Simultaneous assessment of cognitive and affective functions in multiple system atrophy and cortical cerebellar atrophy in relation to computerized touch-panel screening tests

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Abbreviations used: AD, Alzheimer disease; ALS, amyotrophic lateral sclerosis; ANOVA, analysis of variance; CCA, cortical cerebellar atrophy; CNS, central nerve system; DSM-IV, diagnostic and statistical manual of mental disorders, 4th edition; eZIS, easy Z-score imaging system; FAB, frontal assessment battery; GDS, geriatric depression scale; HDS-R, Hasegawa dementia scale-revised; IS, ischemic stroke; MMSE, mini-mental state examination; MoCA, Montreal cognitive assessment; MRI, magnetic resonance imaging; MSA, multiple system atrophy; MSA-C, MSA with predominant cerebellar ataxia; MSA-P, MSA with predominant parkinsonism; NC, normal controls; PD, Parkinson disease; rCBF, regional cerebral blood flow; SD, standard deviation; SPECT, single-photon emission tomography; ^{99m}Tc-ECD, ^{99m}Tc labeled ethyl cysteinate dimer; VI, vitality index.

ABSTRACT

Cognitive impairment and affective dysfunction of multiple system atrophy (MSA) and cortical cerebellar atrophy (CCA) have not been simultaneously examined comparing standard test batteries and a sensitive tool to detect subtle cognitive decline in patients. In the present study, we simultaneously examined cognitive and affective ability in MSA with predominant cerebellar ataxia (MSA-C, n = 25), MSA with predominant parkinsonism (MSA-P, n = 8), and CCA (n = 14) patients using computerized touch panel screening tests. Mini-mental state examination (MMSE), Hasegawa dementia scale-revised (HDS-R), frontal assessment battery (FAB), and Montreal cognitive assessment (MoCA) scores were significantly lower in MSA-C patients than in age-and gender-matched normal controls. One MSA-C patient showed a decrease in the regional cerebral blood flow (rCBF) of the frontal lobe. MSA-P patients showed no such cognitive decline. Only FAB and MoCA scores were significantly lower in the CCA patients. MSA and CCA patients also showed a mild to moderate depressive state. Touch-panel screening tests demonstrated a significant decline of beating devils game in all three disease groups including MSA-P patients, and a significant extension of the flipping cards game only in MSA-C patients. The present study demonstrated different cognitive and affective functions among MSA-C, MSA-P, and CCA patients, and a sensitive screening method for cognitive assessment using touch-panel tests.

Keywords: multiple system atrophy, cortical cerebellar atrophy, cognitive impairment, affective disorder, touch panel screening test, regional cerebral blood flow

1. INTRODUCTION

Multiple system atrophy (MSA) is an adult-onset, sporadic, progressive neurodegenerative disease characterized by cerebellar ataxia, parkinsonian features, autonomic failure, urogenital dysfunction, and corticospinal disorders [1]. The neuropathological findings include widespread and abundant central nerve system (CNS)-synuclein–positive glial cytoplasmic inclusions (Papp–Lantos inclusions) in association with neurodegenerative changes in striatonigral or olivopontocerebellar structures [2]. On the other hand, cortical cerebellar atrophy (CCA) has been considered as a disease entity that develops cerebellar cortical lesions mainly in the cerebellar vermis, but a collective view on the distribution of idiopathic CCA has not yet been established [3].

Recent reports [4-10] suggested that cognitive impairment of MSA is more frequent than previous reports. However, few studies compared MSA with predominant cerebellar ataxia (MSA-C) to MSA with predominant parkinsonism (MSA-P) in relation to cognitive assessment. Only one study reported significant declines of the mini-mental state examination (MMSE) score, verbal memory, visuospatial functions, and speech and language ability in MSA-C patients than in normal controls, and significant declines of verbal memory and executive function in MSA-C patients than in MSA-P patients [11]. A previous report showed a frontal dysfunction in CCA [12]. As for affective functions, MSA and CCA patients were reported to be depressive [13, 14], but no report simultaneously compared cognitive and affective functions between MSA and CCA.

We have reported a computerized touch panel-type screening test for early

detection of ischemic stroke (IS), Parkinson disease (PD), and amyotrophic lateral sclerosis (ALS) [15-17]. However, such a computerized touch panel test has never been applied to MSA-C, MSA-P, and CCA patients. The aim of the present study was, therefore, to simultaneously examine cognitive and affective functions in MSA-C, MSA-P, and CCA patients in relation to the computerized touch panel screening test.

2. PATIENTS AND METHODS

2.1. Participants

Twenty-five MSA-C patients (12 male, 13 female; age at exam., 63.2 ± 7.2 years; age at onset 60.4 ± 8.2 years), 8 MSA-P patients (1 male and 7 female; age at exam., 66.4 ± 4.7 years; age at onset, 62.4 ± 5.7 years), and 14 CCA patients (6 male, 8 female; age at exam., 65.3 ± 12.6 years; age at onset, 50.9 ± 21.2 years), who obtained medical care in Okayama University Hospital from April 2010 to May 2012 participated in this study. The MSA patients were divided into cerebellar (MSA-C) or parkinsonian (MSA-P) type based on the diagnostic criteria for MSA [1]. The CCA patients were diagnosed by clinical symptoms and exclusion diagnosis [18]. One hundred and six age- and gender-matched individuals who lacked any history of neurological or psychiatric disorders were included as normal controls (NC) (50 male, 56 female; age at exam., 64.6 ± 6.6 years) in this study. Clinical details for each group are shown in Table 1.

