

博士学位論文

Neuropsychological characteristics and their association with higher-level functional capacity
in Parkinson's disease

(パーキンソン病患者における神経心理機能と高次生活機能との関連)

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Abstract

Background/Aims: Little is known about the relationship between cognitive functions and higher-level functional capacity (e.g., intellectual activity, social role, and social participation) in Parkinson's disease (PD). The purpose of this study was to clarify neuropsychological characteristics and their association with higher-level functional capacity in PD patients.

Methods: Participants were 31 PD patients and 23 demographically-matched healthy controls. Neuropsychological tests were conducted. One year later a questionnaire survey evaluated higher-level functional capacity in daily living.

Results: The PD group scored significantly lower than the control group in all cognitive domains, particularly executive function and processing. Executive function, processing speed, language, and memory were significantly correlated with higher-level functional capacity in PD patients. Stepwise regression showed that only executive function (TMT-B), together with disease severity (HY stage), predicted the higher-level functional capacity.

Conclusion: Our findings provide evidence of a relationship between executive function and higher-level functional capacity in patients with PD.

Introduction

An important part of successful aging is the strengthening of various functions such as motor function, sensory function, and physiological function. Medical researchers and healthcare professionals should support elderly people to maintain both their physical and mental health so that they can remain highly motivated and make full use of their abilities. However, individual differences in physical function, mental health, and cognitive function increase with age. Moreover, in patients with chronic illnesses, disease-specific factors affect various functions. Therefore, the factors related to successful aging need to be considered on a disease-specific basis.

Parkinson's disease (PD) is a chronic and progressive neurodegenerative disorder that is mainly caused by dopaminergic neuron loss in the substantia nigra. PD typically develops after late middle age, and incidence rates increase with age. The most common symptoms include resting tremor, rigidity, bradykinesia, and postural instability. In recent years, recognition of the importance of non-motor PD symptoms (e.g., cognitive impairment, emotional problems, and sleep problems) has increased. Cognitive impairment is a particular problem, as it reduces quality of life (QOL) [1, 2, 3].

In one multicenter cohort study, 25.8% of patients with PD were classified as having mild cognitive impairment (MCI) [4]. Another survey reported that 18.9% of patients with drug-naïve PD were classified as having MCI [5]. Cognitive function problems in PD are diverse, including executive functions, attention, memory, language, and visuospatial function. These impairments represent fronto-striatal neuronal circuitry dysfunction; the impairment of frontal executive function constitutes the core feature of neuropsychological dysfunction in PD. In many cases, patients are often not aware of their own cognitive dysfunction, but comprehensive neuropsychological tests can detect even

subtle impairments. Since the primary symptoms in PD relate to motor function, it is possible that cognitive impairments are less salient, making it difficult to discern their impact on daily life.

One study of community-dwelling elderly people indicated that problems with cognitive, as well as physical, function significantly impact the maintenance of daily function, even when demographic variables and illness variables are controlled for [6]. Relatively few studies have examined the association of daily function and cognitive function in PD patients without dementia [7, 8, 9, 10]. Cahn et al. [7] reported that motor functioning was a significant independent predictor of physical activities of daily living (ADL; e.g., eating, grooming), whereas executive functioning was not. In contrast, executive functioning (particularly sequencing), but not motor functioning, was a significant independent predictor of instrumental ADLs (e.g., shopping, dialing a telephone number). Rosenthal et al. [8] found relationships between cognitive impairment and activities of daily living, including difficulties in instrumental activities of daily living (IADL), in patients with PD. Martin et al. [9] reported impairment of financial capacity in Parkinson disease with mild cognitive impairment (PD-MCI), indicating that cognitive function is associated with IADL. Another study demonstrated that performance-based measures of IADL, particularly medication management ability, are sensitive to subtle functional declines in PD-MCI [10]. However, these authors suggest that IADL and cognitive functioning may be separate domains of functioning in PD-MCI, as IADL measures did not correlate with performance on neuropsychological measures.

