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Cognition with magnetic resonance imaging findings and social activities in patients with multiple sclerosis in a Japanese cohort

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BICAMS scores and the Expanded Disability Status Scale, gender, age at examination, education, and disease duration. The dependent variable was the "social activity."
Results: Analysis of variance indicated that patients with MS and more cerebral lesions on MRI had lower scores in all three domains of the BICAMS (the Symbol Digit Modalities Test, the second edition of the California Verbal Learning Test, and the revised Brief Visuospatial Memory Test). Scores of all three domains were also significantly lower in patients with cerebellar lesions. Concerning social activities, patients who were unemployed because of MS had lower BICAMS scores compared with employed patients. However, the BICAMS domain scores did not independently affect the other social activities.
Conclusions: Higher numbers of cerebral lesions and the presence of cerebellar lesions evaluated by MRI affect cognitive function based on the BICAMS. Cognitive function may affect social activities in patients with MS.

Cognition with magnetic resonance imaging findings and social activities in patients with multiple sclerosis in a Japanese cohort

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Abstract

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Methods: Cognition was evaluated by the Brief International Cognitive Assessment for MS (BICAMS), using previously published data for 156 Japanese patients with MS. The BICAMS results were analyzed with available MRI data, focusing on hyperintense lesions on T2/fluid-attenuated inversion recovery images. Logistic regression analysis was used to assess associations between the BICAMS scores and social activities (i.e., "student," "employed full time," "employed part time," "homemaker," and "unemployed because of MS"). The independent variables were the BICAMS scores and the Expanded Disability Status Scale, gender, age at examination, education, and disease duration. The dependent variable was the "social activity."

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Conclusions: Higher numbers of cerebral lesions and the presence of cerebellar lesions evaluated by MRI affect cognitive function based on the BICAMS. Cognitive function may affect social activities in patients with MS.

Keywords: cognition, employment, multiple sclerosis

Running Title: BICAMS in MS

Introduction

Patients with multiple sclerosis (MS) often report cognitive impairment, yet this symptom garnered little interest in the clinical and neuroscience literature until the early 1980s. At that time, neuroimaging technology developed to the point where it could provide reliable metrics of neuropathology, and psychometric procedures improved to enable reliable quantification of cognitive abilities.[1] Neuropsychological investigations have shown that 40%–65% of patients with MS experience cognitive impairment, typically with prominent involvement of memory, sustained attention, and information processing speed, rather than global cognitive decline.[2] In Japan, we have previously reported on cognitive dysfunction in MS using the Brief Repeatable Battery of Neuropsychological tests (BRB-N), which revealed that impaired cognitive function, particularly in information processing speed, was present among Japanese patients.[3]

Given the essential role of magnetic resonance imaging (MRI) in MS diagnosis and disease surveillance, MS research is often at the forefront of novel and innovative MRI tools for investigating cognitive deficits.[4] Many of the cognitive deficits in patients with MS can be related to a disconnection syndrome caused by involvement of white matter tracts,[5] with research showing the importance of white matter lesion sites, microstructural injury, gray matter lesions, and cortical and subcortical gray matter brain atrophy.[4] Our previous study using BRB-N demonstrated that patients with MS who had more cerebral lesions on MRI had lower scores in most of the BRB-N tests; moreover, the BRB-N scores were significantly lower in patients with brainstem and cerebellar lesions.[6] Conflating the clinical, radiological, and pathological data, both gray and white matter pathology appear to play unique and likely additive roles in the pathogenesis of MS-related cognitive impairment. However, MRI studies to date have been limited by poor resolutions for detecting disease in brain areas critical for cognition.[7]

Most individuals with MS (>90%) have a history of working before diagnosis, and approximately 60% are employed at time of diagnosis; however, only a small percentage (20%–40%) remain employed after diagnosis.[8] Improvements in mortality rates and in the preservation of physical capabilities have led to increasing interest in cognitive outcomes and quality of life in these patients.[1] Cognitive impairment limits activities of daily living[9] and may negatively affect employment status. In fact, declining performance over time in tests of attention and verbal memory are predictive of impaired employment status.[10] Our previous study indicated that patients categorized as being unemployed because of MS had lower BRB-N scores than other for social activity groups.[6]

Recently, we validated the Japanese version of the Brief International Cognitive Assessment for MS (BICAMS). This test comprises the Symbol Digit Modalities Test (SDMT),[11] and elements of the second edition of

the California Verbal Learning Test (CVLT2)[12] and the revised Brief Visuospatial Memory Test (BVMTR).[13] In the present study, we aimed to evaluate the associations of MRI findings and working status with cognitive function among Japanese patients with MS based on the BICAMS data reported in that validation study.

