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Clinical usefulness of scales for evaluating cognitive impairment in patients with amyotrophic lateral sclerosis

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ABSTRACT

Cognitive impairment is a common non-motor symptom of amyotrophic lateral sclerosis (ALS); however, scales suitable for detecting cognitive impairment in ALS patients in clinical practice are unclear. In this study, the Mini-Mental State Examination, Frontal Assessment Battery, and Montreal Cognitive Assessment (MoCA) were evaluated in 68 patients with ALS. The patients were classified into 3 groups based on the results of these clinical scales: group N, patients with scores higher than the cut-offs in all clinical scales; group M, patients with a score lower than the cut-off in one clinical scale; and group D, patients with scores lower than the cut-offs in two or three clinical scales. Clinical data were compared among the groups. Age at onset was significantly lower, and educational period was longer in group N than in group D. MoCA test reported the highest number of patients with a score lower than the cut-off value. The evaluation item of language in MoCA showed the lowest correct answer rate in group N, and evaluation items of executive function and memory in MoCA showed the lowest correct answer rates in group D. MoCA is the most sensitive clinical scale for evaluating cognitive impairment in ALS among the three scales.

1. Introduction

Amyotrophic lateral sclerosis (ALS), a devastating neurodegenerative disorder, is fatal within a few years from onset without artificial respiratory and nutritional supports [1,2]. ALS is clinically characterized by progressive weakness of upper and lower limbs, which is relatively confined to motor involvement at the early stage. However, recent studies have reported that pathological changes, such as ubiquitin-positive inclusions, are commonly found beyond motor systems in ALS with frontotemporal dementia (FTD) [3]. Previous reports have also shown that the neuropsychological and neuropathological features of patients with ALS are similar to those of patients with FTD [3,4]. Up to 15% of patients with ALS fulfilled the criteria for FTD, and almost 50% reported some cognitive impairment [5,6]. Patients with ALS exhibit dysphagia and respiratory failure at an advanced stage, after which a decision is required as to whether they should receive medical interventions such as gastrostomy or mechanical ventilation *via* tracheostomy. Due to the incidence of cognitive decline in patients with ALS, it is necessary to assess their ability to make decisions regarding interventions at an advanced stage. Therefore, it is important to evaluate cognitive functions in patients with ALS for informed consent. Examinations in clinical practice often have limited time constraints; therefore, a simplified neuropsychological scale would be useful to assess cognitive functions in ALS. In this study, we evaluated the clinical usefulness of three clinical scales: the Mini-Mental State Examination (MMSE) [7], Frontal Assessment Battery (FAB) [8], and Montreal Cognitive Assessment (MoCA) [9], and confirmed that the MoCA can specifically assess the neuropsychological aspect of cognitive impairment in ALS.

2. Patients and methods

In total, 138 consecutive patients with ALS who had been hospitalized from March 2013 to July 2017 in the Department of Neurology, Gunma University Hospital were enrolled in this study. All the participants were diagnosed with possible, probable, or definite ALS using the revised El Escorial criteria [10]. Among these, 84 patients with ALS were examined their cognitive functions using the MMSE, FAB, and MoCA. The remaining 54 patients could not be examined on all three clinical scales due to severe motor or bulbar symptoms. Among 84 patients with ALS, the final evaluation included 68 patients with ALS who had completed all evaluation items of three clinical scales. Patients who could not complete all items of the three clinical scales due to severe weakness of the upper limbs, fatigue or unwillingness were excluded from this study.

The cut-offs for a confirmation of cognitive impairment on each

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scale were < 24, < 11, and < 26 on MMSE [7], FAB [11], and MoCA [9], respectively. Patients were classified into 3 groups following cognitive assessment: group N, patients with scores higher than the cut-offs in all clinical scales; group M, patients with a score lower than the cut-off in one clinical scale; and group D, patients with scores lower than the cut-offs in two or three clinical scales. In addition, clinical characteristics, such as age at onset, age at examination, disease duration from onset to cognitive assessment, educational period, survival period, gender, initial site of motor symptoms, presence or absence of subjective cognitive decline, ALS functional rating scale-revised (ALSFRS-R) [12], and Norris Scales (the Limb Norris Scale and Norris Bulbar Scale) [13] scores were compared among three groups. All items evaluated in the MMSE, FAB, and MoCA were also compared among three groups.

