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Research article

The effect of deep brain stimulation of the subthalamic nucleus on executive functions: impaired verbal fluency and intact updating, planning and conflict resolution in Parkinson's disease

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HIGHLIGHTS

- The effect of bilateral STN DBS on executive functions was tested in PD.
- The focus was on three different executive functions known to be involved in PD.
- Results were compared to a DBS wait-listed PD control group.
- Impaired fluency and intact updating, planning and conflict resolution was found.

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ABSTRACT

Although the improvement of motor symptoms in Parkinson's disease (PD) after deep brain stimulation (DBS) of the subthalamic nucleus (STN) is well documented, there are open questions regarding its impact on cognitive functions. The aim of this study was to assess the effect of bilateral DBS of the STN on executive functions in PD patients using a DBS wait-listed PD control group. Ten PD patients with DBS implantation (DBS group) and ten PD wait-listed patients (Clinical control group) participated in the study. Neuropsychological tasks were used to assess general mental ability and various executive functions. Each task was administered twice to each participant: before and after surgery (with the stimulators on) in the DBS group and with a matched delay between the two task administration points in the control group. There was no significant difference between the DBS and the control groups' performance in tasks measuring the updating of verbal, spatial or visual information (Digit span, Corsi and N-back tasks), planning and shifting (Trail Making B), and conflict resolution (Stroop task). However, the DBS group showed a significant decline on the semantic verbal fluency task after surgery compared to the control group, which is in line with findings of previous studies. Our results provide support for the relative cognitive safety of the STN DBS using a wait-listed PD control group. Differential effects of the STN DBS on frontostriatal networks are discussed.

1. Introduction

In Parkinson's disease (PD), beside the motor symptoms, several cognitive domains are also affected: in 20–40% of patients in the early stage of the disease mild cognitive impairment (MCI) is also present [1]. Based on previous studies it seems that the central cognitive deficit in PD is related to executive dysfunction [2].

One interesting possibility to gain further data regarding the nature of executive dysfunctions in PD focuses on the differential effect of deep brain stimulation (DBS) on specific executive functions. In the past decades DBS became a widely used and accepted procedure in the symptomatic treatment of PD [3].

DBS of the subthalamic nucleus (STN) in PD is associated with a clear motor benefit, and with minimal or no changes in cognitive functions [4,5]. There are studies reporting declines in certain

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executive [6–8] and memory tasks after STN DBS [4,8–10], studies reporting improvement on certain executive [4,6,10] and memory tasks [11] and studies reporting no change in specific tasks measuring these cognitive domains [7,12–14]. One of the most systematically reported decline is in verbal fluency tasks after STN DBS surgery [6,9,14] with this pattern of performance deteriorating further in the long term [8,15].

Our aim in this study was twofold. First, we hoped to gather further evidence regarding the effect of STN DBS on the three main executive components (updating, conflict resolution and planning) [16], within one experimental study. Second, we wanted to overcome the methodological problems faced in the majority of previous studies regarding the use of a relevant clinical control group. In general, we can find two main approaches in the literature regarding control groups in the study of DBS effects on cognitive outcomes: a) those comparing the performance of PD patients after DBS with the stimulators switched on either to the preoperative or to the postoperative state without DBS stimulation [4,6,10,13], and b) those comparing the performance of PD patients after DBS with the stimulators turned on to the performance of a clinical control group with PD diagnosis, but without a planned DBS intervention [7,17].

To overcome some of these methodological problems (e.g. deterioration of cognitive functions with time in PD, differences in symptoms, medication dosage, applied treatment methods across patients, etc.) we designed a study with a so called *wait-listed PD* control group. In this group, PD patients with DBS indication were investigated twice during the period between their referral to DBS and surgery. This way we could control cognitive changes related to both (a) cognitive deterioration over time and (b) different patient populations, and thus this design enables us to focus more closely on possible changes related to the DBS procedure in itself. In sum, the aim of this study was to assess the effect of bilateral STN DBS on executive functions with widely used cognitive tasks in PD patients using a DBS wait-listl to DBS and surgery. This way we could control cognitive changes related to both (a) cognitive deterioration over time and (b) different patient populations, and thus this design enables us to focus more closely on possible changes related to the DBS procedure in itself. In sum, the aim of this study was to assess the effect of bilateral STN DBS on executive functions with widely used cognitive tasks in PD patients using a DBS wait-listed PD control group.

