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Fatigue influences embodiment perception and motor performance in multiple sclerosis subjects: a cross-sectional immersive virtual reality study

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Abstract

Background Multiple sclerosis (MS) represents a major cause of acquired disability in adults worldwide. Fatigue and upper limb (UL) impairments are common and disabling symptoms in people with MS (pwMS), even in the early stage of the disease. Rehabilitation proved to be effective in ameliorating Fatigue and UL function in pwMS. In particular, virtual reality (VR) represents a promising tool for delivering treatments in a highly engaging way, reproducing real-life gestures in a naturalistic manner. Immersive VR (IVR) tools can boost subjects' immersion and presence, but very scarce evidence is currently available on IVR effects in this population.

Aim This study aims to test the feasibility of an IVR system for UL training in pwMS, analyzing clinical correlations of embodiment, fatigue, and UL motor performance.

Methods We conducted a cross-sectional study involving pwMS and age- and sex-matched healthy controls. pwMS under 65 years old reporting uni- or bilateral UL impairment were enrolled; no restrictions were applied regarding sex, MS phenotype, and disease severity (EDSS scores). All subjects underwent a single session of IVR UL training (Oculus Quest 2) using a previously developed and clinically tested IVR system. PwMS were assessed through the Modified Ashworth Scale (MAS), the Nine-Hole-Peg-Test (NHPT), and the Modified Fatigue Impact Scale (MFIS). Moreover, we collected measures of hand peak velocity during task execution and responses to a standardized questionnaire related to embodiment perception, (i.e. subjects' feeling of being part of the virtual context) in terms of body ownership and motor agency, administered after the training session.

Results 25 pwMS were enrolled (Females: 56%, mean age: 53 ± 7 years) with EDSS scores ranging from 3.5 to 8 and with a mean score at the Modified Fatigue Impact Scale (MFIS) (0–84) of 35 ± 14 . None of our subjects reported symptoms of cybersickness or any other adverse effects. All patients reported very high satisfaction rates (median score = 5 on a 5-point Likert scale, interquartile range (IQR) = 4–5); they also experienced strong subjective impression of both body ownership and motor agency (median score on a 9-points rated scale: body ownership = 9 (IQR = 8–9),

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motor agency = 9 (IQR = 8–9)). The median peak velocity of all patients exhibited a significant correlation with MFIS ($\rho = -0.57, p = 0.036$). The MFIS score showed a significant correlation with embodiment and, specifically, a moderate correlation with agency ($\rho = -0.57, p = 0.036$). Notably, low and high-fatigued pwMS showed significant differences in hand peak velocity achieved ($p = 0.005$) and in embodiment perception on the motor agency domain ($p = 0.004$) and body ownership one ($p = 0.024$), which means that higher MS-related fatigue seems associated with weaker embodiment perception, particularly affecting the experienced sense of motor interaction. No statistically significant differences in satisfaction, embodiment, and peak velocity rates were found when comparing pwMS and healthy controls.

Conclusions IVR use in pwMS seems feasible and well-tolerated. Additionally, MS-related fatigue showed a significant role in determining the rate of perceived embodiment, thus conditioning UL kinematics, in pwMS exposed to an IVR session.

Keywords Immersive virtual reality, Multiple sclerosis, Rehabilitation, Embodiment, Kinematics

Background

Multiple sclerosis (MS) represents a major cause of acquired disability in adults worldwide, mostly in females, with the European area registering the highest incidence rate [1]. People affected by MS (pwMS) usually experience both motor and non-motor dysfunctions [2], with a potentially very wide range of symptoms [3].

Fatigue is a common and disabling symptom in pwMS, with an estimated prevalence rate of 36.5 to 78%. It heavily impacts on the perceived quality of life, employment status, and related economic burden [4]. The pathophysiology of MS-related fatigue is presently not fully understood. It seems to be caused by myelin damage, compromised neurotransmitter regulation, and altered cellular metabolism [4], resulting in sleep disturbances, depression, and physical deconditioning [5]. Furthermore, it is plausible that pwMS might activate compensatory strategies that involve the engagement of alternative neural networks compared to what is observed in healthy subjects, thus inducing energy-demanding mechanisms that could further exacerbate fatigue onset in pwMS [5, 6].

Upper limb (UL) impairments are common in pwMS, even in the early stage of the disease [7]. Nearly a third of pwMS shows UL uni- or bilateral dysfunctions such as muscle weakness, decreased manual dexterity, and tremors [8] that heavily impact on the subjects' psychological well-being [9], and related health-care costs [10]. Thus, UL functioning is a clinically relevant predictor for determining the risk of activity limitations and social participation level in this population type [11]. Even if evidence on UL rehabilitation strategies is lacking compared to research on lower limb interventions, rehabilitation proved to be effective in ameliorating UL function in pwMS [12, 13].

