Prefrontal dysfunction following unilateral posteroventral pallidotomy in Parkinson's disease

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Object. Pre- and postoperative cognitive function were evaluated in 25 patients with Parkinson's disease (PD) who underwent unilateral posteroventral pallidotomy (PVP) to clarify the effects of this operation on cognitive function.

Methods. Cognitive function was assessed before surgery and 1 month and 3 months afterward by using a battery of neuropsychological tests consisting of orientation, digit span (forward and backward), digit learning, 5-minute memory of five words, similarities, serial sevens, animal name listing, and the kana pick-out test, as well as the Japanese version of the Mini-Mental State. Preoperative evaluation revealed that patients experienced difficulties in performing the neuropsychological tasks of reasoning and abstraction, working memory of numerals, word fluency, and concept formation compared with 36 healthy volunteers ($p < 0.05$). A simple regression analysis showed strong relationships in a negative fashion between preoperative ($r = 0.81$, $p = 0.002$) and 1-month ($r = 0.79$, $p = 0.0059$) and 3-month ($r = 0.85$, $p = 0.0016$) postoperative gross-total scores and Hoehn and Yahr staging. Preoperative and postoperative scores at 1 month and 3 months were analyzed by analysis of variance, but only the Fisher's post hoc test revealed the source of difference. All tasks except orientation ($p = 0.0292$) were unchanged in the 10 patients who underwent surgery on the right side. The scores for this task at 1 month postsurgery were significantly lower ($p = 0.0203$) but improved to preoperative values by 3 months. In the 15 patients who underwent surgery on the left side significant differences among tasks were revealed for serial sevens ($p = 0.0471$) and animal naming ($p = 0.0425$). The scores for these tasks were significantly lower at 1 month postoperatively ($p = 0.0431$ for serial sevens and $p = 0.0408$ for animal naming), but improved by 3 months after the operation.

Conclusions. The present data revealed that cognitive dysfunction in patients with PD relates to advancement of Hoehn and Yahr stage, but PVP is not associated with significant long-lasting cognitive deficits.

Key Words * cognitive impairment * frontal lobe * basal ganglion * Parkinson's disease * pallidotomy

Neuropsychological studies have demonstrated that Parkinson's disease (PD) is associated with various cognitive deficits, ultimately leading to the development of dementia in approximately 30% of patients.[1] These deficits have been reported to be detected even during the early stage of PD[17,24,25,33] and are thought to be derived from disturbance of frontobasal ganglia circuits.[29,33,34,38,39] Many authors have reported that posteroventral pallidotomy (PVP) effectively alleviates rigidity, bradykinesia, and tremor and has therefore become a common surgical treatment for PD.[6,11,16,18,22] However, lesioning of the globus pallidus internus during PVP is anticipated to affect postoperative cognitive function in patients with PD. Much attention has recently been focused on cognitive changes that occur following PVP, in an effort to reveal the procedure's effects on cognitive function and neuropsychological properties of the basal ganglia.[26,27,36,37] To elucidate these effects, we studied pre- and postoperative cognitive function in patients who underwent PVP.

We retrospectively analyzed pre- and postoperative cognitive function, as assessed using a neuropsychological battery of tests known as Hamamatsu Higher Brain Function Scales[19,21,40,41] in patients who underwent unilateral PVP to clarify its effects on cognitive function.

CLINICAL MATERIAL AND METHODS

Patient Population

Among 37 patients who underwent unilateral PVP, 25 right-handed patients whose cognitive function was evaluated 1 week before and 1 month and 3 months after surgery served as the participants in this study. The group was composed of 13 men and 12 women ranging in age from 54 to 80 years with a mean age of 65.1 ± 6.6 years (mean $\pm$ standard deviation). The remaining 12 patients were excluded from this study because they had bilateral lesion sites; in seven patients the second site was located in the ipsilateral thalamus and in five patients it was in the contralateral globus pallidus internus.

Surgical Technique

After application of a local anesthetic, the patient's head was secured to a Todd-Well's stereotactic frame and a frontal burr hole was made 3 cm lateral to the midline and just in front of the coronal suture. The initial target was determined on the basis of ventriculography of the third ventricle, 2 to 3 mm anterior to the midintercommissural point, 5 mm below the intercommissural line, and 18 to 20 mm lateral to the midline. The location of the optic tract was first determined using intracerebral recordings of visual evoked potentials,[45] and the target was coordinated 1 to 2 mm lateral to the midpoint of the optic tract, which was usually located at the lateral end of the optic tract, 5 mm above its dorsal surface. The neural activities along this trajectory were recorded with the aid of a microelectrode. Finally, one or two lesions were made using an electrode with a diameter of 1.1 mm and a 5-mm bare tip (Radionics, Burlington, MA) set at 70°C for 1 minute.

