**Deep brain stimulation of the subthalamic nucleus in Parkinson's disease: Relationship between the electrode trajectory and cognitive decline**

# Deep brain stimulation of the subthalamic nucleus in Parkinson's disease: Relationship between the electrode trajectory and cognitive decline

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**Abstract**

*Introduction*

It remains to be clarified whether penetration of the caudate nucleus increases the risk of cognitive decline in patients with Parkinson's disease (PD) undergoing deep brain stimulation (DBS) of the subthalamic nucleus (STN).

*Methods*

A retrospective analysis of pre/postoperative neuropsychological changes was performed with 46 consecutive patients with PD who underwent DBS of the STN. In particular, to evaluate the possible relationship between cognitive changes and DBS lead trajectories, repeated-measures ANCOVAs were conducted to analyze the effects of group (23 patients with vs 23 patients without penetration of the caudate nucleus) and time (T0 vs T1) for each neuropsychological test.

*Results*

A statistically significant main effect of time was observed in the Trail Making Test-Part B (TMT-B), as well as in both the phonemic and semantic ($F$ [1, 44] = 35.59, $p < 0.001$, $PrtEta^2 = 0.447$) verbal fluency tasks, and the results suggested postoperative cognitive decline. However, no significant interaction effects of time and group were observed. The results indicated that the extent of the decline was comparable between the nC and C groups, and no relationship was found between cognitive changes and caudate penetration.

*Conclusion*

Although postoperative cognitive decline was observed in some attentional-executive functions, which were assessed by the verbal fluency and TMT-B tasks, the trajectory passing through the caudate appeared not to increase the risk of cognitive decline in patients with PD undergoing DBS of the STN.

## Highlights

- Cognitive changes were analysed in 46 PD patients undergoing DBS of the STN
- Two groups were defined according to presence/absence of caudate penetration
- No relationship was found between cognitive changes and caudate penetration
- Caudate penetration did not increase cognitive decline risk in DBS-STN PD patients

## 1. Introduction

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is a widely applied treatment procedure for patients with moderate to advanced Parkinson's disease (PD) and has well-documented therapeutic effects on motor function and quality of life [1]. However, this procedure evidently has vastly different neuropsychological consequences, and diminished verbal fluency is reportedly the most common postoperative neuropsychological change [2, 3].

Both preoperative factors, such as a more advanced disease stage in which cognitive decline is more likely to be accelerated by the natural course of the disease, and postoperative factors, such as stimulation-related side effects and reductions in dopaminergic medication, have been considered as possible mechanisms involved in cognitive decline in patients with PD after DBS [4]. In addition, implant-related complications, such as microlesional effects due to intraoperative microrecording and the electrode implantation trajectory, have been suggested as causes of impaired cognition [4]. Recently, the relationship between the lead trajectories and electrode location and neuropsychological outcomes has started receiving attention. Particularly, some studies have focused on the role of the caudate given its well-known role in cognition. The caudate nucleus is part of the corticostriatal circuitry and is connected with both prefrontal areas (the anterior part) and the motor and premotor cortices (the posterior tail) [5]. It is therefore closely related to cognition and, in particular, to executive function [5, 6]. The caudate plays a central role in planning and execution of goal-directed strategies and behaviors necessary for achieving complex goals [5, 6].

A recent study assessed the impact of the electrode trajectories, particularly those penetrating the caudate nucleus, on neuropsychological changes in patients with PD after DBS [7]. The results of this randomized trial suggested that the number of

microelectrodes is not correlated with neuropsychological changes, but caudate penetration by the stimulating lead increases the risk of global cognitive decline and working memory impairment [7].

Two other recent studies showed no relationship between caudate penetration and cognitive decline in patients with PD after DBS [8, 9], but some methodological issues cast doubt on the strength of this evidence.

