Deficiency in Mental Rotation of Upper and Lower-Limbs in Patients With Multiple Sclerosis and Its Relation With Cognitive Functions

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Abstract- Mental rotation is a cognitive motor process which was impaired in different neurologic disorders. We investigated whether there were deficits in response pattern, reaction time and response accuracy rate of mental rotation in multiple sclerosis (MS) patients compared to healthy subjects and whether cognitive dysfunctions in MS patients were correlated with mental rotation deficits. Moreover, we showed whether there was a difference between upper and lower-limbs mental rotation in MS patients. Thirty-five MS patients and 25 healthy subjects performed hand mental rotation (HMR) and foot mental rotation (FMR) tasks. Visual information processing speed, spatial learning and memory ability, and visuospatial processing were assessed by Symbol Digit Modalities Test (SDMT), Brief Visuospatial Memory Test–Revised (BVMT-R), and Judgment of Line Orientation Test (JLO) respectively in MS patients. Reaction time for both hand and foot stimuli increased, and response accuracy rate for hand stimuli decreased in MS patients compared to healthy subjects, but response pattern of mental rotation in MS patients persisted. Similar to healthy subjects, MS patients performed upper-limbs mental rotation more easily than a lower-limbs mental rotation with more speed and response accuracy rate. Reaction time and response accuracy rate were correlated with the mentioned cognitive functions. MS patients made use of the correct response pattern for problem solving of increasing orientation from upright stimuli. Reaction time and response accuracy rate altered in these patients and this alteration might occur along with impairment in motor planning. Subjects' better responding to hand stimuli was due to more familiarity with hand stimuli. The correlation of mental rotation ability with cognitive functions indicates the possible role of cognitive functions in mental rotation.

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Keywords: Multiple sclerosis; Mental rotation; Motor imagery; Cognitive function

Introduction

Mental rotation, an index of implicit motor imagery, is similar to the real movement in terms of temporal characteristics, physical rules and neural mechanisms (1-3). In addition, motor imagery as a higher-level cognitive function (4) also engages high-level visual processing (5), visual perceptual mechanisms (6) and working memory (7).

In mental rotation task, subjects determine the laterality of the human body parts presented in different orientations (8). Patients' decision becomes more difficult with increasing orientation of the upright stimulus in line with biomechanical constraints of real movements imposed by their joints (8-10). The correct strategy for responding is that the subjects move mentally their own body parts to judge the stimulus orientation (10).

There were contrasting reports about the alteration of mental rotation ability in different neurological diseases with lesions in various areas of the brain. For example, in one study reaction time of mental rotation

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significantly increased on the affected side in asymmetrical Parkinson's patients compared to healthy subjects (11) but in another study, the reaction time in Parkinson's patients did not change compared to healthy subjects (12). Also, a study on subjects with hemiparetic cerebral palsy showed that deficits in response pattern of HMR existed in right hemiplegia while left hemiplegia performed this task similar to normal individuals (13). Another study on patients with hemiparesis revealed that both left and right hemiplegia performed a typical pattern of mental rotation with longer reaction time compared to the control group (14).

MS as a common chronic disease of the central nervous system (15), can lead to a variety of cognitive, sensory and motor dysfunctions due to demyelination and axonal loss (16). Studies on mental rotation ability in MS patients revealed decreased response accuracy rate of HMR in 30 hospitalized MS patients (17) and increased reaction time and decreased response accuracy rate of HMR in MS patients with mild disability (18).

According to our knowledge, up to now the difference of mental rotation between upper and lower limbs has not been investigated in MS patients. In the present study we investigated response pattern to stimuli in order to explore correct strategy in mental rotation task, reaction time and response accuracy rate in HMR and FMR in MS patients. Moreover, we compared lower and upper-limbs mental rotation in the patients. Also, the relationship of mental rotation ability and visual information processing speed, spatial learning and memory ability, and visuospatial processing was studied.

Materials and Methods

Participants

The sampling was done for a period of six months from January 2013 from among relapsing-remitting (RR) MS patients admitted to the MS society of Kerman/Iran. An expert neurologist used the Modified McDonald's criteria for the diagnosis of MS disease (19) and determined patients' motor function and disability according to the Kurtzke Expanded Disability Status Scale (EDSS) (20) and mental status of patients according to Mini-Mental State Examination (MMSE) (21). The neurologist also evaluated visual acuity and visual field in MS patients. Handedness was assessed by the Edinburgh inventory (22). Fatigue and depressive symptoms in the MS patients were assessed using the Fatigue Severity Scale (FSS) (23) and Beck Depression Inventory-II (BDI-II) (24) respectively. Thirty-five right-handed RR MS patients (20-40-year-old) with an MMSE score>24 and an EDSS score<3.5 were included in this study. The patients had normal or corrected-to-normal vision. Patients with FSS>4, BDI-II>21, recent relapse, other neurological diseases (stroke, seizure, *etc.*), history of head trauma, chronic psychiatric disorder, severe visual deficiency and those who had received corticosteroids during the 12 weeks prior to the study were excluded.