In addition to fatigue, a second important characteristic that has also been described in pwMS, is motor fatigability, which is defined as: “the magnitude or rate of change of motor performance or an objectively reference

criterion after any type of voluntary activity or exercise” [14]. Fatigue and motor fatigability are different and often unrelated concepts [15–17], both impacting on the quality of life in pwMS. Motor fatigability, specifically, influences the possibility to perform sustained therapeutic or daily activities [18]. Due to the current limited information on psychometric properties of the available clinical tools, no recommended reference standard has been identified so far to fully assess motor fatigability in pwMS [17].

Among the presently available rehabilitation interventions used for pwMS, Virtual Reality (VR) represents a promising tool to provide treatments in a highly engaging way, reproducing real-life gestures in a naturalistic manner. VR consists of computer-generated two- or three-dimensional environments where the user can perform tasks and activities with rehabilitation purposes. A key feature of VR environments is “immersion”, defined as “the overall sensation of experiencing the virtual world” [19, 20]. Based on the degree of perceived immersion VR tools can be classified into three categories: non-immersive, semi-immersive, and immersive (IVR) [21]. Notably, *higher immersion seems related to greater levels of motivation and engagement* [22]. The degree of immersion is strictly linked to the sense of embodiment, which is defined as the sensation of being inside, having, and controlling the virtual body [23]. Crucially, alterations of the sense of embodiment might lead to perceptual and behavioral modifications that influence how the user interacts with the virtual context [24].

VR, as a clinical tool, has been receiving increasing attention for the past decades, although mainly in neurological conditions other than pwMS, such as brain injuries and stroke [25, 26]. Systematic reviews found beneficial effects of VR application in the rehabilitation treatment of pwMS in terms of balance [27–29], fear of falling [27, 28], fatigue [30], MS impact [30], and quality of life [30]. Few studies have been conducted to investigate the clinical effect of VR in improving UL function

in this population, although promising results have been reported [19].

However, most of the clinical applications of VR tools in pwMS have used non immersive systems; thus, very scarce evidence is currently available on the effects of IVR on this population type.

The present study aimed to test the feasibility of an IVR system for UL training in pwMS, exploring the correlations in terms of embodiment, fatigue, and motor performance through a controlled cross-sectional design.

Methods

This interventional cross-sectional study has been performed at the Ferrara University Hospital between January and April 2023. All the related procedures were previously approved by the local Ethical Committee (Comitato Etico Area Vasta Emilia Centro, approval number EM606-2022_897/2020/Oss/AOUFe_EM2, September 14th, 2022).

Subjects

We enrolled 25 subjects aged 18–65 years, with a diagnosis of multiple sclerosis, and self-reported uni- or bilateral upper limb impairment. We excluded patients with clinical conditions that could have undermined the possibility to execute the study procedures safely, and people who could not provide informed consent due to cognitive alterations. No exclusion restrictions were applied with respect to sex, MS phenotype, or disease severity according to Extended Disability Status Scale (EDSS) classification [31].

A sex- and age-matched (± 5 years) control group was also involved, including healthy subjects with no upper limb impairments.

Experimental procedures

Written informed consent was collected from all participants prior to the experimental session.

All subjects underwent a single session of IVR upper limb training, lasting approximately 30 min. The system developed for Oculus Quest 2 (Meta, USA) was previously described and tested in stroke patients [26]. During the IVR session, participants sat in front of a table, wearing the Head-mounted device (HMD) and executing motor tasks in the virtual environment. All subjects performed 3 training blocks consisting of 4 exercises each (Glasses, Cloud, Rolling Pin, Ball in Hole as described in our previous work [26]) with 15 repetitions for every task, resulting in a total of 180 trials, 90 for each side, randomly distributed between right and left arm.

Outcomes measured (before session)

At the beginning of the experimental session, demographic and clinical data were obtained from

participating patients. The following information was recorded: age, sex, hand dominance, disability score according to EDSS classification [31], MS type (relapsing-remitting, primary or secondary progressive), more affected body side (if present), comorbidities (if present).

The Modified version of the Ashworth Scale (MAS) was applied to quantify pathological alterations of the upper limb muscle tone [32], and the Nine-Hole-Peg-Test (NHPT) for analyzing manual dexterity [33]. We collected information on perceived MS-related Fatigue through the Modified Fatigue Impact Scale (MFIS), a validated clinical questionnaire aimed to detect subjective trait fatigue, exploring mental and physical components, total score ranges from 0 to 84 where higher scores are related to more severe symptom intensity. In agreement with published literature, we used a cut-off value of 38 to sort subjects into two classes: fatigued and non-fatigued [34].

