients, good responsiveness to L-DOPA was preserved.

Another condition for enlistment in the DBS program was at least 130 points in the Mattis dementia rating scale (MDRS), absence of severe depression according to the Beck depression scale (BDI-II) and absence of psychotic symptoms in the medical history.

Each patient was examined within one month before the implantation of DBS and the control testing was done within 11–44 months after the implantation. The neuropsychological examination was always done in the optimal motor status of the patient. General cognitive level was measured by MDRS. An additional more detailed neuropsychological examination was mainly focused on memory, attention and executive functions.

For memory testing, basic subtests from the Wechsler Memory Scale (WMS-III) were used: Logical memory (LM), Verbal Paired Associates (VePA), Faces (F) and Family Pictures (FP). The LM subtest measures the ability of immediate and delayed recall of a text the patients listen to. The VePA subtest measures the ability to associate words with unrelated meanings during a process of auditive-verbal learning. Both auditive-verbal subtests measure, apart from free recall, also the ability of recognition, which reflects the degree of memory retrieval. The F subtest measures the ability of recognition of retained visual information in memory. The FP subtest measures free recall of visually presented interpersonal situations and visual-spatial memory. Attention and executive functions were assessed by the Trail Making Test (TMT) and the Stroop test (ST). The TMT-A measures psychomotor speed on a visual lookup task and the TMT-B measures the mental set shifting in a task with two sets of stimuli. The ST measures the ability to inhibit reactions to undesired stimuli and the inhibition of an automatic learnt behaviour. In the Victoria version of the ST, the first part examines the psychomotor speed and simple attention (naming of color dots, ST-D), in the second (naming of color print of noncolor words (ST-W) and third part (naming of color print of color words, ST-CW), the ability to suppress automatic reaction on stimuli presented in a non-standard way is tested as well as the interference susceptibility. Initiation and ability of self-activation was measured by phonemic verbal fluency (VF) using the same initial letter before DBS and after DBS The planning ability was assessed by the Tower of London test (TOL). The resulting score was calculated according to the speed of answer and number of faulty attempts when solving 12 tasks. In case the time limit of 60 seconds in each task was exceeded, the result was not counted in.

Descriptive statistics and Wilcoxon signed-rank test for comparison of the performance before and after DBS/STN were done by means of statistic software SPSS 11.5 (Chicago, Illinois). The results of the Wilcoxon test were corrected post-hoc using the Bonferroni correction for multiple comparisons.

Results

By the time of the control examination, we managed to set the DBS parameters for optimal influence on the motor state. The medication was stable in all patients.

Average daily dose of L-DOPA decreased after DBS/STN from 769±341 to 510±270 mg and no other dopaminergic drugs were taken by the time of the control testing. Four out of 19 patients remained without any medication. The degree of depression symptoms after DBS/STN did not change according to BDI-II (15.3±6.3 points before to 15.6±8.1 points after DBS).

After DBS/STN, the performance declined in immediate recall, delayed recall and in recognition in the LM subtest of WMS-III. In the other memory subtests of WMS-III, the performance did not change significantly. Significant worsening occurred in the tasks TMT-B, ST-W and ST-CW. A trend towards worsening of performance was also noted in the VF and TOL tests (Table 1).

General cognitive performance measured by MDRS and performance in tests focusing especially on psychomotor speed (TMT-A, ST-D) were not significantly changed after DBS/STN.

After Bonferroni correction, only the differences in delayed recall and recognition in LM, ST-W and ST-CW remained significant and there remained only trends towards significance in immediate recall in LM and in VF tests (Table 1).