Twenty-five right-handed subjects with normal or corrected-to-normal vision and no neurological diseases participated in the HMR and FMR tasks.

Ethics Committee of Kerman University of Medical Sciences approved the current study which conforms to the Declaration of Helsinki. All patients signed the informed consent form for participation in the study.

Procedure

The order of tests given to all patients during the study was similar, beginning with HMR task, followed by FMR task, SDMT, BVMT-R and ending with JLO. To control for the learning effect, all subjects were naive about the tests and they had no contact with each other.

In order to evaluate implicit motor imagery of the upper and lower extremities, patients performed the HMR and the FMR tasks respectively. Visual angle of patients was approximately 5.7°. At the beginning of each trial of HMR and FMR tasks, we presented a fixation cross for 250 milliseconds (ms) and then the stimulus for 3000 ms and followed by an interval of 1500 ms. The stimuli which were line drawings of both back and palm views of right and left hands and feet were presented in six angular orientations (0°,60°,120°,180°,240°, and 300°). Each picture was shown three times with a total of 72 trials (6 orientation×2 laterality×2 views×3 repetition) were presented in a random order. We asked patients to determine whether hand or foot image was of the right or left as quickly and accurately as possible by pressing right or left arrow keys. Two variables in the mental rotation task were recorded via key press: reaction time (the time between the appearance of the stimulus on the monitor and the onset of the correct response by patients in ms) and response accuracy rate (proportion of correct responses in %).

The Minimal Assessment of Cognitive Function in MS (MACFIMS) comprised seven neuropsychological tests that assessed five cognitive abilities (25,26). Based on our aim of this study, we used three tests of MACFIMS (SDMT, BVMT-R, and JLO). In SDMT, which assesses visual information processing speed and working memory, patients articulated numbers associated with unpaired symbols based on the key at the top of the paper in 90 seconds (25). We explored visual learning and memory ability of patients by BVMT-R. In the first part of this test, we showed six simple figures to patients in 10 seconds and then asked patients to draw correct figures incorrect locations on the answer sheet. We repeated this trial three times. After 25 minutes in a delayed recall trial which assesses visual memory, we asked patients to remember and draw figures (25,26). The JLO test assesses visuospatial processing (27). In this test, we asked the patients to identify the orientation of pairs of partial lines based on a numbered visual array of 11 lines. The examiner recorded the total number of correct responses (25,26).

Statistical analyses

The outcomes were reaction time and response accuracy rate of HMR and FMR, the number of correct responses of SDMT, summation scores of three trials of total recall of BVMT-R, the score of delayed recall of BVMT-R and the number of correct responses of JLO.

Results were reported via mean±standard deviations (SD) or standard error of the mean (SE) for continuous variables. Age, educational level, and gender were compared between healthy subjects and MS patients using independent *t*-test and chi-squared test.

Two-way repeated measures ANOVAs with stimulus type (hand, foot), and stimulus orientations (0°,60°,120°,180°,240°, and 300°) as within-subject factors and groups (MS patients, healthy subjects) as between-subject factor were used for comparing the reaction time and response accuracy rate in the two groups and Bonferroni's post hoc test was used for multiple comparisons. Pearson correlation was used to investigate the relationship between variables of mental rotation (reaction time and response accuracy rate for hand and foot stimuli) and cognitive function scores. We used SPSS V.17 (Version 17.0. Chicago: SPSS Inc) for statistical analyses. In all tests, we used a significance level of 0.05.

Results

Demographic characteristics

Twenty-five healthy subjects and 35 MS patients enrolled in this study. Two groups were well-matched for gender, age, and education. The demographic and clinical characteristics of the participants are shown in Table 1.