There are various levels of daily function. Lawton [11] developed a hierarchical model of competence comprising seven sublevels: life maintenance, functional health, perception and cognition, physical self-maintenance, instrumental self-maintenance,

effectance, and social role. Based on Lawton's model, Koyano and colleagues developed the Tokyo Metropolitan Institute of Gerontology index of competence (TMIG-IC) [12]. The TMIG-IC was designed to measure three higher-level functional capacities. Higher-level competence, which indicates a higher-level functional capacity above basic activities of daily living, corresponds to the 5th, 6th, and 7th sublevels of Lawton's hierarchical model. Expanding on the concept of the three TMIG-IC categories, Masui et al. [13] developed the Japan Science and Technology Agency Index of Competence (JST-IC). This measures a higher level of daily function that includes newly added components, such as social participation and life management. To promote successful aging in an elderly society, it is important to maintain not just ADL and IADL, but also a higher level of daily function. Higher-level functional capacity reflects a more active and healthy aging, and independent living, compared with ADL and IADL. However, many studies on PD have focused on ADL and IADL rather than higher-level functional capacity.

While there is no clear definition of "successful aging," Rowe & Kahn [14] have enumerated three important characteristics: 1) low probability of disease, 2) high cognitive and physical function, 3) active engagement with life. As PD is a chronic, progressive neurological disorder that mainly affects motor function, physical function gradually deteriorates. Thus, the key to successful aging might be the maintenance of cognitive function and everyday function.

Accordingly, we focus on the following questions: (a) What are the features of neuropsychological function and higher-level functional capacity in patients with PD? (b) Do neuropsychological characteristics affect higher-level functional capacity after 1 year in patients with PD? (c) What cognitive domains affect higher-level functional capacity in PD patients? Investigating the relationship between neuropsychological characteristics and

higher-level functional capacity in PD in older people might help improve QOL, and facilitate successful aging in patients with PD. We hypothesized that 1) PD patients would score significantly lower on all cognitive domains, particularly executive function and attention, than healthy controls, 2) Cognitive function would impact the subsequent daily life functions of PD patients.

Materials and Methods

Participants

Summary statistics (mean, SD) of the participants' demographic and clinical characteristics are reported in Table 1. For the comparison of neuropsychological function we had available the data of 57 participants (PD group: 32, NC group: 25; Figure 1). For the questionnaire component of the study, three participants were excluded, leaving 31 patients with PD (PD group: 9 men, 22 women) and 23 demographically-matched healthy controls (HC group: 9 men, 14 women). The patients were recruited from the outpatient department at Toyama University Hospital. The HC participants were recruited from the community. Participants were excluded from the study if they had (a) a Mini-Mental State Examination–Japanese (MMSE) total score below 25, (b) a history of any other neurological disorder and/or acquired brain injury, and (c) a history of serious mental illness.

Table 1. Demographic and Clinical Characteristics of Study Participants

	PD (<i>n</i> = 32)	HC (<i>n</i> = 25)
Age (years)	67.8 (7.4)	66.9 (7.2)
Men/Women	10/22	9/16
Education (years)	12.0 (1.6)	13.2 (2.6)
Premorbid IQ*	97.0 (12.4)	104.6 (10.4)
MMSE-J	28.5 (1.6)	29.3 (1.1)
Disease duration (years)	5.6 (4.6)	—
LEDD (mg)	318.9 (187.6)	—
H&Y distribution		—
1/2/3/4/5	0/9/23/0/0	

Note. All values represent mean (*SD*).

* Premorbid IQ estimated using the Japanese version of the NART (JART).

PD = Parkinson's disease; HC = Healthy controls; MMSE-J = Mini-Mental State Examination–Japanese; LEDD = L-dopa equivalent daily dose; H&Y = Hoehn and Yahr.

Study design

This study was designed to clarify neuropsychological characteristics of PD, and their association with higher-level functional capacity. The following tests were conducted to identify neuropsychological characteristics in patients with PD: the Wisconsin Card Sorting Test (WCST) [15], the Trail Making Test (TMT) [16,17] the Digit Span Test (DST) [18], the Verbal Fluency Test (VFT) [17,19], and the Japanese Verbal Learning Test (JVLT) [20].

About one year after testing, we performed a questionnaire survey to evaluate higher-level functional capacity in daily living. The average period between the neuropsychological testing and the higher-level functional capacity evaluation was 479.3 days.

All patients with PD were medicated with anti-parkinsonian drugs at the time of neuropsychological testing and questionnaire evaluation. Doses of dopaminergic medication were converted to L-dopa equivalent daily dose (LEDD) [21]. All evaluations were approved by the Ethics Committee of the University of Toyama, and all participants

signed a written consent form before undergoing the assessment. A flow-chart of the study is presented in Figure 1.