2.2. Cognitive and Affective Assessments

Cognitive functions were assessed using the MMSE [19], Hasegawa dementia

scale-revised (HDS-R) [20], frontal assessment battery (FAB) [21], and Montreal cognitive assessment (MoCA) [22] scores. Affective functions such as depression and vitality were assessed using the geriatric depression scale (GDS) [23, 24] and the vitality index (VI) [25].

MMSE evaluates seven aspects of cognition such as orientation, registration, attention and calculation, recall, comprehension of spoken language (naming objects, spoken language ability, following commands), writing, and construction drawing [19]. HDS-R evaluates orientation, immediate recall, serial subtraction, backward digit recitation, recall of three words, recall of five objects, and verbal fluency (generating names of vegetables) [20]. FAB is a six-item scale designed to evaluate frontal deficits, including conceptualization (similarities test), mental flexibility (lexical fluency), motor programming (Luria's "fist–edge–palm" test, conflicting instructions, and Go–No go tests), and environmental autonomy (prehension behavior) [21]. MoCA evaluates visuospatial and executive ability, naming, memory, attention, language, abstraction, delayed recall, and orientation with a maximum of 30 points and a cutoff score of 26 (25 or below indicating impairment). This has superior sensitivity for detecting patients with MCI and also reflects frontal function including attention, concentration, working memory and abstract thinking [22, 26]. GDS involves a screening questionnaire for depression and anxiety. Total scores range from 0 to 15, with higher scores indicating more symptoms of depression [23, 24]. VI is composed of five subscales relating to common basic activities of inpatients with long-term care, with a maximum performance score of 10 [25].

2.3. Touch-Panel Screening Test

A touch-panel screening test for the early diagnosis of dementia (the Ryokansan, Ohtsu Computer Corp, Ohtsu, Japan) was administered to all subjects. The touch panel was large and the test did not include tasks such as writing that require fine manual dexterity. The screening test consisted of the following four games: beating devils, flipping cards, arranging pictures, and finding mistakes. We recorded accuracy (percent correct) in the beating devils game and the time to complete the game for the other three games. In the beating devils game, patients were instructed to distinguish between the emergence of heroes and devils, and we measured their accuracy in exterminating only the devils during a 30-sec period (Fig. 1a). In the flipping cards game, we measured the time (sec) to turn over all pairs of matching picture cards (Fig. 1b). In the arranging pictures game, we measured the time (sec) to arrange four scenes from a famous fairy tale in the correct order (Fig. 1c). In the finding mistakes game, we measured the time (sec) to find all three mistakes between panels (Fig. 1d). Although the specific cognitive functions reflected by each task are unclear, in broad terms the flipping card game reflects recent memory, the arranging pictures game reflects processing ability and remote memory, the finding mistakes game reflects discrimination ability, and the beating devil game reflects judgment ability [15].

2.4. SPECT examination

Regional cerebral blood flow (rCBF) of the patients was measured with ^{99m}Tc

labeled ethyl cysteinate dimer (^{99m}Tc-ECD) - single-photon emission tomography (SPECT) at the time of diagnosis. Before 10 min of imaging, 700 MBq of ^{99m}Tc-ECD was injected intravenously. The images were anatomically standardized using the easy Z-score imaging system (eZIS) [27], and then an averaged SPECT image was created from these images. A Z-score map was obtained by comparison of the mean and standard deviation (SD) for each voxel obtained after anatomical standardization and voxel normalization to global mean values between the averaged SPECT image of the patient and SPECT images of age-matched healthy volunteers, using the follow equation: Z-score = ([control mean] − [individual value]) / (control SD)). The mean Z scores for values more than 2.0, which shows a reduction in rCBF [28], were calculated and displayed on the anatomically standardized magnetic resonance imaging (MRI) template as brain surface values. The extent of significant rCBF reduction, which indicates the rate (%) of voxels with a positive Z-score (> 2) in the anatomical segmentation in accordance with Talairach Daemon [29], was acquired with a voxel-based stereotactic extraction estimation (vbSEE) program [30].

SPECT scans of three patients were unavailable because there was no data. Only an MSA-C patient with marked cognitive impairment was studied chronologically.

2.5. Statistical analysis

Statistical analyses were performed using GraphPad Prism version 6.0 for Windows (GraphPad Software, San Diego, CA). We performed one-way factorial analysis of variance (ANOVA) to compare cognitive and affective assessments and

touch panel screening tests between each disease group and a control group. Pearson product-moment correlation coefficient tests was conducted for examining the correlation between touch panel tests and SARA in MSA-C and CCA, touch panel tests and UMSARS-II scores in MSA-P patients, the MMSE score and rCBF, or touch panel tests and rCBF in all disease groups. P-values < 0.05 were considered significant.

3. RESULTS

3.1. Cognitive and Affective Assessments

Compared with NC (MMSE 28.4 ± 2.1, HDS-R 28.6 ± 1.8), MMSE (26.8 ± 3.2, *p < 0.05 vs NC) and HDS-R (27.0 ± 3.0, *p < 0.05 vs NC) scores in MSA-C patients were significantly lower (Fig. 2a, b). MMSE scores in MSA-P (26.7 ± 2.4) and CCA patients (26.8 ± 4.1) were not significantly lower than NC, and HDS-R scores in MSA-P (27.6 ± 1.4) and CCA patients (27.3 ± 3.7) were also not significantly lower than NC. Compared with NC (FAB 15.8 ± 2.1; MoCA 25.4 ± 1.0), FAB (13.3 ± 2.9, **p < 0.01 vs NC) and MoCA (20.8 ± 3.2, **p < 0.01 vs NC) scores in MSA-C patients, and FAB (13.0 ± 4.4, *p < 0.05 vs NC) and MoCA (22.1 ± 4.8, *p < 0.05 vs NC) scores in CCA patients were significantly lower (Fig. 2c, d). FAB (15.2 ± 1.3) and MoCA (25.5 ± 3.5) scores in MSA-P patients were not significantly lower than NC.

