

# The effect of cognitive rehabilitation for post-stroke depression in long-term care health facilities: A randomized controlled trial

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## Abstract

**Objective:** The purpose of this study is to examine the effects of the cognitive rehabilitation on the depressive symptoms, cognitive function, activities of daily living (ADL), quality of life (QOL), and customer satisfaction in Post-Stroke Depression (PSD) patients.

**Design:** Randomized controlled trial

**Setting:** Long-term care health facilities in Ibaraki Prefecture, Japan.

**Subjects:** Total of 30 participants with either cognitive rehabilitation (intervention group, n = 15) or additional low-intensity exercise therapy (control group, n = 15) completed the randomized controlled trial

**Intervention:** The participants were randomly divided into 2 groups and given 36 sessions of low-intensity exercise therapy, (3 sessions a week for 12 weeks) with either cognitive rehabilitation (intervention) or additional low-intensity exercise therapy (control).

**Main Measures:** Measurements were performed before and after the 36 rehabilitation sessions. Primary outcome measures were severity scores evaluations of depression (the Geriatric Depression Scale [GDS], Zung Self Depression Scale [SDS], Japan Stroke Scale - Depression Scale [JSS-D], Japan Stroke Scale - Emotional Disturbance Scale [JSS-E]). Secondary outcome measures included Frontal Assessment Battery (FAB), ADL, QOL and Customer Satisfaction.

**Results:** Participants who received cognitive rehabilitation showed significantly more improvement in the GDS (95% confidence interval [CI], -0.67–5.47; P = .02), SDS (95% CI, 3.68–18.32; P = .01), JSS-D (95% CI, 0.92–3.11; P = .00), and JSS-E (95% CI, -.59–4.64; P = .04) than those in the control group.

**Conclusions:** To the best of our knowledge, this is the first randomized trial to show the efficacy of cognitive rehabilitation to improve the depressive symptoms and cognitive function for PSD patients.

## Introduction

Stroke survivors often encounter severe cognitive and emotional consequences [1]. Post-stroke depressive symptoms occur frequently in the chronic phase after stroke [2-6]. Approximately 15 to 60% of stroke survivors are likely to experience post-stroke depression (PSD). PSD is one of the most important sequela of stroke and adversely affects for cognitive function, ADL, and QOL [7-9]. Patients with PSD were reported to have more functional disability [10], poorer rehabilitation outcomes [11], and increased morbidity and mortality in the first year after stroke onset [12]. Furthermore, in a previous study, we found that patients who were depressed after stroke reported low levels of facility service satisfaction and rehabilitation customer satisfaction [13].

Physioanatomic factors that have been of great interest and of some controversy are the relationships between stroke neuroanatomical

localization, overall stroke burden, stroke subtype, and the formation and severity of PSD [14,15]. Two studies led by Robinson reported that acute stroke patients with left frontal or left basal ganglia lesions had a significantly higher frequency of major or minor depression than patients with other lesion locations [16,17]. Taken together, these findings indicate that frontal lobe function is significantly involved in PSD.

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Studies on the treatment of PSD have generally focused on pharmacological interventions [18,19], while non-pharmacological interventions for PSD have hardly been investigated. Pharmacotherapy has been shown to relieve PSD, however, its usefulness is limited because of frequent adverse effects [20]. There are numerous treatments for depression and anxiety with varying degrees of effectiveness. Physical activity has been shown to be associated with a decrease in depression and anxiety symptoms. Physical activity has been consistently shown to be associated with improved physical health, life satisfaction, cognitive functioning, and psychological wellbeing [21]. Several reports suggest that exercise is a promising, low-risk intervention that might be helpful in prevention and treatment of depression in elderly residents of care homes [22,23].

Cognitive rehabilitation is a rehabilitation program that involves repeated practice of standardized tasks that target particular cognitive functions, what might be referred to as 'cognitive stimulation [24]'. Cognitive rehabilitation stimulates different brain areas that are activated by each task to be performed. Hwi-Young Cho and colleagues [25] reported that computer cognitive training led to activation of the frontal lobe and improvement of memory and attention of stroke patients. Given the association between PSD and frontal lobe function, it is possible that activation of the frontal lobe function through cognitive rehabilitation could lead to improvement of PSD, which, in turn, is likely to lead to an improvement in ADL and QOL patients with PSD.

