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Gender Difference in Explicit and Implicit Motor Imagery Ability in Multiple Sclerosis Patients

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Abstract

Background: Gender differences, in favor of males, exist in motor skills and motor imagery (MI) ability in healthy people. The MI ability in multiple sclerosis (MS) patients was altered; however, the reduction rate in the two genders has not been compared. Knowing the gender difference in MI may be used in rehabilitation programs based on MI.

Objectives: Therefore, the present study aimed to investigate whether gender difference in MI is evident in MS patients.

Methods: Forty-nine relapse-remitting MS patients (23 men) and also 51 healthy subjects (21 men) participated in this case-control study. The MI ability can be measured by Kinesthetic and Visual Imagery Questionnaire-20 (KVIQ-20), mental chronometry based on Box and Block test, and hand mental rotation task.

Results: Healthy men performed most MI tasks better than healthy women. Unlike healthy participants, no gender differences were observed in the KVIQ-20 scale (P=0.904), mental chronometry duration (right hand, P=0.199; left hand, P=0.374) and reaction time of hand mental rotation (right-hand stimuli, P=0.057; left-hand stimuli, P=0.059). However, MS men responded to hand stimuli significantly more accurately than MS women (right-hand stimuli, P=0.007; left-hand stimuli, P=0.027).

Conclusion: Our findings showed that MS men exhibit MI abilities similar to MS women. Perhaps motor deficit in MS males was influenced more by neurocognitive impairment. Perhaps in MS men as compared to MS women, MI practice as motor rehabilitation, could better improve their physical performance.

Keywords: Gender difference, Hand mental rotation, KVIQ-20, Mental chronometry, Motor imagery, Multiple sclerosis

1. Background

Motor imagery (MI) can be defined as a dynamic state in which a subject mentally simulates a determined action (1) or as the mental rehearsal of a motor act in the absence of obvious motor output (2). The MI is related to a subliminal activation of the motor system that is not only involved in producing movements but also in imagining actions, learning by observation, recognizing tools, and also in understanding other peoples' behavior (1). Several findings indicate that MI is related to the same neural mechanisms which are involved in programming and preparing actual actions (1). Furthermore, MI has two aspects: explicit and implicit representation of action (3). Consciously imagining an action, such as imagining yourself running or raising your hand, is known as explicit MI (3). Unlike explicit MI, individuals do not have knowledge of using MI during mental rotation tasks, so it is recognized as implicit MI (3, 4).

Earlier studies have focused on the comparison of the MI ability in men and women, but no clear results have been achieved. Some studies showed that either gender is more capable in one type of mental rotation task (5). Other studies revealed that in some aspects of MI, there is no significant difference between the two genders (6). However, it has been stated that women need more cognitive effort for the MI ability than men (7).

Studies on multiple sclerosis (MS) suggest that the MI ability in this disease was altered (8, 9). The MS patients showed lower reaction speed and accuracy rate in hand mental rotation task than healthy subjects (8, 9). It has recently been shown that male MS patients performed cognitive function more poorly than female patients did. The male gender can be considered a risk factor for cognitive impairment (10).

2. Objectives

So far, the difference between implicit and explicit MI ability between the two genders in MS patients has not been investigated; therefore, in the present study, we aimed to examine whether gender differences in explicit and implicit MI ability in MS patients exhibit. The results of this study

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may be useful in rehabilitation programs based on MI.

3. Methods

3.1. Study design and participants

In this case-control study, the sample size was determined based on a standard deviation of group 1 (547.8) and group 2 (572.3) (11), the effect size of 310, a test power of 80%, a confidence interval of 95%, and therefore the sample size of 52 participants in each group was calculated. The participants were selected through convenience sampling among patients referring to neurology clinics or MS society in Rafsanjan, Iran, in 2020. The selected participants were between the ages of 20 and 50 years old. Individuals who entered the study met the following criteria: having a definite diagnosis of the MS disease, belonging to the subgroup of relapsing-remitting MS, having a stable condition of the disease in the last three months, being right-handed, and having the Expanded Disability Status Scale (EDSS) score range between 0.5 and 3.5.