We therefore performed a retrospective analysis of the pre/postoperative neuropsychological changes in patients with PD who underwent DBS of the STN. In particular, we evaluated the possible relationship between cognitive changes and the DBS lead trajectories in patients with and without penetration of the caudate nucleus.

## 2. Methods

### *2.1. Participants*

Neuropsychological and imaging data obtained from 52 consecutive patients with PD, who underwent bilateral DBS of the STN at the Stereotactic and Functional Neurosurgical Unit of the "Città della Salute e della Scienza" hospital of Turin during 2011–2014, were retrospectively analyzed.

The inclusion criteria for surgery were as follows: 1) diagnosis of idiopathic PD, 2) presence of severe motor fluctuations and drug-related dyskinesia, 3) age younger than 70 years, 4) absence of marked atrophy or focal brain abnormalities on magnetic resonance imaging (MRI), 5) absence of dementia or severe cognitive decline, and 6) absence of clinically-relevant depression or severe psychiatric disorders. The surgical procedures consisted of preoperative computed tomography (CT)-MRI surgical planning to decide on a safe trajectory, followed by a single-session bilateral

stereotactic leading implantation performed under local anesthesia by a single primary surgeon (ML) (for a detailed description of the surgical procedure, see [10, 11]).

On the seventh postoperative day, all patients underwent MRI to evaluate the relative position of the electrodes and the presence/absence of bleeding or other complications. The pre/postoperative motor evaluation of the patients was performed according to the Core Assessment Program for Surgical Interventional Therapies in Parkinson's Disease. In particular, disease severity in each patient was evaluated with the Unified Parkinson's Disease Rating Scale section III (UPDRS-III) and the Hoehn and Yahr (H&Y) stage both in the medication OFF (MED-OFF) state and while the patients were under daily optimal dosage of dopaminergic drugs (Medication ON, MED-ON). The total amount of antiparkinsonian dopaminergic medications was expressed as the levodopa equivalent daily dosage (LEDD). The cognitive status of all patients was evaluated before and after surgery using a standardized neuropsychological test battery. Patients were included in the study if they underwent a successful procedure, without surgery-related complications, and participated in the follow-up evaluation between 6 and 18 months after surgery. The final enrolled cohort was composed of 46 patients with PD.

### *2.2. Procedures*

Preoperative computed tomography and MRI were coregistered with postoperative three-dimensional MRI, and the lead trajectory was traced using all three planes and a "probe's eye view" tool in the I-Plan Stereotaxy software (Brain Lab, AG, Feldkirchen, Germany).

The patients were divided into two groups, the caudate (C) and non-caudate (nC) penetration groups, according to presence or absence of caudate penetration of the electrode trajectory on either hemisphere.

### *2.3. Neuropsychological evaluation*

All patients underwent neuropsychological evaluation under optimal clinical conditions: MED-ON before surgery (baseline evaluation, T0) and MED-ON/stimulation-ON (STIM-ON) after surgery (follow-up, T1). The neuropsychological evaluation included a standardized cognitive test battery: verbal (Bi-syllabic Words Repetition test), numerical (Digit Span test), and spatial (Corsi's Block Tapping test) short-term memory; visuo-spatial reasoning (Raven Color Progressive Matrices), verbal learning (Paired Associate Learning subscale of the Wechsler Memory Scale), and attentional-executive functions (Visual Search Test, Trail Making Test, part B (TMT-B), Nelson Modified Card Sorting test, and Phonemic and Semantic Verbal Fluency tasks taken from the Spinnler and Tognoni handbook) (for a full description, please refer to the paper by Castelli et al [12]).

### *2.4. Statistical analysis*

Independent sample t-tests and chi-squared tests were used to compare baseline demographic, clinical, and neurocognitive variables between the two groups. Several repeated-measures ANCOVAs were conducted to evaluate the main effects of group (nC vs C) and time (T0 vs T1), as well as the interaction effect of time and group, for each neuropsychological test. Given that the follow-up evaluation took place between 6 and 18 months postoperatively, the number of months passed from the surgery to the follow-up neuropsychological evaluation was inserted as a covariate.