Table 1. Participant characteristics

Variable	MS patients (n=35)	Healthy subjects (n=25)	Difference between 2 groups
Age (years)	30.6 ±7.4	31.2±6.5	NS
Gender (females/males proportion)	26/9	20/5	NS
Education (years)	13.4±3	13.6±2.8	NS
Duration of disease (months)	41.9±37.1	--	--
EDSS score	1.6±0.8	--	--
FSS	3.3±1.6	2.5±0.8	*P*=0.02
BDI-II	10.4±5.6	10±3.8	NS
MMSE	29.8±0.5	29.8±0.6	NS

Data represent mean±SD. Abbreviations: MS: multiple sclerosis, EDSS: Expanded Disability Status Scale, FSS: Fatigue Severity Scale, BDI-II: Beck Depression Inventory-II, MMSE: Mini-Mental State Examination, NS: non-significant.

Mental rotation analysis

Reaction time data of mental rotation

Figure 1 displays reaction time for hand and foot stimuli in mental rotation task with six different orientations in the two groups.

Repeated measures ANOVA on reaction times demonstrated significant main effects of group [F (1,58)=25.9; *P*<0.001]. These findings point out that reaction time in MS patients (2226.4 ms±25.1 SE) was higher than reaction time in healthy subjects (2020.9 ms±31.7 SE). The main effect of stimulus type was significant [F (1,58)=56.2; *P*<0.001] indicating that reaction time for hand stimuli (1977 ms±17.5 SE) was lower than reaction time for foot stimuli (2270.4 ms±35.7 SE).

The main effect of stimulus orientation was significant [F (5,54)=51.7; *P*<0.001] which implies that reaction time increases with the increase in angle of rotation. Reaction time needed for the rotation of 180° (2470.6 ms±37.6 SE) was higher than the other five orientations (0°=1875.3 ms±34.3 SE, 60°=1966.9 ms±34.4 SE, 120°=2212.7 ms±33.2 SE, 240°=2208.3 ms±29.8 SE, 300°=2008.4 ms±32.5 SE).

The interaction effect of group×stimulus type was significant [F (1,58)=10.8; *P*=0.002]. Planned comparisons showed that there was a significant difference between MS patients and healthy subjects in terms of reaction time to hand and foot stimuli (for hand, *P*=0.03 and for foot, *P*<0.001).

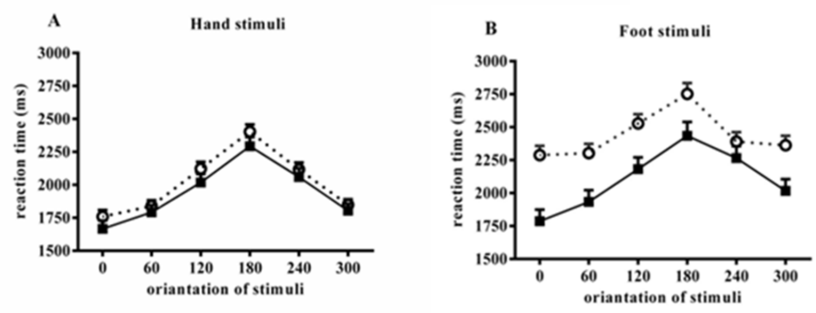

Figure 1. Reaction time (ms) is represented at different stimulus orientations in MS patients (white circles with dotted line) and healthy subjects (black squares with continues line). Graph A represents reaction time for hand stimuli. Graph B represents reaction time for foot stimuli. The error bar shows standard error of the means.

There was no significant interaction effect of group×stimulus orientation [F (5,54)=0.7; *P*=0.4] due to similar response patterns across different orientations between the two groups. In both groups, the shortest reaction time was related to 0 and the longest reaction time for 180°.

Finally, the interaction effect of group×stimulus type×stimulus orientation for the reaction time analysis was not significant [F (5,54)=.6; *P*=0.7]. Planned comparisons showed that there was no significant difference between MS patients and healthy subjects in terms of reaction time for a hand at each stimulus orientation. Reaction time for a foot in five stimulus orientations (for 0°, *P*>0.001; for 60°, *P*=0.002, for 120°, *P*=0.003; for 180°, *P*=0.02 and for 300°, *P*=0.004) differed significantly in MS patients from healthy subjects. Reaction time for hand in the 180° angle increased significantly compared to the other five stimulus orientations in MS patients and healthy subjects. Reaction time for a foot in the 180° angle increased significantly compared to the other five stimulus orientations in MS patients and compared to 0°, 60°, 120°, and 300° in healthy subjects.

Response accuracy rates data of mental rotation

Figure 2 represents response accuracy rate for hand and foot stimuli in mental rotation task with six different orientations in the two groups.