Single photon emission computed tomography (SPECT) with a ^{99m}Tc-ethyl cysteinate dimer (^{99m}Tc-ECD) was performed in 35 patients with ALS. The SPECT images were analyzed using a fine stereotactic region of interest (ROI) template (Fine SRT), which could precisely measure regional cerebral blood flow (rCBF) according to the setting of a fixed universal ROI group based on an anatomical standard image obtained from Statistical Parametric Mapping (SPM99) [14,15]. The constant ROIs from the Fine SRT analysis on each brain hemisphere were composed of 812 ROIs grouped into 52 areas. This comprised 1624 ROIs grouped into 104 areas for both hemispheres [16].

This study was approved by the Ethical Committee at Gunma University Graduate School of Medicine. Informed consent was obtained from all patients with ALS participated in this study.

2.1. Statistical analysis

Statistical analysis was conducted using SPSS®25 (IBM Japan, Tokyo, Japan). Quantitative data are expressed as means ± standard deviations. Quantitative parameters among three ALS groups (group N, M, and D) were compared using the *post hoc* Kruskal-Wallis test with Bonferroni correction, and categorical parameters were compared using chi-square test. Adjustment of the scores of three neuropsychological scales by age at onset and educational period was performed using multiple logistic regression analysis. In addition, correct answer rates for each evaluation item in all three neuropsychological scales were evaluated. Statistical significance was set at $p < .05$.

3. Results

Among the 68 ALS patients evaluated in this study, 34 were male and 34 were female. The mean age at onset was 65.4 ± 11.9 years, and mean age at examination was 66.6 ± 11.9 years. The mean duration from onset to cognitive assessment was 13.9 ± 8.8 months. There were 22 patients with upper limbs onset, 22 patients with lower limbs onset, and 24 patients with bulbar onset. Regarding cognitive function, 48.5% patients had subjective cognitive decline. Further, 38 patients scored lower than the cut-offs in one or more scales among 68 ALS patients; 6 patients scored lower than the cut-offs in the MMSE, 6 patients in the FAB, and 37 patients in the MoCA. There were 28 patients with a score lower than the cut-off in one clinical scale, 27 out of 28 patients scored lower than the cut-off in the MoCA, and one patient scored lower in the FAB. A summary of the clinical characteristics of the groups is shown in Table 1. The numbers of patient in each group were 30 in group N, 28 in group M, and 10 in group D. Four of the 68 patients with ALS fulfilled the diagnostic criteria of the frontotemporal lobar degeneration (FTLD) [17], and one patient fulfilled the diagnostic criteria of Alzheimer's disease [18]; these five ALS patients belonged to group D. An additional five patients in group D had not demonstrated any clinical symptoms of dementia at the time of examination. The age at onset and age at examination of patients were significantly younger in group N than in group D, and the educational period of patients was significantly longer in group N than in group D. There were no significant differences in duration from onset to cognitive assessment, survival period, gender, and initial sites of motor symptoms among three groups. Although the number of the patients with bulbar onset was more frequent in Group D, there was no significant difference between the ALS groups, measured by the chi-square test.

A summary of the cognitive and motor assessments in three groups is shown in Table 2. The presence of subjective cognitive decline was different among three groups; however, there were no statistically significant difference. Using the clinical evaluations of cognitive function, there were statistically significant differences among three groups in MMES and MoCA, and between group N and group M or D in FAB. However, even after adjustment by age at onset and educational period, the trend of results did not change except for the loss of the statistically significant differences between Groups N and D in the MMSE and MoCA. Conversely, no significant differences in motor functions, evaluated by the ALSFRS-R and the Norris Bulbar Scale, were found among three groups. There was only a significant difference between group N and group D in the Limb Norris Scale.

The correct answer rates of each evaluation item in the MoCA, FAB, and MMSE are shown in Tables 3–5, respectively. The correct answer rates of all items in the MoCA and FAB, except the environmental autonomy item in the FAB, were highest in group N, followed by group M and group D (Tables 3 and 4).

With regard to the evaluation items in MoCA (Table 3), the correct answer rates of all items, except a naming item, were significantly higher in group N than in group D. Further, the correct answer rates of items of attention or orientation were significantly higher in group M than in group D.

As for FAB (Table 4), the correct answer rates of the evaluation items of conceptualization, mental flexibility, programming, or inhibitory control were significantly higher in group N than in group M or D. In addition, the correct answer rate of the mental flexibility item was significantly higher in group M than in group D. Interestingly, conceptualization showed the lowest correct answer rates in all three ALS groups.

The analysis of evaluation items in the MMSE revealed that the correct answer rates of the evaluation items of orientation, attention and calculation, and recall were significantly higher in group N than in group D (Table 5). In addition, the correct answer rate of the orientation item was significantly higher in group M than in group D. Notably, the correct answer rates of all evaluation items, except attention and calculation, and recall, were > 75% in group D.

