Cognitive functions in Parkinson's disease: Relation to disease severity and hallucination

Takaaki Wakamori [a], Takashi Agari [a,*], Takao Yasuhara [a], Masahiro Kameda [a], Akihiko Kondo [a], Aiko Shinko [a], Susumu Sasada [a], Tatsuya Sasaki [a], Tomohisa Furuta [b], and Isao Date [a]

[a] *Department of Neurological Surgery, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Japan*

[b] *Department of Psychology, Kibi International University, Japan*

* Corresponding author: Takashi Agari

Department of Neurological Surgery, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, 2-5-1 Shikata-cho, Okayama 700-8558, Japan. Tel.: +86 235 7336

E-mail: agarit@cc.okayama-u.ac.jp

Keywords: Parkinson's disease; cognitive functions; disease severity; hallucinations; SPECT.

Short Title: Cognitive functions in Parkinson's disease

Word count: 2,594 words, **Abstract:** 247 words

Number of references: 26

Abstract

Objective: We wished to relate severity of Parkinson's disease (PD) with cognitive function in relation to cerebral blood flow (CBF).

Methods: Eighty-one consecutive PD patients were enrolled in this study. We used Mini-Mental State Examination (MMSE) and Wechsler Adult Intelligence Scale-Third edition (WAIS-III) to evaluate cognitive functions, and three-dimensional stereotactic ROI template (3DSRT) and Statistical Parametric Mapping (SPM) 8 to evaluate single photon emission CT (SPECT) recordings of regional CBF.

Results: The mean MMSE score of PD patients was 27.4 ± 2.4. The scores of most patients were higher than 23/30. On the other hand, the mean Full-scale IQ of PD patients was 88.4 ± 17.3 in WAIS-III, which was lower than that of normal controls. In particular, visuospatial function score of most patients was lower. There were significant correlation between cognitive scores and Hoehn & Yahr stage and hallucinatory episodes. PD Patients with stage III and IV showed significant deterioration in cognitive functions compared to stage II patients. Analysis of CBF revealed relative reductions in perfusion in the cerebral cortex

relative to that in normal control. SPM 8 showed that cognitive functions in PD patients were positively correlated with rCBF in the thalamus and cingulate gyrus.

Conclusions: This is the study to demonstrate the cognitive impairments in PD patients using WAIS-III. Visuospatial dysfunction might be caused by decrease in rCBF in the parietal and occipital lobes and dorsolateral prefrontal cortex. The severity of cognitive impairments in PD patients was correlated with disease severity and hallucinatory episodes.

1. Introduction

Cognitive impairments are one of the most common non-motor symptoms in patients with Parkinson's disease (PD). Subtle cognitive impairments that usually progress to more severe cognitive impairments and dementia may exist from the initial stage of PD. Cognitive impairments may be ascribed to dopaminergic depletion and failure of the fronto-striatal basal ganglia circuits [1]. Patients with PD have a four- to six-fold increase in the risk of developing dementia compared to the age-matched general population [2]. In a follow-up study, the prevalence of PD with dementia (PDD) was 20% at 5 years after the onset, and increased to 45% at 15 years and 83% at 20 years [3]. Since the mortality is higher in patients with PDD than in non-demented patients [4], the evaluation of cognitive functions in patients with PD is very important.

In the present study, we evaluated the cognitive functions in patients with PD and examined the correlation between cognitive functions and patient-related factors, motor symptoms, and mood states. Additionally, the regional cerebral blood flow (rCBF) in patients with PD was assessed in terms of the results of cognitive functions. We hypothesized that rCBF in patients with PD may be

lower than that of normal controls and that the results of cognitive functions and rCBF may be correlated.