To test this hypothesis, we previously conducted a pilot-study of cognitive rehabilitation for patients with PSD, which included pre- and post-evaluation, but not a control group. Results of this pilot-study indicated that cognitive rehabilitation has favorable effects on depression, frontal lobe function, and QOL [26]. However, recently, the favorable effects of exercise therapy on depression have been reported [23]. Therefore, we considered that it is necessary to compare cognitive rehabilitation and low-intensity exercise therapy, as typically used in rehabilitation programs, to compare their respective therapeutic effects on PSD. The purpose of the current study was to conduct a randomized controlled trial (RCT) to examine the effects of cognitive rehabilitation (intervention group) and low-intensity exercise therapy (control group) on depression status, ADL, and QOL in patients with PSD. Furthermore, we examined the effects of cognitive rehabilitation on customer satisfaction with long-term care facility services and rehabilitation programs for PSD patients.

## Methods

### Participants

Participants in this study were recruited between March 2015 and July 2016. They were residents of 5 long-term care health facilities (LTCHFs) in Ibaraki prefecture, Japan. The inclusion criteria were as follows: (1) cerebral infarction or history of cerebrovascular disorders such as cerebral hemorrhage; (2) mood disorders with 2 or more symptoms according to the Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-IV) [27]; and (3) depression, according to the Geriatric Depression Scale (GDS) [28] (more than 5 points), the Japan Stroke Scale - Depression Scale (JSS-D) [29] ( $\leq 2.4$  points).

Exclusion criteria were as follows: (1) taking antidepressants; (2) diagnosis of dementia according to the revised Hasegawa dementia rating scale (HDS-R) [30] (10 points or less) or Independence degree of daily living for the demented elderly (rank IV-M); and (3) participants with higher degrees of brain dysfunction (such as aphasia).

Sample size was calculated using G\*Power. 3.1.9.2 [31]. The calculations revealed that 14 participants in both groups was the minimum sample size required [32]. Figure 1 shows a flow chart of patients' participation in this study. A total of 40 patients were assessed for eligibility. Of those 40 patients, 8 did not consent to the study and the remaining 32 patients were randomized. Of the 16 patients allocated to the intervention group, 1 could not continue the rehabilitation owing to being discharged before completing all 12 sessions. Likewise, 1 of the 16 patients allocated to the control group could not continue rehabilitation owing to being discharged before completion of the sessions. We could not obtain the postintervention outcomes for these 2 patients who withdrew. Finally, a total of 30 patients completed the cognitive rehabilitation program (intervention group,  $n = 15$ ) or low-intensity exercise therapy program (control group,  $n = 15$ ). There were no adverse events in this study.

### Study design

This study was designed as an RCT, with an intervention group and control group. A computer-generated sequence was used to randomize the participants into the control and intervention groups. All participants underwent 36 20-minute low-intensity exercise therapy sessions (3 sessions per week for 12 weeks) and an additional 36 20-minute rehabilitation sessions (3 sessions per week for 12 weeks) with either cognitive rehabilitation (intervention group) or further low-intensity exercise therapy (control group). Interventions were carried out by skilled and experienced physical therapists or occupational therapists. Baseline measures of each participant's demographics and characteristics were assessed prior to the interventions. Outcome measures were evaluated at 2 points: prior to training (pre-training evaluation), and after the 36 sessions (post-training evaluation).

### Cognitive rehabilitation program (intervention group)

The intervention program consisted of: the Stroop Color-Word Test, Kana Pick-out Test, Digit Span, and the Serial Sevens Test.

#### Stroop Color-Word Test

The Stroop Color and Word Test (SCWT), useful in both clinical and experimental contexts, is a neuropsychological test that uses combinations of colors and words to assess ability to inhibit cognitive interference [33]. In this test, the participant says aloud the color of 4 different colored circles. Next the participant reads aloud the names of colors printed in the same colors (for example the word "red" printed in red ink). Finally, the participant reads about the names of colors printed in different colored inks (for example the word "red" printed in blue ink).

#### Kana Pick-out Test

The Kana Pick-out Test (KPT), so called because it involves participants "picking out" Japanese *Kana* symbols from a text, is a useful tool for assessing frontal lobe function. It is often used in Japan for identifying mild dementia [34]. The test involves the dual task of reading a text while (1) identifying as many *kana* vowel symbols as possible within 2 minutes and (2) understanding the meaning of the text, which is evaluated by answering 10 questions about its contents [34].