Neuropsychological Examination

The battery of neuropsychological tests consisted of orientation, digit span (forward and backward), digit learning, 5-minute memory of five words, similarities, serial sevens, animal name listing, and the kana pick-out test,[19,21,40,41] as well as the Japanese version of the Mini-Mental State (MMS).[8,12,28] Kanas are Japanese phonetic letters that consist of five-vowel letters, 46 consonant-vowel letters, and one consonant letter. In the Japanese kana pick-out test,[21] a story written only with kanas is presented to the examinee who is asked to circle only vowel letters, as many as possible within 2 minutes (kana pick-out, story), while at the same time retaining the meaning of the story (kana pick-out, meaning). Our

neuropsychological battery was designed primarily to assess prefrontal or frontal lobe function with tasks presumed to be related to these functions (digit span, digit learning, similarity, serial sevens, animal naming, and kana pick-out), as well as gross cognitive function of parietotemporal areas (5-minute memory and MMS), and to accomplish the test within 20 to 30 minutes to maintain the patient in a relatively constant state of alertness throughout the examinations. With the exception of the MMS, the battery of tasks has been called the Hamamatsu Higher Brain Function Test in our country and has proved to be useful for evaluating prefrontal or frontal lobe function in more than 500 patients.[19,21,40,41]

Control Data

Control data for this study were obtained from 36 healthy volunteers aged 60 to 70 years (mean 65.5 ± 4.2 years) who were tested on neuropsychological tasks with instruments other than the MMS and from 12 of the 36 volunteers (mean age of 66.6 ± 2.2 years) who were tested using the MMS. The volunteers' ages matched those of the patients. The distribution of raw scores for each task undertaken by the healthy volunteers was converted into a scale with a mean scaled score of 10 and a standard deviation of 3 except for the MMS.[42] These scaled scores were used for converting patients' raw scores to scaled scores, which allowed easy assessment of the patient's task performance. The cognitive domains of our neuropsychological tasks and the mean scores obtained from control volunteers are presented in Table 1. The cognitive domain of working memory[5,13,29,32] was classified into three types according to content matter, that is, working memory of numerical, verbal, and concept formation tasks.

TABLE 1		
COGNITIVE DOMAINS AND SCORES FOR RESPECTIVE TASKS IN HEALTHY VOLUNTEERS*		
Cognitive Domains	Neuropsychological Tasks	Mean Score
temporal orientation	orientation	10.0 ± 0
numerical working memory	digit span	10.8 ± 1.8
numerical working memory	digit span (back ward)	10.0 ± 2.1
immediate memory	digit learning	7.4 ± 5.6
immediate memory	immediate recall (5 words)	8.5 ± 2.7
short-term memory	5-minute memory (5 words)	7.8 ± 5.1
reasoning & abstraction	similarity	10.3 ± 2.2
numerical working memory	serial sevens	11.1 ± 1.8
word fluency	animal naming	12.3 ± 3.6
verbal working memory	kana pick-out (story)	10.3 ± 3.5
concept working memory	kana pick-out (meaning)	11.3 ± 3.6
gross cognitive functions	MMS	29.0 ± 1.2
* Values are expressed as the mean ± standard deviation.		

RESULTS

The patients were classified into two groups according to the side on which surgery had been performed: the left side in 15 patients and the right side in 10 patients. The patients' ages, preoperative modified Hoehn and Yahr stage,[23] and mean dose of levodopa and carbidopa are presented in Table 2. There were no significant differences in patient age, Hoehn and Yahr stage, or medication dose between the two groups (unpaired t-test, p < 0.05).