Materials and Methods

Patients with MS

The clinical characteristics of the patients included in this study have been described in an earlier report.[14] Briefly, 156 Japanese patients with MS (107 females and 49 males) were included, but those with neuromyelitis optica spectrum disorders were excluded. The clinical profiles of the study participants are shown in Table 1.

The BICAMS

The BICAMS[15] was performed for neuropsychological evaluations. This test is actually a battery three individual tests: the SDMT for cognitive processing speed, the first five recall trials of the CVLT2 for auditory/verbal learning and memory, and the first three recall trials of the BVMTR for visual or spatial memory.[15] The test battery was administered in the following order, which was fixed: the SDMT, the five CVLT2 trials, and the three BVMTR trials.[16]

Assessment of MRI findings

MRI scans obtained within a year of performing the BICAMS tests were evaluated for each patient (one patient had an MRI performed 1.5 years before undergoing the BICAMS test). In terms of cerebral lesions, patients were classified into three groups: ≥9 lesions, 4–8 lesions, and ≤3 lesions. We also checked whether there were brainstem and cerebellar lesions. The MRI scans were obtained by axial slices (5 or 6 mm intervals) at 1.5 or 3 Tesla for each subject, and the scan sets per subject contained T2-weighted images and/or T2-weighted fluid-attenuated inversion recovery images.

Social activities

When receiving the BICAMS tests, participants were requested to provide information on their status with regards the following work status: “student,” “employed full time,” “employed part time,” “homemaker,” and

"unemployed because of MS".

Statistical analysis

All data are expressed as means ± standard deviation. Statistical analyses were performed using either SAS 9.4 (SAS Institute Inc., Cary, NC) or GraphPad Prism (GraphPad Software, Inc., La Jolla, CA, USA). Raw data for the three component tests (i.e., the SDMT, CVLT2, and BVMTR) were analyzed to identify associations with the MRI findings. Cerebral, brainstem, and cerebellar lesions on MRI were then evaluated by analysis of variance (ANOVA) followed by Tukey's multiple comparison test. Next, logistic regression analysis was used to assess the presence of causal relationships between social activities and the BICAMS scores. The independent variables were the BICAMS scores, the Expanded Disability Status Scale (EDSS) scores, gender (female = 0; male = 1), age at examination, duration of education, and disease duration, whereas the dependent variables were the social activities, as specified above. P values of <0.05 were considered statistically significant.

Results

MRI findings and BICAMS scores

Cognitive function and cerebral, brainstem, or cerebellar lesions

In our cohort, 117 patients had ≥9 cerebral lesions, 30 had 4–8 lesions, and 9 had ≤3 or lesions. There was a trend for lower BICAMS scores in association with higher numbers of cerebral lesions. Only differences between patients with ≥9 lesions and with 4–8 lesions were statistically significant in each battery of the BICAMS (Fig. 1a). We also identified 102 and 54 patients without brainstem lesions, respectively. Of note, patients with brainstem lesions had significantly lower scores in all three test batteries of the BICAMS (Fig. 1b). Finally, there were 55 and 101 patients with and without cerebellar lesions, respectively. Patients with cerebellar lesions had significantly lower scores in all three test batteries of the BICAMS (Fig. 1c).

We used the general linear model to assess the presence of causal relationships between MRI lesions and BICAMS scores to control for the effects of age at examination, sex, and EDSS. The results revealed significant differences in BICAMS scores among the three groups of cerebral lesions (SDMT: F [2, 150] = 5.66, P<0.05; CVLT2: F [2, 150] = 7.01, P<0.05; BVMTR: F [2, 150] = 5.2, P<0.05) and between the groups with and without cerebellar lesions (SDMT: F [1, 151] = 7.56, P<0.05; CVLT2: F [1, 151] = 5.42, P<0.05; BVMTR: F [1, 151] =

12.25, $P<0.05$). In contrast, there was no significant difference in BICAMS scores between the groups with and without brainstem lesions (SDMT: F [1, 151] = 1.9, P=0.171; CVLT2: F [1, 151] = 1.95, P=0.165; BVMTR: F [1, 151] = 0.77, P=0.382).

