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Circulating neuroplasticity-related biomarkers and functional recovery after rehabilitation in relapsing-remitting multiple sclerosis: a secondary analysis of a randomized trial

Abstract

Background: Exercise and virtual reality (VR) rehabilitation may improve function in people with multiple sclerosis (MS), but the relationship between changes in circulating neuroplasticity-related biomarkers and individual recovery remains unclear. We examined whether changes in brain-derived neurotrophic factor (BDNF), insulin-like growth factor 1 (IGF-1), and neurofilament light chain (NfL) were associated with functional improvement after rehabilitation.

Methods: The secondary analysis used an openly available data set from a randomized trial of 48 persons with relapsing-remitting multiple sclerosis randomized to a supervised home-based exercise program (n=19), an immersive virtual reality rehabilitation program (n=19), or a wait-list control group (n=10) for 8 weeks. Serum brain-derived neurotrophic factor (BDNF), insulin-like growth factor 1 (IGF-1), and neurofilament light (NfL) were measured pre and postintervention with Expanded Disability Status Scale (EDSS), Timed Up and Go, 3-minute step test, 10-m walk test, standing balance, flexibility, Integrated Cognitive Assessment (ICA), and Symbol Digit Modalities Test (SDMT). A composite score was created using a six-item standard motor-recovery battery. Multivariable regression analyses used heteroscedastic-consistent (HC3) standard errors.

Results: The six-measure motor-recovery composite had a Cronbach alpha of 0.86 in this dataset. The exercise group showed greater mean improvement across motor measures, whereas the VR group showed greater mean improvement in the assessed cognitive outcomes. After adjustment for intervention, age, sex, baseline IGF-1, and baseline motor status, IGF-1 change was nominally associated with motor recovery (standardized beta=0.238, 95% CI 0.027–0.448; p=0.027). This association did not remain significant after false-discovery-rate correction (q=0.080) and weakened in sensitivity analyses. Changes in BDNF and NfL were not independently associated with motor recovery.

Conclusions: There was no reliable correlation between peripheral biomarker responses to interventions and individual recovery in this secondary exploratory analysis. Until further clinical and central nervous system evidence is available, peripheral BDNF, IGF-1 and NfL should not be regarded as valid surrogate markers of central neuroplasticity.

Keywords: Multiple sclerosis, neuroplasticity, rehabilitation, BDNF, IGF-1, neurofilament light chain, virtual reality, exercise

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Introduction

Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative disease of the central nervous system that involves demyelination of axons, damage to synapses, and loss of neurons. Although focal lesions and neurodegeneration are major contributors to disability, the impact of structural injury on clinical function is modulated by the ability of the nervous system to reorganize and compensate. Adaptive neuroplasticity thus emerges as an important mechanism through which people living with MS can preserve or restore neurological function in spite of ongoing pathological injury.[1,2]

Exercise and rehabilitation have been increasingly recognized as promising interventions for promoting adaptive functional response. Exercise can result in improvement in walking, balance, fatigue, fitness, and quality of life in individuals with multiple sclerosis (MS) and is now considered a critical element of comprehensive MS care.[3,4] Nonetheless, demonstrating an improvement in function does not prove that plasticity (or "adaptive change") has occurred. Stronger mechanistic causal inferences require that intervention-related changes in the dependent variable (function) are demonstrated to be mediated by independent plastic changes within the central nervous system (CNS).[5,6]

Circulating neurotrophic factors can serve as useful biomarkers of the body's response to rehabilitation. Brain-derived neurotrophic factor (BDNF) plays a role in the survival of neurons, synaptic transmission, learning, and activity-dependent plasticity. An increase in BDNF concentrations following an exercise intervention has been reported in persons living with multiple sclerosis (MS).[7] However, the results are inconsistent across studies, and different factors may affect BDNF levels depending on the type of intervention, MS-related characteristics, exercise doses, and assessment methods.[8] Similarly, insulin-like growth factor-1 (IGF-1) is a neurotrophic hormone with metabolic functions. Recent literature suggests that this factor may mediate some of the beneficial effects of physical activity on the brain. Increased serum IGF-1 levels following a standardized training

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program and a positive association between IGF-1 and physical fitness in people with MS were also reported.[9]

Neurofilament light chain (NfL) has a conceptually different role, being primarily a marker of neuroaxonal injury, rather than being a neurotrophic mediator. Blood NfL is increasingly used as an adjunctive biomarker of disease activity, prognosis and response to therapy in MS.[10] Exercise studies have reported reductions in NfL in some populations with MS,[11] however other investigations have not observed significant changes in neuro-specific blood biomarkers following aerobic training.[12] Thus, change in NfL as a result of an intervention should not automatically be interpreted as being indicative of neuroplasticity.