Compared with NC (2.7 ± 3.3), GDS scores in all three disease groups were significantly higher (MSA-C: 9.6 ± 3.9, **p < 0.01 vs NC; MSA-P: 8.3 ± 2.1, *p < 0.05 vs NC; CCA: 6.9 ± 2.8, *p < 0.05 vs NC) (Fig. 3a). On the other hand, VI scores in all three disease groups were not significantly different from the scores in NC (NC: 9.8 ±

0.5; MSA-C: 9.2 ± 0.8; MSA-P: 9.5 ± 1.0; CCA: 8.8 ± 1.0) (Fig. 3b).

3.2. Touch-Panel Screening Test

Compared with NC (93.1 ± 13.9 %), all three disease patients had significantly lower accuracy in the beating devils game (MSA-C: 84.1 ± 17.2 %, *$p < 0.05$ vs NC; MSA-P: 65.7 ± 35.4 %, **$p < 0.01$ vs NC; CCA: 77.6 ± 18.4 %, *$p < 0.05$ vs NC) (Fig. 4a). Compared with NC (20.4 ± 16.8 sec), time for the flipping cards game in MSA-C patients was significantly extended (34.3 ± 23.7 sec, *$p < 0.05$ vs NC) (Fig. 4b) except for MSA-P (34.6 ± 38.4 sec) and CCA (28.4 ± 16.7 sec) groups.

Time for the arranging pictures game (NC: 16.6 ± 16.0 sec; MSA-C: 23.2 ± 19.5 sec; MSA-P: 28.6 ± 37.8 sec; CCA: 27.9 ± 21.3 sec) (Fig. 4c) and for the finding mistakes game (NC: 45.2 ± 35.0 sec; MSA-C: 51.6 ± 31.2 sec; MSA-P: 54.9 ± 44.5 sec; CCA: 48.2 ± 32.9 sec) was not significantly different in all three disease groups relative to NC (Fig. 4d).

The beating devils game in CCA patients was significantly correlated with SARA scores ($R= -0.77$, $p < 0.05$). However, the other games in CCA patients and all four games in MSA-C patients were not correlated with SARA scores, and all four games in MSA-P patients were not correlated with UMSARS scores.

3.3. SPECT examination

Fig. 5A shows chronological eZIS images of an MSA-C patient with marked cognitive impairment. In contrast to the remarkable decrease in the cerebellum, the eZIS

images showed only a slight decrease of rCBF in a part of the frontal lobe at an early stage with an MMSE score of 22 (Fig. 5A a-c). Half a year later, the eZIS images revealed an apparent spreading and worsening of the rCBF decrease in the frontal lobe (Fig. 5A d-f, arrows). One year later, the rCBF that had decreased became wider and worse in the frontal lobe with an MMSE score of 19 (Fig. 5A g-i, arrows).

Observing the rCBF data of 43 patients, MSA-P and CCA patients did not display a significant correlation with MMSE scores while only MSA-C patients showed a significant negative correlation (Fig. 5B; $R = -0.53$, $*p < 0.05$). No touch panel screening tests were correlated with the significant decrease of rCBF in all 43 patients, and only the finding mistakes game was weakly correlated with MSA-C ($R = 0.36$, $p = 0.09$).

4. DISCUSSION

The present study revealed that MMSE, HDS-R, FAB, and MoCA scores were significantly lower in MSA-C patients (Fig. 2, dotted bar) than the scores of normal controls, but only FAB and MoCA scores were significantly lower in CCA patients (Fig. 2, horizontal-striped bar). MSA-P patients did not show a significant difference in all cognitive measures (Fig. 2, diagonal-striped bar) from the scores of normal controls. In addition, all patients showed significantly higher scores of GDS than normal controls (Fig. 3, upper panel) while the VI score was not significantly different from the score of normal controls in all three disease groups (Fig. 3, lower panel). Accuracy for the beating devils game was significantly lower in all three disease groups (Fig. 4a), and

time for the flipping cards game was extended only in MSA-C patients (Fig. 4b). The SPECT examination showed that the rCBF of an MSA-C patient with cognitive impairment progressively decreased over the course of the disease in bilateral frontal lobes (Fig. 5A) as well as a significant correlation between rCBF and cognitive impairment (Fig. 5B).

Although dementia is consistent with the diagnostic and statistical manual of mental disorders, the 4th edition (DSM-IV) is a non-supporting feature for the diagnosis of MSA [1], and some studies have reported that MSA patients display a cognitive decline compared with controls [4-10], in particular MSA-C patients [11]. On the other hand, degeneration of the cerebellum contributed to frontal dysfunction in CCA patients characterized by an impairment of the inhibitory system [12], consistent with the present study (Fig. 2c-d, 4a).

Cognitive impairment in MSA patients was associated with pre-frontal lobe atrophy and a decrease in rCBF in the prefrontal cortices and cerebellar hemisphere in MSA-C patients [31]. The present study also showed an association between cognitive impairment and rCBF reduction in frontal lobes (Fig. 5) [11]. In terms of affective functions, our MSA and CCA patients showed a mild to moderate depressive state (Fig. 3a), as previously described [13, 14]. Although vitality in MSA patients was more impaired than in PD patients [32], the present study showed no difference of VI between normal controls and MSA patients (Fig. 3b). Vitality in CCA was first reported in the present study, but also showed no decrease (Fig. 3b).