ANOVA model of the main effects of cerebral, brainstem, or cerebellar lesions

We further explored whether each lesion site was associated with decreased BICAMS scores after controlling for the effects of the other two lesions. Brainstem lesions were not associated with the BICAMS. However, cerebral lesions were associated with decreased CVLT2 scores and cerebellar lesions were associated with decreased BVMTR scores (Table 2).

Social activities and BICAMS scores

Among the patients, 60 were employed full time, 35 were employed part time, 36 were homemakers, and 25 were unemployed because of MS, but there were no students. The raw scores for the three BICAMS test batteries by social activity class are shown in Fig. 2. One-way ANOVA was performed with social activity as the independent variables and each BICAMS test as dependent variables. Multiple comparison of patients with MS using Tukey's honestly significant difference test revealed significant differences between the "unemployed because of MS" group and the other social activity groups for each component of the BICAMS ($P < 0.05$) (Fig. 2).

Several potential factors affect social activities and needed to be considered in the analysis. Initially, logistic regression analysis was performed with the three BICAMS tests, the EDSS scores, gender, age at examination, education duration, and disease duration as independent variables and with each social activity as the dependent variables. Subsequently, a model was generated to explain the relationship of a dependent variable with several significant independent variables selected using a stepwise method. A higher estimated value signified that the social activity group, such as "employed full time" and "unemployed because of MS," had a higher significance with a parameter, especially with EDSS (Table 3). Other factors, such as gender and education, also had independent effects on social activities (Table 3), but the none of the components of the BICAMS affected the social activities status.

Discussion

Given that brain MRI is a cornerstone of MS diagnosis, differential diagnosis, and disease monitoring, it is reasonable to ask whether neuroimaging could also be used to predict cognitive function and impairment in this group.[17] Indeed, patients with more severe MS disease burdens (i.e., greater lesion load and cerebral atrophy on MRI) are known to be at increased risk of cognitive impairment.[18] Several studies in Western countries have also demonstrated that patients with greater lesion frequencies and volumes have significantly greater cognitive impairments compared with patients who have lower lesion burdens.[19-21]

The current study using the BICAMS obtained similar results to those in our previous study using the BRB-N, indicating that cognitive impairment worsened as the number of cerebral lesions increased in patients with MS.[6] Although patients who had ≥9 cerebral lesions in the current study had significantly lower scores in each BICAMS test than patients with 4–8 lesions, no significant differences in scores were found between patients who had ≤3 cerebral lesions and patients who had >3 lesions. This could be explained by the small sample size of the group with ≤3 lesions. Significant correlations have been shown between cognitive function and brain volumes, especially gray matter volume.[22,23] However, a longitudinal study over 17 years demonstrated that atrophy of the corpus callosum was strongly associated with decreased performance in cognitively demanding information processing tasks.[24] Studies of normal-appearing white matter involvement have lent further support to the notion of a disconnection syndrome in patients with MS, which could be the cause of cognitive and physical deficits.[5] Further research is needed to clarify the associations between cognitive dysfunctions and MRI findings and to understand cognitive impairment in patients with MS.

Our previous study using the BRB-N demonstrated that patients with brainstem or cerebellar lesions had lower scores than patients without those lesions.[6] Similar results were obtained in the current study when using the BICAMS, although there was no significant difference in BICAMS scores in patients with and without brainstem lesions after adjusting for age at examination, sex, and EDSS. It may be that patients with cerebellar lesions have more cerebral lesions, and that those patients had lower scores compared with patients without cerebellar lesions. However, in the previous study using the BRB-N, cerebellar lesions were associated with decreased SDMT and Paced Auditory Serial Addition Test scores after controlling for the effects of cerebral and brainstem lesions.[6] By contrast, in the current study, cerebellar lesions were not statistically associated with decreased SDMT scores after controlling for the effects of those lesions, though the same tendency was shown ($P = 0.097$).