#### Digit Span Test

The digit span test is a memory test, which assesses a participant's ability to hold a sequence of numbers in their memory. Digit sequences are presented beginning with a length of 2 digits.

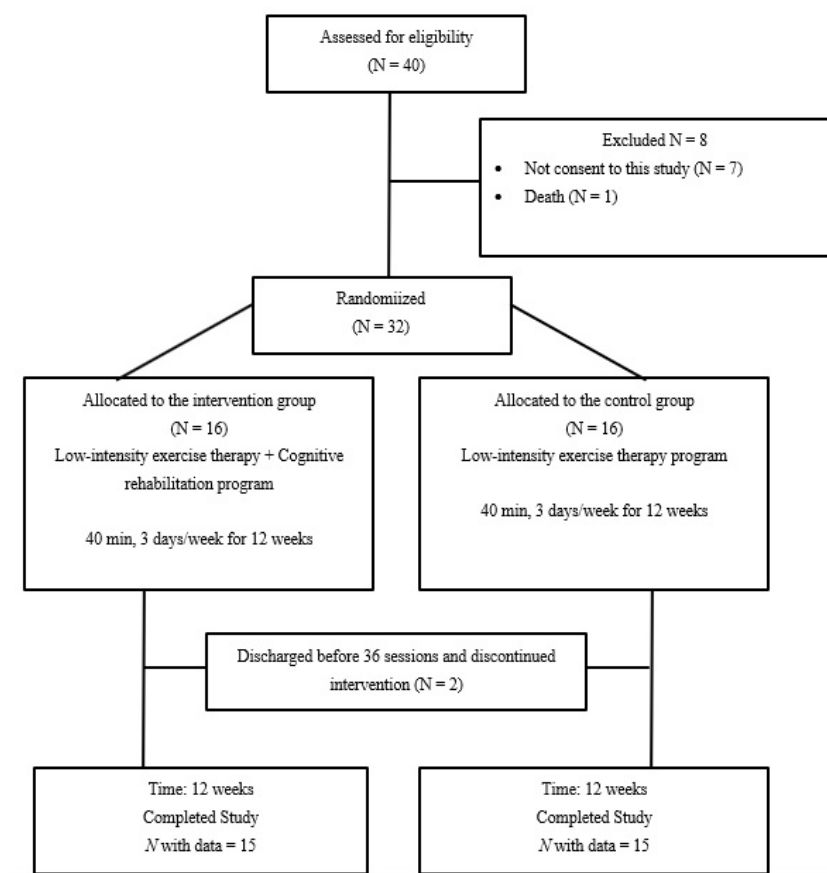


Figure 1. Flow of participant participation

### Serial Sevens Test

The Serial Sevens Test is used in clinical settings to test mental function, perhaps after head trauma or dementia screening. The test involves the participants subtracting 7 from the given number (usually 100), and continuing to subtract 7 from successive answers, until told to stop.

### Low-intensity exercise therapy program (control group)

The low-intensity exercise therapy program consisted of the following: (1) range of motion exercise and (2) low-intensity aerobic exercise in the supine position aimed at level 13 of the Borg scale (slightly tight).

### Assessment

All assessment was done by physical therapists or occupational therapist trained to perform standardized assessment procedures. For primary outcome measures, GDS, the Zung Self Depression Scale (SDS) [35], JSS-D, Japan Stroke Scale - Emotional Disturbance Scale (JSS-E) [36] were used to evaluate depression. Secondary outcome measures were HDS-R, Mini-Mental State Examination (MMSE) [37], Frontal Assessment Battery (FAB) [38], Trail Making Test (TMT part A and B) [39], Barthel Index (BI) [40], independence degree of daily living for the demented elderly, Rehabilitation Customer Satisfaction (the Customer Satisfaction Scale based on Need Satisfaction [CSSNS]) [41], Facility Service Satisfaction, and SF-8 [42]. The Facility Service Satisfaction instrument uses a 50-point scale (0 points [dissatisfaction] to 49 points [satisfaction]) and is composed of 23 items across 6 categories: impression of life in general, care of health, service

contents, leisure activity, life task, and comprehensive evaluation. The Customer Satisfaction Scale based on Need Satisfaction (CSSNS) uses a 75-point scale (0 points [dissatisfaction] to 75 points [satisfaction]) and is composed of 15 items across 5 categories: competence, autonomy, relatedness to participant, relatedness to service provider, and physiological need. The evaluators were blinded to intervention allocation. Participants and therapists were not blinded to intervention allocation.