TABLE 2 CHARACTERISTICS OF PATIENT GROUP				
Op Side	No. of Patients	Mean Age (range)	Modified Hoehr & Yahr Stage (range)	Levodopa & Carbidopa (mg)
lt	15	65.1 ± 5.8 (56–76)	2.6 ± 0.7 (1.5–4.0)	333.3 ± 175.9
rt	10	64.1 ± 8.3 (54–80)	2.4 ± 0.7 (1.5–4.0)	350.0 ± 117.8
total	25	65.1 ± 6.6 (54–80)	2.5 ± 0.7 (1.5–4.0)	340.0 ± 152.7
* Values are expressed as the mean ± standard deviation. There were no significant differences in age, Hoehr and Yahr stage, or medication dosage between groups (p > 0.5, unpaired t-test).				

Preoperative scores for each task undertaken by patients are presented in Table 3. No statistically significant differences in the mean scores of respective tasks were noted between patients in whom lesions were made on the left side and those in whom lesions were made on the right side (unpaired t-test, $p < 0.05$). However, the scores for similarity, animal naming, and MMS in the patients who underwent surgery on the right side and those of similarity, serial sevens, animal naming, and kana pick-out, meaning, in patients who underwent surgery on the left side were significantly lower than those of the healthy volunteers (unpaired t-test, $p < 0.05$). This demonstrates that our patients encountered difficulties in performing the neuropsychological tasks of reasoning and abstraction (similarity), word fluency (animal naming), and working memory of numerals (serial sevens) and concept (kana pick-out, meaning) compared with healthy volunteers of the same ages.

TABLE 3 COMPARISON OF PREOPERATIVE SCORES OF PATIENTS WITH SCORES OF HEALTHY VOLUNTEERS*			
Neuropsychological Tasks	Healthy Control Scores	Preop Scores	
		Rt Side Op (10 patients)	Lt Side Op (15 patients)
orientation	10.0 ± 0	9.6 ± 0.5	9.3 ± 1.0
digit span	10.8 ± 1.8	10.8 ± 1.6	10.5 ± 2.7
digit span (back ward)	10.0 ± 2.1	7.5 ± 3.4	9.7 ± 2.7
digit learning	7.4 ± 5.6	5.7 ± 3.1	6.1 ± 3.1
immediate recall (5 words)	8.5 ± 2.7	6.8 ± 2.8	7.4 ± 3.3
5-minute memory (5 words)	7.8 ± 5.1	9.0 ± 5.3	9.0 ± 5.2
similarity	10.3 ± 2.2	8.5 ± 2.4†	7.6 ± 3.8†
serial sevens	11.1 ± 1.8	9.3 ± 2.8	8.8 ± 3.5
animal naming	12.3 ± 3.6	8.2 ± 2.7†	8.7 ± 2.7†
kana pick-out (story)	10.3 ± 3.5	7.8 ± 1.6	8.0 ± 3.2
kana pick-out (meaning)	11.3 ± 3.6	7.7 ± 3.0	6.8 ± 3.4†
MMS	29.0 ± 1.2	27.7 ± 1.9†	28.5 ± 5.1
* Values are expressed as the mean ± standard deviation.			
† Significantly lower than those of healthy control scores ($p < 0.05$, unpaired t-test).			

Cognitive function before and after surgery was studied by correlating the sum of the respective task scores with patient age and Hoehn and Yahr stage before surgery. A simple regression analysis showed no significant relationships between the scores obtained at the three periods and age ($r = 0.284$ – 0.31 , $p = 0.1608$ – 0.1999), but did show strong inverse relationships between preoperative ($r = 0.81$, $p = 0.002$), 1-month ($r = 0.79$, $p = 0.0059$), and 3-month ($r = 0.85$, $p = 0.0016$) postoperative periods and the patient's Hoehn and Yahr stage (Fig. 1). In general, the higher the Hoehn and Yahr stage before surgery, the lower

the neuropsychological scores, indicating that pre- and postoperative cognitive function impairment depended on the state of the patient's PD.

Fig. 1. Scatterplots showing preoperative (left) and postoperative (right) neuropsychological scores, for comparison with Hoehn and Yahr (H & Y) staging. Solid lines and open squares indicate scores before the operation (left) or at 1 month after surgery (right) and dotted lines and solid circles indicate those at 3 months postoperatively (right). A simple regression analysis showed strong inverse relationships between the preoperative period ($r = 0.81$, $p = 0.002$) and the 1-month ($r = 0.79$, $p = 0.0059$) and 3-month ($r = 0.85$, $p = 0.0016$) postoperative periods and H & Y staging.