Outcomes measured (during session)

The Oculus Quest 2 provides a real-time estimate of subject's hands kinematics [35]. These measures are used, during task performance, to allow interactions with virtual objects. They were also stored and offline analyzed by an assessor blinded to participants' allocation. The estimates of hand kinematics provided by the Oculus Quest 2 are obtained by exploiting stereoscopic depth information from the different cameras and proprietary computer vision routines. The specific details of this process are patented and, thus, not publicly available.

In a previous study, we compared the estimates of peak hand velocity during task performance, a clinically relevant UL kinematic measure, provided by the Quest 2 to their ground-truth values simultaneously measured by means of a commercial high-precision marker-based system [36]. This comparison showed that Oculus' estimates of peak hand velocity are in very close agreement with their ground-truth values with their regression line having a slope close to 1. This result was confirmed and further expanded in a subsequent study in a healthy participant [35].

Outcomes measured (after session)

At the end of the experimental session, the degree of satisfaction and embodiment perceived by the subjects were assessed by means of questionnaires. An ad-hoc developed questionnaire was used for satisfaction [26] (see Supplementary Material for related questions and obtained results), and a subset of the questionnaire proposed by Gonzalez-Franco and Peck, comprising body ownership and motor agency items [37], was used for embodiment. As in our previous study involving stroke patients [26], the indices of body ownership and agency were computed as follows:

Body Ownership: $(Q1 - Q2) - Q3$.

Motor Agency : $Q4 + Q5 - Q6$.

Data analysis

The normality of distributions was assessed using Shapiro–Wilks tests, while the relationship between numerical and ordinal variables was assessed using the Spearman's rank correlation coefficient. To account for multiple testing, p-values were adjusted using the Benjamini–Hochberg false discovery rate (FDR) procedure. MS descriptive and clinical characteristics were compared between high and low subjective fatigue groups using Wilcoxon rank sum test for numerical variables and the chi-squared test for categorical variables. Correlation coefficients were interpreted following a conventional approach: $\rho < 0.4$ was considered weak, moderate when ρ was between 0.4 and 0.7, and strong when $\rho > 0.7$ [38]. Effect size for group comparison was calculated using the Rosenthal formula [39] and interpreted following the Cohen convention [40] where $r \approx 0.10$ is considered a small effect, $r \approx 0.30$ is considered a moderate effect, and $r \approx 0.50$ a large one.

Two-way mixed ANOVA was used to examine the effect of *MFIS class, training block, and their interaction on mean peak velocity*. The between-subjects factor was MFIS level, and the within-subjects factor was training. All model assumptions were met: normal distribution was checked using qqplot, homogeneity of variance was checked using Levene's test, and homogeneity of covariance was checked using Box's test.

The magnitude effect of each factor in the two-way mixed ANOVA was interpreted using Cohen's guideline for eta-squared (η^2) [40]: it was considered weak when $\eta^2 < 0.06$, moderate with η^2 between 0.06 and 0.14, and strong when $\eta^2 > 0.14$.

All statistical analyses were performed using R (version 4.2.2), and the significance level was set at the $p < 0.05$ level.

Results

Our sample consisted of 25 patients (58% female, mean age 53 ± 7 years) with EDSS scores ranging from 3.5 to 8 and a mean subjective trait fatigue score on the Modified Fatigue Impact Scale of 35 ± 14 (Table 1).

Feasibility (satisfaction, adverse events)

The median level of patients' satisfaction, as indicated by their responses to the question "Did you enjoy this type of training?" on a 5-point Likert scale, was 5 (IQR = 4–5). A similar pattern was observed for enjoyment, whose median rate was also 5 (IQR = 5–5), assessed by the question "How much fun did you have?". No subject reported cybersickness symptoms or other adverse effects. The satisfaction questionnaire, together with plots of the responses, can be found in the supplementary material (Figure S1).

Embodiment

Our immersive VR system induced strong subjective feelings of both body ownership and motor agency as shown by results in Fig. 1 (body ownership: median = 9, IQR = 8–9; agency: median = 9, IQR = 8–9). Both indices were computed on a scale ranging from –9 to 9. No statistically significant correlations were found between satisfaction and either motor agency ($\rho = 0.17$, $p = 0.532$; Spearman's rho) or body ownership ($\rho = 0.11$, $p = 0.570$; Spearman's rho).

Clinical and instrumental measures (MFIS-peak velocity-NHPT)

No statistically significant difference was observed between the median peak velocity of less and more impaired hand in pwMS (t-test, $p = 0.990$) during task performance. That is, we found no clinically relevant differences in hand kinematics between the two body sides.

