Neuropsychological and psychiatric assessments following bilateral deep brain stimulation of the sub-thalamic nucleus in Japanese patients with Parkinson's disease

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Running title: Mental changes in PD with STN-DBS

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Abstract

The physical benefits of sub-thalamic nucleus deep brain stimulation (STN-DBS) in Parkinson's disease (PD) patients are well documented, but the mental benefits are uncertain, particularly in Japanese patients. This study evaluated the clinical and neuropsychological characteristics before and after STN-DBS surgery in Japanese PD patients. PD patients (n=13, age 67.0 ± 7.8 years) were evaluated pre-surgery (baseline) and at one and six months post-surgery by two trained psychiatrists . The motor symptoms were assessed by the Unified Parkinson's Disease Rating Scale (UPDRS) motor score. The neuropsychological and psychiatric tests performed were the Mini-Mental State Examination, the Wisconsin card sorting test (WCST), the verbal fluency test (VFT), the Hamilton Depression Rating Scale and the Hamilton Anxiety Rating Scale (HAM-A). The UPDRS motor score ($P<0.001$) and HAM-A score ($P=0.004$) showed significant improvement at one month post-surgery, but a significant decline was observed in the WCST total error ($P=0.005$) and the semantic VFT score

(P<0.001) . The phonetic VFT also showed a substantial decline (P=0.015) at one month post-surgery. At six months post-surgery, the improvement in the UPDRS motor score was maintained, and the scores on the neuropsychological and psychiatric tests had returned to baseline. Although bilateral STN-DBS did not appear to have long-term effects on the neuropsychological and psychiatric outcomes, the microlesion effects associated with STN-DBS appear to increase the risk of transient cognitive and psychiatric complications. These complications should be monitored by careful observation of neurological and psychiatric symptoms.

Keywords: Parkinson's disease, deep brain stimulation, subthalamic nucleus, cognitive function, anxiety

Introduction

Parkinson's disease (PD) typically develops between the ages of 55 and 65 years, and approximately 0.15% of the general population in Japan is diagnosed with PD. Treatment of the advanced stages of PD is a major challenge for modern medicine, and deep brain stimulation (DBS) of the sub-thalamic nucleus (STN) represents the most important innovation for treatment of advanced PD since the discovery of levodopa. STN-DBS is a valid and safe advancement in the treatment of patients with idiopathic and refractory PD. Several studies have shown a significant reduction of the motor symptoms, dopaminergic treatment dose and duration and severity of dyskinesia in STN-stimulated PD patients [1].

Neuropsychological evidence supports the safety of STN-DBS. A meta-analysis revealed that the most common cognitive side effect after STN-DBS surgery was a reduction in verbal fluency in the phonemic and semantic domains[2]. This decrease in verbal fluency is hypothesised to be an effect of surgical electrode implantation rather than an effect of stimulation[3].

Modest but significant improvements in symptoms of depression have been shown after STN-DBS[4]; however, both depression and mania can occur after STN-DBS[5]. Apathy or lack of motivation has been described after STN-DBS[6]. Comparisons of pre-

and post-operative neuropsychological and psychiatric characteristics do not permit the determination of whether the observed changes are related to the surgical intervention, changes in medication or the stimulation itself. Comparisons over a long period of time must take into account the evolution of the disease.

An alternative method for studying the effects of STN-DBS on neuropsychological and psychiatric function is to compare the patients' performance when the stimulators are turned on with the performance when the simulators are turned off. Studies using this methodology have shown that STN-DBS could improve some executive functions, with improved scores observed on the trail making test, the random generation test, the Wisconsin card sorting test (WCST) and the working memory test[7, 8]. Visual conditional learning is impaired by STN-DBS, and patients make a greater number of errors on the interference condition of the Stroop test when stimulators are turned on[8]. Acute changes of mood that are specifically related to STN-DBS have been reported. An assessment of the acute subjective psychic effects of STN-DBS showed psychic stimulation, euphoria, increased motivation, and decreased fatigue, anxiety, and tension when stimulators were turned on[9, 10]. These psychological changes have the potential to influence performance on the cognitive tests. The aim of this study was to assess simultaneously the effects of bilateral STN-DBS on cognitive function, depression and anxiety in Japanese PD

patients.