In addition, healthy subjects who matched the group of patients in terms of age, gender, and education were entered into this study through a public call. These people were not suffering from any neurological disease and did not have routine use of medicine or supplements in the last three months. They also did not participate in mental exercises.

3.2. Data collection

3.2.1. Explicit motor imagery

To evaluate the explicit MI ability in participants, KVIQ-20 was used. The reliability and validity of this questionnaire were approved in 2013 for MS patients (12). This questionnaire assesses the ability to distinguish the clarity of the image and the intensity of the sensations of imagined motions on a five-point ordinal scale. The questionnaire included visual imagery scale and an MI scale. The KVIQ-20 has 20 items (10 moves per stage). From the KVIQ-20 questionnaire, the total score, visual subscale, and kinesthetic subscale by percentage were obtained. For more information, refer to the study performed by Tabrizi et al. (12).

3.2.2. Mental chronometry

To determine the explicit MI, participants performed mental chronometry based on Box and Block Test (BBT). The mental chronometry was calculated from the difference between the physical execution and MI duration. By recording the MI duration of the BBT as well as its execution duration and calculating the absolute value of the difference between these two variables in each hand, two variables of mental chronometry in minutes were obtained. For more information, refer to the study conducted by Rezaian et al. (13).

3.3.3. Implicit motor imagery

By performing hand mental rotation tasks, implicit MI was evaluated in participants. Initially, using the PSYTASK software, a hand mental rotation task was designed. The task was shown on the computer screen, and the participants were asked to determine which side of the hand was being shown by pressing the right or left arrow keys. For example, the image of the back of the right hand and the palm of the left hand at an angle of 180 degrees is shown in Figure 1. The reaction time was recorded in milliseconds (the time between the appearance of the stimulus and the response of the participants in the task that he/she responded correctly to), and the percentage of correct responses indicated the response accuracy rate. The hand mental rotation test obtained four variables: the reaction time to the right and left-hand stimuli and the response accuracy rate to the right-and left-hand stimuli. For more information, refer to the study carry out by Rezaeinasab et al. (14).

3.3.4. Ethical considerations

This study was confirmed by the Ethics Committee of Rafsanjan University of Medical Sciences (permit number: IR.RUMS.REC.1397.237) and is pursuant to the tenets of the Helsinki Declaration. All Participants signed the informed consent to participate in the study.

3.3.5. Statistical analysis

Data between the two groups were compared using an independent sample t-test. All statistical assessments were two-tailed, and a P < 0.05 was considered statistically significant. The collected data was analyzed in SPSS statistical software (version 21, Chicago, IL, USA).

4. Results

Forty-nine MS patients and 51 healthy individuals who matched the patient group criteria in terms of gender, age, and level of education participated in this study. Three of the MS patients and one of the healthy subjects withdrew from the study. Some MS patients did not complete several tasks; therefore, in the statistical analysis, the number of patients was 46 to 49.

The results of the comparison between the two MS patients and healthy participant groups was presented in Table 1. The speed of response to rightand left-hand stimuli (reaction time) in healthy individuals was significantly faster than MS patients. However, the response accuracy rate to right- and left-hand stimuli was not significantly different between the two groups. The absolute value of the difference of execution and MI duration between the two groups was statistically significant. The most minor difference between the MI and execution duration indicates normal mental chronometry. In