The data were analyzed using the Statistical Package for the Social Sciences version 24 (IBM Corp., Armonk, NY).

## 3. Results

Postoperative MRI revealed that the electrode trajectory penetrated the right caudate in 17 (37%), left caudate in 2 (4.3%), and both right and left caudate in 4 (8.7%) of the

46 patients with PD. These 23 patients constituted the C group, and the remaining 23 patients constituted the nC group, in which the electrode trajectory did not intersect with the caudate nucleus. Demographic and clinical characteristics are listed in **Table 1**. The comparison between the nC and C groups showed that they were matched for sex, age, years of education, disease duration, LEDD, and disease severity as assessed by the UPDRS-III and the H&Y Stage (**Table 1**).

The T0 and T1 neuropsychological test scores in both groups are described in **Table 2**. The baseline neuropsychological test-score comparison between the two groups, performed using a series of independent samples t-test, showed no statistically significant results (all $p > 0.05$), suggesting that the preoperative cognitive profiles of the two groups were comparable.

A series of repeated-measures ANCOVAs were then performed for each neuropsychological test score to analyze the time (pre vs post-surgery), group, and their interaction effects, controlling for the number of months passed from the surgery to the follow-up examination. The repeated-measures ANCOVAs revealed no statistically significant covariate or interaction effects (all $p > 0.05$), but a statistically significant main effect of time was observed for three of the test. Specifically, the results showed a statistically significant medium-sized increase in the TMT-B scores from T0 to T1 ($F(1, 43) = 5.715$, $p = 0.021$, $PrtEta^2 = 0.117$), suggesting that there was decline in attentional set-shifting in both groups. Performance deterioration was also found in the verbal fluency tasks in both groups, with a statistically significant medium-sized main effect of time in both the phonemic ($F(1, 42) = 4.615$, $p = 0.038$, $PrtEta^2 = 0.099$) and the semantic ($F(1, 43) = 6.838$, $p = 0.012$, $PrtEta^2 = 0.137$) domains. The lack of significant interaction effects confirmed that the extent of the decline in these three tests was comparable between the nC and C groups, and no relationship was found between

cognitive changes and caudate penetration. In all other neuropsychological tests, no changes between the T0 and T1 scores and no differences between the nC and the C groups were observed.

## 4. Discussion

In patients with advanced PD, DBS of the STN has been established as an effective treatment strategy when motor fluctuations, dyskinesia, and tremor can no longer be controlled by drug therapy [1]. However, the growing recognition of the importance of non-motor symptoms, observed in 100% of patients with PD and identified as the most important factor in determining quality of life, has led to increasing investigation of the DBS effects on non-motor symptoms [13].

The cognitive and behavioral effects of DBS of the STN have been investigated by numerous studies; some evidence appears to be consolidated, such as the detrimental effect on verbal fluency [2–4], but some relevant issues remain unresolved. For example, why do some patients experience clinically-relevant cognitive decline, but others do not [12]? What are the causes of the adverse cognitive outcomes? Considering these clinically-outstanding open issues, further studies are needed to clarify the role of the potential variables possibly influencing the cognitive outcomes.

Recently, some studies investigated a relatively neglected potential cause, the microlesional effects of the target area and the anatomical structures involved in the microrecording and electrode implantation trajectory [7-9]. The standard lead trajectory passes through the dorsolateral prefrontal cortex, subcortical white matter, thalamus, anterior limb of the internal capsule, and the basal nuclei [7, 14]. One of these anatomical structures, the caudate nucleus, has recently been implicated in cognitive decline following DBS [7-9, 14]. The caudate is part of the corticostriatal circuitry and

is closely related to cognition [5, 6]. The caudate plays a key role in reward-based behavior, working memory, and goal-directed strategies, as suggested by the results of several studies [5, 6]. Studies on the earliest stages of Huntington's disease, in which neuronal loss begins with the head of the caudate nucleus, have shown that the cognitive deficits are relatively circumscribed and include impairments in several tasks of attentional set-shifting, planning, and working memory [6].