Methods

Patients

Thirteen consecutive patients (six male, seven female; 67.0 ± 7.8 years old, mean duration of disease 8.1 ± 4.4 years) who had been experiencing levodopa-sensitive PD with severe on/off fluctuations and who were scheduled for surgery for bilaterally implanted STN-DBS at Naruto Health Insurance Hospital in Tokushima, Japan between May 2003 and July 2004 participated in the study. All the patients provided written and informed consent. The inclusion criteria were the absence of relevant cognitive decline and the absence of a clinical diagnosis of mental disorders, including major depression. Quadripolar DBS electrodes were implanted bilaterally with stereotactic guidance under local anaesthesia. The target localisation was based on the atlas and on direct visualisation on the magnetic resonance image using surgical planning software. The target was further identified physiologically by intraoperative microelectrode recording. The optimal contact for stimulation was selected based on the best motor response. The PD patients underwent motor, cognitive, mood and anxiety assessments pre-surgery (baseline) and one and six months post-surgery in the medication-on and stimulation-on

condition. The motor symptoms were assessed using section III of the Unified Parkinson's Disease Rating Scale (UPDRS). The motor improvement induced by STN-DBS was assessed using the UPDRS section III in the pre-operative medication-on condition as the baseline condition. The dose of antiparkinsonian medication was calculated as the levodopa equivalent daily dosage (LEDD). Table 1 shows the clinical characteristics of the PD patients.

Neuropsychological and psychiatric assessments

The neuropsychological and psychiatric tests performed were the Mini-Mental State Examination (MMSE) for general cognitive function, the Wisconsin card-sorting test (WCST) and the verbal fluency test (VFT) for frontal executive function, the Hamilton Depression Rating Scale (HAM-D) for depression and the Hamilton Anxiety Rating Scale (HAM-A) for anxiety. The same trained psychiatrists (M.S. and S.U.) conducted all the evaluations.

Statistical analysis

A one-way repeated measures analysis of variance was used to compare the results across time (pre-surgery, one month post-surgery, six months post-surgery). The P values were adjusted using the Bonferroni correction. If there were a significant effect of time ($P<0.01$), post hoc comparisons were performed using Dunnett's test.

Spearman's test was used to quantify the correlations among the changes in the WCST total error, the semantic VFT and the HAM-A scores from baseline to one month post-surgery, the changes in the UPDRS section III score and the LEDD from baseline to one month post-surgery, the stimulation parameters (right and left STN voltage), the age of the patient and the duration of illness.

Results

Motor symptoms and LEDD

A significant improvement in motor symptoms from baseline to one month post-surgery (Dunnett's test $P<0.001$; Table 1) was observed. The improvement in motor symptoms was maintained at six months post-surgery (Dunnett's test $P<0.001$; Table 1). The LEDD values at one month and six months post-surgery were 76.6% and 96.9% of the pre-surgery LEDD value, respectively (Table 1). We adjusted the medication and the stimulation based only on the motor symptoms. The preoperative mean LEDD of 289 mg is quite smaller than those observed in other studies. In other studies, the patients appear to be offered surgery only when medication therapy had failed (highly advanced and refractory stage PD with a high LEDD), whereas we offered surgery to patients in a less advanced stage of PD. The mean duration of disease

of 8.1 years was relatively shorter than those observed in other studies.

Neuropsychological and psychiatric tests

A significant main effect of time on the WCST total error ($P=0.005$), the semantic VFT score ($P<0.001$) and the HAM-A score ($P=0.004$) was evident. The phonetic VFT score showed a substantial change ($P=0.015$). A post hoc analysis revealed that the WCST total error and the semantic VFT score were worse at one month post-surgery than at baseline; however, these changes were diminished at six months post-surgery (Table 1). The HAM-A score had improved at one month post-surgery (Table 1). No effects of time on the MMSE or the HAM-D score (Table 1) were found.

Correlations

The UPDRS motor score at baseline did not show a correlation between the neuropsychological or psychiatric tests at baseline. The change in the UPDRS motor score from baseline to one month post-surgery did not correlate with the change in any neuropsychological or psychiatric test. The change in the WCST total error from baseline to one month post-surgery was not correlated with the change in the semantic VFT score or any other neurological or clinical variables. The change in the semantic VFT score from baseline to one month post-surgery was positively correlated with the change in the phonetic VFT score ($r=0.65$, $P=0.015$) and negatively correlated with the

change in the HAM-A score (r=-0.55, P=0.05).

Discussion

There are two major findings of our investigation. First, mild cognitive declines in frontal executive function (assessed by the VFT and the WCST) were observed at one month post-surgery but had diminished at six months post-surgery. Second, a transient improvement in anxiety (assessed by the HAM-A) and a tendency for improved depression levels (assessed by the HAM-D) were observed at one month post-surgery.

The first finding suggests that cognitive declines at one month might be because of microlesion effects, such as focal oedema, that reflect a traumatic tissue reaction induced by the insertion of the electrodes[11]. The cognitive decline could not be because of a reduction in dopaminergic treatment, depressive mood, apathy or state of confusion because the decline in the VFT and the WCST scores was not correlated with the decline in the LEDD, the HAM-D and HAM-A scores that changed in the opposite direction, and the MMSE score at one month post-surgery was similar to that at baseline.