2. Methods

2.1. Patients

The subjects were 81 patients with PD that visited our institute between July 2008 and November 2011. Disease severity of patients with PD in this study was determined by Hoehn & Yahr (H&Y) stage. Hallucinations, ADL, and motor symptoms were evaluated by the Unified Parkinson's Disease Rating Scale (UPDRS). Mood states were evaluated by a profile of mood states (POMS) [5]. The mean age of patients was 62.8 ± 7.4 years. Mean disease duration was 11.9 ± 5.4 years. Levodopa equivalent daily dosage (LEDD) was 966.5 ± 390.7 mg. The mean H&Y stage score in the drug-on condition was 2.8 ± 0.7. When we classified patients with PD according to H&Y stage, there were 32 stage II patients, 38 stage III patients, and 11 stage IV patients. In the evaluation of UPDRS, the hallucinations score was 0.4 ± 0.5; the ADL score was 7.8 ± 6.3; the motor score was 13.1 ± 10.4; the tremor score was 0.5 ± 1.1; the rigidity score

was 2.5 ± 2.8; the akinesia score was 3.8 ± 4.3; and the postural instability score was 3.0 ± 2.5. In the evaluation of POMS, the *Tension-Anxiety* score was 51.5 ± 9.1; the *Depression* score was 50.1 ± 9.4; the *Anger-Hostility* score was 44.3 ± 7.7; the *Vigor* score was 40.1 ± 8.2; the *Fatigue* score was 47.9 ± 8.4; and the *Confusion* score was 56.7 ± 10.6.

Written informed consent was obtained from every patient before the study. The ethical committee of Okayama University Hospital has approved the use of human subjects for this study.

2.2. Evaluation of cognitive functions

All patients with PD were assessed using the Mini-Mental State Examination (MMSE) and the Wechsler Adult Intelligence Scale-Third edition (WAIS-III). Trained clinical psychologists and speech therapists conducted the neuropsychological tests for all patients. Neuropsychological tests were performed for patients with drug-on condition. When we evaluated the cognitive functions of patients with PD with motor fluctuation, we performed neuropsychological tests for patients with the drug-on condition as judged by the

patient's self-report. We stopped the tests when patients with PD presented with motor fluctuations.

Twelve subtests in WAIS-III were conducted for patients with PD in this study. We excluded *Object assembly* and *Symbol search* in order to reduce patient fatigue. In accordance with the protocol for WAIS-III, raw scores were converted to age-corrected scaled scores in the normal control group, which consists of 1381 healthy adult Japanese selected randomly [6]. The mean IQ of normal control in WAIS-III is set from 90 to 109 [6]. WAIS-III scores are shown as comparison of IQ with scores of normal control [6]. Next, we calculated the summary scores of Full-scale IQ (FIQ), Verbal IQ (VIQ), and Performance IQ (PIQ), and group indexes for Verbal Comprehension (VC), Working Memory (WM), and Perceptual Organization (PO).

2.3. rCBF study

Single-photon emission computed tomography (SPECT) was performed as reported previously [7]. All patients with PD received ^{99m}Tc ethyl cysteinate dimer SPECT (Fujifilm RI Pharmaceuticals Ltd., Tokyo, Japan). SPECT was

performed for patients with the drug-on condition. We used the Patlak plot method to quantify the rCBF in patients with PD [8]. After all patients underwent SPECT, we evaluated rCBF by using the three-dimensional stereotactic ROI template (3DSRT) and Statistical Parametric Mapping (SPM) 8 (Department of Cognitive Neurology, UCL, London, UK).

3DSRT is a fully automated rCBF quantification program with 636 regions of interest (ROIs) in total [9]. We quantified the blood flow in each ROI as the value in millilitres per 100 g/min and showed it in 12 segments: callosomarginal, precentral, central, parietal, angular, temporal, occipital, pericallosal regions, lenticular nucleus, thalamus, hippocampus, and cerebellum. The 3DSRT values of patients with PD are compared to the normal control in these segments (rCBF of PD patient's / rCBF of normal control × 100 [%]). We used the scores of normal control of healthy adult Japanese in 3DSRT research shown in a previous study by Matsuda [10].