the group of healthy individuals, the difference



The palm of the left hand at 180 °



The back of the right hand at 180 °

Figure 1. An example of hand images used in the PSYTASK software

Table 1. Comparison of MI variables in two groups of healthy and MS groups

Variable	MS group (n=47)	Healthy group (n=51)	P-value*
Reaction time of HMRT to right-hand stimuli (ms)	1993.92 ± 513.91	1711.16 ± 358.73	0.002
Reaction time of HMRT to left-hand stimuli (ms)	2029.15 ± 501.68	1746.53±347.36	0.002
Response accuracy rate of HMRT to right-hand stimuli (%)	77.36 ± 25.59	77.44 ± 18.06	0.676
Response accuracy rate of HMRT to left-hand stimuli (%)	74.31 ± 18.91	75.97± 16.88	0.644
Absolute difference of execution and motor imagery duration related to right hand in mental chronometry task (min)	5.70 ± 3.83	1.74 ± 1.56	< 0.001
Absolute difference of execution and motor imagery duration related to left hand in mental chronometry task (min)	5.91 ± 4.22	1.65 ± 1.48	< 0.001
KVIQ-20 score (%)	63.93 ± 13.03	73.91 ± 12.13	< 0.001
Visual subscale of KVIQ-20 (%)	32.47 ± 6.28	37.58 ± 6.17	< 0.001
Kinesthetic subscale of KVIQ-20 (%)	31.45 ± 7.10	36.32±7.03	0.001
* To device device an only to test			

* Independent sample t-test

Abbreviations: MI: motor imagery, MS: multiple sclerosis, HMRT: hand mental rotation task, KVIQ-20: Kinesthetic and Visual Imagery Questionnaire-20, ms: millisecond, min: minutes

between the two variables of MI and execution was less than MS patients. The KVIQ-20 score, visual subscale of KVIQ-20, and kinesthetic subscale of KVIQ-20, were significantly higher in healthy participants than MS patients.

The comparison of two groups of healthy participants and MS patients by gender is shown in Table 2. The MI ability of healthy men was statistically better than that of the MS men in all variables, except the variable of accuracy rate to hand stimuli. Comparing the MI ability of MS women with healthy women showed a significant difference in the variables of mental chronometry and reaction time to hand stimuli between the two groups. In the healthy participants group, men performed all the tasks better than women (Table 2). This means that there was less reaction time, more response accuracy rate, less difference between MI and execution duration, and higher KVIQ-20 score in healthy men than healthy women, most of which were statistically significant. The results in the healthy group indicated the superiority of men in the MI ability.

In the group of MS patients, the MI ability of men showed no statistically significant difference from women except for the response accuracy rate (Table 2). The results of comparing MS men and women in terms of the MI ability showed reduced superiority of the MS men regarding this ability. In the MS patients group, men performed the hand mental rotation task better than women and had less reaction time and a higher response accuracy rate. Of course, only the difference in the response accuracy rate was statistically significant. Although in the male patients, the difference between MI and execution was less than in women, there was no significant difference between women and men in terms of this variable. The KVIQ score in MS women was better than in MS men, although the difference was not significant.

 Table 2. Comparison of MI variables in healthy and MS participants by gender

Variable	Groups							
		Healthy			MS			<i>P</i> -value*
	Gender	N	Mean ± SD	P-value* Within group	N	Mean ± SD	P-value* Within group	Between groups
Reaction time of HMRT to right-hand stimuli(ms)	Female	30	1873.05± 285.53	<0.001	24	2133.03 ± 509.55	0.057	0.021
	Male	21	1479.87± 328.67		23	1848.76± 487.48		0.006