### Statistical analysis

SPSS version 21.0 was used for all statistical analyses. Fisher exact test and Mann-Whitney U test were used to compare the characteristics between intervention group and control group (Table 1). Comparisons were made using Wilcoxon signed-rank test and Mann-Whitney U test for intervention group and control group (BI, HDS-R, MMSE, FAB, GDS, SDS, JSS-D, JSS-E, Facility Service Satisfaction, CSSNS, SF-8) (Table 2). Adjustment was made using the Bonferroni method for multiple testing (Tables 2 and 3). Sample size was calculated using the effect sizes. The sample size of this study has sufficient detection power. Statistical significance was set at  $P < .05$ .

### Ethical considerations

This study was conducted with the approval of the ethics committee of the University of Tsukuba (approval number: 943). All participants provided written informed consent after receiving a full written description of the study. The trial was prospectively registered through Clinical Trial Registry (University hospital Medical Information Network (UMIN) number: 000029117 [https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr\\_view.cgi?recptno=R000033266](https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno=R000033266)).

**Table 1.** Demographic characteristics of subjects who completed study

Characteristics		Intervention group (N = 15)		Control group (N = 15)		P value
Sex <sup>a</sup>	Female(%)	12	(80.0%)	8	(53.3%)	.25
Age <sup>b</sup>		82.6±9.2	(56 to 93)	77.9±9.8	(59 to 95)	.10
Residents period (Day) <sup>b</sup>		721.9±810.0	(62 to 2687)	844.0±995.5	(333 to 3938)	.36
Certified as requiring care (levels) <sup>b</sup>		3.1±0.9	(2 to 5)	3.0±1.5	(2 to 5)	.79
Independence degree of daily living for the demented elderly <sup>c</sup>	Not applicable	10	(66.7%)	11	(73.3%)	.63
	Rank I	0	(0.0%)	1	(6.7%)	
	Rank II	4	(26.7%)	2	(13.3%)	
	Rank III	1	(6.7%)	1	(6.7%)	
Hasegawa dementia rating scale-revised <sup>b</sup>	(HDS-R)	23.3±5.2	(12 to 30)	22.1±5.8	(11 to 28)	.63
The Geriatric Depression Scale <sup>b</sup>	(GDS)	8.5±1.8	(5 to 12)	8.7±3.0	(5 to 13)	.52
Zung Self Depression Scale <sup>b</sup>	(SDS)	44.5±7.4	(31 to 58)	45.3±10.2	(29 to 66)	.90
Japan Stroke Scale - Depression Scale <sup>b</sup>	(JSS-D)	6.2±3.8	(2.4 to 14.1)	4.4±1.2	(2.6 to 6.9)	.32
Japan Stroke Scale – Emotional Disturbance Scale <sup>b</sup>	(JSS-E)	3.38±4.18	(-0.55 to 13.95)	4.0±3.1	(-0.3 to 7.78)	.31
Time since stroke(Day) <sup>b</sup>		2224.5±1534.3	(721 to 5990)	2829.8±1838.7	(441 to 5110)	.69
Side of paresisa	Right	2	(13.3%)	4	(26.7%)	.65
Complications (Multiple answers) <sup>c</sup>						
	Diabetes mellitus	2	(13.3%)	3	(20.0%)	.60
	Hypertension	7	(46.7%)	7	(46.7%)	
	Osteoarthritis	1	(6.7%)	2	(13.3%)	
	Fracture	2	(13.3%)	5	(33.3%)	
	Heart disease	0	(0.0%)	2	(13.3%)	
	Respiratory disease	0	(0.0%)	2	(13.3%)	

NOTE. Values are N(%), mean ± SD, or as otherwise indicated.