Repeated measure ANOVA analysis for group×stimulus type×stimulus orientation displayed a significant main effect of group [F (1,58)=4.9, *P*=0.03], stimulus type [F (1,58) = 162.8, *P*<.001], and stimulus orientation [F (5,54) = 26.5, *P*<0.001].

These results suggest that response accuracy rate in MS patients (76.3%±0.9) was significantly lower than healthy subjects (79.3%±1.1); subjects responded to hand stimuli (84.9%±0.8) with more accuracy than foot stimuli (70.6%±1); response accuracy rate decreases with increase in angle of the rotation. Response accuracy rate for the rotation of 180 (66.5%±1.4) was lower than the other five orientations (0°=83.1%±1.1, 60°=82.6%±1.1, 120°=76.4%±1.2, 240=76%±1.6, 300=82.2%± 1.1).

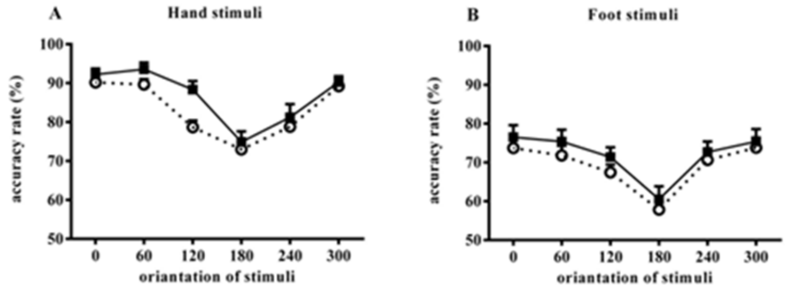

Figure 2. Response accuracy rate (%) are presented at different stimulus orientations in MS patients (white circles with dotted lines) and healthy subjects (black squares with continues lines). Graphs A and B represent Response accuracy rate for hand and foot stimuli. The error bar shows standard error of the means

The interaction effect of group×stimulus type was not significant [F (1,58) =.06; *P*=0.8] which indicated that there were increased response accuracy rate in responses for hand stimuli compared to foot stimuli in both groups (for both groups: *P*<0.001).

Planned comparisons showed that patients responded to hand stimuli with significantly less response accuracy rate than healthy subjects (*P*=0.04) but not for foot stimuli (*P*=0.2).

There was no significant interaction effect of group×stimulus orientation [F (5,54)=0.8; *P*=0.6] due to similar response patterns across different orientations between the two groups. In both groups, the lowest response accuracy rate was observed in response to 180 rotation of stimuli.

Finally, the interaction effect of group×stimulus type×stimulus orientation was insignificant [F (5,54)=0.3; *P*=0.9]. Planned comparisons showed that response accuracy rate for a hand in the orientation of 120° in MS patients differed significantly from healthy subjects. There was no significant difference between MS patients and healthy subjects in terms of response accuracy rate for foot stimuli in each of six stimulus orientations. Response accuracy rate for a hand in the 180° angle significantly differed from 0°, 60°, 240° and 300° orientations in MS patients and compared to 0°, 60°, 120° and 300° in healthy subjects. Reaction time for a foot in the 180° angle significantly differed from the other five stimulus orientations in both groups.

Correlation analysis

Table 2 shows the correlation results of reaction time and response accuracy rate for hand and foot stimuli with cognitive scores.

There was a significant negative correlation between reaction time for both hand and foot stimuli and all of the following: SDMT score, total recall, and delayed recall scores of BVMT-R and JLO score. Response accuracy rate for hand and foot stimuli was correlated positively with cognitive function scores.

Table 2. Correlation of mental rotation ability with cognitive function in MS patients

variable	SDMT	Total recall (BVMT-R)	Delayed recall (BVMT-R)	JLO
Reaction time to hand stimuli	r= -.46 *P*= .009	r= -.33 *P*= .04	r= -.45 *P*= .03	r= -. 4 *P*= .03
Accuracy rate to hand stimuli	r= .54 *P*= .001	r= .56 *P*<.001	r= .52 *P*= .01	r= .52 *P*= .01
Reaction time to foot stimuli	r= -.41 *P*= .02	r= -.32 *P*= .043	r= -.59 *P*= .002	r= -.53 *P*= .003
Accuracy rate to foot stimuli	r= .52 *P*= .002	r= .32 *P*= .046	r= .46 *P*= .02	r= .5 *P*= .007

Abbreviations: SDMT: Symbol Digit Modalities Test, BVMT-R: Brief Visuospatial Memory Test – Revised, JLO: Judgment of Line Orientation Test.