The median peak velocity of all patients exhibited a moderate significant correlation with MFIS ($\rho = -0.57$, $p = 0.036$). This suggests that higher levels of subjective trait fatigue are related to reduced peak velocity, as illustrated in Fig. 2. In particular, the physical MFIS subscale exhibited a significant correlation with median peak velocity ($\rho = -0.53$, $p = 0.04$), while the cognitive subscale did not reach significance ($\rho = -0.45$, $p = 0.084$). No statistically significant correlation was observed between median peak velocity and either motor agency ($\rho = -0.45$, $p = 0.084$) or body ownership ($\rho = -0.11$, $p = 0.650$).

The MFIS showed a moderate correlation with motor agency ($\rho = -0.57$, $p = 0.036$) and a non-statistically significant correlation with body ownership ($\rho = -0.40$, $p = 0.084$). This suggests that higher levels of subjective trait fatigue are associated with a lower subjective feeling of motor agency but a relatively normal feeling of ownership of a virtual body.

Table 1 Demographic characteristics of study participants

	pwMS (n = 25)
Age	53 ± 7
Sex (F)	14 (56%)
EDSS 3–4, 5	10 (40%)
EDSS 5–6, 5	13 (52%)
EDSS 7–8, 5	2 (8%)
MFIS	35.3 ± 14.4
Years since diagnosis	15.6 ± 11.0
More affected limb (R)	13 (52%)
Dominance (R)	22 (88%)

Mean ± Standard Deviation; frequency (%)

MFIS Modified Fatigue Impact Scale, F female, R right

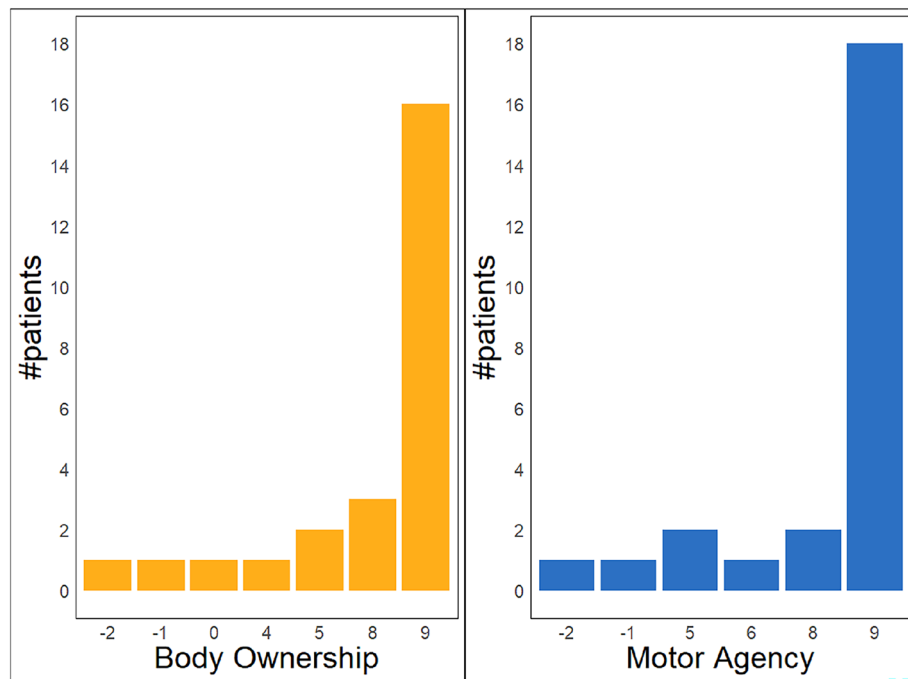


Fig. 1 Distribution of the patients' scores for body ownership and agency. Patients' perceptions for body ownership and motor agency experienced as assessed by a standardized questionnaire (see "Methods" section for further details). Both indices can be in the range [-9; +9] and each bar represents the number of patients who obtained the score indicated on the horizontal axis. For both indices, As can be seen, most patients gave the highest scores for both body ownership (16) and motor agency (18)

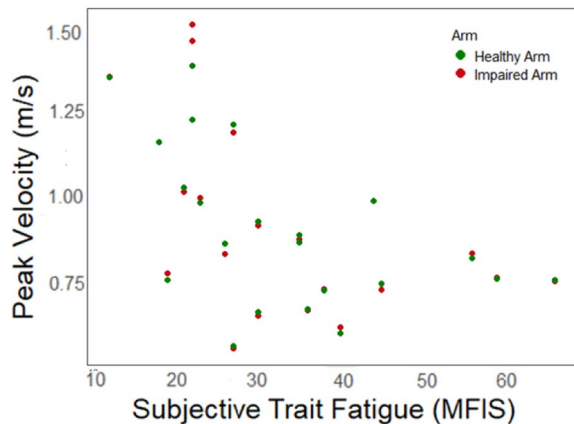


Fig. 2 Relationship between patients' subjective trait fatigue and median peak velocity of the two arms. The correlation between MFIS score and peak velocity achieved was moderate ($\rho = -0.057, p = 0.036$), indicating that more severe subjective trait fatigue was significantly associated with lower hand peak velocity

Considering the relationship between median peak velocity and the NHPT, no statistically significant correlations were found both on the left ($\rho = -0.42, p = 0.084$), and on the right hand ($\rho = -0.19, p = 0.532$).