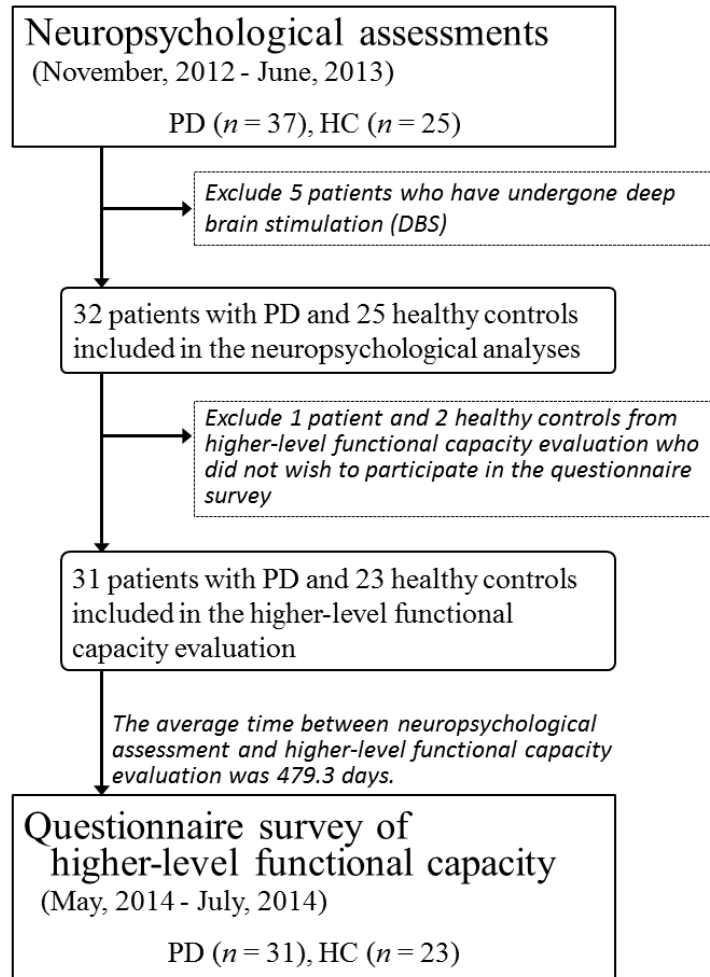


Figure 1. Flow chart showing study design.

Assessments

Clinical characteristics

The severity of disease was rated by at least one neurologist using the Hoehn and Yahr (HY) rating scale. Before performing the neuropsychological tests, the level of global cognitive function was confirmed using the MMSE. Premorbid intelligence was estimated using the Japanese Adult Reading Test (JART) [22]. The level of apathy was assessed using

the Japanese version of the Apathy Scale [23]. Other patient characteristics were collected from electronic medical records.

Neuropsychological characteristics

Details of the neuropsychological assessment are as follows. Executive function was assessed using the WCST and TMT-B. The WCST consists of 4 stimulus cards and 2 identical decks of 64 response cards. The response cards display different numbers of figures of varying forms and colors. Participants must match a set of response cards to one of the stimulus cards. They are not told how to match the cards (by the rule of color, form, or number), but are told which matches are correct or incorrect. The WCST measures executive functions, mental flexibility, problem-solving ability, and set-shifting ability [19]. The TMT consists of two parts. In part B, the participant must connect circles with alternating numbers and letters. Part B measures executive function, cognitive flexibility, and alternating attention because it requires the capacity to switch from one stimulus to another. The TMT (B-A) is able to accurately evaluate PD patients' ability to switch attention, because it eliminates the influence of motor speed [24]. Attention and working memory were assessed using the Digit Span from the Wechsler Adult Intelligence Scale–Third Edition. The DST measures auditory attention by requiring repetition of a series of digits immediately following presentation. Processing speed was assessed using the TMT-A, which requires participants to connect numbered circles scattered across a page. Part A measures visual scanning, numeric sequencing, and visuomotor speed. The VFT (category and letter) was used to assess language. Individuals must generate as many words as possible, according to particular rules, during a specified time interval. Participants were asked to generate words within both a semantic category (animal), and a phonemic

category (beginning with “ka”). Verbal memory and learning was assessed using the JVLT. This is the original Japanese verbal learning test referring to specific characteristics of the unblocked list of another previous study [25], similar to the California Verbal Learning Test (CVLT) [26]. The examiner reads aloud a list of 16 words at one-second intervals in a fixed order over three trials. After each trial, participants must recall as many words as they can in any order. Delay free recall was tested after a 15–20 min interval (in which the subject was occupied with other tests).