The correlation between cognitive functions and rCBF was analyzed using SPM 8 [11]. All SPM calculations were performed using Matlab version 2012a (MathWorks, Sherborn, Massachusetts, USA). The SPECT images were

spatially normalized to the standardized brain template [12]. The normalized images were smoothed to account for variations in subtle anatomic structures [13]. Statistical correlation between cognitive functions and rCBF was explored voxel by voxel by setting each patient's IQ as a covariate of interest. Significance was accepted if the clusters survived a corrected threshold of $p < 0.05$. We showed anatomical regions with correlation between cognitive functions and rCBF using Talairach Daemon software [14].

2.4. Statistical analysis

First, all data are shown as mean ± standard deviation (SD) in MMSE and WAIS-III. Second, we used a two-tailed Pearson's correlation coefficient test between cognitive functions (MMSE, WAIS-III) and patient-related factors (age, disease duration, LEDD, hallucinations), motor symptoms (H&Y stage and UPDRS), and mood states (POMS). We conducted Bonferroni corrections for multi-factor analyses in UPDRS items. Finally, we focused on the H&Y stage that was most strongly correlated with cognitive functions. We conducted a one-way analysis of variance (ANOVA) to assess the significance of mean

differences in demographic data and the results of cognitive functions in three groups (II, III, and IV) classified by H&Y stage and then performed a post hoc Bonferroni test. All statistical analyses were performed with SPSS 15.0 for Windows. Statistical significance was set at $p < 0.05$.

3. Results

3.1. Cognitive functions in patients with PD

The mean MMSE score of patients with PD was 27.4 ± 2.4 (range: 21–30). Five patients (6.1%) were under the cut-off point, that is, 23/30. The scores of most patients were more than 23/30 in MMSE.

The mean FIQ of patients with PD was 88.4 ± 17.3 (range: 57–125) in WAIS-III (Supplementary Table 1). The mean FIQ was lower than that of normal controls. The VIQ and PIQ were 92.9 ± 16.4 (range: 65–129) and 85.2 ± 17.4 (range: 53–120), respectively. The VIQ was within the normal range; however, the PIQ was lower than that of normal controls. In the group index, the VC index was 93.7 ± 15.9 (range: 65–129). The WM index was 93.1 ± 13.3 (range: 60–130).

The VC and WM indexes were within the normal range. The PO index was 88.2 ± 17.7 (range: 52–125). The PO index was lower than that of normal controls. All verbal subtest scores of patients with PD were within the normal range. The *Block design*, *Picture arrangement*, and *Digit symbol cording* scores were lower than those of normal controls.

3.2. Correlation between cognitive functions and factors in patients with PD

MMSE score was correlated with age, H&Y stage, and hallucinations (Table 1). FIQ was correlated with H&Y stage and hallucinations. VIQ was correlated with H&Y stage, hallucinations, and Anger-Hostility. PIQ was correlated with H&Y stage and hallucinations. VC index was correlated with H&Y stage and Anger-Hostility. WM index was correlated with H&Y stage and Confusion. PO index was correlated with H&Y stage and hallucinations.

3.3. Cognitive impairments and H&Y stage in patients with PD

The demographics were not significantly different in groups of each H&Y stage (mean age: stage II: 62.6 ± 8.7, III: 63.0 ± 5.3, IV: 63.8 ± 9.4; years of education: II: 12.7 ± 2.0, III: 12.6 ± 1.5, IV: 12.5 ± 1.7). We evaluated the cognitive functions in each H&Y stage group (II, III, and IV). The mean MMSE score was not significantly different among the three groups (stage II: 27.9 ± 1.9, III: 27.2 ± 2.7, IV: 26.4 ± 2.4). WAIS-III scores in each H&Y stage group are shown in Fig. 1A. The mean FIQ of stage II patients was higher than that of stage III and IV patients. Similarly, the mean VIQ and PIQ of stage II patients were higher than that of stage III and IV patients. In the group index, the mean VC index of stage II patients was significantly higher than that of stage III patients (Fig. 1B). The mean WM and PO indexes of stage II patients were significantly higher than that of stage III and IV patients.

