

Initial cognitive dip after subthalamic deep brain stimulation in Parkinson disease

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Abstract Although many studies have shown no significant change in global cognitive function after subthalamic brain stimulation (STN DBS) in patients with Parkinson disease (PD) and have concluded that STN DBS is generally safe from a cognitive standpoint, some studies have reported a decline in global cognitive function after STN DBS. Interestingly, in some studies, the decline in cognitive function appears to be greater during the initial short period after surgery (within 6 or 12 months after surgery) than the decline thereafter. To this end, we examined whether the rate of change in global cognitive function during the initial 6 months after STN DBS was different from the mean 6-month change that occurred between 6 and 36 months after surgery. Thirty-six PD patients who

underwent bilateral STN DBS and were followed for more than 3 years were included. Change in Mini-Mental Status Examination (MMSE) score during the first 6 months after surgery was compared with the 6-month MMSE score change between 6 and 36 months after surgery. Mean MMSE change during the first 6 months after surgery was significantly greater than the mean 6-month MMSE change between 6 to 36 months after surgery. The levodopa equivalent daily dose at baseline and the score for Stroop Color-word test at baseline were significantly associated with the decline in MMSE score during the first 6 months after surgery. Our result showed that decline in global cognitive function was faster in the first 6 months after surgery, compared with that after 6 months.

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Introduction

While bilateral subthalamic deep brain stimulation (STN DBS) is an established treatment for the motor symptoms of Parkinson disease (PD), there is controversy over its effect on cognition. Many studies have shown no significant change in global cognitive function after surgery and have concluded that STN DBS is generally safe from a cognitive standpoint [1]. However, worsening of frontal executive function after STN DBS is not uncommon [1–4], and some studies have reported a decline in global cognitive function after STN DBS [5, 6]. Interestingly, in some studies, the decline in cognitive function appears to be greater during the initial short period after surgery (within 6 or 12 months after surgery) than the decline thereafter [7–11].

On that basis, we examined whether the rate of change in global cognitive function during the first 6 months after STN DBS was different from that after 6 months of surgery. We also assessed relationships between various factors and the change in global cognitive function after STN DBS.

Methods

Patients with PD who underwent bilateral STN DBS at the Seoul National University Hospital (SNUH) Movement Disorder Center (MDC) and were followed for more than 36 months after surgery were included. Patients with a preoperative MMSE score <25, repositioning of an electrode within 3 years, staged bilateral surgery, or missing follow-up MMSE scores during the 36-month follow-up period were excluded. All patients provided informed written consent and the study protocol was approved by the SNUH Institutional Review Board.

Bilateral STN DBS implantation was performed as previously described [12]. After surgery, the exact locations of the electrodes and contacts were verified using a CT-MRI fusion technique. All contacts within the boundary of the STN were used in a multiple monopolar fashion.

Preoperative and postoperative assessments were performed according to a previously described SNUH MDC protocol [12]. Motor symptoms were evaluated using the Unified Parkinson Disease Rating Scale (UPDRS). The levodopa equivalent daily dose (LEDD) was calculated as previously described [12]. Neuropsychological assessments were undertaken in the *on*-medication state before surgery and in the *ON*-stimulation *on*-medication state at postoperative follow-ups. Global cognitive function was assessed using MMSE scores as a part of a neuropsychological test battery, which includes the modified version of the Trail Making Test (TMT) A and B for attention and executive function respectively, the Korean Boston Naming Test for

language, and the Rey-Kim Memory Battery for memory. For a more thorough evaluation of the frontal executive function, a Stroop test and fluency test was administered. In the Stroop test, patients were asked to name the color of each item on three task boards as quickly as possible, the colored dots (Stroop Color), common words printed in color (Stroop Word), and names printed in colors not corresponding to the words themselves (Stroop Color-word). The fluency test involved animal and fruit names for semantic word fluency, and ‘s’ and ‘g’ sounds for phonemic word fluency [9].

Differences in the rate of change in MMSE score in specific time intervals were analyzed using a paired-*t* test. Correlations between variables and MMSE score changes were examined using Pearson’s correlation coefficient.