The ^{99m}Tc-ECD SPECT study was performed with 35 patients (12 in group N, 15 in group M, and 8 in group D). The results of rCBF for each ROI are shown in Table 6. There was a significant difference in the rCBF of right thalamus between groups N and M; however, the other areas showed no significant differences between ALS groups. In contrast, the mean rCBF of all ALS patients was decreased in 66 of 104 areas (such as the frontal, parietal, occipital, and limbic) when compared with the mean rCBF of the normal database reported previously [19] (data not shown).

4. Discussion

ALS is characterized by progressive weakness and muscle atrophy because of a selective loss of upper and lower motor neurons. Previously, cognitive impairment was believed to be an infrequent extramotor symptom in ALS [6]. The first ALS cases with intellectual decline were reported in France in 1892 [20]. In addition, an ALS case with motor aphasia was reported in Japan in 1893 [20]. Subsequently, cognitive decline in ALS was reported frequently worldwide and current clinical practice recognizes cognitive impairment a common symptom in ALS [5]. Recent studies have reported that TDP-43 is a major component of ubiquitin-positive and tau-negative inclusions in ALS and FTLD [21,22], indicating a common pathological basis of cognitive impairment due to frontotemporal degeneration. Cognitive

Table 1
Clinical characteristics of patients in the ALS groups.

	Group N	Group M	Group D	Total
Number of patients	30	28	10	68
Age at onset (years)	60.3 ± 11.5*	67.0 ± 8.0	73.0 ± 15.8	65.4 ± 11.9
(age range)	38–85	56–85	24–88	24–88
Age at examination (years)	61.4 ± 11.3*	68.2 ± 7.9	74.3 ± 15.9	66.6 ± 11.9
Duration (months)	13.4 ± 9.1	14.2 ± 8.9	14.1 ± 8.4	13.9 ± 8.8
Education (years)	13.1 ± 2.6*	12.1 ± 2.6	10.1 ± 2.6	12.3 ± 2.8
Survival (months)	24.6 ± 16.1 (n = 12)	25.2 ± 14.5 (n = 13)	26.0 (n = 1)	24.9 ± 14.6 (n = 26)
Male: female	13:17	18:10	3:7	34:34
Site of motor onset				
Upper limb	9	11	2	22
Lower limb	11	9	2	22
Bulbar	10	8	6	24

Group N: patients with scores higher than the cut-offs in all clinical scales.
Group M: patients with a score lower than the cut-off in one clinical scale.
Group D: patients with scores lower than the cut-offs in two or three clinical scales.
Duration: disease duration from onset to cognitive assessment.
Age at onset, age at examination, duration, education, and survival are expressed as mean ± SD.
n: number, SD: standard deviation.
* $p < .05$: Group N *vs.* Group D.

Table 2
Cognitive and motor assessments in the three ALS groups.

	Group N (n = 30)	Group M (n = 28)	Group D (n = 10)	Total (n = 68)
Subjective cognitive decline, n (%)				
Yes	9 (30.0%)	18 (64.2%)	6 (60.0%)	33 (48.5%)
No	10 (33.3%)	5 (17.9%)	1 (10.0%)	16 (23.5%)
Undetermined	11 (36.7%)	5 (17.9%)	3 (30.0%)	19 (28.0%)
Cognitive function (n = 68)				
MMSE point (mean ± SD)	28.8 ± 1.5*	27.1 ± 1.8**	24.0 ± 2.1	27.2 ± 2.4
number of subjects with < 24 (%)	0 (0%)	0 (0%)	6 (60%)	6 (8.8%)
FAB point (mean ± SD)	16.1 ± 1.4*	13.4 ± 2.0	10.7 ± 2.7	14.0 ± 2.7
number of subjects with < 11 (%)	0 (0%)	1 (3.6%)	5 (50%)	6 (8.8%)
MoCA point (mean ± SD)	27.7 ± 1.3*	22.7 ± 2.7**	18.6 ± 2.2	23.9 ± 4.0
number of subjects with < 26 (%)	0 (0%)	27 (96.4%)	10 (100%)	37 (54.4%)
Motor function (mean ± SD) (n = 45)	n = 19	n = 19	n = 7	
ALSFRS-R	41.7 ± 4.1	41.1 ± 4.3	41.6 ± 6.8	41.4 ± 4.5
Limb Norris	52.6 ± 6.2***	52.7 ± 11.8	59.9 ± 3.0	53.8 ± 9.0
Norris Bulbar	31.3 ± 10.1	29.8 ± 11.2	24.4 ± 11.3	29.6 ± 10.8