As discussed in our previous study, the cerebellum may be important in cognitive function and information processing.[25-27] In the current study, after controlling for the effects of cerebral and brainstem lesions,

cerebellar lesions were associated with decreased BVMTR scores that evaluate visual–spatial episodic memory. It is known that short-term memory impairments associated with cerebellar deficits include difficulty learning and spontaneously recalling new information; these, in turn, reflect deficient strategies for organizing verbal or visual spatial material for encoding, as well as difficulty in locating information in memory stores.[27] A significant association has also been shown between the total gray and white matter cerebellar volumes and the visual–spatial subdomain in a non-faller group of patients with MS.[28] In the current study, we did not investigate the cerebellar volume in the included patients. However, it is suggested that the cerebellum plays an important role in the control of cognitive functions, being strongly interconnected with the prefrontal, superior temporal, posterior parietal, and limbic cortices. Further research is needed to clarify the associations between cognitive impairment and cerebellar lesions in MS.

Lower SDMT scores were demonstrated in the group of patients who were "unemployed because of MS" in our previous study.[6] The estimated value of SDMT in those data was −0.0627, which was statistically significant, but the effect was small. In the current study, using the same logistic regression analysis as used in our previous study and using SDMT, EDSS, and male sex as independent variables and each social activity as the dependent variable, we found that the estimated value of SDMT was −0.0409 in the group of patients who were "unemployed because of MS". Those data are not so different from the previous data, which implies that some sample sizes or different groups may generate statistically significant or not significant results.

In our previous study, >60% of Japanese patients with MS experienced a change in employment status, which is known to affect quality of life significantly.[29] Cognitive impairment also has a substantial influence on activities of daily living and work capacity,[1] and the worsening of cognitive function could be associated with a loss of employment.[10] Using the BRB-N, we previously showed that patients in the "unemployed because of MS" group had the lowest scores relative to those in the other social activity groups, and this was confirmed in the current study using the BICAMS. Both studies revealed that EDSS scores were highly and negatively associated with the "unemployed because of MS" group,[6] and in addition, the current study demonstrated a positive association for the EDSS score and the "employed full time" group. Constructing a model to explain the relationship of a dependent variable with several significant independent variables via the stepwise method failed to show that cognitive impairments identified by the BICAMS affected social activities in patients with MS. However, it has been considered that cognitive dysfunction in MS contributes significantly to unemployment, accidents, impaired daily function, and loss of social contacts.[30] Prospective studies are needed to evaluate the associations of

cognitive impairments with social activities. Further, social environments and systems differ considerably among countries and regions and may affect the activities of patients with MS, necessitating that further studies be undertaken in different countries or regions.

In conclusion, our current study demonstrated that cognitive impairment evaluated by the BICAMS is associated with greater numbers of brain lesions on MRI and lower scores on the BICAMS domains. This seems to apply to patients with MS who are unemployed because of their condition, rather than those in other social activity groups. Cognitive impairment is an important aspect of MS that can produce functional handicaps and adversely affect a patient's quality of life.[31] Currently, there is no simple approach for improving cognitive function in patients with MS. Social engagement and quality of life are important considerations for patients with MS, and there is a growing evidence base to suggest that clinicians need to pay greater attention to how these are affected by cognitive dysfunctions.

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Disclosure of ethical statement

The study protocol was approved by the Ethics Committee of each participating site, and all participants provided written informed consent.

Conflicts of interest

None declared.

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Figure Legends

Fig. 1. MRI lesions and BICAMS scores

Patients were divided into three cerebral lesion groups (≥9, 4–8, and ≤3) based on MRI findings. The group with ≥9 lesions had significantly lower scores than the group with 4–8 lesions (Fig. 1a). Patients with brainstem lesions had lower scores in all BICAMS tests compared with those who had no brainstem lesions (Fig.1b). Patients with cerebellar lesions had lower scores in all BICAMS tests (Fig.1c). Main bars represent mean values and error bars represent standard deviations. (*$P < 0.05$)

Abbreviations: BICAMS, Brief International Cognitive Assessment for MS; BVMTR, the revised Brief Visuospatial Memory Test; CVLT2, the second edition of the California Verbal Learning Test; MRI, magnetic resonance imaging; MS, multiple sclerosis; SDMT, Symbol Digit Modalities Test.