There were no differences in demographics between pwMS characterized by high and low levels of subjective trait fatigue, as shown in Table 2. The high subjective trait fatigue group ($MFIS \geq 38$) consisted of 10 patients with a mean subjective trait fatigue score on the

Table 2 Descriptive characteristics of PwMS divided by modified fatigue impact scale classes

	F_pwMS (n=10)	NF_pwMS (n=15)	P value
Age	52.4 ± 7.6	53.3 ± 5.9	0.889
Sex (F)	5 (50%)	9 (60%)	0.935
EDSS	5.2 ± 1.3	5.2 ± 1.1	0.461
MFIS	50 ± 9.0	25.5 ± 6.9	< 0.001
Years since diagnosis	14.8 ± 11.1	16.1 ± 11.3	0.846
More affected limb (R)	5 (50%)	8 (53%)	1
Dominance (R)	9 (90%)	13 (87%)	1

Mean ± SD; frequency (%)

MFIS modified fatigue impact scale, F_pwMS fatigued_pwMS, NF_pwMS non-fatigued_pwMS, F females, R right

MFIS of 50 ± 9.02 . The low subjective trait fatigue group ($MFIS < 38$) consisted of 15 patients with a mean MFIS of 25.5 ± 6.9 .

The intensity of subjective trait fatigue does not appear to be relevant in terms of satisfaction ($p = 0.125$) and enjoyment ($p = 0.164$) experienced, as reported in Table 3.

Notably, while subjective trait fatigue did not affect the patients' satisfaction, it however affected embodiment. Specifically, the perceived embodiment in the virtual avatar during task performance in VR was statistically different between the high- and low-fatigued groups both for body ownership ($p = 0.024$ and for motor agency ($p = 0.004$).

Table 3 Differences in satisfaction and embodiment in pwMS with high and low level of subjective trait fatigue

	F_pwMS (n = 10)	NF_pwMS (n = 15)	P value	Effect size (r)
Satisfaction(1st question)	4.5 (IQR = 3.25–5.25)	5 (IQR = 4.5–5.5)	0.125	
Satisfaction(13th question)	5 (IQR = 4.25–5.25)	5 (IQR = 5–5)	0.164	
Agency	8 (IQR = 5–9)	9 (IQR = 9–9)	0.004	0.57
Body Ownership	6.50 (IQR = 1.25–9.25)	9 (IQR = 9–9)	0.024	0.44

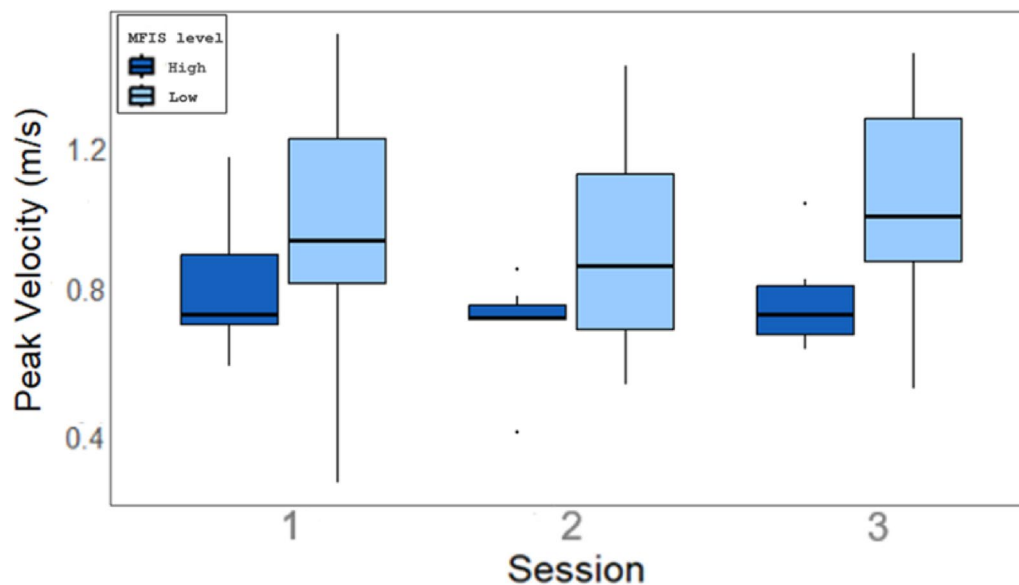
Median (IQR = Interquartile Range)

