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Effects of computer-assisted cognitive rehabilitation in benign multiple sclerosis

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Background/aim: Benign multiple sclerosis (BMS) patients display preserved somatic neurological functions but nevertheless may develop cognitive dysfunction. Our aim was to explore the impact of computer-assisted cognitive rehabilitation (CCR) on cognitive functions of BMS patients.

Materials and methods: Age- and sex-matched BMS patients (n = 21), non-BMS patients (n = 22), and healthy individuals (n = 38) were recruited for evaluation of cognitive functions. CCR was administered to 10 BMS patients and a panel of neuropsychological tests were employed at baseline and 6 months. CCR was based on mental exercise software containing attention, memory, reasoning, visual, and verbal task modules.

Results: BMS and non-BMS patients showed impaired selective reminding, spatial recall, symbol digit modalities (SDMTs), controlled oral word association (COWAT), paced auditory serial addition-3 (PASAT-3), and Stroop tests. Timed 25-foot walk and 9-hole peg test results of BMS patients were comparable to those of healthy controls. BMS patients with CCR showed significantly improved SDMTs, COWAT, and Stroop test results compared to those without CCR.

Conclusion: Several cognitive domains including memory and executive functions are impaired in BMS patients. CCR has an ameliorating impact particularly on sustained attention, information processing speed, verbal fluency, categorical reasoning, and executive functions of BMS patients.

Key words: Benign multiple sclerosis, computer-assisted cognitive rehabilitation, memory, sustained attention, executive functions

1. Introduction

Cognitive impairment is frequently encountered in multiple sclerosis (MS), affecting up to 70% of patients (1). Cognitive functions are affected in both late and early (including clinically isolated syndrome) stages of the disease and continue deteriorating during the disease course (2,3). A broad range of cognitive domains including attention, information processing, learning, memory, executive functions, and visual-spatial functions are negatively affected, ultimately causing poor life quality and reduced participation in social activities (4–6). Several studies have shown that neuropsychological rehabilitation may have favorable effects on cognitive functions of MS patients. There is also accumulating evidence suggesting that computer-assisted cognitive rehabilitation (CCR) programs might improve cognitive skills (7).

Although different descriptions of benign MS (BMS) exist, it is often described as having a relatively lower Expanded Disability Status Scale (EDSS) score (generally ≤3.0) at a disease duration of 10 or more years (8). Despite having preserved visual, motor, and sensory functions (hence low EDSS scores), BMS patients might display substantial cognitive impairment, which likely occurs due to damage in the normal appearing white matter of BMS patients (9). Nevertheless, the impact of cognitive rehabilitation has never been studied in BMS.

In this study, cognitive and motor functions of age-, sex-, and disease duration-matched MS patients with and without benign course were evaluated. Then the influence of a multidomain CCR program on cognitive functions of BMS patients was investigated by baseline and follow-up neuropsychological tests.

2. Materials and methods

2.1. Participants

Twenty-one MS patients with benign disease (EDSS of ≤3.0) more than 10 years after onset were included (8). MS patients with comparable age/sex and EDSS >3.0 more than 10 years after disease onset (non-BMS, n = 22) and healthy individuals (n = 38) were recruited as controls.

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Eight non-BMS patients had secondary progressive MS (SPMS), whereas the remaining non-BMS patients had relapsing remitting MS (RRMS). All MS patients fulfilled the revised McDonald criteria (10). Individuals with severe visual loss, a history of psychiatric disease or dementia, alcohol or substance abuse, education of <8 years, previous cognitive rehabilitation training, a relapse, or steroid treatment within the 3 months prior to inclusion were excluded. Disease-modifying (interferon-beta, glatiramer acetate, or fingolimod) and symptomatic treatments were continued during the study. All participants signed an informed consent form and the study was approved by the institutional review board.

2.2. Neuropsychological assessment

Participants were evaluated by Rao's Brief Repeatable Battery of Neuropsychological Tests (BRB-N) before (baseline) and after (month 6) intervention. The BRB-N contains subtests that assess MS-specific impairments (11) such as immediate verbal recall [(Selective Reminding Test (SRT-IML)], verbal memory acquisition (SRT-TL), delayed verbal learning (SRT-DL), immediate visual recall [10/36 Spatial Recall Test (SPART-IML)], visual memory acquisition (SPART-TL), delayed visual learning (SPART-DL), sustained attention and speed of information processing [Paced Auditory Serial Addition Test-3 (PASAT-3), Symbol Digit Modalities Test (SDMT)], and verbal fluency and categorical reasoning [Controlled Word Association Test (COWAT)]. In addition, the Stroop Color-Word Test was included to evaluate executive functions, the Beck Depression Inventory was administered to evaluate mood, and 9-hole peg and timed 25-foot walk tests were administered to evaluate motor functions. Results of these tests were expressed as mean ± standard deviation of the BMS, non-BMS, and healthy control groups, respectively.