Table 2. Comparison of MI variables in healthy and MS participants by gender

	Groups							
Variable		Healthy			MS			<i>P</i> -value*
	Gender	N	Mean ± SD	<i>P</i> -value* Within group	N	Mean ± SD	<i>P</i> -value* Within group	Between groups
Reaction time of HMRT to left-hand stimuli(ms)	Female	30	1890.10 ± 293.57	<0.001	24	2165.47 ± 510.80	0.059	0.025
	Male	21	1541.42± 318.72		24	1892.82± 463.26		0.006
Response accuracy rate of HMRT to right-hand stimuli (%)	Female	30	69.99 ± 19.35		24	71.29 ± 18.20	0.007	1.00
	Male	21	88/08 ± 8.38	<0.001	25	86.92 ± 25.09		0.394
Response accuracy rate of HMRT to left-hand stimuli (%)	Female	30	68.69 ± 17.98	<0.001	24	68.27 ± 20.75	0.027	0.937
	Male	21	86.36± 7.13		25	80.10± 15.20		0.075
Absolute difference of	Female	30	2.01 ± 1.53		24	6.42 ± 4.24		< 0.001
execution and motor imagery duration related to the right hand in mental chronometry task(min)	Male	21	1.34 ± 1.55	0.130	25	5.00 ± 3.33	0.199	<0.001
Absolute difference of	Female	30	2.07 ± 1.61		24	6.64 ± 4.75		< 0.001
execution and motor imagery duration related to the left hand in mental chronometry task(min)	Male	21	1.05 ± 1.04	0.014	25	5.37 ± 3.66	0.374	<0.001
KVIQ-20 score(%)	Female Male	30 21	70.66 ± 12.42 78.54 ± 10.29	0.021	22 24	64.18 ± 14.58 63.70 ± 11.75	0.904	0.090 <0.001
Visual subscale of KVIQ- 20(%)	Female Male	30 21	35.86 ± 6.50 40.04 ± 4.82	0.016	22 24	32.95 ± 6.87 32.04 ± 5.81	0.628	0.130 <0.001
Kinesthetic subscale of KVIQ-20(%)	Female Male	30 21	34.80 ± 6.92 38.50± 6.75	0.064	22 24	31.22 ± 8.08 31.66± 6.24	0.837	0.093 0.001

* Independent sample t-test

Abbreviations: MI: motor imagery, MS: multiple sclerosis, HMRT: hand mental rotation task, KVIQ-20: Kinesthetic and Visual Imagery Questionnaire-20, ms: millisecond, min: minutes

5. Discussion

The present research has shown that healthy subjects have a stronger implicit and explicit MI ability than MS patients. In the comparison between the two genders, the results of the present study indicated that the MI ability is superior in healthy men compared to healthy women; however, MI ability in MS men is similar to that of MS women. In addition, the results of the comparison of the two groups in terms of gender indicated a greater decrease in the dimensions of the MI ability of MS men compared to healthy men. Although there was a decrease in MS women compared to healthy women, this reduction was not in all dimensions of MI ability. We hope that the results of our research about the difference in the MI ability in males and females will be employed in the rehabilitation of patients.

There are conflicting results regarding gender differences in cognitive and mental functions. The obtained results indicated that men were significantly faster than women at judging hand laterality for the palm hand, while females were much faster at judging hand laterality for the backhand (5). Another study showed that although there was no significant difference in the correct response rate between men and women in the mental

rotation task, in terms of the reaction time to the left hand, women were slower than men (6). The results of the study indicated that women and men have similar performance levels for abstract figure rotation task; however, women make more cognitive efforts to reach the same level as men. For the body mental rotation task, with comparable cognitive efforts, women were faster than men (7). The results of a study have shown that gender impacts the timing of MI without any effect on mental vividness. The score of the vividness of movement imagery questionnaires was similar between men and women; however, women showed better results in the timing of MI performance (15). In addition, a study has determined that men had better imagery capacity than women and better kinesthetic mode of imagery (16). Alfredo Campos observed healthy men have a higher score on the performance tests of mental imagery than women. There were no significant gender differences in the imagery questionnaires (17).

The question arises as to what factors cause differences in the cognitive function of men and women in the present study and previous studies. A previous study has shown a structural and functional difference in the brain of males and females (18). In addition to the structural differences of the brain in different genders, several functional differences also exist. Overall, it can be stated that women are better than men in episodic memory and verbal memory, while men are typically better than women in spatial tasks and route-navigating (19). Studies indicated that males and females use different strategies while doing similar cognitive tasks (20). Speck et al. demonstrated gender differences in the pattern of brain activation associated with working memory Furthermore, illustrated gender tasks they in problem-solving strategies differences or differences in the underlying neural substrate (21).

Similar to our results about MS patients, a new study found that some cognitive functions in MS men, such as information processing speed and verbal memory, are more prone to impairment than women, and the male gender can be considered as a risk factor for cognitive impairment (10). In a mini-review study about gender differences in MS patients in terms of all MS subtypes, males were revealed to be the indicator of more severe disease and disability (22). Cognitive impartment was a specific disability that appears to be worse in male patients than in females. Additionally, cognitive domains in men were affected more than in women (23) for reasons including the presence of the ϵ 4 allele of the APOE gene (genotype different) (24) and the loss of volume in several deep gray matter structures (24).