MFIS Modified Fatigue Impact Scale

Table 4 Analysis of variance on MFIS, training blocks, and related interaction on median peak velocity

	MFIS level effect			Training block effect			Interaction (MFIS level x training block)		
	F	P value	η^2	F	P value	η^2	F	P value	η^2
Peak velocity	8.617	0.005	0.09	0.379	0.686	< 0.01	0.107	0.898	< 0.01

MFIS Modified Fatigue Impact Scale

**Fig. 3** Distribution of hand peak velocity across the three training blocks in high and low-fatigued pwM. Peak velocity was significantly different between high and low-fatigued groups ($p = 0.005$), with no relevant changes during session ($p = 0.686$)

To understand whether the subjective fatigue level had an interaction with a decline in peak velocity over the 30-minute session, we run a mixed ANOVA model. Specifically, we examined the effect of MFIS level and training block and their interaction on the median peak velocity. As illustrated in Table 4; Fig. 3, no interaction was found (MFIS level*training block $p = 0.898$). This means that changes in mean peak velocity across experimental blocks were not significantly different between high and low fatigued pwMS.

There were no differences between pwMS and healthy controls regarding age ($p = 0.924$), sex ($p = 1.000$), and manual dominance ($p = 0.602$).

We compared the median levels of patients' satisfaction and enjoyment rates between pwMS and healthy controls; we found no differences in satisfaction ($p = 0.401$), as assessed by the question "Did you enjoy this type of

training?" and in enjoyment ($p = 0.106$), as assessed by the question "How much fun did you have?"

We compared embodiment rates between all pwMS and healthy controls; we found no differences either in body ownership ($p = 0.117$) and motor agency ($p = 0.109$). This result suggests that it is not MS per se that modulates both rates, but rather whether it is associated with fatigue or not.

We observed no significant differences in median hand peak velocity between pwMS and healthy controls when the factors session and MFIS level were collapsed (Fig. 4).

Discussion

Our experimental study suggests a potential link between subjective trait fatigue in patients with multiple sclerosis and their motor performance and perception of embodiment in a virtual body. Specifically, we found that,

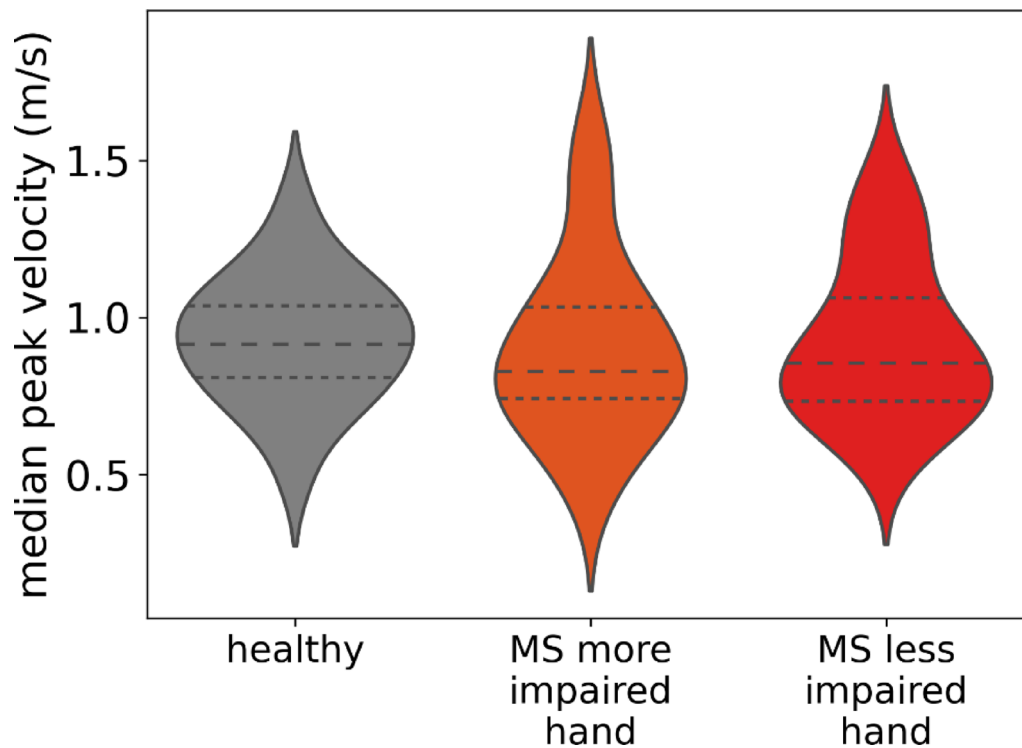


Fig. 4 Distribution of median hand peak velocity between healthy controls and pwMS. Median hand peak velocity distribution during task performance between healthy subjects and pwMS (considering motor impairment side) in the three experimental sessions. No significant differences were found