Fig. 2. Social activities and BICAMS scores

The raw BICAMS test scores are shown for each social activity group (employed full time, employed part time, homemaker, or unemployed because of MS). There were significant differences between the "unemployed because of MS" group and the other social activities groups for all BICAMS tests. Main bars represent mean values and error bars represent standard deviations. (*$P < 0.05$)

Abbreviations: BICAMS, Brief International Cognitive Assessment for MS; BVMTR, the revised Brief Visuospatial Memory Test; CVLT2, the second edition of the California Verbal Learning Test; MRI, magnetic resonance imaging; MS, multiple sclerosis; SDMT, Symbol Digit Modalities Test.

Table 1. Clinical profiles of the included patients with MS

	Patients with MS
Number (Female/Male)	156 (107/49)
Age at examination (years) † (range)	41.4 ± 9.3 (23–70)
Duration of education (years) †, ‡ (range)	14.1 ± 1.9 (12–22)
Age at onset (years) † (range)	31.0 ± 9.2 (10–64)
EDSS † (range)	2.4 ± 2.0 (0.0–8.0)
Clinical course	
Primary-progressive	1
Relapsing-remitting	137
Secondary-progressive	18
MRI findings	
Cerebral lesions	
≥9 lesions	117
4–8 lesions	30
≤3 lesions	9
Brainstem lesions	
Positive	102
Negative	54
Cerebellar lesions	
Positive	55
Negative	101
Social activities	
Student	0
Employed full time	60
Employed part time	35
Homemaker	36
Unemployed because of MS	25

† mean ± standard deviation (SD),

Table 2. ANOVA model in which only the main effects of cerebral, brainstem or cerebellar lesions are hypothesized

	SDMT	CVLT2	BVMTR
Cerebral lesions			
F value (2, 151)	1.80	3.51	1.85
P value	0.169	<0.05	0.16
Effect size (partial η^2)	0.023	0.044	0.024
Brainstem lesions			
F value (1, 151)	1.14	0.39	0
P value	0.287	0.535	0.98
Effect size (partial η^2)	0.008	0.003	0.000
Cerebellar lesions			
F value (1, 151)	2.79	1.38	7.11
P value	0.097	0.243	<0.05
Effect size (partial η^2)	0.018	0.009	0.045

Table 3. Logistic regression analysis on social activities

Social activity	Parameter	Estimated value	Standard error	*P* value	Odds ratio	95% Wald confidence limits for odds ratio
Employed full time	EDSS	–0.2804	0.1130	0.0131	0.756	0.605–0.943
	Gender	1.344	0.4163	0.0012	3.834	1.696–8.671
	Age	–0.0564	0.0231	0.0146	0.945	0.903–0.989
	Education	0.2520	0.1037	0.0150	1.287	1.050–1.577
Employed part time	Gender	–1.232	0.5187	0.0175	0.393	0.106–0.806
Homemaker	Gender	–2.409	0.7564	0.0014	0.090	0.020–0.396
	Education	–0.2675	0.1275	0.0360	0.765	0.596–0.983
Unemployed because of MS	EDSS	0.6504	0.1337	<0.0001	1.916	1.475–2.490
	Gender	1.510	0.5827	0.0096	4.527	1.445–14.183
	Duration	0.0731	0.0351	0.0373	1.076	1.004–1.153