MMSE: mini-mental state examination, FAB: frontal assessment battery.
MoCA: Montreal cognitive assessment, ALSFRS-R: amyotrophic lateral sclerosis functional rating scale-revised.
Group N: patients with scores higher than the cut-offs in all clinical scales.
Group M: patients with a score lower than the cut-off in one clinical scale.
Group D: patients with scores lower than the cut-offs in two or three clinical scales.
n: number, SD: standard deviation.
* $p < .005$: Group N *vs.* Group M or Group D.
** $p < .05$: Group M *vs.* Group D.
*** $p < .05$: Group N *vs.* Group D.

impairment in ALS is characterized by frontal lobe involvement, such as executive dysfunction and language deficits, compared with memory deficits or disorientation [23]. Tanaka et al. investigated the clinical characteristics of the cognitive symptoms in 130 Japanese ALS patients with dementia, and found that 85% patients had FTD-like symptoms, such as disinhibition and emotional blunting, and 15% patients had memory impairment [24]. Furthermore, a recent study reported cognitive dysfunction in nearly 50% patients with ALS [5].

The evaluation of cognitive function in patients with ALS is difficult to complete in clinical practice due to time constraints. The three clinical scales, MoCA, FAB, and MMSE are designed to evaluate cognitive function within 10–15 min.

This study revealed that an older age at onset and lower educational level were associated with cognitive impairment in Japanese patients with ALS, because the differences in MMSE and MoCA between groups N and D were no longer significant after adjusting for age at onset and education period. Cognitive dysfunction is more common in elderly people, and previous studies in several populations have shown that an older age at onset is a risk factor for cognitive impairment in ALS patient [25–27]. Therefore, aging could be a strong risk factor for cognitive impairment in ALS patients, as well as in the general population. Educational level is a protective factor against several cognitive functions, such as executive function, visuospatial ability, and verbal memory, which are impaired in frontal lobe dysfunction [25].

> 50% of patients in this study scored lower than the cut-off in the MoCA, whereas only 8.8% of patients scored lower than the cut-off in the FAB and MMSE. In addition, 96.4% of patients in group M showed a score lower than the cut-off only in MoCA. These findings suggested that the MoCA is more sensitive at detecting the cognitive impairment in patients with ALS compared than are the FAB and MMSE. Interestingly, cognitive impairment was not clearly associated with the severity of motor dysfunction in the patients in this study.

Table 3
Correct answer rates of evaluation items in the MoCA.

Evaluation items	Group N	Group M	Group D	Total
Executive	87.0%*	58.0%	21.0%	63.0%
Visuospatial	95.0%**	76.5%	71.5%	83.0%
Naming	97.7%	93.7%	90.3%	94.7%
Attention	95.0%*	86.0%***	65.5%	85.8%
Language	57.7%*	45.0%	35.5%	46.3%
Abstraction	90.0%**	71.0%	64.5%	77.5%
Memory	88.0%**	34.8%	23.3%	53.0%
Orientation	99.5%*	95.7%***	85.7%	95.3%
Education (> 12 years)	40.0%*	28.6%	10.0%	33.3%

Group N: patients with scores higher than the cut-offs in all clinical scales.
Group M: patients with a score lower than the cut-off in one clinical scale.
Group D: patients with scores lower than the cut-offs in two or three clinical scales.
* $p < .05$: Group N *vs.* Group D.
** $p < .05$: Group N *vs.* Group M or Group D.
*** $p < .05$: Group M *vs.* Group D.

Table 4
Correct answer rates of evaluation items in the FAB.

Evaluation items	Group N	Group M	Group D	Total
Conceptualization	71.0%*	46.3%	38.0%	54.7%
Mental flexibility	86.7%*	70.0%**	45.3%	72.0%
Programming	97.7%*	70.0%	52.3%	77.3%
Sensitivity to interference	97.7%	92.3%	78.7%	92.0%
Inhibitory control	85.7%*	62.3%	43.0%	68.0%
Environmental autonomy	100.0%	100.0%	100.0%	100.0%

Group N: patients with scores higher than the cut-offs in all clinical scales.
Group M: patients with a score lower than the cut-off in one clinical scale.
Group D: patients with scores lower than the cut-offs in two or three clinical scales.
* $p < .05$: Group N *vs.* Group M or Group D.
** $p < .05$: Group M *vs.* Group D.