Results

Thirty-six patients (18 men) were enrolled. Patient characteristics at baseline and follow-up are displayed in Table 1. Baseline MMSE scores were not correlated with age, disease duration, education years, *off*-UPDRS motor score, axial subscore of *off*-UPDRS motor score, or Beck Depression Inventory (BDI) score. During the first 6 months, mean MMSE score changed from 28.0 ± 1.6 to 27.0 ± 2.4 . Among orientation, memory registration, attention, recall, language, and visuospatial function subscores of MMSE, subscore for recall was most affected. At 36 months, mean MMSE score was 26.7 ± 2.7 . Two of 36 patients had converted to dementia at 36 months.

To determine whether the rate of change in global cognitive function during the first 6 months after STN DBS differed from that in longer-term (after 6 months) periods after surgery, we compared mean change in MMSE scores during the initial 6 months after surgery to the mean 6-month change that occurred between 6 months and 36 months after surgery. Mean change in MMSE score

Table 1 Patient characteristics at baseline and follow-up (*n* = 36)

	Baseline	6 Month	12 Month	36 Month
Age	56.8 ± 8.0			
Age at onset	47.1 ± 8.8			
Disease duration	9.7 ± 4.1			
Values are expressed as mean ± SD				
<i>UPDRS</i> Unified Parkinson Disease Rating Scale, <i>LEDD</i> levodopa equivalent daily dose, <i>BDI</i> beck depression inventory, <i>MMSE</i> mini-mental status examination				
<i>Off</i> -UPDRS motor	36.6 ± 13.6	20.5 ± 12.5	19.7 ± 10.8	21.2 ± 11.0
<i>On</i> -UPDRS motor	16.8 ± 10.0	15.5 ± 9.8	15.8 ± 9.0	17.3 ± 9.6
Axial subscore of <i>off</i> -UPDRS motor	11.3 ± 4.8	6.5 ± 3.6	6.6 ± 3.3	6.9 ± 4.0
LEDD	1038.7 ± 473.9	266.4 ± 287.1	266.0 ± 317.4	296.8 ± 394.8
BDI	18.1 ± 8.5	17.8 ± 9.6	21.5 ± 10.7	24.4 ± 10.7
MMSE	28.0 ± 1.6	27.0 ± 2.4	27.2 ± 2.1	26.7 ± 2.7

during the initial 6 months was significantly greater than the 6-month MMSE change between 6 and 36 months after surgery (1.0 ± 2.1 vs 0.0 ± 0.4 , $p = 0.015$).

Next, we examined several factors that may be related to MMSE score changes during the initial 6-month period. Among the baseline characteristics examined, LEDD ($r = 0.461$, $p = 0.005$) and the axial subscore of *off*-UPDRS motor score ($r = 0.378$, $p = 0.023$) were significantly correlated with the change in MMSE score during the first 6 months, whereas age, disease duration, education years, *off*-UPDRS motor score, BDI, and MMSE score at baseline were not correlated. Postoperative LEDD reduction at 6 months after surgery also showed a correlation with the change in MMSE score during the initial 6 months after surgery ($r = 0.420$, $p = 0.011$), while change in *off*-UPDRS motor score, change in axial subscore of *off*-UPDRS motor score, and change in BDI score during the first 6 months were not correlated. Among the baseline neuropsychological test scores, poor performance in TMT B test, Stroop Word test, and Stroop Color-word test were significantly correlated with the change in MMSE score during the initial 6-month period ($r = 0.462$, $p = 0.006$; $r = 0.424$, $p = 0.012$; $r = 0.411$, $p = 0.016$).

As the initial postoperative decline in MMSE score may be related to possible brain parenchymal damage by recording or permanent electrodes, we assessed the association between the change in MMSE score in the first 6 months after surgery and the number of recording tracts during surgery. Our analysis revealed a positive correlation ($r = 0.332$, $p = 0.048$). Thus, patients with higher LEDD at baseline, higher axial subscore of *off*-UPDRS motor score at baseline, poor performance in TMT B test, Stroop Word test, and Stroop Color-word test at baseline neuropsychological test, greater number of recording tracts during surgery, and greater LEDD reduction at 6 months after surgery exhibited a greater decline in MMSE score at 6 months. Among these, multiple linear regression results indicated that LEDD at baseline and the score for Stroop Color-word test at baseline were significantly associated with the decline in MMSE score during the initial 6 months after surgery ($R^2 = 0.336$).