2. Materials and methods

2.1. Participants

Patients were recruited from the St. John's Hospital, Budapest, Hungary and were assessed by a neurosurgeon (I.V.) and a neurologist (L.F.), both specialized in movement disorders. Only patients who met the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria for PD were included. All patients were assessed first and then those who had surgical intervention during the 4–6-month period between the two assessment points were assigned to the experimental group. The remaining participants (with no surgical intervention) were assigned to the control group. Ten PD patients with bilateral DBS implantation (STN DBS group) and 10 PD wait-listed patients (Clinical control group) participated in the study. Parkinsonian motor symptoms were rated using the motor part III of the Unified Parkinson's Disease Rating Scale (UPDRS) [18] by the same specialist at the first and at the second assessment points in both groups. Daily doses of medications were standardized by a formula for L-dopa-equivalent doses (LED). As inclusion criteria we used a cutoff score of >24 on the Mini Mental State Examination (MMSE) [19] and a cutoff score of >19 on the Beck Depression Inventory (BDI Hungarian version) [20]. Anxiety was assessed by the Spielberger State and Trait Anxiety Inventory (STAI Hungarian version) [21]. We did not include in the study those participants who had a lifetime history of alcohol or drug dependence and who met the criteria for any psychiatric or neurological diagnosis other than PD (see Table 1 for sample characteristics).

The research protocol was approved by the hospital's ethical review board and it was carried out in accordance with the latest version of the Declaration of Helsinki. All patients were assured that participation in the study would not interfere with their clinical treatment and all patients received a detailed description of the study before they signed the informed consent forms.

2.2. Experimental design and procedure

A mixed factorial design was used with group (STN DBS vs. Clinical control) as a between-subjects factor and assessment points (1st vs. 2nd) as a within-subjects factor. Each patient in the DBS group was assessed twice with the same cognitive and neuropsychological task battery: before surgery on medication and after surgery on medication with the stimulators on. Patients in the control group were also assessed twice before the DBS surgery with the same task battery. We made an attempt to maintain a similar time interval between the two assessment points as in the DBS group and this time interval varied between 4 and 6 months.

The position of the implanted electrodes was confirmed on the post-operative CT-scan, and the active contacts' relationship to the STN was confirmed by fusion of the postoperative CT to the preoperative MRI data set on custom-developed Vister-3D planning software. The active contact was positioned 1–2 mm posterior, 10.8–12.0 mm lateral, and 1–2 mm below the mid-comissural point. Eight patients were treated with monopolar stimulation at 130 Hz with 60 or 90 μs pulse duration and 2.6–3.9 mA. In two patients interleaving bipolar stimulation was delivered through two pairs of contacts on both sides.

2.3. Cognitive and neuropsychological assessment

General mental ability was assessed by the MMSE [19]. Widely used neuropsychological tasks were used to assess executive functions, including the updating of verbal (Digit span forward and backward) [22], spatial (Corsi block-tapping task) [23] and visual (letter N-back task with two- and three-back conditions) [22] information. Conflict resolution was tested by the Stroop task [16], while planning and shifting were assessed by the Trail Making Test B [24]. The fluency of information processing was measured by phonemic and semantic verbal fluency tasks [25].

2.4. Statistical analysis

Due to technical problems, the results of one participant in the Clinical control group were not recorded in the Stroop test and in the N-back task. During data analysis, non-parametric statistical methods were used. A change score was determined for each participant and for each task by calculating the difference between scores obtained at the first and second assessment points. Then change scores were compared between the groups (STN DBS vs. Clinical control) by conducting a series of Mann–Whitney U Tests.

For within-subject comparisons (1st vs. 2nd assessment point), a series of Wilcoxon signed-rank tests was conducted in the two groups separately. For between-subjects comparisons (STN DBS vs. Clinical control), a series of Mann–Whitney U Tests was conducted for the two assessment points separately. A Spearman's rank correlation was conducted between the Semantic fluency task change