Table 5
Correct answer rates of evaluation items in the MMSE.

Evaluation items	Group N	Group M	Group D	Total
Orientation	99.0%*	96.8%**	85.7%	95.6%
Registration	100.0%	99.0%	95.3%	98.7%
Attention and calculation	90.6%*	76.2%	52.8%	77.6%
Recall	85.7%*	77.3%	47.7%	75.0%
Naming	100.0%	100.0%	100.0%	100.0%
Repetition	97.0%	90.0%	93.0%	93.0%
3-Stage command	99.0%	92.3%	93.0%	95.0%
Reading	100.0%	97.0%	100.0%	99.0%
Writing	93.0%	97.0%	100.0%	96.0%
Copying	97.0%	97.0%	79.0%	93.0%

Group N: patients with scores higher than the cut-offs in all clinical scales.
Group M: patients with a score lower than the cut-off in one clinical scale.
Group D: patients with scores lower than the cut-offs in two or three clinical scales.
* $p < .05$: Group N *vs.* Group D.
** $p < .05$: Group M *vs.* Group D.

The MoCA was developed to detect mild cognitive impairment and can evaluate cognitive function, including the frontal lobe function, in a multifaceted manner [9]. In this study, the language item of the MoCA had the lowest correct answer rate compared with other items in group N. In addition, the correct answer rates for executive function and memory were < 25% in group D (Table 3). These results are similar to those reported by Osborne et al. who evaluated 39 patients with ALS using the MoCA and FAB [28]. According our results, language function may be impaired in patients with ALS prior to dementia onset; however, executive function and memory may be more frequently affected once cognitive dysfunction had developed. This trend is similar to that observed in patients with frontotemporal dementia but not in patients with other dementias, such as Alzheimer's disease [5,18].

The FAB consists of 6 items and is broadly accepted as a useful test to evaluate frontal lobe function. The FAB results in the present ALS cases showed that the correct answer rate of conceptualization was the lowest among three groups. Notably, the evaluation item of conceptualization may be sensitive for detecting executive dysfunction in patients with ALS. Furthermore, 8.8% (6 patients) of all ALS cases showed the score lower than the cut-off in FAB (Table 2), which is compatible to the previous report showing the executive dysfunction in ALS [29].

MMSE showed the least sensitivity for detecting cognitive impairment. Most evaluation items, except attention and calculation, and recall showed correct answer rates of > 75% in all three groups. However, reduced correct answer rates for memory and recall items in the MoCA and the MMSE, respectively, suggested that verbal memory is preferentially impaired in ALS. This result is confirmed in a recent systematic review on the cognitive profile of ALS [30]. Regarding the items for attention, there was a difference in correct answer rates between MoCA and MMSE, because these scales include different numbers of tasks to evaluate attention. Attention items were evaluated using three tasks (a sustained attention task, a serial subtraction task, and digits forward and backward) in MoCA, and only one task (a serial subtraction task) in MMSE[7,9]. Therefore, the lower correct answer rate on attention items in MMSE relative to that in MoCA may indicate that working memory evaluated by a serial subtraction task is sensitively impaired in ALS.

Previous reports have revealed that writing errors, such as letter omission, substitution, displacement or misuse of postpositions, is sometimes observed in patients with ALS [31,32]. However, writing in the MMSE showed correct answer rates > 90% in the three ALS groups in this study. This item required the spontaneous writing a sentence and most patients wrote only one sentence; therefore, it was hard to detect impairments in this MMSE item.

There was no significant difference in rCBF in the ^{99m}Tc-ECD SPECT analysis, except in the right thalamus between groups N and M. This suggests that cognitive impairment from neuronal degeneration or dysfunction in patients with ALS may be assessed in a more sensitive manner using clinical scales than rCBF analysis.

One limitation of this study is due to the exclusion of some patients from the analysis because some evaluation items from the three clinical scales could not be completed due to severe motor impairment of the upper limbs. This highlights the requirement to develop a scale that can evaluate cognitive functions regardless of upper limb dysfunction. The Edinburgh Cognitive and Behavioral ALS Screen, published in 2013, can evaluate cognitive function regardless of upper limb weakness [33]; however, the completion time of this test is 15–20 min, and a Japanese version has not been established.

In conclusion, the MoCA has the greatest potential of usefulness in a clinical practice among three clinical scales for evaluating cognitive impairment in patients with ALS. In particular, executive function, language, and memory items were sensitive to detect the cognitive impairment in patients with ALS. Altogether, these data suggest that the assessment of cognitive function using MoCA can be used to evaluate the decision-making ability in patients with ALS in clinical practice.