Notably, in a randomized trial, Witt et al. revealed that bilateral DBS surgery had mild but detrimental cognitive effects in patients with PD, and the results showed that the effects were related to the lead trajectory and to the subthalamic location of the stimulating contact [7]. In particular, the lead trajectory passing through the caudate nucleus was found to be associated both with global cognitive decline and with impaired working memory performance 6 months after surgery [7]. The study of Witt et al. [7] had the strength of using caudate lesion volume as a continuous variable, which increased the study sensitivity. Conversely, a relative weakness was the small number of patients, five, with no caudate penetration as opposed to 12 patients with bilateral caudate penetration and 14 with unilateral caudate penetration [7]. Two recent studies [8, 9] have questioned the aforementioned results, failing to show an association between cognitive decline and caudate penetration, but the generalizability of this evidence was reduced by methodological issues [15]. Indeed, most of the 29 patients with PD studied by Morishita et al. underwent only unilateral DBS of the STN [8, 15]. Meanwhile, Isler et al. [9] found that penetration of the caudate nucleus in patients with PD with bilateral DBS of the STN led to decreased cognitive flexibility, as assessed by the TMT-B, 3 months after surgery; however, this effect was no longer present 12 months after surgery. The authors therefore suggested that caudate penetration has a detrimental cognitive effect only in the short-term period after DBS [9], but the sample

size again raises doubt regarding the statistical power of the study and the generalizability of the results.

In the present study, we retrospectively analyzed postoperative changes in different cognitive domains in 46 patients with PD who underwent bilateral DBS of the STN. All included patients underwent neuropsychological assessment 11 months postoperatively on average. Allowing for this time between assessments avoided confounding due to surgery-related inflammatory effects and controlled for long-term cognitive decline due to the normal course of the disease.

Postoperative MRI revealed that in the 46 patients with PD included in the analysis, 23 had a lead trajectory passing through the caudate, either unilaterally or bilaterally, and 23 had a lead trajectory that did not intersect with the caudate. The comparison between the pre/postoperative neuropsychological profiles showed no relationship between cognitive changes and caudate penetration. In fact, the pre/postoperative neuropsychological comparison revealed a medium-sized decline in both the phonemic and the semantic components of verbal fluency and a medium-sized decline in TMT-B performance. However, these findings were comparable between the two groups, suggesting that caudate penetration does not increase the risk of cognitive decline in patients with PD undergoing DBS of the STN. The possible detrimental effect of the caudate penetration on high demanding cognitive tasks should nevertheless be explored by future studies.

In summary, the present results seem to converge with the evidence that a lead trajectory passing through the caudate does not increase the risk of cognitive decline in patients with PD [8, 9, 14]. Further studies are needed to confirm these findings and to investigate possible factors (other than caudate penetration), which more likely contribute to cognitive decline after DBS.

## Author contributions

LC and ML were responsible for the conception and design of the study. LR and ML were responsible for data collection and clinical evaluations. VT and LR were responsible for data analysis. LC, VT, and ML contributed to the interpretation of the data. VT and LC drafted the article, which was critically revised by all authors. All authors have approved the final version of the manuscript.