Although the present study provided novel data on the difference between implicit and explicit MI ability in MS men and women with similar functional disability, it has limitations, such as the lack of the inclusion of other types of MS in the study and lack of examination of MS patients with EDSS > 3.5.

6. Conclusion

In the present research, we found that in healthy men, the MI ability was stronger than in healthy women; however, in male MS patients, this ability was equal to female MS patients. Therefore, it can be suggested that perhaps the motor deficit in men with MS was influenced more by neurocognitive impairment compared with women with MS. Perhaps it can be said that in men with MS, the MI technique of mental practice could better improve their physical performance.

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Footnotes

Conflicts of Interest: The authors declare that they have no competing interests.

Authors' contributions: M.A., H.A., and E.S. devised the project, the main conceptual ideas, and the proof outline.P.A., F.A., and H.A. performed the experiments.Z.A. performed the analysis and interpreted the results.E.S. and M.A. drafted the manuscript.All authors reviewed and commented on the manuscript.

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Ethics approval and consent to participate: This study was confirmed by the Ethics Committee of Rafsanjan University of Medical Sciences (permit number: IR.RUMS.REC.1397.237) and is pursuant to the tenets of the Helsinki declaration. All Participants signed the informed consent to participate in the study.

References

- O'Shea H. Mapping relational links between motor imagery, action observation, action-related language, and action execution. *Front Hum Neurosci.* 2022;16:984053. doi: 10.3389/fnhum.2022.984053. [PubMed: 36466617].
- Ladda AM, Lebon F, Lotze M. Using motor imagery practice for improving motor performance-a review. *Brain Cogn.* 2021;**150**:105705. doi: 10.1016/j.bandc.2021.105705. [PubMed: 33652364].
- Gelding RW. Auditory-sensorimotor brain function during mental imagery of musical pitch and rhythm. [Thesis PhD]. Macquarie University; 2022.
- Osuagwu BA, Zych M, Vuckovic A. Is implicit motor imagery a reliable strategy for a brain-computer interface?. *IEEE Trans Neural Syst Rehabil Eng.* 2017;25(12):223948. doi: 10.1109/TNSRE.2017.2712707. [PubMed: 28682260].
- Conson M, De Bellis F, Baiano C, Zappullo I, Raimo G, Finelli C, et al. Sex differences in implicit motor imagery: Evidence from the hand laterality task. *Acta Psychol (Amst)*. 2020;203:103010. doi: 10.1016/j.actpsy.2020.103010. [PubMed: 31981826].
- Mochizuki H, Takeda K, Sato Y, Nagashima I, Harada Y, Shimoda N. Response time differences between men and women during hand mental rotation. 2019;14(7):e0220414. doi: 10.1371/journal.pone.0220414. [PubMed: 31348807].
- Campbell MJ, Toth AJ, Brady N. Illuminating sex differences in mental rotation using pupillometry. *Biol Psychol.* 2018;**138**:19-26. doi: 10.1016/j.biopsycho.2018.08.003. [PubMed: 30086332].
- Azin M, Zangiabadi N, Tabrizi YM, Iranmanesh F, Baneshi MR. Deficiency in mental rotation of upper and lower-limbs in patients with multiple sclerosis and its relation with cognitive functions. *Acta Med Iran*. 2016;**54**(8):510-7. [PubMed: 27701721].
- Tabrizi YM, Mazhari S, Nazari MA, Zangiabadi N, Sheibani V, Azarang S. Compromised motor imagery ability in individuals with multiple sclerosis and mild physical disability: an ERP study. *Clin Neurol Neurosurg.* 2013;115(9):1738-44. doi: 10.1016/j.clineuro.2013.04.002. [PubMed: 23639730].
- T Uher, M Vaneckova, J Krasensky, JB Dusankova, E Havrdova, D Horakova. Sex differences in cognitive performance in Multiple Sclerosis (4243). *Neurology*. 2020;94(15).
- Azin M, Zangiabadi N, Iranmanesh F, Baneshi MR, Banihashem S. Effects of intermittent theta burst stimulation on manual dexterity and motor imagery in patients with multiple sclerosis: a quasi-experimental controlled study. *Iran Red Crescent Med J.* 2016;**18**(10):e27056. doi: 10.5812/ircmj.27056. [PubMed: 28180015].
- Tabrizi YM, Zangiabadi N, Mazhari S, Zolala F. The reliability and validity study of the Kinesthetic and Visual Imagery Questionnaire in individuals with multiple sclerosis. *Braz J*