2.3. Cognitive intervention

The CCR)was based on the NOROSOFT Mental Exercise Program. NOROSOFT contains five modules: attention, memory, reasoning, visual, and verbal tasks. Patients were asked to practice 5 days a week for 50 min. The sessions had 20 min of a daily exercise section, which allows patients to perform every module, and 30 min of impairment-specific training according to Rao's BRB-N scores for each patient. For the weekly follow-up, patients were supervised by the program's institutional interface. Each patient was evaluated by one of the authors on a monthly basis. CCR was randomly administered to 10 of the 21 BMS patients on the basis of a computerized list of random numbers. A psychologist, blind to the study, administered and evaluated the tests and another psychologist explained the training procedure and supervised the rehabilitation program.

2.4. Statistical analysis

Continuous variables were presented using means and standard deviations. Demographic and clinical features of study groups were compared with ANOVA, the chi-square, Student's t-test, and the Mann–Whitney U test, as required. Differences between test scores of BMS patients, non-BMS patients, and healthy controls were assessed by ANOVA and Tukey's post hoc test. Differences between test scores of BMS patients at baseline and the 6th month were compared with Student's t-test. The effect of CCR on the change in test performances over time was investigated using repeated measures ANOVA. $P < 0.05$ was inferred as statistical significance.

3. Results

3.1. BMS patients show impaired cognitive test scores despite preserved motor functions

BMS patients, non-BMS patients, and healthy controls had comparable age and sex. There were also no differences between MS duration, disease onset age, relapse numbers, and BDI scores of BMS and non-BMS patients. EDSS scores of non-BMS patients (between 3.5 and 6.0) were significantly higher than those of BMS patients (between 1.5 and 3.0), as expected (Table). To compare motor and cognitive functions of BMS and non-BMS patients, a panel of tests were employed for all MS patients. Both BMS and non-BMS patients had significantly lower SRT-IML (5.0 ± 1.4, 4.4 ± 1.3, 6.1 ± 1.5; $P < 0.0001$), SRT-TL (7.9 ± 1.5, 7.3 ± 1.3, 9.2 ± 1.3; $P < 0.0001$), SRT-DL (7.8 ± 2.9, 6.7 ± 2.7, 9.7 ± 2.1; $P < 0.0001$), SPART-TL (4.5 ± 1.5, 4.5 ± 1.5, 6.2 ± 1.4; $P < 0.0001$), SPART-DL (4.8 ± 2.2, 4.9 ± 2.3, 7.0 ± 2.3; $P = 0.0003$), PASAT-3 (41.4 ± 13.0, 33.3 ± 9.1, 48.7 ± 7.7; $P < 0.0001$), SDMT (41.8 ± 15.5, 32.9 ± 15.9, 51.0 ± 12.1; $P = 0.0001$), and COWAT (60.7 ± 19.7, 48.5 ± 18.3, 75.6 ± 17.5; $P < 0.0001$) scores than healthy controls. Although non-BMS and BMS patients showed trends towards reduced SPART-IML (4.3 ± 2.1, 3.9 ± 1.5, 4.8 ± 1.9; $P = 0.2177$) scores, this difference did not attain statistical significance. The Stroop test was also impaired in both non-BMS and BMS patients (47.7 ± 32.4, 65.2 ± 34.2, 36.8 ± 14.7; $P = 0.0006$). However, since BMS patients had relatively better Stroop test scores, two-group comparisons attained significance only among non-BMS patients and healthy controls ($P < 0.001$). There were no significant differences among cognitive test scores of non-BMS and BMS patients, with the exception of PASAT-3 scores, which were relatively improved in BMS patients ($P < 0.05$). While 9-hole peg (20.1 ± 1.9, 27.8 ± 11.2, 18.6 ± 2.1; $P < 0.0001$) and timed 25-foot walk tests (6.7 ± 1.1, 9.2 ± 3.7, 6.1 ± 1.5; $P < 0.0001$) were impaired in non-BMS patients, BMS patients showed scores comparable to those of healthy controls (Figure 1).

Table. Clinical and demographic features of benign MS (BMS) patients, non-BMS patients, and healthy controls (HC).