With touch panel screening tests, both beating devils game and flipping cards

game showed significant decreases in MSA-C, and only the beating devils game showed a significant decrease in MSA-P and CCA, suggesting that the beating devils game was the most sensitive game to discriminate three diseases from the controls (Fig. 4).

The severity of ataxia in MSA-C and CCA patients and motor dysfunction in MSA-P patients was assessed through the scale for the assessment (SARA) and rating of ataxia or unified MSA rating scale part II (UMSARS-II), respectively (Table 1). Although touch panel screening tests could be affected by ataxia and parkinsonism, SARA scores in CCA patients were significantly correlated with only the beating devils game ($R= -0.77$, $p < 0.01$) and SARA scores in MSA-C and UMSARS-II scores in MSA-P were not correlated with any touch panel screening tests. Therefore, the beating devils game could be affected slightly by ataxia in CCA patients but not by motor dysfunction in MSA-P patients. The beating devils game and the flipping cards game in MSA-C patients could reflect cognitive impairment because there was no significant correlation with ataxia.

The beating devils game reflects judgment ability, as well as working memory functions of the frontal and parietal lobes, and basal ganglia, while the flipping cards game reflects recent memory, as well as reference memory functions of temporal and parietal lobes [11]. The present data with touch panels (Fig. 4) may well be related to dysfunction of the frontal lobe in MSA-C, MSA-P, and CCA [5, 7, 8, 10, 12], and bilateral basal ganglia in MSA-P [33, 34], as previously reported. However, there is limited data relating touch panel tests to various diseases and in the future more

analyses and data are expected.

It has been reported that aspiration pneumonia is associated with dementia, especially Alzheimer's disease [35, 36], due to cerebrocortical atrophy. A previous report revealed the association between the brain cortex and swallowing and concluded that the brain cortex is in charge of the initiation and modification of swallowing and sensorimotor integration [37]. Although no report revealed the association between aspiration pneumonia and dementia in MSA, dementia in MSA could cause aspiration pneumonia not only by disturbance of cerebellar and pyramidal tract, but also through a mechanism similar to the brain cortical deficit, mainly a decrease in the frontal lobe function, as indicated by the SPECT study (Fig. 5B). As dementia is the cause of death in 9-27% of MSA patients [38, 39], detecting dementia at an early stage is very important for preventing aspiration pneumonia and for improving the quality of life of MSA patients. Although MMSE, HDS-R, and FAB are widely used measures of cognitive function, patients usually take more than 30 min to complete the entire batteries, often getting tired. We previously reported on the usefulness of touch-panel screening tests in patients with IS [15], PD [16], and ALS [17]. The method is very simple, takes only a few minutes, and patients even enjoy the tests [15-17]. The present study revealed that such a touch-panel screening test was sensitive to detect subtle cognitive decline in MSA and CCA patients (Fig. 4).

In conclusion, the present study showed different features of cognitive and affective impairments in MSA-C, MSA-P, and CCA, with decreased rCBF of the frontal lobe particularly in MSA-C, while features of affective dysfunction were similar among

the three diseases. These touch-panel screening tests may be useful for detecting early cognitive decline and also for repetitive cognitive assessment of MSA-C, MSA-P, and CCA patients.

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Figure legends

Figure 1

Examples of computerized touch panel screen for (a) beating devils, (b) flipping cards, (c) arranging pictures, and (d) finding mistakes games.

Figure 2

Scores of cognitive function measures for (a) MMSE, (b) HDS-R, (c) FAB, and (d) MoCA comparing normal control (open bars), MSA-C (dotted bars), MSA-P (horizontal-striped bar), and CCA (diagonal-striped bar) patients. Note the significant reduction in MMSE, HDS-R, FAB, and MoCA scores of MSA-C patients and in FAB and MoCA scores of CCA patients compared to the control (*$p < 0.05$, **$p < 0.01$ vs control).

Figure 3

Scores of affective function measures (a) GDS and (b) VI comparing normal control (open bars), MSA-C (dotted bars), MSA-P (horizontal-striped bar), and CCA (diagonal-striped bar) patients. Note the significant increase in GDS scores of MSA-C, MSA-P, and CCA patients compared to the control (*$p < 0.05$ and **$p < 0.01$ vs control).

Figure 4

Scores of the touch-panel screening tests (a) beating devils game, (b) flipping

cards game, (c) arranging pictures game, and (d) finding pictures game comparing normal control (open bars), MSA-C (dotted bars), MSA-P (horizontal-striped bar), and CCA (diagonal-striped bar) patients. Note the significantly low accuracy in beating devils game for MSA-C, MSA-P, and CCA patients, and extended time of the flipping cards game for MSA-C patients compared to the control (*$p < 0.05$, **$p < 0.01$ vs control).

Figure 5

A: Chronological eZIS images of an MSA-C patient with cognitive impairment; first time (a-c), 6 months (d-f), and 18 months later (g-i). Note a progressively widespread and strong decrease in rCBF in the frontal lobe (arrows). B: Scatter plots of MMSE scores and rCBF showing the extent of decrease in MSA-C, MSA-P, and CCA patients. Only MSA-C showed a significant correlation between MMSE scores and the decrease in rCBF (left; $R = -0.53$, *$p < 0.05$).

