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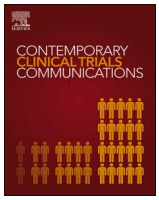

TRACking health behaviors in people with Multiple Sclerosis (TRAC-MS): Study protocol and description of the study sample

Ruchika S. Prakash [a,b,*], Heena R. Manglani [a], Elizabeth J. Duraney [a], Anita Shankar [a], Megan E. Fisher [a], Alisha Janssen [a], Lauren Cea [a], Rick Petosa [c], Rebecca Andridge [d], Jacqueline Nicholas [e]

[a] Department of Psychology, The Ohio State University, Columbus, OH, USA
[b] Center for Cognitive and Behavioral Brain Imaging, The Ohio State University Columbus, OH, USA
[c] Department of Human Sciences, The Ohio State University, Columbus, OH, USA
[d] Department of Biostatistics, The Ohio State University, Columbus, OH, USA
[e] Ohio Health Multiple Sclerosis Center, Columbus, OH, USA

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ABSTRACT

Introduction: People with multiple sclerosis (PwMS) experience a range of physical, cognitive, and affective symptoms. Behavioral interventions targeting increased physical activity show promising support as low-cost methods to improve working memory, episodic memory, and processing speed in PwMS. In this randomized controlled trial, we will examine the efficacy of a pedometer-tracking intervention, designed to increase low-to-moderate levels of physical activity, for improving working memory in PwMS.

Methods and Analysis: Eighty-seven PwMS, between the ages of 30–59, have been recruited for the study. Seventy-five of the eligible and interested individuals were randomized to six-month health behavior monitoring groups: a Step-track group or a Water-track group (serving as the active control). Neuropsychological measures, assessing the primary outcome of the study, were administered at pre, midpoint, and post-intervention. Exploratory factor analysis of neuropsychological measures resulted in three factors: a working memory/processing speed factor, a visual episodic memory factor, and a verbal episodic memory factor. Changes in this latent measure of working memory/processing speed is the primary outcome of the current study. Functional MRI data will be analyzed to examine changes in the functional connectivity of the neural network supporting working memory.

Ethics and dissemination: The institutional review board granted approval for the study and all participants provided written informed consent. The results of this study will provide support showing that step-tracking increases overall levels of physical activity, improves working memory and processing speed, and strengthens the neural circuitry that supports better cognition. Evidence from this study will thus offer promising support for the routine use of step-tracking devices to improve cognitive functioning in PwMS. Study results will be disseminated through peer-reviewed publications and presentations at scientific conferences.

Strengths and limitations of the study

- This study will establish the efficacy of a low-cost, pedometer tracking intervention to improve working memory performance in PwMS.
- Changes in the network strength of a previously validated neuromarker of working memory will provide support for this intervention to strengthen the neural circuitry supporting working memory.
- This study only included relapsing-remitting individuals between the ages of 30–59 years.
- The study includes no longitudinal follow-up data.

1. Introduction

Multiple sclerosis (MS) is a neurological disease that impacts nearly one million individuals in the United States alone [1]. MS commonly involves muscle weakness, numbness, fatigue, pain, and spasticity [2,3].

* Corresponding author. Department of Psychology, The Ohio State University, 139 Psychology Building 1835 Neil Avenue, Columbus, OH 43210, USA.
E-mail address: prakash.30@osu.edu (R.S. Prakash).

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In addition to these physical symptoms, declines in cognitive functioning are estimated to affect up to 70% of PwMS [4–7]. These difficulties range from impairments in simple reaction time tasks that require fast processing speed to complex higher-order tasks of cognitive control requiring planning, multi-tasking, and maintenance of task demands [8–10]. Impairments in cognition are a critical predictor of employment status [11,12], social engagement [13], and independence in activities of daily living [14–16]. The resulting economic burden due to lost wages, progression of cognitive disability, and rising healthcare costs is approximated at $10 billion—thus necessitating rehabilitation of cognitive dysfunction in PwMS [17].