Virtual-reality rehabilitation is an additional layer that can provide a significant amount of information. It combines a cognitive challenge, sensory feedback, motor learning, repetition, and task engagement. Clinical studies show that it might have a positive impact on cognitive and motor functions in people with MS, but the outcome depends on the intervention and the domain that is being trained.[13,14] Therefore, it can be concluded that an exercise or a VR intervention might have a differing effect on functional and biological levels.

A major unresolved question is whether circulating biomarker changes really track individual recovery. One biomarker could have significant mean change following an intervention without explaining why some participants recover more than others. Distinguishing these levels of inference is important to biomarkers being considered as indicators of rehabilitation-induced neuroplasticity. The present secondary analysis therefore examined an open randomized-trial dataset containing pre/post BDNF, IGF-1, NfL, motor, disability, and cognitive measurements in people with relapsing-remitting MS. The primary aim was to determine whether within-person biomarker changes were associated with multidimensional motor recovery independently of intervention allocation and baseline characteristics. Secondary analyses examined cognitive outcomes and the robustness of biomarker-function relationships.

Methods

Study design and data source

The research is a secondary analysis of a publicly available dataset, titled "Comparing exercise with virtual reality gaming on gait and cognition in relapsing-remitting multiple sclerosis: a randomized controlled trial." The study by Sadeghi et al.[15] explored the effect of two active treatments – supervised physical exercise, and immersive motor–cognitive virtual reality (VR) gaming – compared to a wait-list/usual-care control condition on participants with relapsing-remitting multiple sclerosis over eight weeks. The dataset can be accessed at the Dryad Digital Repository (DOI: 10.5061/dryad.x69p8czzx).

The sample consisted of 48 participants (exercise n = 19, VR n=19, and wait list n=10). Baseline and post-intervention measures were taken meaning there are 96 data points for 48 people. There were no missing values. Participants were adults with relapsing remitting MS fulfilling inclusion criteria from the original trial and on stable disease modifying therapy (as described in the repository). The small sample size within each group should also be taken into consideration when interpreting results from adjusted analysis, particularly within the control group.

Variables

The demographic variables were age and sex. The clinical and functional variables were Expanded Disability Status Scale (EDSS), Timed Up and Go (TUG), 3-minute step test, 10-metre timed walk test (10MWT), standing balance test, sit-and-reach flexibility test, information processing speed composite (ICA), and Symbol Digit Modalities Test (SDMT). The circulating biomarkers were insulin-like growth factor (IGF-1) in ng/mL, brain-derived neurotrophic factor (BDNF) in pg/mL, and neurofilament light chain (NfL) in pg/mL. The SDMT was retained as an individual cognitive endpoint since it is a sensitive and clinically relevant measure of information-processing speed in multiple sclerosis (MS).[16]

Construction of the motor-recovery composite

An exploratory motor recovery composite was constructed. For EDSS, TUG, 3 minute step test, 10MWT, stand balance and sit and reach flexibility, the change in score from baseline to follow-up was taken. This was divided by the total standard deviation of the score. EDSS and TUG were converted to negative values so that higher values are indicative of improvement. The mean change score for the 6 variables was computed. The internal consistency for the composite was good (Cronbach's alpha=0.86). However, this does not guarantee external validity or unidimensionality. ICA and SDMT were treated separately due to the lack of evidence of a single cognitive composite.

Statistical analysis

Continuous variables were summarised using means and standard deviation. One-way ANOVA was conducted on the baseline group comparisons to explore differences between groups however, this does not represent successful or unsuccessful randomisation due to the nature of p values. Given the exploratory nature, descriptive statistics were used to explore how the groups changed pre-post. There were baseline imbalances in several biomarkers and functional outcomes meaning results cannot be directly compared between groups without adjustment.