Table 1 Demographic data of participants in this study

	Control	MSA-C	MSA-P	CCA
No. of cases	106	25	8	14
Gender (M/F)	50/56	12/13	1/7	6/8
Age at onset (y)	—	60.4 ± 8.2	62.4 ± 5.7	50.9 ± 21.2
Duration of disease (y)	—	2.9 ± 1.8	4.1 ± 3.6	14.4 ± 15.4
Age at exam. (y)	64.6 ± 6.6	63.2 ± 7.2	66.4 ± 4.7	65.3 ± 12.6
SARA	—	17.6 ±5.7	—	15.2 ±6.8
UMSARS-Ⅱ	—	—	25.5 ± 6.4	—

Figure 1

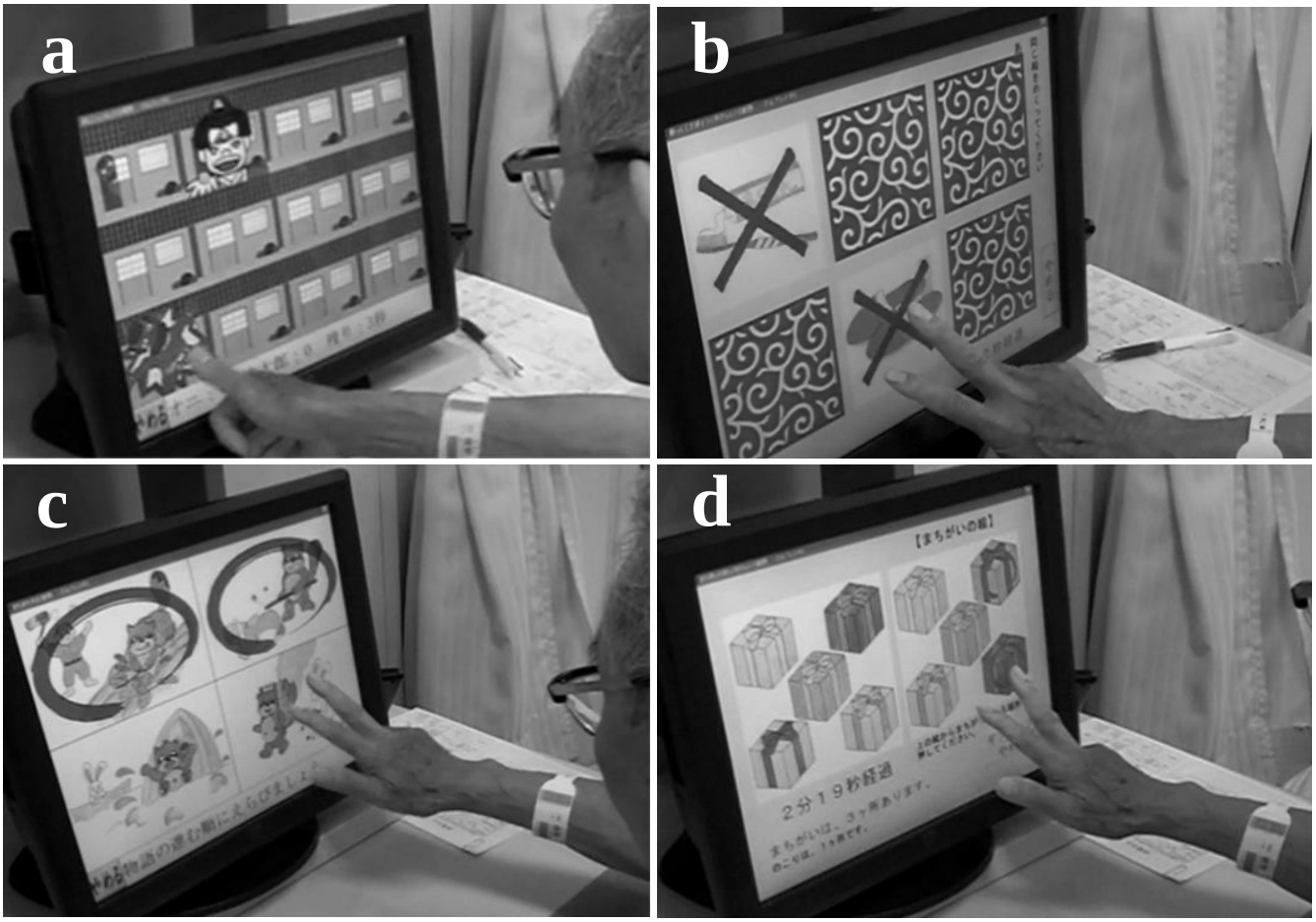


Figure 2

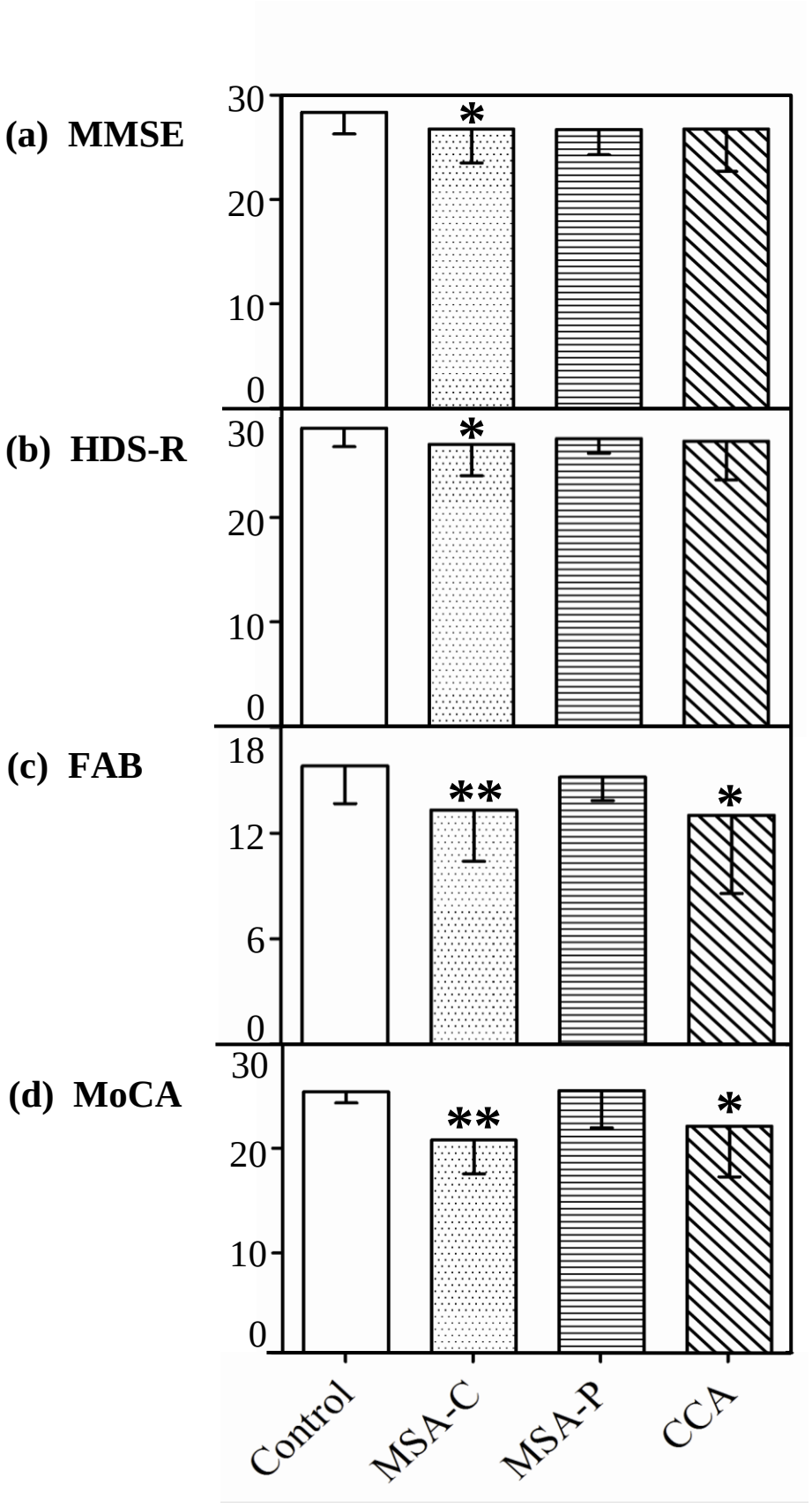

(a) MMSE
30
20
10
0
*
(b) HDS-R
30
20
10
0
*
(c) FAB
18
12
6
0
**
*
(d) MoCA
30
20
10
0
**
*
Control
MSA-C
MSA-P
CCA