Higher-level functional capacity

Higher-level functional capacity was assessed using the Tokyo Metropolitan Institute of Gerontology Index of Competence (TMIG-IC) and the Japan Science and Technology Agency Index of Competence (JST-IC).

The TMIG-IC has been widely used in Japan, and has good validity and reliability [27]. It comprises a 13-item index including three sublevels of competence: Instrumental self-maintenance (e.g., Can you handle your own banking?), intellectual activity (e.g., Do you read books or magazines?), and social role (e.g., Do you visit the homes of friends?). Although the TMIG-IC has become a standard measure of competence in the elderly, its format is now a little dated. In addition, some questions may not be as relevant to elderly people today. For this reason, the JST-IC was created to reflect changes in social conditions and trends. The JST-IC is a 16-item index with four sublevels of competence: Social participation (e.g., Are you active in the neighborhood association and residents' association?), use of new devices (e.g., Can you use the Automated Teller Machine?), information gathering (e.g., Do you watch educational programs?), and life management (e.g., Do you make some small creative arrangements in your daily life?). Used in

conjunction with the TMIG-IC, the JST-IC can be applied to a broader group of people. Both the TMIG-IC and JST-IC were administered to both groups of participants, who were asked to evaluate feasibility or their own independence with respect to the 29 tasks. The response to each item was “yes” (able to do) or “no” (unable to do), and scored as 1 for “yes” and 0 for “no”.

Statistical analysis

Group differences in neuropsychological characteristics

Group differences on neuropsychological measures were analyzed using independent t-tests.

Group differences in higher-level functional capacity

Group differences on higher-level functional capacity measures were analyzed using Mann-Whitney U tests.

Correlation between neuropsychological characteristics and higher-level functional capacity

First, Spearman’s correlational analysis was used to examine relationships between neuropsychological characteristics and higher-level functional capacity in the PD group. Second, neuropsychological variables that significantly correlated with higher-level functional capacity were entered into a stepwise multiple regression analysis to determine their relative contribution to higher-level functional capacity. Third, the raw neuropsychological test scores of the PD group were converted to z-scores using the mean and *SD* of the same generation HC group. PD participants with an observed z-score falling

more than $-1.5 SD$ below the mean were classified as demonstrating cognitive decline. The Kruskal-Wallis test was used to compare subscale scores on the TMIG-IC and JST-IC between the three groups (HC vs. PD with cognitive impairment vs. PD with normal cognitive function). Post hoc analysis used the Mann-Whitney test with Bonferroni adjustment.

Results

Group differences in neuropsychological characteristics

Group comparisons of neuropsychological characteristics are shown in Table 2. Patients with PD performed significantly worse than the HC group in all domains. In the executive function test, the PD group achieved significantly fewer categories, made more total errors, showed higher rates of non-persistent errors, and fewer conceptual level responses on the WCST than did the HC group. In addition, the PD group performed significantly worse than the HC group on TMT-B and TMT (B-A). The PD group had significantly lower scores on attention/working memory in the backward version of the digit span task.

Regarding processing speed, the PD group performed significantly worse than the HC group on TMT-A. In relation to language, the PD group was more impaired on letter fluency tasks than the HC group. Regarding memory and learning, the PD group performed significantly worse on immediate recall than the HC group. There were large effect sizes for completed WCST categories TMT-B, and TMT-A.

Table 2. Neuropsychological Characteristics of Patients with PD and HC, matched for Age and Education

Domain and Measure		PD (n = 32)	HC (n = 25)	t	p-value	Effect Size (Cohen's d)
<i>Executive function</i>						
WCST	Categories Completed	4.7 (2.2)	6.0 (0.0)	3.10	.004**	0.81
	Total Errors	27.8 (22.0)	14.9 (6.5)	-3.01	.005**	0.77
	Perseverative Errors (%)	10.5 (4.5)	8.8 (2.3)	-1.90	.064	0.47
	Non-perseverative Errors (%)	15.0 (11.5)	8.5 (3.1)	-2.91	.006**	0.75
	Conceptual Level Responses (%)	65.6 (22.0)	76.7 (6.7)	2.57	.015*	0.66
TMT	Part B time (s)	154.8 (102.8)	91.2 (29.5)	-3.33	.002**	0.80
	Part B-Part A time (s)	82.2 (64.0)	52.3 (25.3)	-2.41	.020*	0.59
<i>Attention/Working memory</i>						
DST	Forward	5.2 (1.8)	5.5 (1.0)	1.00	.321	0.20
	Backward	3.9 (0.8)	4.4 (1.1)	2.06	.045*	0.53
<i>Processing speed</i>						
TMT	Part A time (s)	72.6 (50.5)	38.9 (10.0)	-3.68	.001**	0.88
<i>Language</i>						
VFT	Letter (Ka)	9.3 (3.2)	11.6 (2.8)	2.92	.005**	0.76
	Category (animal)	16.3 (6.5)	18.0 (5.5)	1.05	.298	0.28
<i>Memory and Learning</i>						
JVLT	Immediate Recall Total	30.1 (7.6)	35.0 (4.9)	2.76	.005**	0.75
	Immediate Recall Trial 1	6.7 (2.9)	7.8 (2.2)	1.63	.108	0.42
	Immediate Recall Trial 2	11.3 (2.8)	13.1 (1.8)	2.87	.006**	0.75
	Immediate Recall Trial 3	12.2 (2.9)	14.0 (1.9)	2.81	.005**	0.72
	Delayed Recall	12.1 (2.8)	13.3 (2.0)	1.89	.065	0.48