Preoperative and postoperative scores at 1 month and 3 months were analyzed by analysis of variance, and Fisher's, Scheffé's, and the Bonferroni post hoc tests were used to reveal the source of difference. Neuropsychological scores of patients in whom lesions were made on the right side are shown in Table 4. Postoperative scores were unchanged, with no statistically significant variance for patients in whom lesions were made on the right side for all tasks except orientation ($p = 0.0292$, Fisher's test). The scores for this task performed at 1 month after the operation were significantly lower than those scores for the task performed preoperatively and 3 months postoperatively ($p = 0.0203$, Fisher's test). In other words, the patients who underwent surgery on the right side demonstrated transient impairment of temporal orientation 1 month after the operation. Table 4 also shows the results of an analysis of scores of patients in whom lesions were made on the left side. Significant differences among tasks were revealed for serial sevens ($p = 0.0471$, Fisher's test) and animal naming ($p = 0.0425$, Fisher's test). The scores for these tasks were significantly lower at 1 month postoperatively ($p = 0.0431$ for serial sevens and $p = 0.0408$ for animal naming, Fisher's test) but improved to preoperative values by 3 months postoperatively. This indicates that numerical working memory (serial sevens) and word fluency (animal naming) were only transiently impaired after surgery. However, it was noted that these significantly lower scores at the 1-month postoperative period were revealed only when Fisher's test was applied and that no difference was discerned with Scheffé's and the Bonferroni tests.

Neuro- psychological Tasks	Healthy Control Scores	Patient Scores			
		Rt Side Op		Lt Side Op	
		Score	p Value	Score	p Value
orientation					
preop	10.0 ± 0	9.6 ± 0.5		9.3 ± 1.0	
1 mo		6.7 ± 1.3	0.0292†	8.7 ± 1.9	0.5311
3 mo		9.1 ± 1.1		9.0 ± 1.3	
digit span					
pre-op	10.8 ± 1.8	10.8 ± 1.6		10.5 ± 2.7	
1 mo		11.0 ± 2.4	0.9915	9.7 ± 3.3	0.7456
3 mo		10.2 ± 3.1		9.6 ± 3.6	
digit span (back)					
preop	10.0 ± 2.1	7.5 ± 3.4		9.7 ± 3.6	
1 mo		8.3 ± 4.7	0.8997	8.2 ± 4.7	0.6405
3 mo		8.3 ± 4.7		9.0 ± 4.1	
digit learning					
preop	7.4 ± 5.6	5.7 ± 3.1		6.1 ± 3.1	
1 mo		5.6 ± 3.9	0.7938	6.2 ± 3.9	0.7013
3 mo		5.9 ± 3.5		5.8 ± 3.7	
5-word recall					

immediate	8.5 ± 2.7				
pre-op		6.8 ± 2.8		7.4 ± 3.3	
1 mo		7.7 ± 4.0	0.1540	5.5 ± 3.3	0.3675
3 mo		6.5 ± 3.9		6.5 ± 3.9	
5 mins	7.8 ± 5.1				
preop		9.0 ± 5.3		9.0 ± 5.2	
1 mo		7.1 ± 2.0	0.2468	6.4 ± 4.2	0.1742
3 mo		7.6 ± 1.8		8.6 ± 4.8	
similarity					
preop	10.3 ± 2.2	8.5 ± 2.4		7.6 ± 3.8	
1 mo		8.3 ± 2.1	0.3470	6.7 ± 3.5	0.7805
3 mo		7.8 ± 1.8		7.4 ± 3.5	
serial sevens					
preop	11.1 ± 1.8	9.3 ± 2.8		8.8 ± 3.5	
1 mo		9.0 ± 2.7	0.8936	6.7 ± 4.7	0.0471†
3 mo		8.9 ± 2.1		8.0 ± 4.4	
animal naming					
preop	12.3 ± 3.6	8.2 ± 2.7		8.7 ± 2.7	
1 mo		8.0 ± 2.8	0.9772	6.8 ± 3.4	0.0425‡
3 mo		7.8 ± 2.3		7.7 ± 3.2	
kana pick-out					
story	10.3 ± 3.5				
preop		7.8 ± 1.6		8.0 ± 3.2	
1 mo		6.6 ± 2.5	0.2326	5.2 ± 3.4	0.0597
3 mo		7.6 ± 1.6		6.2 ± 3.7	
meaning	11.3 ± 3.6				
preop		7.7 ± 3.0		6.8 ± 3.4	
1 mo		5.6 ± 3.4	0.5023	5.7 ± 4.4	0.6268
3 mo		6.6 ± 3.3		5.8 ± 4.5	
MMS					
preop	29.0 ± 1.2	27.7 ± 1.9		28.5 ± 5.1	
1 mo		26.3 ± 2.9	0.4029	24.2 ± 5.4	0.7323
3 mo		25.8 ± 3.2		25.1 ± 5.8	

* Values are expressed as the mean ± standard deviation.