In verbal subtests, the *Similarities* score of stage II patients was higher than that of stage III and IV patients (Fig. 1C). The *Vocabulary* and *Arithmetic* scores of stage II patients were also higher than that of stage III patients. The *Letter number sequencing* score of stage II patients was higher than that of stage IV patients. There was no significant difference in the other subtests, including *Information*, *Comprehension*, and *Digit span*. All of the performance subtest

scores of stage II patients were higher than that of stage III and IV patients in *Picture completion*, *Block design*, *Matrix reasoning*, *Picture arrangement*, and *Digit symbol cording* (Fig. 1D).

3.4. rCBF study

3DSRT demonstrated that the rCBF of patients with PD was lower in the bilateral callosomarginal, precentral, central, parietal, angular, temporal, occipital regions, and cerebellum compared to the normal controls (Table 2). On the other hand, the rCBF of patients with PD was comparatively normal in the pericallosal segment, lenticular nucleus, thalamus, and hippocampus.

SPM 8 showed correlation between FIQ and rCBF in patients with PD (Fig. 2). The strong correlation between FIQ and rCBF, that is, the increased rCBF in patients with high FIQ and the decreased rCBF in patients with low FIQ, is shown in red and yellow. FIQ was positively correlated with rCBF in the thalamus, hypothalamus, and cingulate gyrus. VIQ was positively correlated with rCBF in the frontal lobe, including the frontal and inferior frontal gyrus, left temporal pole, left hippocampus, and pons. PIQ was positively correlated with rCBF in the

frontal lobe (such as the superior frontal gyrus and dorsolateral prefrontal area), the parietal lobe (such as the lingual gyrus), and the occipital lobe.

4. Discussion

We found that the MMSE score of patients with PD was usually high and few patients had a score below 23/30. Another study showed that the mean MMSE score of patients with PD was 27.4 and 17% of patients had a score below 23/30 [15]. The mean MMSE score was almost the same between ours and the study. Cognitive impairments in patients with PD are characterized by memory, visuospatial, and executive dysfunction. However, MMSE may be inadequate to evaluate these cognitive dysfunctions in patients with PD.

In our study, patients with PD had impaired cognitive functions in the evaluation of WAIS-III. Schadt used part of WAIS-III to evaluate cognitive functions in patients with PD [16], but study that was used WAIS-III is few. In our study, the PO index of patients with PD was low scoring, which indicated that most patients with PD had visuospatial dysfunction. Another study showed that visuospatial dysfunction in patients with PD appeared in visuospatial tasks on executive

function such as planning and attention [17]. Visuospatial function in patients with PD may be impaired due to executive dysfunction. Therefore, in our study, patients with PD received significantly low scores in block design of WAIS-III that is visuospatial function tests involving executive function.

The present study found that cognitive functions were significantly correlated with H&Y stage in patients with PD. In other studies, cognitive functions in patients with PD were correlated with age, H&Y stage [3], and neuropathological stage [18]. Patients with stage II PD retained cognitive functions to some extent in our study compared to normal controls. However, patients with stage III and IV PD had significantly impaired cognitive functions, including language function, working memory, and visuospatial function than that of stage II patients.

Cognitive functions were also significantly correlated with hallucinations in our study. Hallucinations may occur in the course of degenerative dementias besides PDD, such as dementia with Lewy bodies and Alzheimer's disease [19]. The prevalence of hallucinations is approximately 40% in patients with PD and the emergence of visual hallucinations is high [19]. The performance of PD patients with hallucinations was significantly worse in terms of cognitive

functions when compared to patients without hallucinations [20]. Therefore, hallucinations in patients with PD may be a predictor of cognitive impairments, although further investigations with dedicated assessment tools for hallucinations are needed.

3DSRT revealed that patients with PD had hypoperfusion in the callosomarginal segment and the cerebral cortex, including the frontal, temporal, parietal, and occipital lobes. In the previous research in meta-analysis of quantitative results, global CBF of cerebral cortex was decreased in patients with PD [21]. SPM 8 showed that cognitive functions in patients with PD, in the WAIS-III evaluation, were correlated with rCBF in the thalamus and cingulate gyrus. The thalamus is the main area in the fronto-striatal basal ganglia circuits. These circuits may be critical for cognitive functions and behavior control [22]. Dysfunction of these circuits may cause cognitive impairments, especially in language and executive dysfunctions [23]. Therefore, the cognitive function decline in patients with PD may be caused by a decrease in rCBF in the thalamus and cingulate gyrus.