Working memory deficits are an integral part of the cognitive sequelae of MS, and there is strong evidence supporting the consequential downstream effects of working memory decrements [9,18,19]. Working memory, involving the maintenance and manipulation of contextual information, acts as a selection mechanism, facilitating and guiding behavior by mitigating interference between competing representations [20]. Our meta-analytic review of cognitive dysfunction in multiple sclerosis [10], along with more recent reviews [21–23], reveals a large effect size (g = -0.515) for working memory impairment in PwMS compared to healthy controls. Furthermore, neuroimaging investigations of working memory tasks in PwMS unequivocally show the lack of load-dependent modulation of the prefrontal-parietal circuitry [24–27].

Interventions to increase physical activity are some of the few behavioral treatment options available to improve cognitive functioning—specifically for the domain of working memory. Within MS, there is growing literature on physical activity interventions with some studies supporting the claim that such interventions improve processing speed [28,29], working memory [29], and episodic memory [29–31]. Other studies, however, have found no evidence for improvements in cognitive functioning [32–34]. Only a few studies, to our knowledge, have examined the efficacy of pedometer-tracking interventions as a low-cost strategy for promoting low-to-moderate intensity physical activity with the potential for downstream effects on cognition. Studies in clinical and community populations have provided unequivocal evidence for increased physical activity engagement after a theoretically similar pedometer-based tracking intervention [35–37]. An internet-based 12-week psychoeducation intervention aimed at increasing overall physical activity, but not step count specifically, illustrated a change of almost 1,400 steps/day in PwMS [38] and provided evidence for the feasibility of the current design.

For our pedometer-tracking intervention, we developed an in-house mobile application to show behavioral goals and offer motivational materials. Each week, participants were asked to increase their daily walking by 500 more steps than their previous week average, until they reached the next category of activity according to pedometer indices for public health and/or 12,500 steps per day [39]. Furthermore, given the abundance of research showing that individuals who walk between 7,500 and 10,000 steps per day accumulate the most health benefits [39–41], our pedometer-tracking intervention is hypothesized to improve working memory with such improvements evident in both paper-and-pencil measures and neural correlates of working memory. Finally, the current clinical trial also includes an active control group: the water-tracking group. This group monitors their daily water intake with the goal of increasing daily water consumption by 8 oz each week until total daily consumption reaches 64 oz/day for women and 87.5 oz/day for men [42]. Including an adequate placebo control group enables us to significantly contribute to evidence-based clinical practices by providing gold-standard evidence for a low-cost, viable method for increasing physical activity to improve cognitive and brain health.

2. Methods

2.1. Study design

In this single-blind, randomized controlled trial (RCT), we were interested in comparing the impact of a six-month step-tracking intervention (Step-track) relative to a water-tracking (Water-track) active control group on behavioral and neural measures of working memory (ClinicalTrials.gov: NCT03244696). Power analysis for this study was based on a pilot trial examining the effect of physical activity training on cognitive processing speed in PwMS [43]. Participants in the physical activity training group demonstrated a significant increase in cognitive functioning performance, specifically performance on the Symbol Digit Modalities Test, compared to participants in the waitlist control group ($\eta_p^2 = 0.11$). Using an alpha level of 0.05, a total sample of 66 participants would be required for an estimated power of 0.80 for the Group × Time interaction in the linear mixed model. We expected to lose participants to attrition in this six-month RCT. Based on our previous experience, we anticipated attrition to remain under 20% of the sample, thus requiring 80 participants for our proposed study and desired power. Eighty-seven PwMS, between the ages of 30–59, were recruited for the study. All participants were recruited from the United States of America. Of these, 75 of the eligible and interested individuals were randomized to one of two 6-month health behavior monitoring groups: a Step-track group or a Water-track group. Differences between the groups will be assessed at baseline, three months after randomization, and at the conclusion of the six-month intervention period (controlling for any baseline measurement differences). Fig. 1 illustrates a timeline for study participation and includes all assessment sessions.