The transient cognitive decline observed is consistent with a meta-analysis that revealed significant declines in the semantic (Cohen's d=0.73) and the phonemic

(d=0.51) VFT that were not related to the patient age, disease duration, and stimulation parameters or the change in the LEDD[2]. Previous reports have shown that the WCST improved with STN-DBS, whereas it declined with deep brain stimulation of the internal segment of the globus pallidus (GPi-DBS)[8] and did not change at six months and one year after STN-DBS surgery[12].

The transient declines in the neurocognitive domains after STN-DBS did not interfere with everyday functioning in our study (assuming the decline does not propel a patient beyond the threshold associated with disability or handicap). The verbal fluency performance makes significant independent contributions to the prediction of the instrumental activities of daily living as reported by a caregiver[13], and the WCST significantly predicts the instrumental activities of daily living in older adults[14].

The second finding about transient improvement in anxiety and a tendency for improved depression levels is consistent with previous reports showing that the favourable effects of STN-DBS on anxiety and depression were transient[15-17]. The improvement in the HAM-A score at one month post-surgery was negatively correlated with the decline in the semantic VFT score. The role of the STN in the regulation of emotional responses and behaviour is becoming increasingly clear, and several neuroimaging studies have reported DBS-induced changes at the level of the cortical

and subcortical associative and limbic regions[18-20]. Such a potent influence on associative, limbic, and motor functions has not been observed with other DBS targets such as the GPi or the thalamus.

We did not find any correlations between the improvement of each item of the HAM-A or the HAM-D and the improvement of the UPDRS motor score; however, a significant main effect of time on anxiety and somatic (muscular), cardiovascular and gastrointestinal symptoms in the HAM-A items was evident (data not shown). The transient improvement of the HAM-A score might be associated with the direct effects on STN-DBS and with the improvement of somatic symptoms. Studies have shown the presence of the microlesion effect in the early postoperative period (approximately six months), and the effect is greater with STN compared with GPi[21, 22].

Acknowledgements

The authors are extremely grateful to the patients for participating in this research. A Health and Labor Science Research Grant from the Japanese Ministry of Health, Labour and Welfare supported this work. The authors have no conflicts of interest.

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Table 1: Clinical characteristics of the 13 Parkinson's disease patients who underwent STN-DBS

	Baseline	one month	six months	ANOVA P
Clinical characteristic				
LEDD (mg/day)	281.9 ± 154.4	215.9 ± 104.6	273.3 ± 172.0	0.224
UPDRS III	27.8 ± 12.4	11.3 ± 7.1 *	18.7 ± 10.2*	**0.001**
Right STN Voltage (V)	-	2.5 ± 0.7	3.3 ± 1.0	
Left STN Voltage (V)	-	2.3 ± 0.5	3.4 ± 1.1	
Neuropsychological tests				
MMSE	26.3 ± 1.6	24.6 ± 3.6	26.8 ± 2.4	0.043
WCST categories achieved	2.9 ± 1.9	2.1 ± 1.9	3.1 ± 1.9	0.129
WCST total error	19.7 ± 9.1	27.5 ± 9.3 *	20.2 ± 9.8	**0.005**
WCST perseverative errors in Nelson	6.1 ± 5.8	11.1 ± 9.4	6.9 ± 5.9	0.029
WCST perseverative errors in Milner	3.3 ± 5.8	4.6 ± 7.1	2.8 ± 5.1	0.429
Phonetic verbal fluency	19.5 ± 6.5	14.2 ± 6.2	17.4 ± 7.5	0.015
Semantic verbal fluency	31.9 ± 5.7	22.8 ± 6.8 *	29.2 ± 9.3	**0.001**
Psychiatric tests				
HAM-D 17	4.8 ± 2.5	3.4 ± 2.2	3.7 ± 2.2	0.152
HAM-D 21	5.5 ± 2.8	3.5 ± 2.5	3.8 ± 2.3	0.037
HAM-A	8.9 ± 5.0	5.1 ± 3.3*	6.2 ± 3.3	**0.004**

The data are presented as the mean ± SD. The P values are from a one-way repeated analysis of variance. * indicates $P<0.05$ when compared to baseline using Dunnett's test. LEDD=L-dopa equivalent daily dose; UPDRS III=unified Parkinson's disease rating scale III; MMSE=mini mental state examination; WCST=Wisconsin card sorting test; HAM-D= Hamilton rating scale for depression; HAM-A= Hamilton rating scale for anxiety