a Fisher exact test

b Mann–Whitney U test

c Chi-Square Test

**Table 2.** Differences within groups, differences between groups

Measures		Intervention group (N=15)					P value <sup>b</sup>		Control group (N=15)				P value <sup>b</sup>	
		Pre-	Post-	Differences within group (95%CI) <sup>a</sup>		Pre-			Post-	Differences within group (95%CI) <sup>a</sup>				
Barthel Index	(BI)	55.3±20.7	58.0±19.8	2.7	(-3.24 to 8.57)	.60		53.0±20.9	53.0±20.9	0.0	(0.00)			
Hasegawa dementia rating scale-revised	(HDS-R)	23.3±5.2	24.3±5.8	1.0	(-1.30 to 3.30)	.29		22.1±5.8	21.5±5.3	-0.6	(-1.15 to 2.35)	.73		
Mini-Mental State Examination	(MMSE)	23.0±4.5	24.7±4.9	1.7	(-0.30 to 3.64)	.11		22.3±4.8	23.3±4.0	1.1	(-0.43 to 2.57)	.15		
Frontal Assessment Battery	(FAB)	9.5±3.3	12.5±3.5	2.9	(1.28 to 4.59)	.01	**	9.7±3.4	10.7±3.5	1.0	(-0.26 to 2.26)	.09		
The Geriatric Depression Scale	(GDS)	8.5±1.8	5.1± 2.5	-3.5	(2.32 to 4.61)	.00	**	8.7±3.0	8.1±3.8	-0.6	(-0.63 to 1.83)	.33		
Zung Self Depression Scale	(SDS)	44.5±7.4	34.1±7.1	-10.3	(5.46 to 15.21)	.00	**	45.3±10.2	45.1±11.9	-0.2	(-4.15 to 4.55)	.82		
Japan Stroke Scale – Depression Scale	(JSS-D)	6.2± 3.8	2.1± 1.3	-4.1	(2.06 to 6.14)	.00	**	4.4±1.2	4.1± 1.6	-0.3	(-0.29 to 0.88)	.22		
Japan Stroke Scale – Emotional Disturbance Scale	(JSS-E)	3.4± 4.2	1.1± 3.2	-1.3	(-1.26 to 4.72)	.16		4.0±3.1	3.6± 3.1	-0.4	(-0.54 to 1.32)	.46		
Facilities Service Satisfaction Total score		39.4±6.8	42.0±4.3	2.9	(-0.36 to 6.23)	.06		37.0±5.6	38.2±6.9	1.2	(0.75 to 3.15)	.21		
Rehabilitation Customer Satisfaction Total score	(CSSNS)	36.2±4.9	37.6±6.8	5.5	(0.10 to 10.97)	.07		47.3±9.3	46.9±10.4	-0.3	(-4.57 to 5.24)	.86		
SF-8														
Physical functioning	(PF)	33.5±17.7	44.5±14.2	10.9	(-2.10 to 22.65)	.01	**	38.5±14.1	34.2±18.6	-4.3	(-6.61 to 15.2)	.41		
Role physical	(RP)	37.0±15.6	47.8±11.7	10.8	(-0.99 to 21.36)	.01	**	42.3±13.6	37.6±17.6	-4.8	(-6.50 to 16.0)	.39		
Bodily pain	(BP)	43.9±13.0	51.5±9.3	7.6	(-5.51 to 12.56)	.00	**	50.3±13.8	47.9±14.4	-2.3	(-4.37 to 9.05)	.42		
General health	(GH)	45.4±8.7	53.5±7.9	8.1	(-1.02 to 12.07)	.00	**	47.5±7.8	47.9±9.5	0.4	(3.59 to 4.37)	.40		
Vitality	(VT)	44.3±9.1	52.7±8.3	8.4	(-3.04 to 8.21)	.00	**	46.3±6.6	50.1±6.7	3.8	(-0.63 to 8.23)	.07		
Social functioning	(SF)	32.7±14.7	50.1±7.7	17.4	(-1.76 to 19.42)	.00	**	43.0±11.7	39.5±14.8	-3.5	(-4.23 to 11.06)	.37		
Role emotional	(RE)	50.2±6.4	51.0±7.8	0.8	(-5.80 to 5.80)	.50		45.2±10.0	51.0±7.8	5.8	(1.23 to 10.31)	.02	*	
Mental health	(MH)	46.5±10.5	51.6±9.2	5.1	(-0.21 to 15.19)	.02	*	42.6±10.7	44.1±11.3	1.5	(-0.74 to 3.77)	.14		
Physical component summary	(PCS)	34.9±14.7	46.6±9.9	11.7	(-1.11 to 17.72)	.00	**	43.5±12.8	38.3±14.8	-5.3	(-4.25 to 14.75)	.28		
Mental component summary	(MCS)	48.2±8.3	52.3±8.4	4.1	(-2.76 to 9.20)	.01	**	44.0±8.5	49.1±7.5	5.1	(3.20 to 6.92)	.00	**	