Note. Groups were compared by independent t-test. Values represent mean (SD). * $p < .05$. ** $p < .01$. Cohen's d: ≥ 0.8 = Large, 0.5–0.8 = Medium, 0.2–0.5 = Small.

PD = Parkinson's disease; HC = Healthy controls; WCST = Wisconsin Card Sorting Test; DST = Digit Span Test; TMT = Trail Making Test; VFT = Verbal Fluency Test; JVLT = Japanese Verbal Learning Test.

Group differences in higher-level functional capacity

Group comparisons of higher-level functional capacity are shown in Table 3. The mean TMIG-IC score for the PD group was 10.6 ± 2.9 , and for the HC group it was 12.4 ± 1.2 .

The PD group showed significantly lower total TMIG-IC scores than the HC group. PD patients had significantly lower scores than the HC group on the Instrumental

self-maintenance and the Intellectual activity subscales, but not on the Social role subscale.

The mean JST-IC score for the PD group was 10.8 ± 3.6 , and for the HC group it was 13.6 ± 2.9 . PD patients had significantly lower scores than the HC group on the Social participation, Use of new devices and Information gathering subscales, but not on the Life management subscale.

Table 3. Scores of the Tokyo Metropolitan Institute of Gerontology Index of Competence and the Japan Science and Technology Agency Index of Competence: Comparison between PD and HC.

	PD (n = 31)	HC (n = 23)	p-value
<i>TMIG-IC</i>	10.58 (2.93)	12.43 (1.20)	.002**
Instrumental self-maintenance	4.06 (1.39)	4.96 (0.21)	.002**
Intellectual activity	3.39 (0.84)	4.00 (0.00)	.000***
Social role	3.13 (1.26)	3.48 (1.20)	.054
<i>JST-IC</i>	10.84 (3.56)	13.65 (2.89)	.003**
Social participation	1.65 (1.50)	3.09 (1.35)	.000***
Use of new devices	2.90 (1.25)	3.61 (0.66)	.032*
Information gathering	3.23 (0.85)	3.57 (0.95)	.041*
Life management	3.06 (1.06)	3.39 (0.89)	.257

Note. Groups were compared using Mann-Whitney *U*-tests. Values represent mean (SD). * $p < .05$. ** $p < .01$. *** $p < .001$.

PD = Parkinson's disease; HC = Healthy controls; TMIG-IC = Tokyo Metropolitan Institute of Gerontology Index of Competence; JST-IC = Japan Science and Technology Agency Index of Competence.

Correlation between Neuropsychological characteristics and Higher-level functional capacity

The results of this analysis are presented in Table 4 and Table 5. Higher-level functional capacity (Integration score = sum of TMIG-IC and JST-IC) was significantly correlated with the following neuropsychological characteristics: Executive function (WCST total errors and TMT-B), Processing speed (TMT-A), Language (VFT category), and Memory (JVLTL). We conducted a stepwise multiple regression analysis to evaluate the influence of these neuropsychological characteristics on higher-level functional capacity. Age, HY stage, and LEDD were also included in this analysis. Regression results revealed significant

changes in R^2 at the first and second steps. At Step 1, HY stage accounted for 41% of the variance. When TMT-B was added at Step 2, a further 11% of the variance was accounted for (R^2 total = .52).