Phys Ther. 2013;**17**(6):588-92. doi: 10.1590/S1413-35552012005000124. [PubMed: 24271091].

- Rezaeian M, Assadollahi Z, Azin H, Kaeidi A, Azin M. Assessment of reliability and validity of the mental chronometry task based on the box and block test in multiple sclerosis patients. *IRCMJ*. 2021;23(3). doi: 10.32592/ircmj.2021.23.3.274.
- 14. Rezaeinasab M, Estahbanati MF, Chermahini SA, Shamsizadeh A, Assadollahi Z, Hasanshahi A, et al. Effect of tactile stimulation on hand mental rotation among young healthy adults: A randomized controlled trial. *Arch Neurosci.* 2020;7(2):e99078. doi: 10.5812/ans.99078.
- Subirats L, Allali G, Briansoulet M, Salle JY, Perrochon A. Age and gender differences in motor imagery. *J Neurol Sci.* 2018;**391**:114-7. doi: 10.1016/j.jns.2018.06.015. [PubMed: 30103958].
- Mendes P, Marinho D, Petrica J. Comparison between genders in imagery ability in Portuguese basketball practitioners. *JPES*. 2015;15(3):391-5. doi: 10.7752/jpes.2015.03058.
- 17. Campos A. Gender differences in imagery. *Pers Individ Differ*. 2014;**59**:107-11. doi: 10.1016/j.paid.2013.12.010.
- Ingalhalikar M, Smith A, Parker D, Satterthwaite TD, Elliott MA, Ruparel K, et al. Sex differences in the structural connectome of the human brain. *Proc Natl Acad Sci U S A*. 2014;**111**(2):823-8. doi: 10.1073/pnas.1316909110. [PubMed: 24297904].

- Asperholm M, Högman N, Rafi J, Herlitz A. What did you do yesterday? A meta-analysis of sex differences in episodic memory. *Psychol Bull.* 2019;**145**(8):785-821. doi: 10.1037/bul0000197. [PubMed: 31180695].
- Wang L, Carr M. Working memory and strategy use contribute to gender differences in spatial ability. *EdPsychJournal*. 2014;**49**(4):261-82. doi: 10.1080/00461520.2014.960568.
- Speck O, Ernst T, Braun J, Koch C, Miller E, Chang L. Gender differences in the functional organization of the brain for working memory. *Neuroreport.* 2000;**11**(11):2581-5. doi: 10.1097/00001756-200008030-00046. [PubMed: 10943726].
- Golden LC, Voskuhl R. The importance of studying sex differences in disease: The example of multiple sclerosis. J Neurosci Res. 2017;95(1-2):633-43. doi: 10.1002/jnr.23955. [PubMed: 27870415].
- Schoonheim MM, Popescu V, Lopes FCR, Wiebenga OT, Vrenken H, Douw L, et al. Subcortical atrophy and cognition: sex effects in multiple sclerosis. *Neurology*. 2012;**79**(17):1754-61. doi: 10.1212/WNL.0b013e3182703f46. [PubMed: 23019265].
- Savettieri G, Messina D, Andreoli V, Bonavita S, Caltagirone C, Cittadella R, et al. Gender-related effect of clinical and genetic variables on the cognitive impairment in multiple sclerosis. J Neurol. 2004;251(10):1208-14. doi: 10.1007/s00415-004-0508-y. [PubMed: 15503099].