† We found that in patients who underwent surgery on the right side, the postoperative scores for all tasks except orientation ($p = 0.0292$, Fisher's test) were unchanged with no statistically significant variance. The scores for this task at 1 month after the operation were significantly lower ($p = 0.0203$, Fisher's test), but improved to preoperative values by 3 months after the operation.

‡ In patients who underwent surgery on the left side, analysis of variance showed a significant difference among tasks for serial sevens and animal naming. The scores for these tasks were significantly lower at 1 month after the operation ($p = 0.0431$ for serial sevens and $p = 0.0408$ for animal naming), but improved by 3 months after the operation.

DISCUSSION

Extensive neuropsychological studies in patients with PD and other basal ganglia disorders have revealed a syndrome of subcortical dementia that relates to cognitive dysfunction associated with impaired activities of the basal ganglia.[1,15,20,24,26,33,34,39] These studies revealed numerous cognitive disturbances of working memory,[13,29] word fluency,[15] procedural memory,[4] visuospatial memory,[33] and attention,[9,10,31,43,44] suggesting the importance of brain dopamine to cognitive functioning. The results of recent neuroanatomical studies suggest that regions of the striatum are linked via a neuronal loop involving the thalamus to the dorsolateral prefrontal, lateral orbitofrontal, and anterior cingulate areas.[2,3] This indicates that depletion of brain dopamine in patients with PD results in impairment of frontal lobe function. However significant the cognitive dysfunction is reported to be in patients who have PD, as assessed by various neuropsychological tests,[1,15,24,26,33,35,39] it remains unclear which cognitive components depend on prefrontal or other frontal cortical functions. Recent studies in which positron emission tomography scanning and/or regional cerebral blood flow

measurement have been used have revealed that tasks related to word fluency were associated with increased activity in the prefrontal lobe,[14] and the prefrontal lobe has been considered to play an important role in performing numerical and verbal working memory tasks in conjunction with the parietal or temporal lobe.[30,32,35] Other cognitive domains are considered to reflect primarily frontal lobe functions, a determination based on clinical studies;[7,19,34,40,41] the corresponding tasks have not been applied to functional imaging because they are complicated to perform and it is difficult to maintain the patient in a constant cognitive state for several minutes. Our patients demonstrated preoperative cognitive dysfunction in word fluency (animal naming) and working memory of numerical (serial sevens) and verbal (kana pick-out, meaning) tasks and a linear relationship between the Hoehn and Yahr stage and the sum of respective task scores. This relationship was also observed after the operation, suggesting that cognitive dysfunction in patients with PD is associated with impaired activities of the prefrontal lobe, and prefrontal function deteriorates as the Hoehn and Yahr stage of the disease advances.

Recently studies on cognitive function following PVP have been increasing in number and there have been a few brief reports and one full study.[26,27,36,37] Discrepant results have been reported with no cognitive deficits found in two studies[26,36] and deficits of working memory and word fluency after PVP found in two others.[27,37] Our 1-month postoperative follow-up data showed working memory of numerical task and word fluency to be disturbed in patients in whom the lesion was made on the left side, whereas only temporal orientation was disturbed in those in whom the lesion was made on the right side. However, it is noteworthy that these statistically significant differences appeared only when the less conservative Fisher's test was applied and disappeared when more conservative tests (Scheffé's test and the Bonferroni test) were used. We infer from our data that the discrepant results of studies on postoperative cognitive function[26,27,36,37] are probably derived from the test used for statistical analysis, that is, a significant long-lasting cognitive effect of pallidotomy was not evident when the more conservative test was applied to reveal the source of statistically significant difference. However, it should be noted that patients with advanced PD may have a potential risk for postoperative cognitive dysfunction, because cognitive dysfunction in patients with PD is associated with advancement of Hoehn and Yahr stage.

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