compared to low-fatigued pwMS, high-fatigued ones showed impaired UL kinematics during reaching tasks execution (quantified through hand peak velocities), and statistically lower levels of self-reported motor agency and body ownership in an IVR scenario.

Historically, research efforts in the rehabilitation of pwMS have been focused on the lower extremity (and related functions; gait, balance, mobility), despite upper limb (UL) dysfunctions being a widely reported impairment, heavily impacting on the patients' independence and quality of life [9, 11]. VR seems to be a promising tool for increasing UL function in pwMS [19]. Consequently, HMDs have been receiving increasing attention in the research community due to the possibility that they offer to boost task relevance and improve patients' engagement and examples of applications of IVR for UL treatment in pwMS have been reported in the literature [41–47].

In the present study, very high enjoyment and satisfaction rates have been reported by patients. The high acceptance rate of IVR devices that we found in pwMS is in agreement with previous reports by Pau [45, 47] and Kamm [44] and our previous study in stroke patients [26]. Clinicians' feedback further supports the high HMD usability [41], and they might be well-tolerated even in multisession programs, as described by Bertoni [42]. As reported in the literature, specific features of IVR games are more susceptible to inducing cybersickness

phenomena, such as timeframe acceleration, rotation, and camera movement [48]. Our system was specifically designed to minimize discomfort symptoms caused by VR exposure. In particular, we specifically designed our tasks such that they can be performed with the patients comfortably seated and we used a cozy home interior as virtual environment to increase subjects' immersion and avoid unpleasant feelings.

The novel element revealed by our study is the potential existence of a link between MS-related fatigue, embodiment, and upper limb kinematics. In our experiments, subjective trait fatigue seems to have a significant role in determining the rate of immersion achieved by patients; high-fatigued pwMS experienced significantly weaker feelings of both motor agency and body ownership. Indeed, in the whole MS sample, significant correlations were found between MFIS and median hand peak velocity, and between MFIS and motor agency scores.

Delving deeper the biobehavioral and functional mechanisms which can underline the sense of embodiment experienced, the concept of “motor agency” could be synthesized in the “sensation that self-actions lead to ensuing perceptual consequences” [49], which is implicitly related to motor imagery and motor representation. Considering motor behavioral functioning, the action execution timing is strongly correlated to the time to mentally simulate the same task, which is approximately similar in healthy adults, named isochrony [50–52]. This coupling between

the timing of executed and imagined movements has shown to be compromised in pathological conditions due to neurological disorders [53–55]. This phenomenon is called anisochrony and, as detailed by Tacchino et al., it is present in MS people during UL motor tasks, where a temporal dissociation between actual and imagined movements is observed, particularly for the non-dominant arm [56]. This difference appears related to a greater cognitive effort in imagining movements performed with the non-dominant side [57], which requires compensatory brain network activation, thus energy-consuming strategies, plausibly impaired by central fatigue and contemporarily generators of it. It is reasonable to suppose that “motor agency” perception could be implicitly associated to the temporal congruency between mental and actual movement execution (i.e. isochrony concept), which might be exploited in an artificial, experiential-highlighting scenario.

In our sample, the significant correlation between MFIS scores and hand peak velocities in both arms suggests an association between fatigue, that is indexed by the MFIS, and UL motor characteristics, which may furtherly impact the resulting embodiment perception, as revealed by the correlation found between MFIS and motor agency scores.

It is plausible to hypothesize that MS-fatigue might alter the subject’s ability to immerse him/herself into the virtual world and interact with it; thus, a sensory mismatch between mental motor representation and motor output may influence the consequent perceptive congruency (embodiment rate), and it can accordingly shape hand movement velocities. In fact, in our investigations, high-fatigued pwMS experienced significantly reduced levels of perceived embodiment, as shown by their lower scores in both motor agency and body ownership scores compare to low-fatigued ones. These results suggest that subjective trait fatigue could cohesively affect motor interaction in a VR environment, as revealed by between-group hand kinematic differences, and it could impact on virtual body ownership sensation.