Figure 3

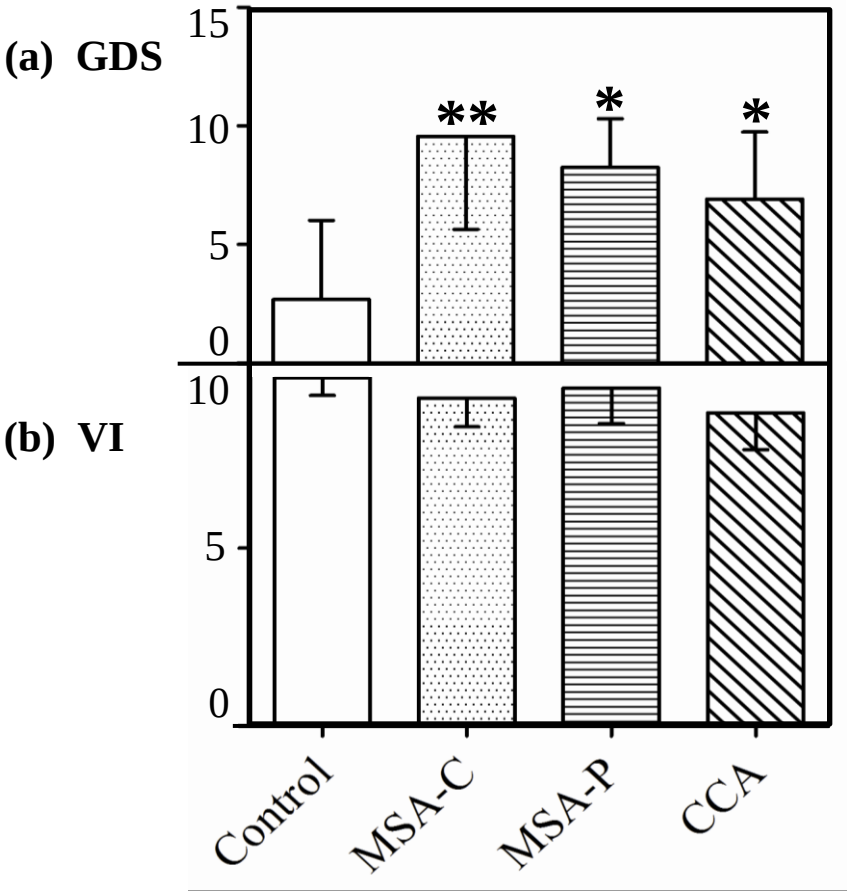


Figure 4

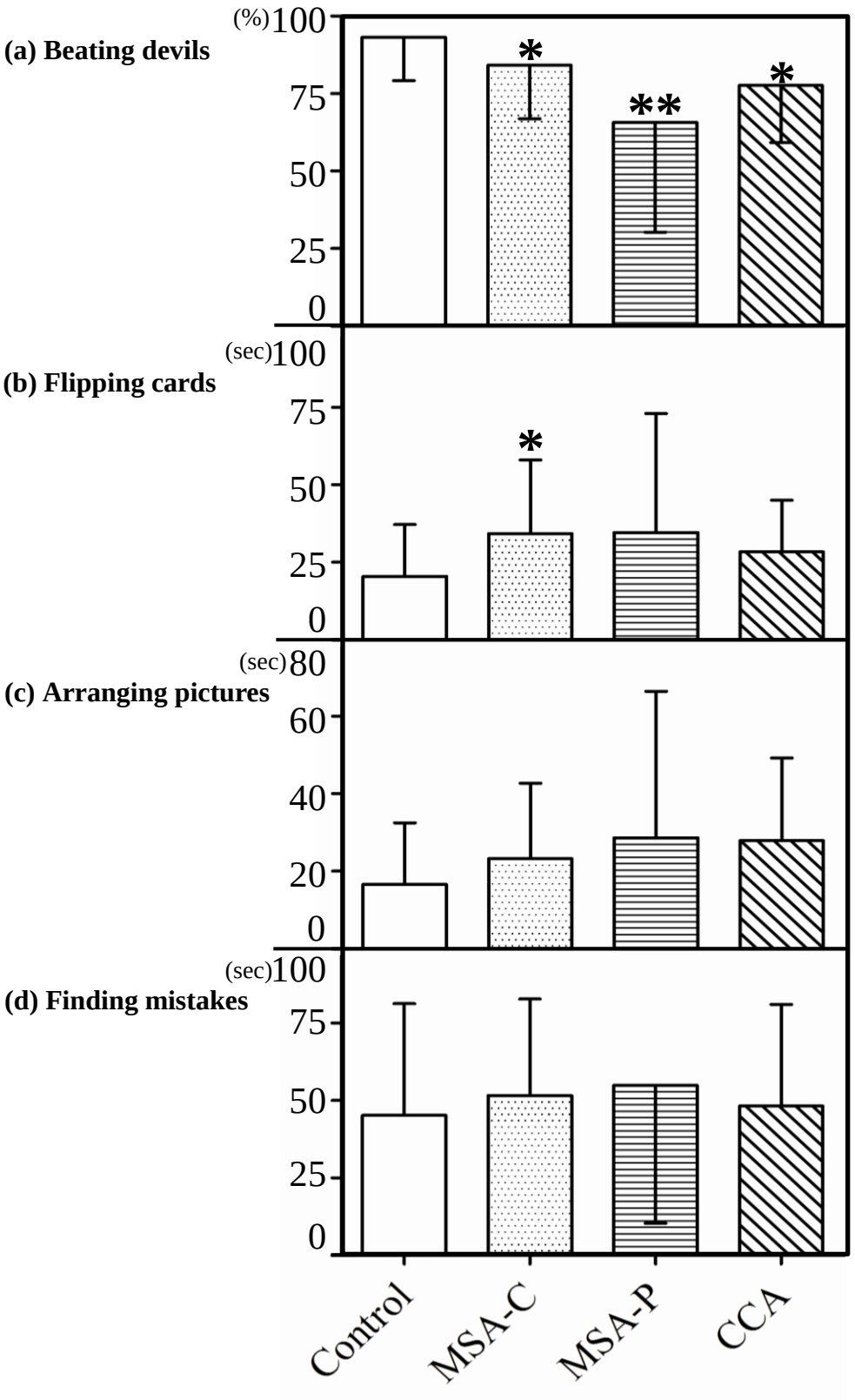
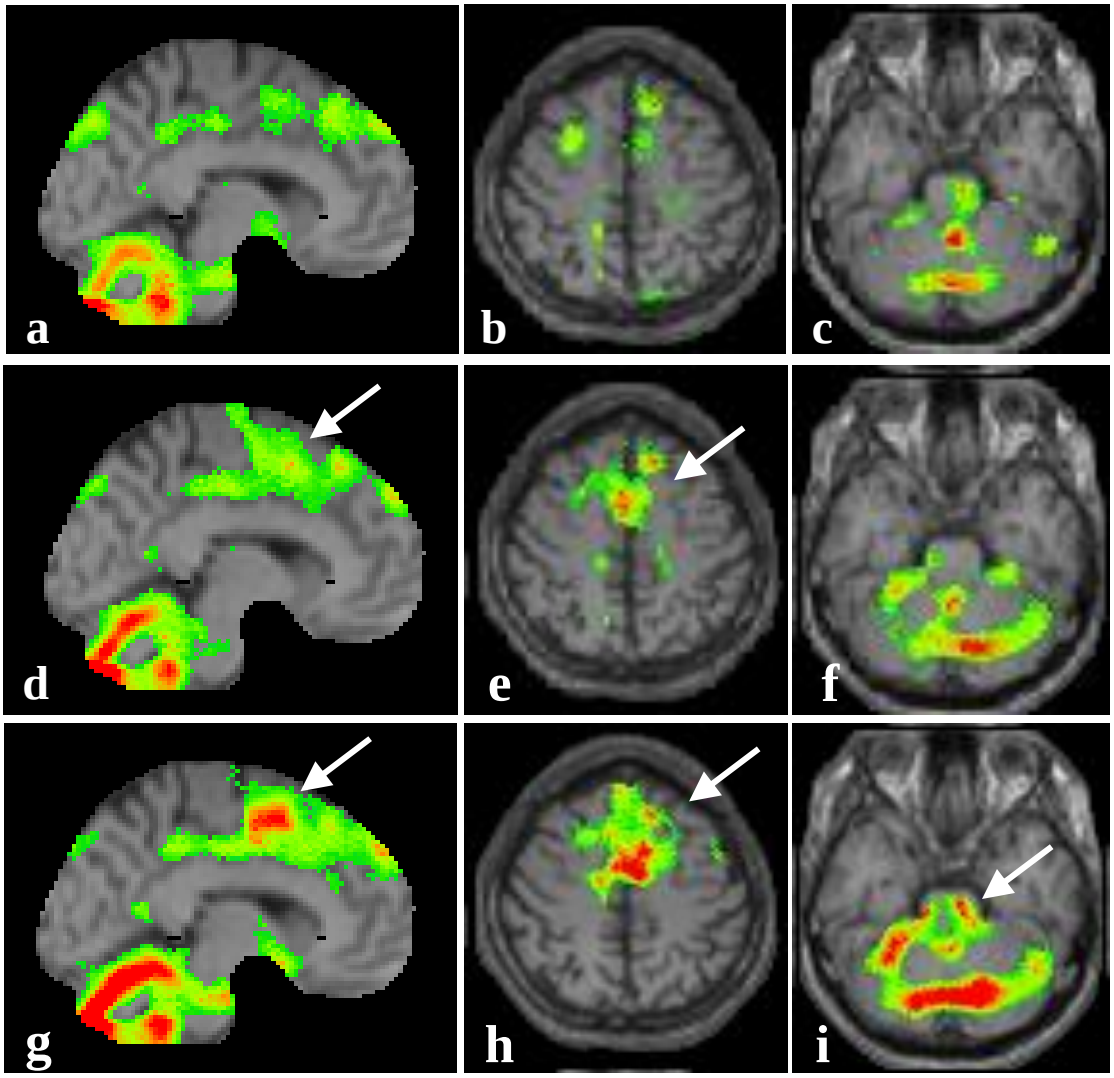
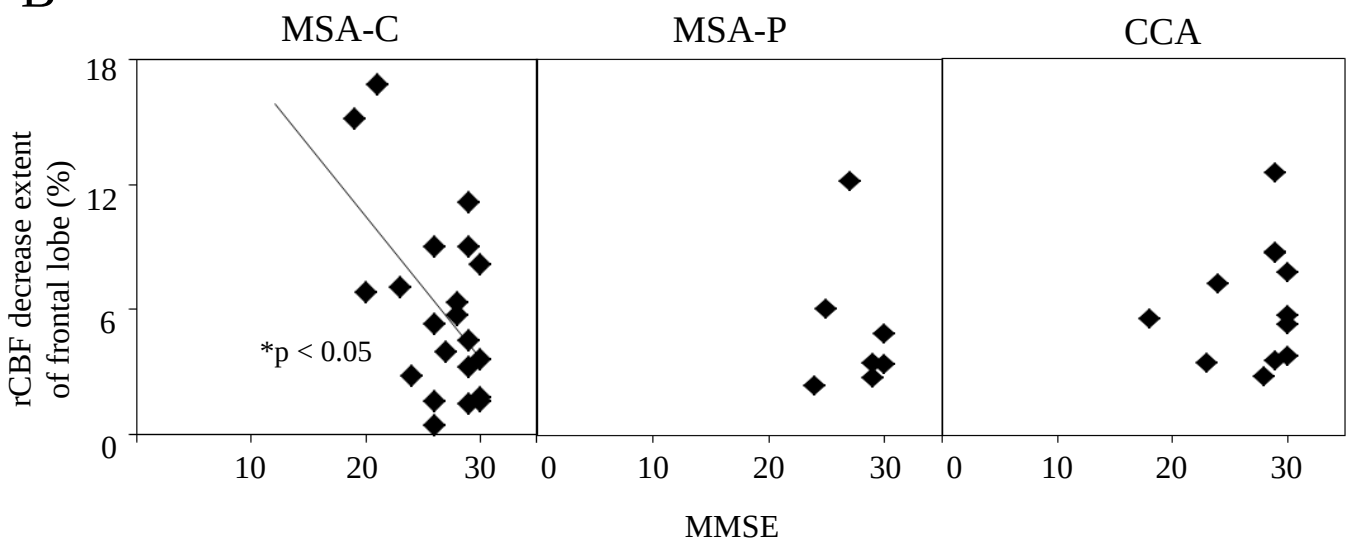

(a) Beating devils
(%)
100
75
50
25
0
*
**
*
(b) Flipping cards
(sec)
100
75
50
25
0
*
(c) Arranging pictures
(sec)
80
60
40
20
0
(d) Finding mistakes
(sec)
100
75
50
25
0
Control
MSA-C
MSA-P
CCA

Figure 5

A


a
b
c
d
e
f
g
h
i

B


MSA-C
MSA-P
CCA
18
12
6
0
rCBF decrease extent of frontal lobe (%)
*p < 0.05
10
20
30
0
10
20
30
0
10
20
30
MMSE