Declaration of Competing Interest

The authors report that they have no conflicts of interest.

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Table 6
Regional CBF (ml/100 g/min.) in three ALS groups analyzed with Fine SRT.

Brain regions	ROI	Group N (n = 12)		Group M (*n* = 15)		Group D (*n* = 8)		Total (*n* = 35)	
		Rt.	Lt.	Rt.	Lt.	Rt.	Lt.	Rt.	Lt.
Frontal	Superior frontal	36.6 ± 6.1	36.4 ± 5.9	38.5 ± 3.9	38.5 ± 4.4	38.8 ± 5.7	38.9 ± 5.6	37.8 ± 5.0	37.7 ± 5.1
	Medial frontal	40.6 ± 6.1	40.6 ± 6.2	42.2 ± 5.3	42.2 ± 5.8	44.7 ± 7.5	45.1 ± 8.0	42.1 ± 6.0	42.2 ± 6.4
	Paracentral lobule	44.6 ± 6.2	45.6 ± 7.3	45.6 ± 4.8	45.1 ± 5.9	50.8 ± 9.2	52.5 ± 9.5	46.7 ± 6.7	47.2 ± 7.6
	Anterior cingulate	37.3 ± 6.0	36.6 ± 5.9	37.6 ± 4.6	36.8 ± 4.8	35.5 ± 6.0	35.1 ± 5.9	37.0 ± 5.3	36.3 ± 5.3
	Subcallosal	40.7 ± 6.4	41.9 ± 7.6	42.1 ± 3.6	42.2 ± 4.2	42.0 ± 8.9	41.1 ± 8.5	41.7 ± 5.9	41.9 ± 6.4
	Orbital	38.4 ± 6.9	37.4 ± 5.6	39.8 ± 5.2	39.2 ± 5.4	38.7 ± 6.6	37.8 ± 5.8	39.1 ± 6.0	38.4 ± 5.4
	Rectal	36.7 ± 6.2	36.7 ± 6.2	38.3 ± 4.8	38.6 ± 5.1	37.2 ± 7.4	36.6 ± 6.9	37.4 ± 5.8	37.3 ± 5.8
	Middle frontal	41.0 ± 7.1	41.3 ± 7.1	42.9 ± 4.2	42.9 ± 3.9	43.0 ± 5.3	42.6 ± 5.5	42.2 ± 5.5	42.2 ± 5.4
	Inferior frontal	41.3 ± 7.1	41.8 ± 6.8	42.7 ± 4.1	42.9 ± 4.2	41.9 ± 6.0	41.7 ± 6.3	42.1 ± 5.6	42.3 ± 5.5
	Precentral	39.7 ± 5.4	40.1 ± 5.3	40.3 ± 3.9	40.7 ± 3.6	44.1 ± 7.7	43.6 ± 6.6	41.0 ± 5.5	41.2 ± 5.0
	Insula	42.9 ± 6.8	42.4 ± 6.4	43.1 ± 4.5	42.7 ± 4.2	42.8 ± 8.5	41.1 ± 7.9	43.2 ± 6.0	42.4 ± 5.7
Parietal	Postcentral	38.5 ± 5.2	38.9 ± 5.0	38.6 ± 2.9	39.6 ± 3.4	41.1 ± 6.2	41.1 ± 5.8	39.0 ± 4.6	39.6 ± 4.5
	Superior parietal	34.7 ± 4.2	35.4 ± 4.5	35.6 ± 3.2	36.1 ± 3.4	36.8 ± 7.4	37.0 ± 7.0	35.4 ± 4.7	35.9 ± 4.6
	Inferior parietal	39.1 ± 5.4	39.7 ± 5.3	40.5 ± 3.0	40.1 ± 3.7	41.3 ± 6.9	40.9 ± 6.1	40.1 ± 4.9	40.1 ± 4.8
	Supramarginal	39.9 ± 5.5	39.2 ± 5.9	41.6 ± 4.5	40.5 ± 4.2	41.4 ± 7.7	40.0 ± 7.3	41.0 ± 5.5	40.0 ± 5.4
	Angular	40.3 ± 5.4	40.0 ± 5.5	41.8 ± 3.4	42.0 ± 3.4	41.7 ± 8.0	41.9 ± 7.2	41.3 ± 5.3	41.3 ± 5.1
Temporal	Superior temporal	38.2 ± 5.8	38.8 ± 5.8	39.4 ± 3.1	39.1 ± 3.6	38.7 ± 7.1	37.8 ± 6.5	38.9 ± 5.0	38.7 ± 5.0