To see whether the above factors were also related to the postoperative decline in global cognitive function over the longer term, we searched for factors that were significantly related to the decline in MMSE score during the 36-month period. In contrast to the results for the initial 6-month period, axial subscore of *off*-UPDRS motor score at baseline, postoperative LEDD reduction, and the number of recording tracts were not significantly correlated with the decline in MMSE score during the 36-month follow-up. Among the baseline neuropsychological test scores, poor performance in TMT B test, Stroop Color-word test, and phonemic fluency test were significantly correlated with

the decline in MMSE score during the 36-month follow-up. Multiple linear regression results indicated that age at surgery and the score for TMT B test at baseline were significant predictors of decline in MMSE score during the 36-month follow-up period ($R^2 = 0.371$).

Discussion

Our results show that the decline in global cognitive function as assessed by MMSE scores is faster during the first 6 months after STN DBS than in the period from 6 to 36 months and that baseline LEDD is independently associated with this decline. In line with our results, previous studies have also described an apparently greater initial decline in cognitive function after STN DBS, although statistically not significant [7–11]. It can be argued that a faster decline during the initial period after surgery is a natural course of cognitive decline unrelated to STN DBS in PD (i.e., the higher the MMSE score, the faster its decline). However, in this study, the MMSE score at baseline was not correlated with the decline in MMSE score during the initial 6 months after surgery. Moreover, the rate of change in MMSE score during the 6-month to 12-month postoperative period and the 12-month to 36-month period were not different ($p = 0.866$). Taken together, our results indicate that an initial faster decline in MMSE scores is not reflective of a natural course of cognitive decline unrelated to surgery.

On the basis of our limited data, especially the lack of a control group and the absence of preoperative follow-up data on cognitive function, it is not clear why our patients exhibited an initial faster decline in global cognitive function followed by a slower decline. One possibility is that the greatest reduction in LEDD after surgery occurred within 6 months, and the reduction is greater (74 %) than in previous studies. Given that dopamine influences cognitive function in PD [13], an initial excessive reduction in LEDD followed by a stable dosage may explain the initial rapid decline in global cognitive function in our study. In this sense, although a large reduction in LEDD after STN DBS may be indicative of successful surgery with regard to motor symptoms, the cognitive aspect should also be considered when adjusting medications for optimal patient care. The positive correlation between the decline in MMSE score and the number of recording tracts in the initial phase after surgery suggests that transient effects of surgery, such as reversible parenchymal damage or transient brain edema by electrode, may also explain the initial rapid decline.

In addition to the number of recording tracts, baseline LEDD level, and axial subscore of the *off*-UPDRS motor score at baseline, LEDD reduction at 6 months was

significantly correlated with the decline in MMSE score during the first 6 months after surgery. Although these factors have been implicated in cognitive change in previous studies [9, 10, 14], as those studies were focused primarily on frontal executive functions, the relationship of those factors to global cognitive function has not yet been fully described. Correlation of poor performance in the tests for attention and executive function at baseline with global cognitive decline after surgery has also been shown in the studies with longer follow-up periods [6, 7]. This might indicate that the poor frontal lobe function should be taken into consideration when evaluating and selecting patients for DBS for better outcomes in terms of cognition or quality of life, although it cannot be an exclusion criterion for surgery [7]. Furthermore, given that LEDD at baseline and the score for Stroop Color-word test at baseline explain only 33.6 % of the variance in the change in MMSE score, research into additional factors should be conducted.

Interestingly, factors significantly related to global cognitive decline were different at 6 and 36 months; thus, indicating that the mechanism of cognitive decline during the initial short-term postoperative period is different from that over the long term after surgery.

This study has some limitations. First, we assessed global cognitive function using MMSE, which bears some problems evaluating global cognitive function in PD. Second, due to the lack of a control group, we could not distinguish between the observed findings due to the effect of STN DBS versus the natural course. Lastly, we excluded patients with missing follow-up MMSE scores. If missing an MMSE is related to a patient's cognitive status, our results would have been biased.

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