Individual-level models were created using ordinary least squares regression to investigate associations between the change in individual biomarkers (IGF-1, BDNF and NfL). Models included intervention group, age, sex, baseline biomarker concentration and baseline motor function. Continuous variables and the outcome variable were standardised. To account for potential heteroscedasticity, HC3 heteroscedasticity-consistent standard errors were used. However, this does not account for lack of stability in small samples or confounding. The Benjamini-Hochberg false discovery rate method was implemented across the 3 main biomarker models. These results represent associations and not evidence of mediation or causality.

The sensitivity analyses included rank based methods, ln (post/pre) log response ratio for biomarkers and excluding the outlier BDNF. P values with $p<0.05$ were considered nominal evidence. The false discovery rate adjusted q values were used to help interpret the results from the main tests. The results presented in this manuscript only show the direction of the sensitivity analyses. To fully report the results, these should be included once the original analysis has been reproduced. This was a small post-hoc secondary analysis therefore emphasis was placed on effect size, confidence intervals and consistency between models.

Ethical considerations

The repository of the article Dryad states that the original study was approved by the Royan Institute Ethics Committee (IR.ACECR.ROYAN.REC.1396.98). The study also received written informed consents from the participants. The current study is a secondary analysis of the de-identified public data, thus, no new participants were recruited for it.

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Results

Participant characteristics

The mean age of the 48 participants was 34.13 +/- 8.50 years. Thirty-one participants (64.6%) were female and 17 (35.4%) were male. The baseline EDSS was 2.95 +/- 0.92. Baseline differences were seen among groups, particularly for IGF-1, BDNF, SDMT, TUG, and the 3-minute step test, and therefore baseline marker and functional values were explicitly included in adjusted association models (Table 1).

Table 1 Baseline characteristics of participants

Variable	Exercise (n=19)	VR (n=19)	Control (n=10)	p
Age, years	34.53±8.29	31.37±8.21	38.60±8.15	0.088
EDSS	2.71±0.84	2.97±1.01	3.35±0.85	0.209
IGF-1, ng/mL	291.56±47.52	384.38±32.70	444.99±39.07	<0.001
BDNF, pg/mL	7444.00±237.80	7210.43±162.36	8285.71±462.06	<0.001
NfL, pg/mL	57.52±37.70	66.44±38.34	76.63±33.06	0.417
ICA	65.11±14.67	61.26±15.71	57.30±13.69	0.401
SDMT	47.37±9.76	40.11±10.70	35.50±13.29	0.019
TUG, s	9.20±1.69	9.99±2.10	11.33±2.15	0.028
3-minute step test	41.16±12.37	33.74±12.77	25.30±11.13	0.007
10MWT, s	8.91±2.49	9.18±2.81	10.56±2.85	0.284
Standing balance, s	67.28±11.99	68.96±8.37	68.90±9.04	0.857
Sit-and-reach, cm	5.35±1.14	5.69±0.79	5.48±1.22	0.589

Values are mean±SD. p values are from one-way analysis of variance and are descriptive. EDSS, Expanded Disability Status Scale; ICA, Integrated Cognitive Assessment; SDMT, Symbol Digit Modalities Test; TUG, Timed Up and Go; 10MWT, 10-metre timed walk test.

Treatment-associated functional and biomarker profiles

On average those in the exercise group improved more on the motor outcome measures. They had reductions in mean TUG time (1.11s) and 10MWT time (2.41s). They also increased in 3 minute step score (15.68), stand balance (17.27s) and flexibility (2.91cm). Those using VR showed greater improvements on average on the two cognitive outcome measures (ICA: +6.21, SDMT: +1.95). The control group generally deteriorated on many outcomes. The exercise group improved in their mean IGF-1 (+100.25ng/mL). However, VR and control groups decreased in mean IGF-1. These are descriptive values from the data collected (Table 2) and shouldn't be interpreted as a new adjusted analysis of efficacy between groups.