Table I – Results of neuropsychological tests before and with DBS

N=19	Before DBS	with DBS	Z score	P value uncorrected
MDRS	140.8 (2.7)	139.7 (5.2)	0.5	0.574
WMS-III-LM immediate recall	36.9 (8.3)	30.6 (9.2)	2.8	0.005
WMS-III-LM delayed recall	24.7 (7)	17.5 (6.6)	3.3	0.001x
WMS-III-LM delayed recognition	25.4 (3.1)	22.5 (2.9)	3.1	0.002x
WMS-III-VePA immediate recall	16.2 (7.2)	17.2 (8.1)	1.1	0.293
WMS-III-VePA delayed recall	5.6 (2.0)	5.3 (2.6)	0.4	0.659
WMS-III-VePA delayed recognition	23.9 (0.2)	23.9 (0.5)	0.4	0.655
WMS-III-F immediate recognition	34.7 (4.2)	33.6 (6.3)	1.1	0,264
WMS-III-F delayed recognition	33.8 (5.1)	34.5 (5.1)	0.5	0,631
WMS-III-FP immediate recall	28.9 (8.7)	26.6 (11.1)	0.8	0.409
WMS-III-FP delayed recall	29.2 (8.9)	24.9 (11.3)	1.4	0.153
VF	16.5 (5.8)	10.8 (4.4)	2.8	0.005
TMT-A	59.8 (31.4)	69.2 (42.1)	0.5	0.619
TMT-B	150.6 (88.1)	226.6 (189.5)	2.3	0.022
ST-D	13.9 (1.8)	16 (5.5)	1.6	0.103
ST-W	16.8 (3.2)	21.7 (9.4)	3.1	0.002x
ST-CW	29.6 (8.9)	44.1 (25.3)	3.6	0.0004xx
TOL total score	69.4 (10.9)	61.1 (17.9)	2.2	0.031

Results before DBS and with DBS are presented as means and (SD).
Z score and P value Wilcoxon test, significance after Bonferroni correction (x $P<0.05$, xx $P<0.01$).
N = number of subjects, MDRS = Mattis Dementia Rating Scale, WMS-III = Wechsler Memory Scale, LM = Logical Memory, VePA = Verbal Paired Associates, F = Faces, FP = Family Pictures, VF= Verbal Fluency Test, TMT-A, TMT-B = Trail Making Test part A and B (see details in Methods), ST-D, ST-W, ST-CW = Stroop Test part D, W, and C (see details in Methods), TOL = Tower of London Test.

Discussion

Memory

Our results imply that patients after DBS/STN show a tendency to worsening of declarative memory measured in Logical memory WMS-III subtest. We have noticed no performance impairment in the other memory subtests of WMS-III. Performance in the LM test probably requires larger involvement of executive functions than other subtests of WMS-III. With respect to the fact that the performance in LM test deteriorated in short–term recall, long-term recall as well as long-term recognition we suppose that especially the ability to imprint in memory worsened. LM requires fast processing of a larger information volume at the same time unlike VePa, where larger number or presentations of the same stimuli repeat. In other words, these results may indicate a partial weakening of complex verbal stimulus processing in encoding the information into declarative memory. The LM subtest, which has not been previously used to test PD patients after DBS/STN, seems to be a particularly suitable method for the assessment of verbal memory. Unlike various other tests that rather assess the general ability to memorize lists of words, the LM subtest brings information on the ability to remember complex information, which is more often used in daily life.

Former studies brought different findings of memory functions after DBS/STN. In some studies, no differences in verbal as well as non-verbal memory were found [6, 8]. Two studies found slight deficit in delayed recall three months after the DBS STN implantation, which did not further worsen within one year after the implantation [4, 5]. Other studies observed general impairment of declarative verbal and non-verbal memory that was explained mainly as a result of the surgery [2, 9]. However, it is also possible that some memory components may be affected by the stimulation itself. In the study of Halbig et al. [10] it was established that patients with the stimulator switched off had worse declarative memory test results in comparison with those whose stimulator was switched on. The authors assume that the STN has a specific role in memory systems activation. The influence of STN stimulation on memory functions may be related to functional connections of the STN in the association circuits among basal ganglia and temporal cortex [11]. However, the differences in memory performance can be caused by different discrimination power of the methods used in various DBS/STN studies. Visually presented verbal memory tests [7] are less demanding than auditory verbal memory tests [2, 9].