Verbal function in patients with PD was correlated with rCBF in the left temporal and left hippocampus in our study. The role of the left hippocampus is

associated with verbal memory [24]. The MMSE score was significantly correlated only with left hippocampal perfusion [25]. We found normal rCBF in the left hippocampus in patients with PD. Therefore, in our study, verbal function in patients with PD may be preserved in WAIS-III, and patients with PD may score high in MMSE, in which the verbal function fairly affects the scores.

Visuospatial function was correlated with rCBF in the parietal and occipital lobes and the dorsolateral prefrontal area. The lingual gyrus and occipital lobe play an important role in patients attempting spatial recognition. The dorsolateral prefrontal cortex plays a critical role in executive function after spatial recognition. A decrease in rCBF in these areas reflects dysfunction in cortical visual processing [26]. Therefore, hypoperfusion of the parietal and occipital lobes and the dorsolateral prefrontal cortex in patients with PD may cause visuospatial dysfunction in our study.

Funding

This study received no funding.

Conflict of interest

The authors report no conflict of interest.

Acknowledgments

The authors thank Mr. Yuuki Watanabe and Mr. Yoshio Kubo (Department of Psychology, Kibi International University, Takahashi, Japan) for their help as advisors of neuropsychological tests and statistical strategy.

Appendix A. Supplementary data

The following are the supplementary data related to this article:

Supplementary Table 1.

References

[1] Pagonabarraga J, Kulisevsky J. Cognitive impairment and dementia in Parkinson's disease. Neurobiol Dis 2012;46:590-6.

[2] Aarsland D, Kurz MW. The epidemiology of dementia associated with Parkinson's disease. Brain Pathol 2010;20:633-9.

[3] Hely MA, Reid WG, Adena MA, Halliday GM, Morris JG. The Sydney multicenter study of Parkinson's disease: the inevitability of dementia at 20 years. Mov Disord 2008;23:837-44.

[4] Fall PA, Saleh A, Fredrickson M, Oisson JE, Grannerus AK. Survival time, mortality, and cause of death in elderly patients with Parkinson's disease: a 9-year follow-up. Mov Disord 2003;18:1312-6.

[5] McNair DM, Loor M, Droppleman LM. Manual for the profile of mood states. San Diego, CA: Educational and Industrial Testing service, 1992.

[6] Wechsler D. WAIS-III Administration and Scoring Manual. San Antonio: The Psychological Corporation, 1997.

[7] Imon Y, Matsuda H, Ogawa M, Kogure D, Sunohara N. SPECT image analysis using statistical parametric mapping in patients with

Parkinson’s disease. J Nucl Med 1999;40:1583-9.

[8] Patlak CS, Blasberg RG, Fenstermacher JD. Graphical evaluation of blood-to-brain transfer constants from multiple-time uptake data. J Cereb Blood Flow Metab 1983;3:1-7.

[9] Takeuchi R, Matsuda H, Yoshioka K, Yoshioka K, Yonekura Y. Cerebral blood flow SPET in transient global amnesia with automated ROI analysis by 3DSRT. Eur J Nucl Med Mol Imaging 2004;31:578-89.

[10] Matsuda H. Cerebral blood flow SPECT (NouketuryuuSPECT). Diagnostic imaging 2002;22:718-26.

[11] Friston KJ, Holmes AP, Worsley KJ, Poline JP, Frith CD, Frackowiak RSJ. Statistical parametric maps in functional imaging: a general linear approach. Hum Brain Mapp 1994;2:189-210.

[12] Friston KJ, Ashburner J, Frith CD, Poline JB, Heather JD, Frackowiak RSJ. Spatial registration and normalization of images. Hum Brain Mapp 1995;3:165-89.