Table 2 Mean pre-to-post changes by intervention group

Outcome (post - pre)	Exercise	VR	Control
EDSS	-0.21±0.35	-0.03±0.31	+0.35±0.34
IGF-1, ng/mL	+100.25±46.88	-26.95±28.24	-22.53±17.22
BDNF, pg/mL	+1074.43±290.81	+1475.15±271.29	+6862.84±22851.54*
NfL, pg/mL	-2.07±6.41	-0.59±5.87	+6.10±6.33
ICA	+2.42±3.96	+6.21±6.14	-1.50±3.87
SDMT	+0.63±2.11	+1.95±1.39	-0.80±2.70
TUG, s	-1.11±0.47	-0.02±0.26	+0.22±0.22
3-minute step test	+15.68±4.98	+0.11±3.53	-1.60±2.22
10MWT, s	-2.41±0.70	-0.21±0.59	+0.41±0.42
Standing balance, s	+17.27±6.79	+4.04±3.96	+2.84±1.23
Sit-and-reach, cm	+2.91±0.84	-0.01±0.09	-0.01±0.09

*The control-group BDNF mean and SD were strongly influenced by one extreme observation. Negative changes indicate improvement for EDSS, TUG, and 10MWT; positive changes indicate improvement for the remaining performance measures

Multidimensional motor recovery

The exploratory recovery score using a six-component motor measure showed greater recovery in the exercise group compared to the VR and control groups (Figure 1). This demonstrates the large differences between the motor recovery results observed. However, the score was created within this dataset and as such has not been externally validated. Therefore, the figure is descriptive only.

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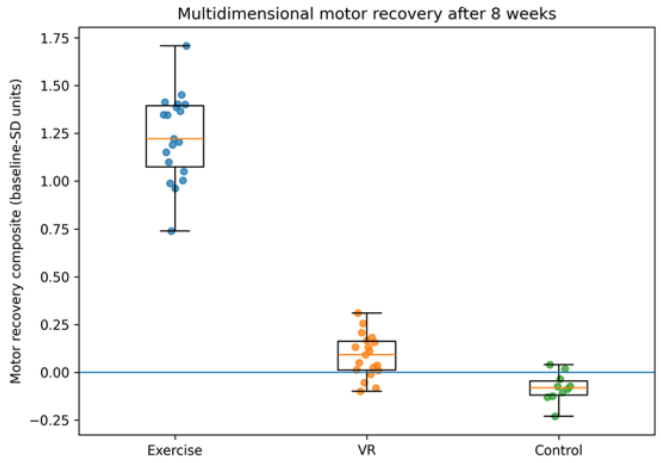


Figure 1 Multidimensional motor recovery by intervention group. Positive values indicate improvement; values are expressed in baseline-standard-deviation units averaged across EDSS, TUG, 3-minute step test, 10MWT, standing balance, and flexibility.

IGF-1 and motor recovery

IGF-1 increased on average in the exercise group, but decreased in the VR and control groups. Greater change in IGF-1 levels was nominally associated with greater motor recovery in the adjusted model (standardized β=0.238, 95%CI: 0.027-0.448, p=0.027). However, this did not reach statistical significance after adjustment for multiple comparisons between the three primary biomarkers (FDR q=0.080) and the association was weaker when different models were fitted. The data in Figure 2 are raw and should not be interpreted as reflecting the regression coefficient from the adjusted model. This is an exploratory result only.

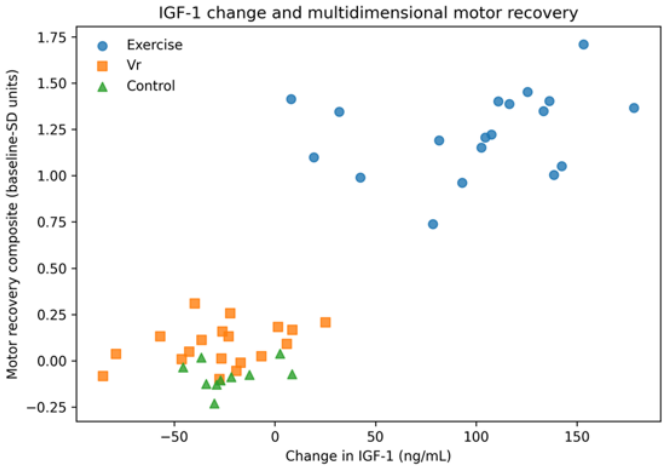


Figure 2 Change in IGF-1 and multidimensional motor recovery. The plot shows unadjusted participant-level values by randomized group; inferential results were obtained from adjusted multivariable models.

BDNF and NfL

Mean BDNF was increased in intervention groups. There was no consistent independent association between within-subject change in BDNF and motor recovery. One control subject had an increased post-intervention BDNF concentration of 80,291pg/mL compared to 8,392.5pg/mL. This value was included in the main analysis as it could not be verified that there was a data entry or laboratory input error based on the publicly available information. However, this had a strong effect on the distribution and precision of values. A sensitivity analysis excluding this point did not produce a consistent association between BDNF and motor recovery. The assay result could not be independently validated. If this analysis is repeated the estimates for the model without the outlier should be reported.