Executive functions

Cognitive initiation

We found only a trend to impaired VF performance, which is otherwise one of the most frequently repeated results in patients with DBS/STN [2, 5, 7, 9]. Indeed, VF requires more self-activation in comparison with the other tests of executive functions [4]. The VF performance decrease observed shortly after the DBS

implantation had not further deteriorated and has mostly been considered as a result of the surgery [4, 7, 8, 12]. Cognitive performance can be negatively influenced by the size and location of the lesions including the exploration electrodes tracks [3, 4]. The definitive location of the stimulation electrodes and stimulation parameters can also be important factors [3]. However, Brusa et al [23] doubt the specific effect of lesions on cognitive functions in patients treated by DBS/STN, as they observed a similar decrease in VF also in patients with DBS of the globus pallidus internus, where the trajectories of electrodes are in different locations. These authors assume that the VF performance decrease is caused by a non-specific disturbance of cortico-subcortical circuits. On the other hand, Funkiewiez et al. [7] suggest that the impaired performance in VF might be also related to the lack of self-activation, resulting from increased apathy, which can be observed in patients following reduction of dopaminergic medication after DBS/STN [14].

Cognitive inhibition

We observed a significant impairment of cognitive inhibition in interference tasks ST-W a ST-CW. By "cognitive inhibition" we mean volitional control of cognitive processes in terms of suppression of undesired stimuli and maintaining certain mental setup. In the inhibition of ongoing reactions, frontal lobes and basal ganglia take part [15, 16]. We assume that DBS/STN impairs the ability to resolve conflict situations that are more demanding on cognitive inhibition. In patients with the stimulator switched on, Schroeder et al. [17] observed an impaired performance in the interference part of the ST, accompanied by decreased activation in the right ventral striatum and right anterior cingulum (ACC). These authors suggest that DBS/STN induces functional blockade of cortico-subthalamic afferents from ACC and leads to an impairment of self-regulatory cognitive inhibition. Jahanshahi et al. [3], observed (with the stimulator switched on) an amelioration of the psychomotor speed in the first part of ST but in the interference part of the ST, the performance showed no significant change in the speed of performance, only the number of self-corrected errors increased. A worsening of ST performance was observed also in other DBS/STN studies [18, 19].

Influence of the surgery as opposed to the influence of the stimulation

Since we tested our patients on dopaminergic medication and only in their optimal state before the surgery and after the DBS/STN implantation, we are not able to distinguish whether the impairment of cognitive functions is the result of the surgery or an effect of stimulation. During the surgery, the patients' motor performance has been evaluated, but the effects on cognitive and behavioural processes have never been systematically examined. The effects of the surgery on cognitive functions immediately after surgery i.e prior to the initiation of permanent stimulation are unknown. Similarly, the effect of stimulation parameters

on cognitive and behavioural processes has not been satisfactorily clarified. This problem was not resolved even by the study with the DBS/STN switched on/off, because it was not possible to rule out persisting long-term effects of chronic stimulation [4].

In both rats and humans, the association and limbic areas are located in the medial part of the STN as well as the lateral motor area [20]. Studies on rats showed different effects of DBS/STN parameters on motor and behavioural functions. In rat model of PD, Temel et al [11] found that motor functions improved at higher amplitudes of stimulation, while behavioural regulation in terms of inhibition of premature reactions improved at lower amplitudes. This suggests that different influence of DBS/STN on motor and cognitive functions may be related to different electrophysiological qualities of STN cell subpopulations and to localization of electrodes. Although the human STN is structurally and functionally heterogeneous [21], we may assume that premature reactions established in rats [22] might, to a certain degree, correspond with impairment of cognitive and behavioural regulation in humans as reflected by ST performance. Electrical stimulation amplitudes that improve motor functions might, on the other hand, impair cognitive regulation in PD patients.

It might be argued that the decrease of cognitive performance at a time period exceeding one year after the stimulator implantation is a result of a spontaneous disease progression. However, such decreases were not found in control groups of PD patients who were not operated [24, 25].

Conclusion

The effects of DBS/STN on cognitive functions of patients with PD are different from its effects on motor functions. Although a negative influence of DBS/STN on global cognitive performance was not proved, our results show, in concordance with previous studies, a slight but significant impairment of executive functions and in certain aspects of declarative memory. The impairment may be related to the surgery itself, to different influences of stimulation parameters on motor and cognitive functions and/or to decreased dopaminergic treatment in PD patients on DBS/STN.

Acknowledgments: We thank Dr. Petr Mečíř, Dr. Markéta Volfová, Dr. Olga Ulmanová, PhD and Dr. Tereza Serranová for their clinical follow up and referrals of patients. We thank Olga Kučerová for her technical assistance.

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