NOTE. Values are N, mean ± SD, or as otherwise indicated

Abbreviations: CI, confidence intervals

\*Significant difference between pre- and post-test values,  $P < 0.05$ , \*\*Significant difference between pre- and post-test values,  $P < 0.01$ 

a Wilcoxon signed-rank test, b Adjusted using the Bonferroni method for multiple testing

**Table3.** Differences between groups

Measures		Differences between two groups (95%CI) <sup>a</sup>		P value <sup>b</sup>		Effect Size <sup>a</sup>
The Geriatric Depression Scale	(GDS)	2.9	(-0.67 to 5.47)	.02	*	0.623
Zung Self Depression Scale	(SDS)	10.1	(3.68 to 18.32)	.01	**	0.686
Japan Stroke Scale - Depression Scale	(JSS-D)	3.8	(0.92 to 3.11)	.00	**	0.799
Japan Stroke Scale - Emotional Disturbance Scale	(JSS-E)	0.9	(-0.59 to 4.64)	.04	*	0.532
SF-8						
Physical functioning	(PF)	-15.3	(-2.10 to 22.65)	.12		0.400
Role physical	(RP)	-15.5	(-0.99 to 21.36)	.09		0.438
Bodily pain	(BP)	-9.9	(-5.51 to 12.56)	.58		0.144
General health	(GH)	-7.7	(-1.02 to 12.07)	.11		0.414
Vitality	(VT)	-4.6	(-3.04 to 8.21)	.24		0.305
Social functioning	(SF)	-20.9	(-1.76 to 19.42)	.04	*	0.525
Role emotional	(RE)	4.9	(-5.80 to 5.80)	1.00		0
Mental health	(MH)	-3.5	(-0.21 to 15.19)	.07		0.468
Physical component summary	(PCS)	-17.0	(-1.11 to 17.72)	.21		0.321
Mental component summary	(MCS)	1.0	(-2.76 to 9.20)	.05	*	0.514

NOTE. Values are N, mean± SD, or as otherwise indicated

Abbreviations: CI, confidence interval

\*Significant difference between pre and post test values,  $P < 0.05$ , \*\*Significant difference between pre and post test values,  $P < 0.01$

a Mann–Whitney U test, b Adjusted using the Bonferroni method for multiple testing.

## Results

At the pre-training evaluation, no differences in patient characteristics or baseline clinical data were observed between the 2 groups (Table 1). The secondary measures did not differ between the 2 groups. The amount of rehabilitation during the intervention period did not differ between the 2 groups (Table 1).

Tables 2 and 3 shows the outcome measures of the 2 groups. The intervention group showed significant increases in FAB (95% confidence interval [CI], 1.28–4.59;  $P = .01$ ), GDS (95% CI, 2.32–4.61;  $P = .00$ ), SDS (95% CI, 5.46–15.21;  $P = .00$ ), JSS-D (95% CI, 2.06–6.14;  $P = .00$ ), Physical component summary (PCS) of SF-8 (95% CI, -1.11 - 17.72;  $P = .00$ ) and MCS of SF-8 (95% CI, -2.76 –9.20;  $P = .01$ ) whereas in the control group, no difference was observed except for the MCS of SF-8 (95% CI, 3.20 –6.92;  $P = .00$ ). The intervention group showed significantly greater improvement in the GDS (between-group difference = 2.9; 95% CI, -.67–5.47;  $P = .02$ ), SDS (between-group difference = 10.1; 95% CI, 3.68–18.32;  $P = .01$ ), JSS-D (between-group difference = 3.8; 95% CI, .92–3.11;  $P = .00$ ), JSS-E (between-group difference = .90; 95% CI, -.59–4.64;  $P = .04$ ) and MCS of SF-8 (between-group difference = 1.0; 95% CI, -2.76 –9.20;  $P = .05$ ) than did the control group.