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**Table 1.** Demographic and clinical characteristics of the patients at baseline.

| | Total | nC group | C group | | p |
|---|---|---|---|---|---|
| **Sex** | | | | | |
| **M** | 27 (58.7%) | 65.2% (15) | 52.2% (12) | $\chi^2$ (1) = 0.807 | 0.369 |
| **F** | 19 (41.3%) | 34.8% (8) | 47.8% (11) | | |
| **Age** | 59.5 (7.29) | 59.7 (7.0) | 59.3 (7.7) | t(44) = 0.160 | 0.874 |
| **Years of education** | 8.7 (4.02) | 8.2 (4.4) | 9.1 (3.6) | t(44) = -0.803 | 0.426 |
| **PD duration** | 12.3 (3.55) | 12.4 (3.7) | 12.2 (3.5) | t(44) = 0.164 | 0.870 |
| **LEDD (mg)** | 1044.5 (357.7) | 1108 (319.6) | 981.1 (388.8) | t(44) = 1.21 | 0.233 |
| **UPDRS-III** | | | | | |
| **MED-OFF** | 39.6 (13.1) | 40.3 (10.9) | 39 (15.2) | t(44) = 0.351 | 0.727 |
| **MED-ON** | 14.3 (5.9) | 14.9 (6.4) | 13.7 (5.4) | t(43) = 0.665 | 0.510 |
| **Hoehn and Yahr Stage** | | | | | |
| **MED-OFF** | 2.8 (0.9) | 2.8 (0.7) | 2.9 (1.1) | t(41) = - 0.494 | 0.624 |
| **MED-ON** | 1.8 (0.7) | 1.8 (0.6) | 1.8 (0.8) | t(38) = 0.098 | 0.922 |
| **Number of micro-electrodes** | | | | | |
| **Right side** | 1.24 (0.4) | 1.22 (0.4) | 1.26 (0.4) | t(44) = -0.339 | 0.737 |
| **Left side** | 1.2 (0.4) | 1.13 (0.3) | 1.26 (0.4) | t(41.2) = -1.11 | 0.275 |
| **Caudate penetration** | | | | | |
| **Non** | 23 (50%) | | | | |
| **Right** | 17 (37%) | | | | |
| **Left** | 2 (4.3%) | | | | |
| **Bilateral** | 4 (8.7%) | | | | |

All the data are expressed in mean (SD) or number (%). Comparison between the non-caudate (nC, N=23) and the caudate (C, N=23) groups was performed using the t-test or the $\chi^2$, as appropriate. LEDD, levodopa equivalent daily dosage; PD, Parkinson's disease; UPDRS-III, unified Parkinson's disease rating scale section III; MED-ON, medication ON; MED-OFF, medication OFF; SD, standard deviation.

**Table 2.** Baseline and follow-up neuropsychological tests scores divided by group (non Caudate - nC vs Caudate - C penetration group).