Table 4. Correlations between Neuropsychological Characteristics and Higher-level Functional Capacity in Patients with PD ($n = 31$)

		Integration score ^a
<i>Executive function</i>		
WCST	Categories Completed	.454*
	Total Errors	-.398*
	Perseverative Errors (%)	-.130
	Non-perseverative Errors (%)	-.415*
	Conceptual Level Responses (%)	.324
TMT	Part B time (s)	-.605**
	Part B-Part A time (s)	-.521**
<i>Attention/Working memory</i>		
DST	Forward	.360
	Backward	.209
<i>Processing speed</i>		
TMT	Part A time (s)	-.649**
<i>Language</i>		
VFT	Letter (Ka)	.250
	Category (animal)	.528**
<i>Memory and Learning</i>		
JVLT	Immediate Recall Total	.405*

Note. ^a Integration score is sum of TMIG-IC and JST-IC. * $p < .05$. ** $p < .01$.

WCST = Wisconsin Card Sorting Test; DST = Digit Span Test; TMT = Trail Making Test; VFT = Verbal Fluency Test; JVLT = Japanese Verbal Learning Test.

Table 5. Results of Stepwise Multiple Regression Analysis of Factors influencing Higher-level Functional Capacity of Patients with PD ($n = 31$)

Dependent variable: Integration score ^a	R^2	Change in R^2	adjusted R^2	β	t	p -value
Step1	.41		.39			
HY stage				-.637	-4.455	.000***
Step 2	.52	.11	.49			
HY stage				-.369	-2.562	.016*
TMT (Part B)				-.484	-3.357	.002**

Final model: $R = .720$, $F(2,28) = 15.11$, $p < .001$

Note. ^a Integration score is sum of TMIG-IC and JST-IC. * $p < .05$. ** $p < .01$. *** $p < .001$.

Comparison among HC, PD with cognitive decline, and PD without cognitive decline groups on each TMIG-IC and JST-IC subscale

Patients with PD were classified into “PD-executive impairment” and “PD-normal executive function” based on the TMT-B z-score, because TMT-B is related to higher-level functional capacity. Group comparison of TMIG-IC and JST-IC subscales are shown in Table 6. There were significant differences among the three groups for all subscales. The PD-executive impairment group scored significantly lower than the HC and PD-normal executive function groups on the Instrumental self-maintenance, Intellectual activity, Use of new devices, and Life management subscales. The PD-executive impairment group scored significantly lower than the HC group on the Social role subscale. Both PD groups scored significantly lower than the HC group on the Social participation and Information gathering subscales.

Table 6. Comparison of TMIG-IC and JST-IC Subscales across Groups

	HC (<i>n</i> = 23)	PD- normal executive (<i>n</i> = 19)	PD- executive impairment (<i>n</i> = 12)	Kruskal-Wallis χ^2	<i>p</i> -value	Post hoc
<i>TMIG-IC</i>						
Instrumental self-maintenance	33.5	29.0	13.6	21.8	.000***	HC, PD-normal executive > PD-executive impairment
Intellectual activity	34.0	28.8	12.9	25.7	.000**	HC, PD-normal executive > PD-executive impairment
Social role	31.6	27.9	19.5	6.4	.040*	HC > PD-executive impairment
<i>JST-IC</i>						
Social participation	35.8	24.9	15.7	14.5	.001***	HC > PD-executive impairment, PD-normal executive
Use of new devices	32.3	29.7	14.8	12.8	.002**	HC, PD-normal executive > PD-executive impairment
Information gathering	32.0	27.5	18.9	7.0	.030*	HC > PD-executive impairment, PD-normal executive
Life management	30.1	31.5	16.2	9.6	.008**	HC, PD-normal executive > PD-executive impairment

Note. Groups were compared using the Kruskal-Wallis test. Bonferroni adjusted Mann-Whitney *U*-tests were used as post hoc analysis. Values represent Mean rank. * *p* < .05. ** *p* < .01. *** *p* < .001.

TMIG-IC = Tokyo Metropolitan Institute of Gerontology Index of Competence; JST-IC = Japan Science and Technology Agency Index of Competence; HC = Healthy controls; PD-executive impairment = Parkinson's disease with executive impairment; PD-normal executive = Parkinson's disease without executive impairment.