## Discussion

To the best of our knowledge, this is the first randomized trial to show the efficacy of cognitive rehabilitation to improve the depressive symptoms and cognitive function for PSD patients. Pre-training evaluation revealed that the participants in our study were depressed and had declined frontal lobe function. Post-training evaluation demonstrated that for participants in the intervention group both their depressive symptoms and frontal lobe function were improved after completing the cognitive rehabilitation intervention. The results obtained in this trial indicate that depressive symptoms and frontal lobe function can be improved by the addition of cognitive rehabilitation to the usual exercise-based rehabilitation programs.

Van Eeden and colleagues [43] reported an economic evaluation of cognitive behavioral therapy (CBT) intervention versus computerized cognitive training for PSD symptoms. Both interventions consisted of

13–16 sessions over a period of 4 months. The computerized cognitive training was an individual, patient-tailored computerized cognitive training program in which patients executed computer tasks on their own cognitive level. As a result of the intervention, they reported that both treatments showed a therapeutic effect on PSD symptoms. Based on their report, cognitive rehabilitation was considered effective for patients with PSD, however, we could not find other studies that reported the effects of cognitive rehabilitation on patients with PSD symptoms.

In Japan, cognitive rehabilitation is generally provided by occupational therapists or clinical psychologists. In this study, the cognitive rehabilitation program consisted of common attention-related work tasks rather than computer-based exercises and it was shown to be effective in improving depressive symptoms.

Sou and colleagues [44] reported that computerized cognitive training (CCT) attenuated decline in memory performance in patients with mild cognitive impairment, and showed, using function MRI, that the effect was mediated by enhanced functional connectivity between the hippocampus and superior frontal cortex. Brain changes of patients with major depression were characterized by diffuse bilateral grey matter loss in the ventrolateral and ventromedial frontal systems extending into the temporal gyri and hippocamp compared to healthy controls [45]. Considering these findings, it seems reasonable to suggest that cognitive rehabilitation acts upon the areas of the brain related to depression and thereby ameliorates depressive symptoms.

In this study, the control group performed a typical rehabilitation, which consisted of exercise therapy. Recently, favorable effects of exercise therapy on depression have been reported [26]. One study reported that resistance training exercise leads to improvement of cognitive function in patients with mild cognitive impairment [46]. The exercise therapy performed in our control group was of a low intensity. While there was a positive effect on QOL, it was not effective for improving depression or cognitive function. Underwood and colleagues<sup>22</sup> reported that at aged 65 years or older, a moderately intense exercise program did not reduce depressive symptoms in residents of care homes. It seems that the effect of exercise therapy for elderly patients with depression might be different from its effect on depression in general.



In our study, the QOL of patients with PSD was improved as a result of cognitive rehabilitation. Cumming and colleagues [47] showed that cognitive impairment and poorer attention were associated with lower QOL among post-stroke patients after 3 and 12 months after onset. In addition, Cao and colleagues [48] showed that there was a negative correlation between QOL and depression among elderly people. Therefore, in addition to its benefit for ameliorating depression, cognitive rehabilitation may also be effective for improving the QOL of patients with PSD.

Apathy has been reported as one of the primary clinical features among post-stroke patients. Starkstein and colleagues [49] reported that major depression was associated with an increased frequency of apathy and that apathy was also significantly associated with older age, cognitive impairment, and impairment of ADL. Okada and colleagues [50] estimated the severity of apathy using an Apathy Scale and regional cerebral blood flow in stroke patient and demonstrated that apathy may be accompanied by cognitive impairments, depressive state, and frontal dysfunction. Further, they reported the hypoactivity in the frontal lobe and anterior temporal regions. In our study, results of the pre-training evaluation showed that the patients with PSD were also apathetic. However, post-training evaluation demonstrated that this apathetic condition improved significantly in the intervention group compared to the control group. Based on these findings, cognitive rehabilitation seems to be effective for reducing apathetic symptoms by promoting frontal lobe function.

This study has some limitations. Questions remain about the optimal duration of rehabilitation, the best duration for a training session, intervention frequency, exercise load, and long-term effects of cognitive rehabilitation and low-intensity exercise. We will attempt to answer these questions in future investigations.

## Clinical messages

The results obtained in this randomized controlled trial suggest that the inclusion of cognitive rehabilitation to the usual low-intensity exercise therapy rehabilitation program could improve depressive symptoms in patients with PSD more efficiently than exercise rehabilitation alone. Further randomized controlled studies on a larger scale are needed to clarify its effectiveness.

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## Conflict of interest

The authors have no conflict of interest to declare.

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