	Middle temporal	37.8 ± 6.0	37.9 ± 5.7	38.9 ± 3.3	38.5 ± 3.5	39.0 ± 7.6	38.9 ± 7.1	38.6 ± 5.3	38.5 ± 5.0
	Inferior temporal	34.2 ± 5.4	34.4 ± 5.3	37.5 ± 3.8	37.4 ± 4.6	35.8 ± 6.7	36.0 ± 6.8	35.7 ± 4.9	35.6 ± 4.9
	Transverse temporal	47.1 ± 7.2	46.6 ± 7.7	46.7 ± 5.3	47.9 ± 5.7	44.6 ± 9.9	42.6 ± 9.2	46.6 ± 6.8	46.6 ± 7.2
Occipital	Superior occipital	37.4 ± 5.3	37.6 ± 5.1	38.8 ± 3.7	38.9 ± 3.4	41.2 ± 7.5	40.5 ± 7.1	38.8 ± 5.3	38.8 ± 5.0
	Middle occipital	38.3 ± 5.6	38.5 ± 5.4	39.7 ± 3.5	39.6 ± 3.5	42.5 ± 8.6	41.1 ± 6.9	40.0 ± 5.7	39.7 ± 4.9
	Inferior occipital	37.4 ± 5.5	38.0 ± 6.2	39.2 ± 4.8	40.2 ± 4.4	41.2 ± 8.6	40.7 ± 7.9	38.5 ± 5.6	39.0 ± 5.5
	Precuneus (lower)	52.5 ± 6.9	53.3 ± 6.7	52.8 ± 4.3	52.8 ± 4.1	54.1 ± 9.9	53.9 ± 9.5	53.1 ± 6.5	53.4 ± 6.3
	Cuneus	47.3 ± 5.6	47.3 ± 5.3	46.9 ± 5.4	47.5 ± 6.0	49.4 ± 8.6	49.5 ± 8.5	48.0 ± 5.6	48.4 ± 5.6
Limbic	Hippocampus	30.8 ± 3.4	30.0 ± 4.8	32.1 ± 4.2	31.9 ± 4.1	30.6 ± 6.3	31.4 ± 7.3	31.1 ± 4.3	30.9 ± 4.8
	Fusiform	40.4 ± 6.0	42.0 ± 6.4	42.8 ± 3.1	43.1 ± 3.5	44.2 ± 7.8	44.3 ± 8.3	42.2 ± 5.5	42.9 ± 5.8
	Lingual	46.1 ± 5.6	46.8 ± 5.3	46.4 ± 4.7	47.0 ± 4.5	49.3 ± 8.1	48.9 ± 7.3	47.2 ± 5.5	47.6 ± 4.9
	Parahippocampal	33.5 ± 5.4	33.8 ± 5.9	35.4 ± 3.3	35.1 ± 3.5	36.0 ± 6.5	35.9 ± 6.4	35.0 ± 4.8	34.9 ± 5.0
	Amygdaloid body	27.7 ± 4.1	28.1 ± 5.2	30.0 ± 5.2	28.0 ± 4.7	29.0 ± 8.9	29.6 ± 8.5	28.6 ± 5.3	28.2 ± 5.5
	Thalamus	34.9 ± 3.2*	34.9 ± 4.2	40.4 ± 5.2	38.2 ± 4.9	35.6 ± 7.0	35.3 ± 6.6	37.3 ± 5.4	36.1 ± 4.9
Corpus striatum and globus pallidus	Putamen	47.0 ± 7.6	46.2 ± 6.6	47.8 ± 4.4	47.2 ± 4.5	45.9 ± 8.6	44.8 ± 7.0	47.3 ± 6.4	46.4 ± 5.7
	Globus pallidus	38.6 ± 5.2	39.1 ± 5.9	40.4 ± 5.1	40.2 ± 5.1	37.9 ± 6.7	39.0 ± 5.8	39.4 ± 5.4	39.8 ± 5.3
	Caudate head	32.1 ± 7.7	31.0 ± 6.3	31.2 ± 5.2	29.9 ± 6.3	26.9 ± 7.9	26.4 ± 7.5	30.8 ± 6.9	29.8 ± 6.6
	Caudate tail	27.2 ± 3.5	26.4 ± 4.9	28.8 ± 5.6	27.6 ± 6.0	24.8 ± 5.7	23.1 ± 5.4	26.7 ± 3.9	25.5 ± 4.4
Pericallosal and cerebellum	Precuneus (upper)	45.0 ± 7.0	44.9 ± 7.4	44.8 ± 4.1	44.6 ± 4.6	47.9 ± 9.0	48.7 ± 8.8	45.7 ± 6.3	45.8 ± 6.7