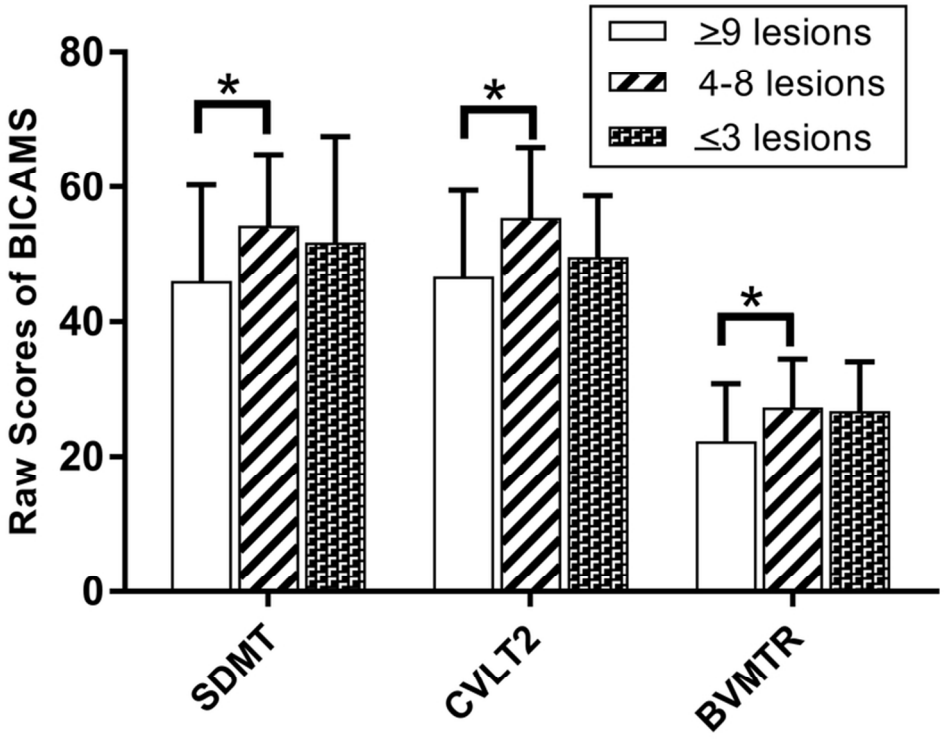

Fig1a

75x61mm (300 x 300 DPI)

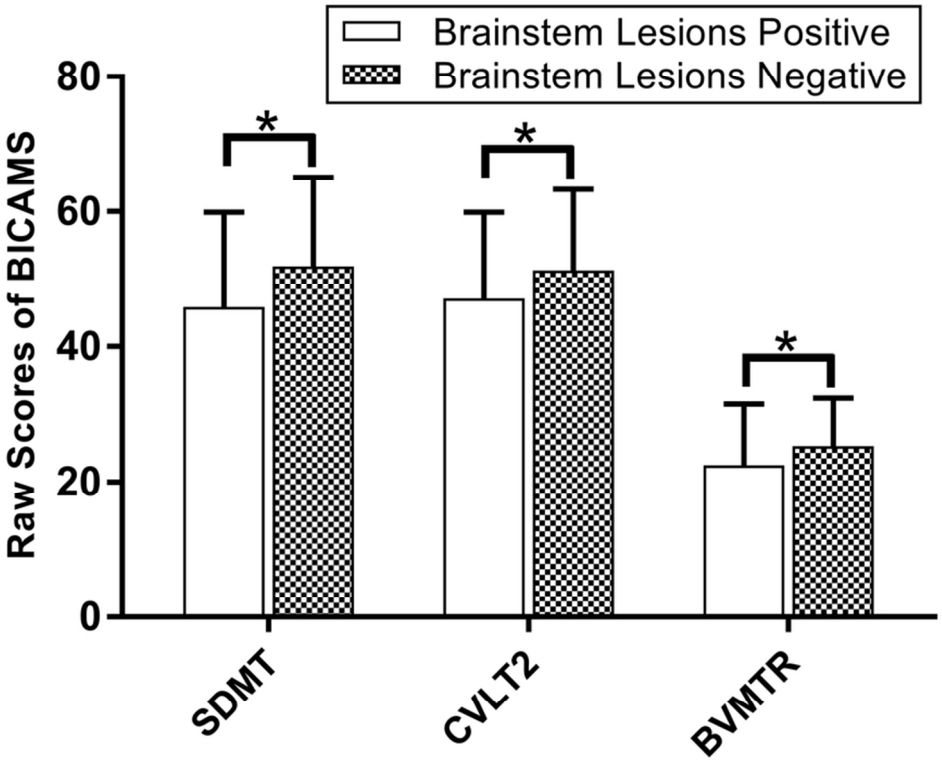

Fig1b

78x64mm (300 x 300 DPI)