Discussion

In this study, we investigated whether mental rotation ability in RR-MS patients was impaired, whether upper and lower extremities mental rotation was different in MS patients, whether cognitive impairment was related to mental rotation ability in MS patients and whether response accuracy rate and reaction time for different angles of rotation were similar.

The results of the current study on 35 RR MS patients are as follows: for the first time, our findings imply that MS patients responded to hand stimuli with higher response accuracy rate and less reaction time compared to foot stimuli but the same differences in response to foot stimuli were observed in healthy subjects. Correct response pattern of mental rotation in RR-MS patients was preserved, but speed and response accuracy rate of response in the patients were impaired. Response accuracy rate and reaction time correlated with visual information processing speed, visual learning, and memory ability, and visuospatial processing in MS patients.

In the current study, hand, and foot mental rotation were chosen because the change of stimuli orientation easily affects the difficulty of mentally stimulated movement. Previous studies showed that aging (28), depression (18) and fatigue (29) can interfere with the mental rotation performance. To control for potential confounders such as depression, fatigue and age in the present study, patients with FSS>4, BDI-II>21 and age>40 were excluded.

Our findings revealed that MS patients and healthy subjects responded more easily to hand stimuli than foot stimuli because hand stimuli were more familiar than foot stimuli for subjects and mental spatial transformation of hand stimuli was easier than foot stimuli. Higher reaction time for foot stimuli is mainly due to higher reaction time for palm views which may be explained by subjects' less experience with foot palms than foot backs (No separate data was reported for palm views).

We showed that reaction time and response accuracy rate for hand stimuli in MS patients altered compared to healthy subjects. For foot stimuli, reaction time increased significantly while response accuracy rate remained the same compared to healthy subjects. Even though response accuracy rate remained the same in both groups, reaction time was much longer for MS patients.

Similar to our findings, Heremans *et al*., (17) showed that response accuracy rate in HMR task in MS patients was lower than healthy subjects and Tabrizi *et al*., (18) showed that speed and response accuracy rate for hand stimuli in MS patients decreased compared to healthy subjects.

Previous studies revealed that motor imagery was involved in movement planning (30) and planning deficit in patients with hemiparetic cerebral palsy was caused by motor imagery impairment (31). Therefore, motor imagery deficit in MS patients may cause motor planning impairment, and future studies are required to explore the association between motor imagery deficits and motor planning impairment in MS patients.

Our findings related to response pattern showed that increase in the orientation of upright hand and foot stimuli caused difficulty in judgment for both groups and, as a result, reaction time increased, and response accuracy rate decreased. The response pattern used by healthy subjects and MS patients suggests that both groups used the correct strategy. Namely, the subjects mentally rotated their own hands and feet to match the depicted stimuli. Our findings were consistent with a previous study that showed reaction time increased in the hand postures which are difficult to real movements (8). Also, consistent with our results, previous studies showed that with increasing angle of rotation of the upright picture, reaction time for stimuli increased in healthy individuals and MS patients (9,32,33).

Previous studies showed that motor imagery is linked to cognitive functions (e.g. language and memory) (4), and visuospatial domain of working memory (34). Since there was declined information processing speed (35) and working memory in MS patients (36,37), we can assume that decrease in information processing speed and working memory accounts for mental rotation deficits. our study showed that reaction time and response accuracy rate of mental rotation task correlated with visual information processing speed, working memory, spatial learning and memory ability, and visuospatial processing in MS patients. These correlations indicate that several aspects of cognitive function may be involved in mental rotation performance which is a complex cognitive motor task. These results support the results of previous studies which demonstrated executing HMR task in MS patients was influenced by learning, verbal and visuospatial working memory, visual and auditory information processing speed (17,33). In general, our results indicated that mental rotation performance as implicit motor imagery task in MS patients was related to their cognitive function. These findings can be considered in motor imagery-based MS patients' neurorehabilitation.

There were some limitations. We excluded MS patients with severe cognitive and motor impairment from the study. Therefore, further studies should be conducted to determine the relationship between various aspects of mental rotation ability and cognitive function in more disabled MS patients. Reaction time for hand and foot stimuli was restricted to 4500 ms. Functional MRI is recommended for future studies in order to investigate brain areas activated in mental rotation task in MS patients.

In summary, the current study showed that there was a significant difference between the upper and lower limbs mental rotation ability in MS patients which is similar to the difference in healthy subjects. Mental rotation in MS patients was impaired compared to healthy subjects and correlated with visual processing speed and working memory, spatial learning and memory ability and visuospatial processing.

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