NfL decreased moderately in both the exercise and VR groups, but increased in controls. After adjustment, reduction in NfL was not independently associated with motor recovery (standardized beta=-0.062, 95% CI -0.172 to 0.048, p=0.268; FDR q=0.403) (Table 3).

Table 3 Adjusted associations between biomarker change and multidimensional motor recovery

Biomarker change	Standardized beta	95% CI	p	FDR q	Interpretation
IGF-1	0.238	0.027 to 0.448	0.027	0.080	Suggestive; not FDR-significant
BDNF	-0.009	-6.521 to 6.503	0.998	0.998	No stable independent association
NfL	-0.062	-0.172 to 0.048	0.268	0.403	No independent association

Separate models adjusted for intervention group, age, sex, baseline biomarker concentration, and baseline motor status. Continuous variables were standardized. HC3 robust standard errors were used. The very wide BDNF confidence interval reflects the extreme BDNF observation.

Secondary cognitive analyses

None of the biomarker changes were consistently independently associated with improvements in cognitive performance. The association between IGF-1 change and SDMT change was unclear, with an imprecise association found after adjustment (standardized beta=0.670, 95% CI −0.025 to 1.364, p=0.059). No association was found with ICA change (p=0.826). No consistent associations were found between BDNF and NfL change and cognitive measures. These exploratory outcomes should not be interpreted as an indication of mediation via a biomarker.

Discussion

The main finding from the individual patient data meta-analysis was that there was no reliable correlation between changes in circulating biomarkers and individual patient responses. Although there were wide improvements in motor outcome measures following exercise, and a large mean increase in IGF-1, VR led to greater mean improvements on cognitive tests and an increase in BDNF. However, no strong associations were found when adjusting for covariates. This is important as interventions may affect clinical outcomes via different mechanisms.

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For example, whilst there was an association between greater changes in IGF-1 and improved motor outcomes in the main adjusted model (accounting for intervention group and selected baseline covariates), this was not significant according to our criteria for multiple testing. This was also sensitive to analysis decisions made. It was in the expected direction and may be a physiologically meaningful association. However, there is not enough evidence to conclude that IGF-1 mediated the benefit of the rehabilitation or can be used to predict individual patient recovery. There were also large differences in baseline IGF-1 levels between groups which adds some uncertainty.

The IGF-1 finding is biologically plausible. IGF-1 participates in neuronal survival, metabolic regulation, myelin-related processes, and activity-dependent adaptation. Earlier work in women with MS reported increased IGF-1 following combined functional training and reported relationships between IGF-1 and physical fitness.[9] Systematic review evidence also suggests that exercise can influence neurotrophic pathways in MS, although effects on non-BDNF factors and mechanistic links with neuroprotection remain inconsistent.[17] The present analysis extends this literature by asking whether individual changes in IGF-1 correspond to multidimensional recovery after accounting for the intervention itself. The answer is suggestive but not conclusive.

BDNF is often proposed to be an indicator of an adaptation occurring due to exercise. Previous research has reported increased BDNF in some MS populations in the periphery post-exercise (Shobeiri et al., 2022; Wens et al., 2016). However, BDNF levels are affected by factors external to the CNS. Mean BDNF levels increased across the intervention groups however there was no clear trend between individual increases and improvements in either motor or cognitive function. This was complicated by an outlier within the control group. Whilst this was not excluded due to it being evident there was an error, it was also unable to be independently identified whether this was a valid score or was a product of lab error. Therefore this supports a cautious approach.

Stronger demonstration of rehabilitation-induced neural plasticity would ideally combine biomarkers with functional outcomes and CNS-based measurements, such as functional or structural MRI, diffusion imaging, EEG, or transcranial magnetic stimulation. Reviews of MS rehabilitation neuroplasticity have emphasized precisely this need for direct measures of brain reorganization and for linking those changes to clinically meaningful functional adaptation.[2,5,6]

NfL should be viewed separately to neurotrophic factors given it mainly represents neuroaxonal damage. The small decrease in both intervention groups and increase in controls was not associated with stable individual level associations with motor recovery. Previous MS literature has reported varied responses to exercise interventions.[11,12] The current findings do not tell us if there were changes in neuroaxonal damage during short term rehab periods. Therefore, NfL should not be used as an indicator of direct neuro-adaptive plasticity.