[13] Morbelli S, Rodriguez G, Mignone A, Altrinetti V, Brugnolo A, Piccardo A, et al. The need of appropriate brain SPECT templates for SPM

comparison. Q J Med Mol Imaging 2008;52:89-98.

[14] Yoon HJ, Park KW, Jeong YJ, Kang DY. Correlation between neuropsychological tests and hypoperfusion in MCI patients: anatomical labeling using xjView and Talairach Daemon software. Ann Nucl Med 2012;26:656-64.

[15] Riedel O, Klotsche J, Spottke A, Deuschl G, Forstl H, Henn F, et al. Cognitive impairment in 873 patients with idiopathic Parkinson's disease. Results from the German study on Epidemiology of Parkinson's Disease with Dementia (GEPAD). J Neurol 2008;255:255-64.

[16] Schadt CR, Cox KL, Tramontana MG, Byrne DW, Davis TL, Fang JY, et al. Depression and intelligence in patients with Parkinson's disease and deep-brain stimulation. J Natl Med Assoc 2006;98:1121-5.

[17] Ogden JA, Growdon JH, Corkin S. Deficits on visuospatial tests involving forward planning in high functioning parkinsonians. Neuropsychiatry Neuropsychol Behav Neurol 1990;3:125-39.

[18] Braak H, Rub U, Del Tredici K. Cognitive decline correlates with neuropathological stage in Parkinson's disease. J Neurol Sci

2006;248:255-8.

[19] Fenelon G, Mahieux F, Huon R, Ziegler M. Hallucinations in Parkinson's disease: prevalence, phenomenology and risk factors. Brain 2000;123:733-45.

[20] Katzen H, Myerson C, Papapetropoulos S, Nahab F, Gallo B, Levin B. Multi-modal hallucinations and cognitive function in PD patients. Dement Geriatr Cogn Disord 2010;30:51-6.

[21] Borghammer P, Chakravarty M, Jonsdottir KY, Sato N, Matsuda H, Ito K, et al. Cortical hypometabolism and hypoperfusion in Parkinson's disease is extensive: probably even at early disease stage. Brain Struct Funct 2010;214:303-17.

[22] Cummings JL. Frontal-subcortical circuits and human behavior. J Psychosom Res 1998;44:627-8.

[23] Oishi K, Ogawa M, Oya Y, Kawai M. Whole-brain voxel-based correlation analysis between regional cerebral blood flow and intelligence quotient score in Parkinson's disease. Eur Neurol 2004;52:151-5.

[24] Riekkinen P Jr, Kejonen K, Laakso MP, Soininen H, Partanen K,

Riekkinen M. Hippocampal atrophy is related to impaired memory, but not frontal functions in non-demented Parkinson's disease patients. Neuroreport 1998;9:1507-11.

[25] Ikeda E, Shiozaki K, Takahashi N, Togo T, Odawara T, Oka T, et al. Total Mini-Mental State Examination score and regional cerebral blood flow using Z score imaging and automated ROI analysis software in subjects with memory impairment. Ann Nucl Med 2008;22:539-42.

[26] Abe Y, Kachi T, Kato T, Arahata Y, Yamada T, Washimi, et al. Occipital hypoperfusion in Parkinson's disease without dementia: correlation to impaired cortical visual processing. J Neurol Neurosurg Psychiatry 2003;74:419-22.

Figure Captions

Fig. 1. WAIS-III scores in each Hoehn & Yahr stage group

The mean scores in each Hoehn & Yahr stage group are shown in IQ (A), Group index (B), Verbal subtest (C), and Performance subtest (D). The black bar represents scores in stage II patients. The white bar represents scores in stage III patients. The gray bar represents scores in stage IV patients. The error bar shows standard deviation. The high score indicates good performance. A significant difference was found between stage II and III and stage II and IV patients (** $p < 0.01$, * $p < 0.05$).

Fig. 2. Correlation between cognitive functions and rCBF in patients with PD

The strong correlation between cognitive functions and rCBF in patients with PD is shown in red and yellow ($p < 0.05$).