Discussion

The primary aim of the present work was to clarify the neuropsychological characteristics of PD and their association with higher-level functional capacity. The PD group scored

significantly lower on all cognitive domains compared with the HC group, with large effect sizes for the WCST, TMT-A, and TMT-B tests. These results support our hypothesis that PD patients perform poorly in all cognitive domains, but especially executive function and attention. However, TMT performance is affected by motor function. Since patients with PD experience motor symptoms, their actions were slower compared to the HC group. TMT (B-A) scores showed a small effect size compared to Part B and Part A, although we used the difference score (B-A), which is meant to remove the motor component of the test evaluation. The magnitude of the effect sizes in Part A and Part B suggests that motor function is involved, but it is not clear whether this solely reflects the decrease in executive function. However, the PD group showed significantly lower scores on the digit span test (backward) and letter fluency test than the HC group. Working memory and divided attention are involved in the backward digit span task because this test involves a reversing operation (mental double-tracking) as well as a memory component [19]. In addition, compared with the category fluency, the letter fluency task reflects frontal lobe function to a larger extent. For this reason, it is suggested that frontal lobe function declines in PD groups, and this is supported by a recent meta-analysis [28,29] indicating that attention and executive function are impaired in PD patients.

There has been a recent increase in reports of brain changes associated with cognitive impairment [30,31,32]. In an MRI study, patients with PD-MCI had significantly decreased gray matter density in the right middle frontal area compared with patients with PD-intact cognition [30]. Several studies using diffusion tensor imaging (DTI) have shown that changes in the microstructure of white matter in PD patients are associated with cognitive function. For example, Gallagher et al. [31] showed that fractional anisotropy (FA) within an a priori frontal mask was related to executive composite scores. They

concluded that white matter microstructural abnormalities contribute to cognitive deficits in PD. Zheng et al. [32] investigated the relationship between measures of white matter integrity in regions-of-interest (ROIs) and performance in five distinct cognitive domains (executive function, language, attention, memory, and visuospatial skills). They demonstrated that executive function is primarily correlated with frontal connecting tracts, including the left anterior limb of the internal capsule and genu of the corpus callosum. These results indicate that the executive function impairments in PD are related to anatomical changes in the frontal lobe area. Thus, the prior research suggests that cognitive functions in PD (e.g., executive functions) are impaired by microstructural changes of the frontal area. Future work requires prospective observation of cognitive and brain changes. Investigating longitudinal changes of cognitive impairment in PD patients may be helpful in understanding their cognitive symptoms.

It is important to recognize changes in the functional capacity of patients with PD in order to fully understand their substantial difficulties in daily life. Patients with PD showed a decrease in higher-level functional capacity in comparison with healthy controls. The final regression model significantly predicted higher-level functional capacity, with symptom severity (HY stage) and executive function (TMT-B) the two strongest predictors. It is interesting that Part B was selected as a predictive factor because it is related to executive function. In addition to severity of symptoms, TMT-B showed promise as a predictive factor for higher-functional capacity. Using the TMT-B results, we divided PD patients into those showing executive function impairment, and those not showing executive function impairment.

The group showing executive impairment scored lower on instrumental self-maintenance, intellectual activities, the use of new devices, and life management

compared to those not showing the impairment, and the HC group. However, there was no significant difference in scores between the latter two groups. Our results support the findings of previous studies of MCI [33] and PD [7], which report that executive function is significantly related to instrumental self-maintenance. Because executive function controls the ability to actualize decision-making, planning, executing, and modifying as a sequential cognitive function, IADL—which requires complex and applied behavior in comparison to ADL—is strongly influenced by executive function. A study of Japanese regional senior residents found that higher-level functional capacity correlated positively with cognitive function [34]. In particular, intellectual activities seem largely determined by the cognitive function that controls information processing speed, executive function, and short-term memory or working memory. Example TMIG-IC questions that examine intellectual activities, and involve cognitive functioning aspects, are “Do you read newspapers?” and “Are you able to fill out forms for your pension?” Our findings indicate a correlation between intellectual activity and executive function.

The ability to use new devices is also correlated with executive function. The use of a new device does not simply involve temporarily gathering information. If the new device has a display, for example, the user must remember information while simultaneously reading the screen, necessitating multiple cognitive processes [35]. These simultaneous and parallel functions of storing and modifying are related to working memory capacity. In this study, PD patients who were impaired in their performance on the TMT-B were classified as “PD-executive function impairment,” but TMT-B scores reflect alternative and divided attention, as well as working memory. As elderly individuals age, the decline in executive function and attention becomes more pronounced, and they tend to avoid using devices that require complex cognitive functioning. This indicates that if

executive function is reduced, the use of information and communication equipment can be difficult. That is, elderly patients with PD who demonstrate low executive function are expected to have a higher risk of these cognitive dysfunctions. One survey of senior citizens' adoption of home electronic appliances and information devices revealed that more than 50% owned devices such as personal computers, mobile phones, and DVD players. A national survey in Japan showed that the rate of internet use among people aged 60–79 climbed from 43% in 2008 to 61% in 2012, and the rate is increasing each year [36]. Therefore, elderly people's ability to use information devices and information systems might greatly influence their daily lives. Thus, in order to be able to use information devices and electronics, maintaining cognitive function is necessary and indispensable.