	BMS (n = 21)	**non-BMS (n = 22)**	**HC (n = 38)**	**P**
Sex (F/M)	15/6	12/10	28/10	0.286*
Age, years (SD)	37.0 (7.6)	39.3 (9.0)	36.0 (10.2)	0.355**
Age of MS onset, years (SD)	23.7 (6.9)	27.4 (9.0)	-	0.147***
Duration of MS, years (SD)	13.2 (4.2)	14.8 (5.7)	-	0.327***
EDSS, mean (SD)	2.2 (0.5)	4.2 (0.8)	-	<0.001†
Number of relapses, mean (SD)	7.7 (3.8)	7.5 (4.3)	-	0.889***
BDI scores, mean (SD)	7.9 (4.7)	11.1 (8.5)	7.0 (5.7)	0.144***

F, Female; M, male; SD, standard deviation; EDSS, Expanded Disability Status Scale; BDI, Beck Depression Inventory. *, Chi-square; **, ANOVA; ***, Student's t-test; †, Mann–Whitney U test.

3.2. CCR ameliorates cognitive functions in BMS

To evaluate the impact of CCR on cognitive functions of BMS patients, cognitive test scores of BMS patients with (n = 10) and without (n = 11) CCR were evaluated before and 6 months after initiation of CCR. When scores before and after CCR were compared with Student's t-test, in the BMS group without CCR, SDMT (before 42.1 ± 14.1 vs. after 36.0 ± 10.7; P = 0.031) and Stroop (before 47.7 ± 37.6 vs. after 63.7 ± 49.3; P = 0.043) test scores significantly deteriorated. Alternatively, in the BMS group with CCR, after 6 months of treatment, BMS patients showed significantly improved PASAT-3 scores (before 40.3 ± 12.8 vs. after 46.3 ± 11.3; P = 0.008). Other cognitive and motor test scores remained relatively identical. When all four groups with and without CCR were compared with repeated measures ANOVA, CCR was found to exert a positive influence on SDMT (P = 0.016), COWAT (P = 0.036), and Stroop (P = 0.023) test scores (Figure 2).

4. Discussion

Memory, attention, and frontal lobe cognitive domains of BMS patients are well known to be impaired (12). Moreover, BMS and non-BMS patients show identical cognitive impairment frequency and cognitive deterioration pace (13). Deficits in executive functions, processing speed, and attention have been associated with structural damage of tracts connecting the cortical and subcortical regions of the brain (14). Similar to previous reports, in our study, BMS patients displayed deficits in a wide range of cognitive functions including verbal and visual memory, attention, and executive functions and, as a result, BMS and non-BMS patients showed similar neuropsychological profiles. By contrast, 9-hole peg and timed 25-foot walk tests were not impaired in non-BMS patients, indicating preserved motor functions in this MS subgroup. Thus, our results confirm the notion that regions of the brain associated with cognitive functions are affected in BMS, while those associated with somatic neurological functions are relatively preserved. Notably, while displaying equally impaired scores as non-BMS patients in most cognitive tests, BMS patients' Stroop and PASAT-3 test performances were relatively better than those of non-BMS patients. This might be due to the fact that BMS patients have increased activation of the cognitive network regions involved in executive functions owing to adaptive functional cortical changes (15). To establish a comparable patient control group, non-BMS patients were selected from among MS patients with disease duration of more than 10 years and thus some non-BMS patients were inadvertently in the progressive stage of MS. In future studies, it might be advisable to establish a homogeneous non-BMS control group comprising only RRMS patients. Response of these intermediate RRMS patients (neither BMS nor SPMS despite >10 years of disease duration) to CCR is also worth investigating.

CCR has been widely used for rehabilitation of the cognitive dysfunction of MS patients, improving scores obtained in a broad range of neuropsychological tests (16–18). To our knowledge, our study has shown for the first time that BMS patients also benefit from CCR. The amelioration in PASAT-3, SDMT, COWAT, and Stroop test scores was more pronounced than that observed for verbal and visual memory test scores. Notably, SDMT and Stroop test scores showed trends towards deteriorating in nonrehabilitated BMS patients in a 6-month time span. In CCR-administered patients this deterioration pattern appears to have been reversed, leading to either unaffected or significantly improved test scores. Similar CCR-induced improvements of PASAT and Stroop test scores have been previously shown in non-BMS patients, as well (16–20). It