Going into the role of fatigue on embodiment and motor performance, our patients’ subgroups were different only for MFIS scores, while no other demographic (age, sex, hand dominance) and clinical characteristics (disease severity, years since diagnosis) were significantly different. Considering the existing knowledge on the impact of fatigue on temporal motor congruency in imagined versus actual movements execution in pwMS, i.e., anisochrony phenomenon, fatigue did not show a critical effect, even if partially explored so far [56, 57]. However, it is noteworthy to underline that in these studies, pwMS presented, on average, reduced fatigue rates than what was observed in our sample [56–58]; this difference may explain the larger impact we recorded on fatigue severity

as primary element in modulating embodiment perception and UL kinematics, behavioral elements related to mental gesture simulation and resulting motor output.

Importantly, the role of fatigue investigated here is related to what is self-reported by patients in everyday life tasks, and it is not related to the *fatigability* induced by physical training. Indeed, while hand peak velocities were statistically different between high-fatigued and low-fatigue patients’ groups during the session, this difference did not significantly vary during the three training blocks. The role of fatigability as an early decrease of performance in IVR exposure is still to be explored in multisession trials, since a single 30-minute training execution seems not suitable to trigger these symptoms.

When compared to healthy controls, pwMS, as a group, showed no significant difference in both embodiment perception and motor performance. This result suggests that it is not the presence of MS per se that modulates the feeling of embodiment and alters UL kinematics, but rather its association or not with symptoms of fatigue.

Limitations

The present study has limitations that need to be discussed. Firstly, considering the limited sample size, this finding should be confirmed in larger clinical trials to provide a more general assessment of the potential link between MS-related fatigue, embodiment perception, and UL motor performance. Second, the present investigation is purely behavioral, and future studies might want to consider including also physiological markers of embodiment. Finally, the execution of a multisession clinical trial could contribute to tracking modifications on the role of fatigue in VR immersion and UL kinematics across time. The kinematic analysis of hand peak velocities provides a partial representation of UL motor performance, and a wider instrumental assessment is required to deeply characterize motor behavior (i.e. smoothness parameters, accuracy metrics). Nevertheless, hand peak velocities are recognized as clinically relevant UL kinematic indexes [59], and their comparison between Oculus Quest 2 and a marker-based motion capture system proved to be in close agreement both in neurologically impaired subjects [36] and healthy participant [35]. Notably, despite the limited number of study participants, the outcome assessor blinding on kinematic analysis contributes to reduce the potential bias underlined by our emerging findings. Patient-reported outcomes (i.e. embodiment, satisfaction) investigated by questionnaires may have been affected by expectation-bias, due to itself novelty and engaging nature of IVR. Although, IVR presence is a subjective experience not otherwise explorable except with self-report tools.

As concerned to future investigations, larger, multi-dimensional and quantitative analysis comprising also

neurophysiological correlates are crucial in order to properly target and tailor IVR interventions coherently to individuals' rehabilitation needs.

Conclusions

HMD use in pwMS seems feasible and well-tolerated by pwMS, independent of disease severity and fatigue intensity. In our experiments, MS-related fatigue significantly modulated self-reported measures of embodiment and UL performance, in pwMS exposed to an IVR session. We speculate that this effect might be due to fatigue potentially amplifying sensory mismatch between mental motor simulation and actual gesture execution, revealed by statistically significant differences observed in immersion rates, and hand peak velocities between high-fatigued and low-fatigued MS subjects.

Abbreviations

MS	Multiple sclerosis
PwMS	People affected by MS
UL	Upper limb
VR	Virtual reality
IVR	Immersive virtual reality
EDSS	Extended Disability Status Scale
HMD	Headmounted device
MAS	Modified Ashworth Scale
NHPT	Nine-hole-peg-test
MFIS	Modified Fatigue Impact Scale
F	Female
R	Right

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Author contributions

Conceptualization, S.S., A.C., and G.F.; Data curation, G.F., G.P., and A.C.; formal analysis, G.F., G.P., and A.C.; investigation, G.F., A.B., and A.C.; methodology, S.S., G.F., G.P., A.B., and A.C.; project administration, S.S. and G.F.; supervision, S.S.; validation, S.S., A.C. and G.F.; visualization, S.S., A.C., and G.F.; writing—original draft, G.F.; writing—review and editing, S.S., G.F., G.P., A.B., and A.C. All authors have read and agreed to the published version of the manuscript.

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Data availability

The datasets used during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Area Vasta Emilia Centro, Regione Emilia-Romagna (Italy) (EM606-2022_897/2020/Oss/AOUFe_EM2), and written informed consent was obtained from each participant. All participants were informed of the study's objectives and procedures.

Consent for publication

Consent was obtained from participants for publication of these data.

Competing interests

The authors declare no competing interests.

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