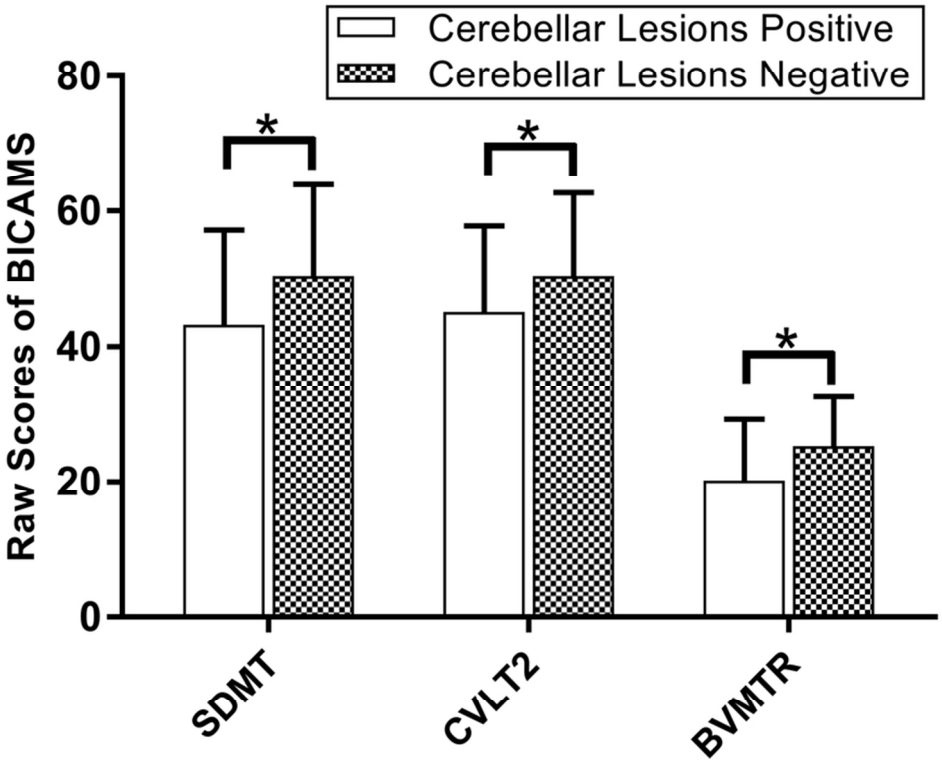

Fig1c

78x65mm (300 x 300 DPI)

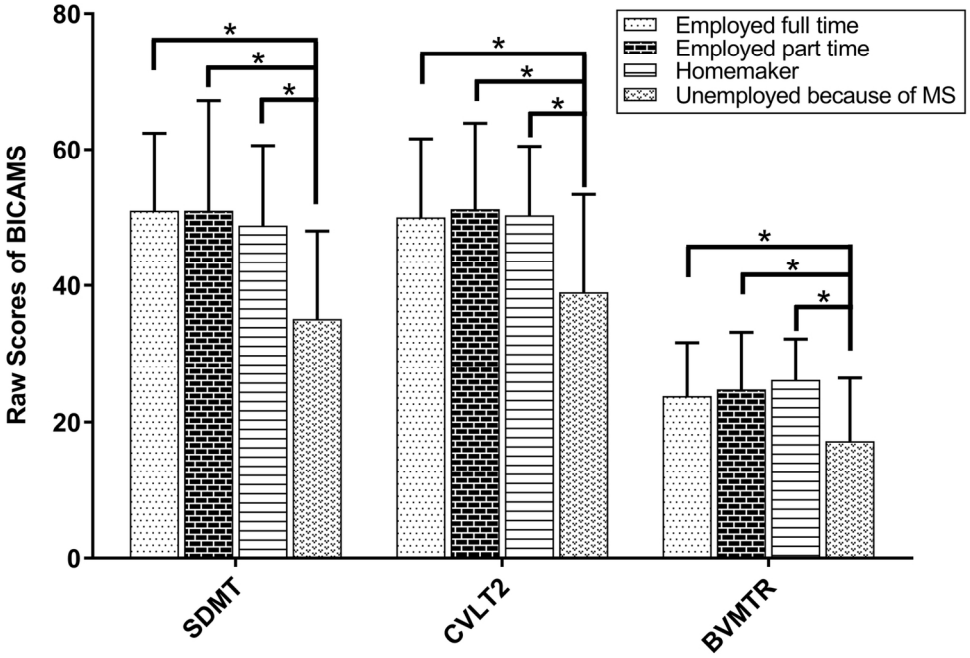

Fig2

137x114mm (300 x 300 DPI)