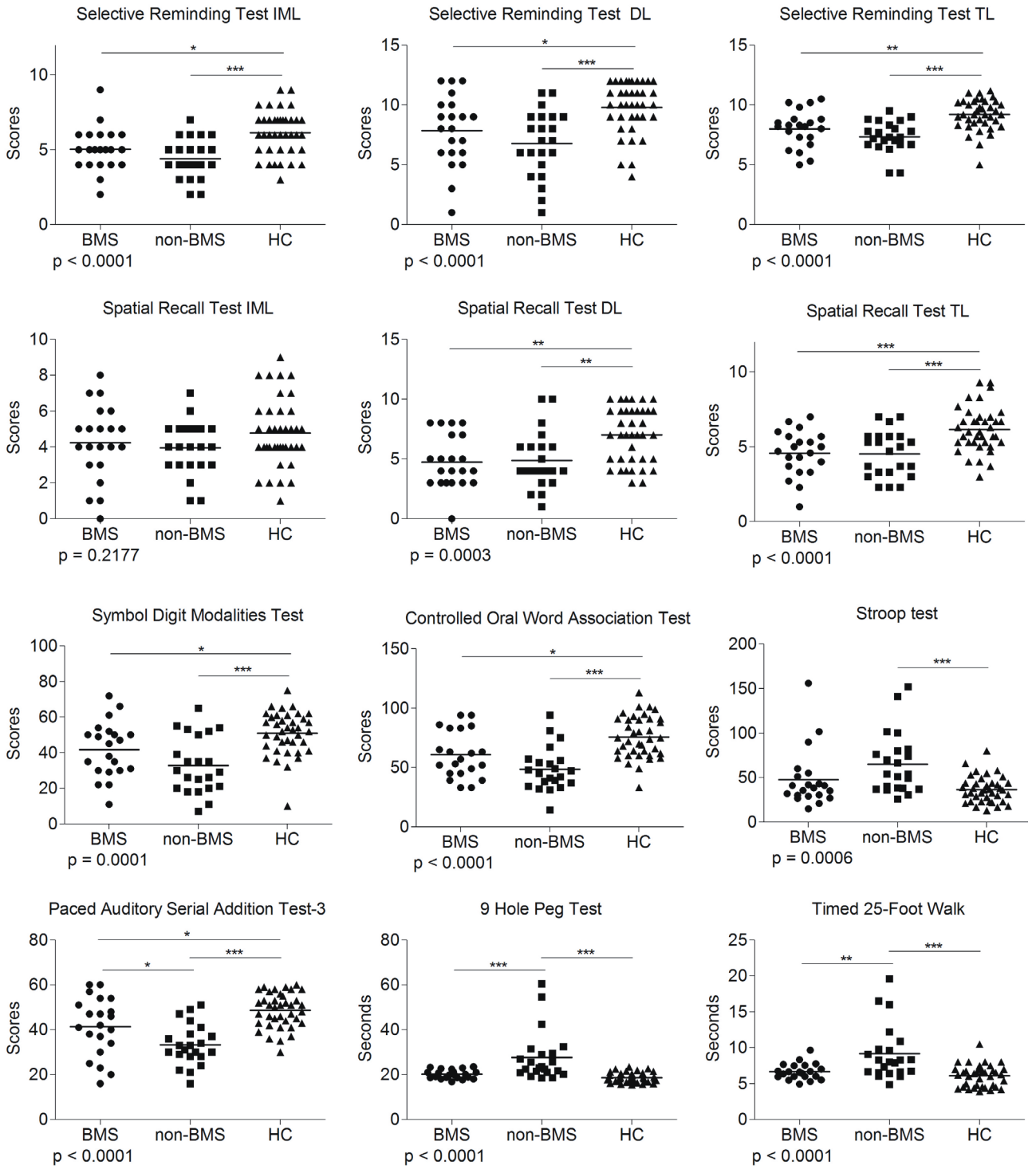

Figure 1. Neuropsychological test results of benign MS (BMS) patients, non-BMS patients, and healthy controls (HC). Horizontal lines indicate mean values. P-values for three-group comparisons (by ANOVA) are indicated at the lower left corner of each panel. Significant two-group comparisons (by Tukey's post hoc test) are denoted at the top of the panels. *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$. IML, Immediate learning; DL, delayed learning; TL, total learning.