	Cingulate	37.3 ± 4.2	37.1 ± 4.3	39.3 ± 4.5	39.0 ± 3.9	36.8 ± 6.5	36.7 ± 5.9	37.9 ± 4.7	37.7 ± 4.5
	Posterior cingulate	49.4 ± 6.5	46.7 ± 5.1	48.8 ± 4.5	46.5 ± 4.4	46.0 ± 6.4	42.2 ± 6.8	48.4 ± 5.6	45.6 ± 5.4
	Vermis	46.1 ± 6.6	46.6 ± 6.8	47.2 ± 5.4	47.5 ± 5.4	50.9 ± 10.8	50.9 ± 11.2	47.9 ± 7.0	48.2 ± 7.2
	Anterior lobe	37.8 ± 4.4	38.4 ± 5.6	40.6 ± 4.4	40.9 ± 3.5	41.9 ± 7.0	42.1 ± 7.3	39.6 ± 5.1	40.0 ± 5.3
	Posterior lobe	48.9 ± 7.2	48.9 ± 7.3	51.7 ± 7.8	51.4 ± 8.1	54.0 ± 10.5	54.2 ± 10.8	51.9 ± 7.0	51.8 ± 7.2
Brainstem	Hypothalamus	22.9 ± 3.4	22.6 ± 3.5	25.0 ± 5.6	25.3 ± 5.2	22.6 ± 6.1	23.1 ± 6.9	23.5 ± 4.8	23.6 ± 4.9
	Quadrigemini	28.2 ± 5.8	29.5 ± 6.7	31.3 ± 4.7	31.3 ± 4.2	32.9 ± 6.9	34.7 ± 7.6	30.3 ± 5.7	31.8 ± 6.0
	Substantia nigra	26.0 ± 5.6	23.5 ± 5.5	28.0 ± 3.5	25.9 ± 4.7	28.5 ± 7.8	28.5 ± 7.0	27.3 ± 5.4	25.4 ± 5.6
	Nucleus ruber	29.9 ± 7.1	30.8 ± 7.9	32.5 ± 4.2	33.1 ± 4.8	33.9 ± 8.5	36.9 ± 9.1	31.9 ± 6.4	33.3 ± 7.2
	Pons	28.7 ± 5.5	29.3 ± 4.6	31.0 ± 4.1	30.5 ± 4.8	31.9 ± 6.2	31.8 ± 6.0	30.1 ± 4.8	30.1 ± 4.5
Brodmann	Broca	41.1 ± 7.0	41.7 ± 6.4	42.8 ± 4.3	43.0 ± 4.9	41.5 ± 5.6	41.3 ± 6.2	41.9 ± 5.5	42.1 ± 5.6
	Wernicke	43.3 ± 5.8	44.4 ± 6.2	45.5 ± 3.8	45.6 ± 4.2	44.1 ± 7.4	43.4 ± 6.8	44.4 ± 5.4	44.6 ± 5.4
	Primary visual	43.8 ± 6.0	44.9 ± 6.0	44.4 ± 4.2	47.1 ± 4.2	47.1 ± 10.1	48.3 ± 9.0	44.8 ± 6.4	46.6 ± 6.1
	Primary auditory	45.3 ± 6.8	45.6 ± 7.9	45.1 ± 4.2	46.7 ± 4.8	43.3 ± 8.7	43.0 ± 8.2	44.9 ± 6.2	45.7 ± 6.7
	Premotor	38.5 ± 6.0	39.3 ± 5.9	40.9 ± 4.1	40.7 ± 3.9	41.2 ± 5.1	40.9 ± 4.8	40.0 ± 4.9	40.1 ± 4.7
	Supplementary motor	41.3 ± 5.5	40.9 ± 5.9	42.1 ± 4.9	38.5 ± 12.0	48.4 ± 9.2	48.3 ± 9.7	43.4 ± 6.7	42.8 ± 7.3

Group N: patients with scores higher than the cut-offs in all clinical scales.
Group M: patients with a score lower than the cut-off in one clinical scale.
Group D: patients with scores lower than the cut-offs in two or three clinical scales.
CBF: cerebral blood flow, ROI: region of interest, Fine SRT: fine stereotactic ROI template.
* $p < .05$: Group N *vs.* Group M.

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