| Tasks | Groups | T0 | T1 | | F value | p | PrtEta$^2$ |
|---|---|---|---|---|---|---|---|
| BWR | nC | 4.13 (0.81) | 4.09 (0.79) | Group | F(1, 43) = 0.360 | 0.552 | 0.008 |
| | C | 4.43 (0.72) | 4.17 (0.89) | Time | F(1, 43) = 1.264 | 0.267 | 0.029 |
| | | | | T × G | F(1, 43) = 1.595 | 0.213 | 0.036 |
| Digit Span | nC | 5.17 (0.89) | 5.09 (0.85) | Group | F(1, 43) = 0.117 | 0.734 | 0.003 |
| | C | 5.43 (1.12) | 5.17 (1.11) | Time | F(1, 43) = 0.24 | 0.877 | 0.001 |
| | | | | T × G | F(1, 43) = 0.477 | 0.494 | 0.011 |
| CBT | nC | 4.48 (0.51) | 4.48 (0.51) | Group | F(1, 43) = 2.61 | 0.114 | 0.057 |
| | C | 4.30 (0.70) | 4.13 (0.82) | Time | F(1, 43) = 0.073 | 0.788 | 0.002 |
| | | | | T × G | F(1, 43) = 0.482 | 0.491 | 0.011 |
| CPM | nC | 28.61 (3.19) | 28.74 (3.78) | Group | F(1, 43) = 0.352 | 0.556 | 0.008 |
| | C | 27.48 (5.25) | 27.91 (4.73) | Time | F(1, 43) = 0.002 | 0.968 | 0 |
| | | | | T × G | F(1, 43) = 0.146 | 0.704 | 0.003 |
| PAL | nC | 12.33 (2.66) | 11.28 (3.25) | Group | F(1, 43) = 0.242 | 0.625 | 0.006 |
| | C | 11.95 (3.23) | 11.94 (3.51) | Time | F(1, 43) = 2.222 | 0.143 | 0.049 |
| | | | | T × G | F(1, 43) = 2.404 | 0.128 | 0.053 |
| Visual search | nC | 46.09 (7.64) | 45.55 (8.22) | Group | F(1, 42) = 0.344 | 0.561 | 0.008 |
| | C | 44.17 (10.57) | 43.52 (11.73) | Time | F(1, 42) = 0.939 | 0.338 | 0.022 |
| | | | | T × G | F(1, 42) = 0.038 | 0.846 | 0.001 |
| TMT-B | nC | 148 (74) | 188.4 (120.1) | Group | F(1, 43) = 0.792 | 0.378 | 0.018 |
| | C | 191.2 (146.5) | 212.1 (155.6) | Time | F(1, 43) = 5.715 | 0.021 | 0.117 |
| | | | | T × G | F(1, 43) = 1.436 | 0.237 | 0.032 |
| MCST-Criteria | nC | 5.74 (1.05) | 5.65 (0.78) | Group | F(1, 41) = 0.001 | 0.970 | 0 |
| | C | 5.71 (0.56) | 5.52 (0.93) | Time | F(1, 41) = 0.058 | 0.811 | 0.001 |
| | | | | T × G | F(1, 41) = 0.389 | 0.536 | 0.009 |
| MCST-Errors | nC | 3.35 (2.29) | 4.74 (3.86) | Group | F(1,41) = 0.399 | 0.531 | 0.010 |
| | C | 5.61 (5.41) | 5.29 (7.07) | Time | F(1, 41) = 1.583 | 0.216 | 0.037 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | T × G | F(1, 41) = 1.776 | 0.190 | 0.042 |
| MCST-Persev. | nC | 1.17 (1.27) | 1.74 (1.54) | Group | F(1, 41) = 2.690 | 0.109 | 0.062 |
| | C | 2.19 (2.48) | 2.48 (2.08) | Time | F(1, 41) = 0.517 | 0.476 | 0.012 |
| | | | | T × G | F(1, 41) = 0.243 | 0.625 | 0.006 |
| PVF | nC | 46.45 (18.14) | 35.59 (16.41) | Group | F(1, 42) = 0.372 | 0.545 | 0.009 |
| | C | 42.17 (15.0) | 33.57 (12.66) | Time | F(1, 42) = 4.615 | 0.038 | 0.099 |
| | | | | T × G | F(1, 42) = 0.570 | 0.455 | 0.013 |
| SVF | nC | 23.02 (6.13) | 20.37 (4.3) | Group | F(1, 43) = 0.720 | 0.401 | 0.016 |
| | C | 21.98 (5.33) | 18.88 (4.55) | Time | F(1, 43) = 6.838 | 0.012 | 0.137 |
| | | | | T × G | F(1, 43) = 0.038 | 0.846 | 0.001 |

Mean (SD) scores and repeated-measures ANCOVAs results are shown in this table. F, p, and partial $Eta^2$ values of group factor (nC vs C group), time factor (T0 vs T1), and time × group (T×G) interaction are reported. The covariate (number of months passed from the surgery to the follow-up neuropsychological evaluations) did not shown any statistical significant effect (all $p > 0.05$), so data are not reported.

BWR, Bi-syllabic Words Repetition test; CBT, Corsi's Block Tapping test; CPM, Raven Color Progressive Matrices; PAL, Paired Associate Learning scale; TMT-B, Trail Making Test, part B; MCST, Nelson Modified Card Sorting test; PVF, Phonemic Verbal Fluency; SVF, Semantic Verbal Fluency.