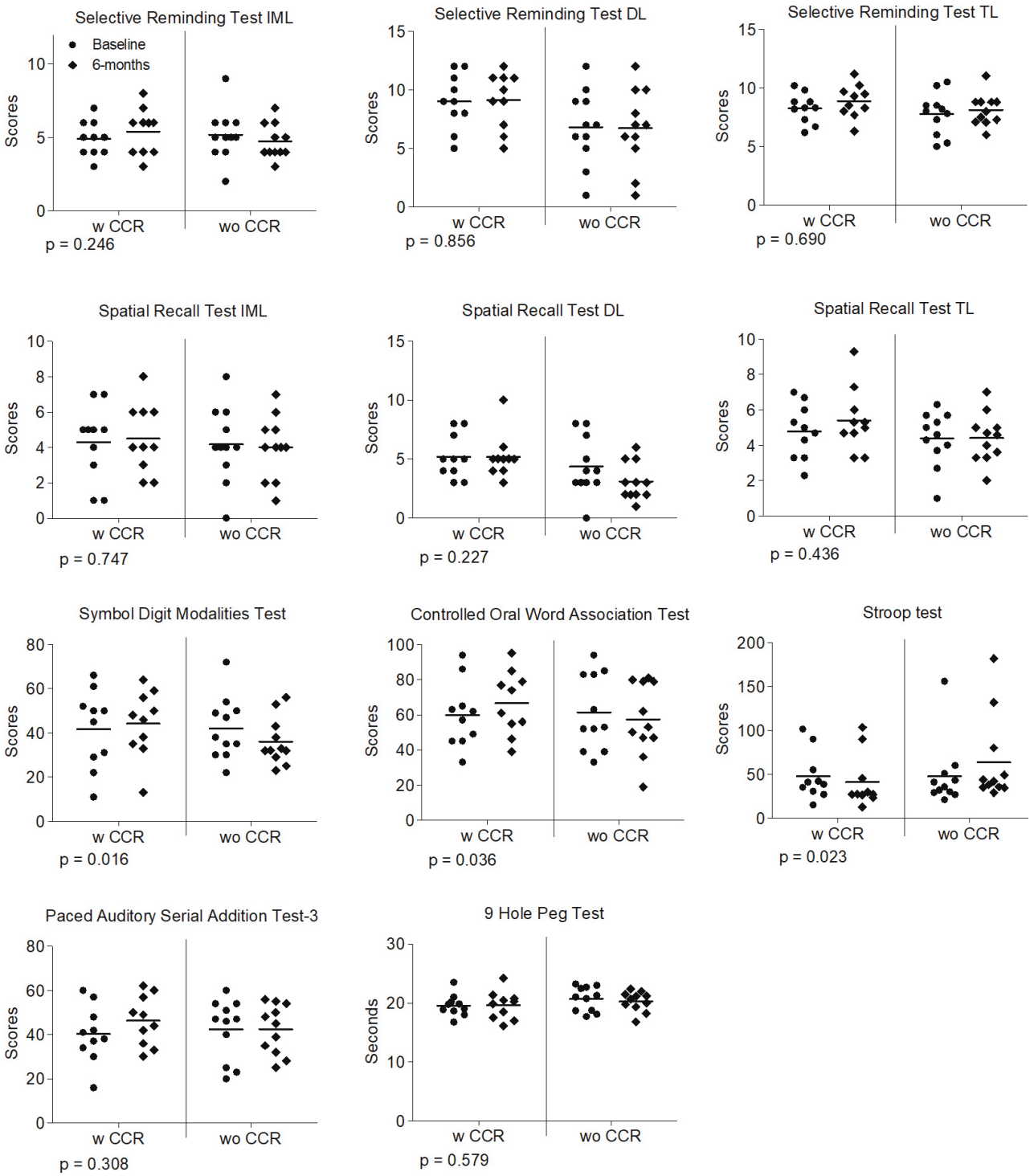

Figure 2. Neuropsychological test results of benign MS patients with (w) and without (wo) computer-assisted cognitive rehabilitation (CCR). P-values for four-group comparisons (by repeated measures ANOVA) are indicated at the lower left corner of each panel. IML, Immediate learning; DL, delayed learning; TL, total learning.

should be noted as a limitation that the tool administered in CCR has similar features with the assessment tools and therefore some of the observed benefits of CCR after 6 months of training could be at least partly due to learning effects.

PASAT-3, SDMT, COWAT, and Stroop tests assess sustained attention, information processing speed, verbal fluency, and categorical reasoning, all of which are known to be mediated by executive functions (21–23). The differential amelioration pattern induced by CCR might be the consequence of the above-mentioned adaptive enhanced activity of executive function regions of the brain (15). Alternatively, these regions might have been less severely afflicted in BMS, providing a cognitive reserve that enables prompt restoration by rehabilitation efforts. In conclusion, BMS patients might show severe cognitive deficits, which may potentially respond to neuropsychological rehabilitation. The long-term effects of CCR and the most ideal cognitive rehabilitation methods for BMS patients need to be further studied.

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