The functional outcome measures should also be cautiously interpreted. The six item motor score had good internal consistency within our sample, and the exercise group showed improvements in all of the domains. However, due to the newness of this score it may be affected by items that correlate well together and the weighting of the items. It would require replication to be considered a valid outcome measure for rehab. The VR group had larger mean changes in ICA and SDMT which is in keeping with the high motor and cognitive demands of VR tasks.[13,14] These are simply descriptive findings in a small secondary data set. They do not provide any conclusive evidence that one intervention is superior in a certain clinical area.

Clinical implications

A positive change in a circulating neurotrophic or neuroaxonal biomarker should not be interpreted in isolation as evidence that an individual patient has undergone meaningful neuroplastic recovery. Rehabilitation response should continue to be grounded in direct measures of function, disability, cognition, and participation, and, when mechanistic inference is intended, assessments of the central nervous system.

IGF-1 may merit further consideration as a candidate marker of motor rehabilitation response, but it requires larger prospective studies with prespecified biomarker endpoints before it can be validated. BDNF may have value as part of a multimodal biological profile, but it cannot discriminate between adaptive central nervous system reorganization and systemic exercise response on the basis of peripheral BDNF alone. NfL may be considered more appropriately as a complementary marker of neuroaxonal integrity rather than a direct indicator of rehabilitation-induced plasticity.

Strengths

A key strength of this study was that we had access to both biomarkers and functional measurements from the same individuals at baseline and post-rehabilitation. We addressed several confounders by accounting for treatment allocation and baseline variables, using false discovery rate correction, and assessing sensitivity to model specification and an extreme value of BDNF. While this improves clarity, it does not address the issues of small sample size, hypotheses generated post-hoc and absence of direct central neuroplasticity measures.

Limitations

Limitations of this analysis include small sample size and post-hoc design. Only 48 individuals completed the models. 10 controls were included within the analysis. There were large differences in IGF-1, BDNF, and multiple functional measures at baseline. Although confounding variables were controlled for this does not remove all bias. This means that any associations or trends observed are exploratory.

The motor composite was developed for this analysis so there has not been external validation. As the cognitive measures did not have justification for a composite score to be developed. The BDNF values were heavily influenced by an outlier value in the control group. It was not possible to verify the source of this outlier using the public dataset. Sensitivity analyses were performed to reduce reliance on one model however it is not clear if it was a true biological value or due to measurement bias or a data entry error.

Circulating BDNF and IGF-1 are peripheral markers. NfL is a marker of neuroaxonal damage. There was no information available on when samples were taken, recent activity, body composition, inflammation, drug information or what batch they were taken from. Without any additional information such as MRI, neurophysiology or long term follow up it cannot be confirmed that the functional improvements seen were due to central neuroplasticity. Future well powered prospective studies with pre-defined biomarker outcomes will be required to confirm this. Both central and functional measures should be collected in order to confirm this.

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Conclusion

In this secondary exploratory analysis of a randomised rehabilitation trial in relapsing remitting MS, exercise resulted in greater mean improvements on motor function and increases in circulating IGF-1. Conversely, VR resulted in greater mean improvements in cognitive function and increased BDNF. However, there were clear signs of individual-level recovery tracking in biomarker changes. There was a nominally positive association between IGF-1 and motor function, although the results were not significant after false discovery rate correction and were dependent on analysis. Neither BDNF nor NfL had consistent associations with recovery after adjustment. These findings suggest that these peripheral markers should not be used as sole surrogates for neuroplasticity induced by rehabilitation. Larger prospective trials incorporating blood biomarkers alongside functional, neuroimaging and neurophysiological outcomes are required.

Declarations

Data availability: The data analyzed in this study are publicly available through the Dryad Digital Repository under the dataset "Comparing exercise with virtual reality gaming on gait and cognition in relapsing-remitting multiple sclerosis: a randomized controlled trial" (DOI: 10.5061/dryad.x69p8czzx).

Ethics statement: The original study received approval from the Royan Institute Ethics Committee (IR.ACECR.ROYAN.REC.1396.98), and participants provided written informed consent, as reported in the repository documentation. The present study involved secondary analysis of de-identified publicly available data.

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None.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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