Previous studies showed that participation in intellectual activities and the use of information devices are linked with a lower risk of developing cognitive impairment and dementia [37][38][39], which suggests a reversal of the assumed direction of influence between cognitive function and higher-level functional capacities. The concept of cognitive reserve has recently been highlighted [40]. Cognitive reserve is characterized by cognitive storage, which appears to help prevent cognitive function decline, and which may be strengthened. Therefore, it is important to increase activities that promote cognitive demands, including intellectual activities and information device usage, to strengthen the cognitive reserve and prevent the decline of cognitive function and the progression of dementia.

With respect to social roles, social participation, and information gathering, there were no significant differences among participants regarding whether executive function was impaired. Overall, patients with PD scored lower than healthy controls on these measures. These findings support previous work indicating that social participation is

affected by several factors other than aging-related physical decline, such as socioeconomic status, lifestyle, age, and gender [41], suggesting that cognitive function is not the only cause of lack of social participation.

Despite these findings, both social participation and intellectual activities seem important in preventing dementia [42]. It has been reported that older adults who have infrequent social interaction have an increased risk of developing dementia. The scale of these social networks is an important factor in preventing dementia [43]. That is, it is possible to indirectly activate cognitive function through participation in social networking and interaction with others. One study of patients with PD reported that habitual leisure-time activities correlate with cognitive function and emotions [44]. The authors suggest that reducing sedentary lifestyles and promoting habitual leisure-time activities (physical and non-physical leisure activities) might be beneficial in preventing cognitive decline and apathy. The maintenance of an active lifestyle, even in PD patients with motor symptoms, might therefore be beneficial. However, in order to promote social participation, it is necessary to first ascertain the factors that inhibit participation in patients with PD.

The present study is the first to clarify the association between neuropsychological characteristics and higher-level functional capacity in patients with PD. However, some limitations must be noted. First, we were not able to categorize participants by gender and duration of symptoms because the sample size was small. Second, healthy controls were mature participants that lived in our region, who agreed to voluntarily participate after having been publicly recruited. Therefore, there is a possibility that participants' motivation and health awareness were generally high, indicating a potential bias in the sample selection. Third, we used a comprehensive neuropsychological battery to evaluate participants, but this did not include visual memory or visual-spatial function examinations.

Since these abilities tend to decline with age, they should be assessed in future studies.

Fourth, the severity of PD symptoms is an important influence on higher-level functional capacity (in addition to executive function). However, our assessment of symptom severity was based on the HY staging system and did not include the Unified Parkinson's Disease Rating Scale (UPDRS). Compared to the HY staging system, the UPDRS permits a more detailed evaluation of severity level. Examining the relationship between higher-level functional capacity and development of PD symptoms using the UPDRS system is desirable. Furthermore, we examined neuropsychological function and higher-level functional capacity only once in this study. Therefore, we do not know how higher-level functional capacity changes with respect to changes in cognitive function.

In conclusion, our results showed that the higher-level functional capacity of patients with PD declines in comparison to that of healthy controls, and that executive function influences the decline. These findings imply that an increase in educational interventions that promote social and intellectual activities might be effective, and psychological interventions involving cognitive training related to cognitive function might be beneficial for PD patients. Hindle et al. conducted a meta-analysis of studies focusing on the effect of non-pharmacological interventions, such as cognitive training, exercises, physical therapy, and DBS, on the cognitive function of PD patients [45]. However, only one study provided a high level of evidence (i.e., using randomized controlled trials and a very low risk of bias). This suggests that research on cognitive training and its influence on cognitive impairment in PD and dementia patients is both quantitatively and qualitatively limited. By way of contrast, there are ample reports of the effectiveness of psychological interventions for patients with psychiatric disorders (e.g., schizophrenia), in which cognitive rehabilitation has been implemented to prevent decline in cognitive function and

to improve social function [46]. It may be possible to learn from such positive interventions and apply them to patients with PD to establish a support system that can help maintain and improve cognitive function and higher-level functional capacity in these patients.

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