2.2. Inclusion/exclusion criteria

The study recruited individuals between the ages of 30–59 with a clinically definite diagnosis of relapsing-remitting MS (RRMS). Individuals older than 60 years were excluded from the study to control for the confounding effect of age on cognitive and neural decline. Additionally, as MS typically onsets in the late 20s to early 30s, we decided to include individuals over the age of 30 years as participants over this age are likely to have completed their education and be employed in their current jobs, thus reducing variance resulting from these confounding factors. Additional inclusionary criteria included: mild-to-moderate disease severity as quantified by a score under 5.5 to ensure adequate ambulation on the self-report measure of the Expanded Disability Status Scale [44], a score >23 on the Mini-Mental Status Examination [45] to rule out significant cognitive impairment, no current use of accelerometer, pedometer, and/or physical activity monitoring equipment to monitor steps, access to an Android/iOS smart device, and internet access for the duration of the study. Exclusion criteria included: presence of neurological disorders other than MS, a psychiatric disorder diagnosed by a licensed mental health provider in the last two years, recreational drug use in the last 6 months, or MS relapse or corticosteroid use in the last 30 days. Finally, as the study included an MRI component, participants were required to be right-handed, and those with ferromagnetic implanted devices or self-reported claustrophobia were excluded from the study. In addition to these criteria, to include individuals with cognitive impairment, we administered the self-reported and informant-reported versions of the Multiple Sclerosis Neuropsychological Questionnaire to all participants. Participants were enrolled in the study if they received a score greater than 24 on the self-reported form or 22 on the informant-reported form. However, partway through the study, based on the absence of a correlation between subjective and objective cognitive impairment, we decided to no longer exclude participants based on this criteria. This amendment to the protocol was submitted and approved by The Ohio State University Institutional Review Board.

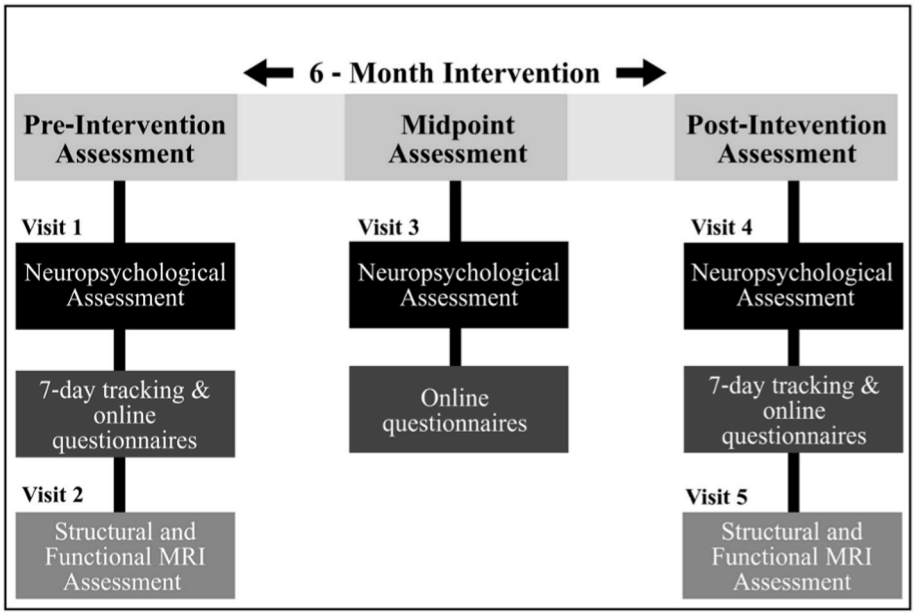

Fig. 1. A timeline for the current study, including all neuropsychological and neuroimaging assessment sessions.

2.3. Procedure

Participants were recruited from Ohio and neighboring states. We implemented a multi-pronged recruitment effort—advertising for the study through print/email communications, in-person recruitment, community outreach, and other opportunities provided by various MS organizations. Table 1 provides a list of our primary recruitment sources for the RCT.

Participants interested in the study either completed a phone screen or an online survey designed to collect basic demographic information, data on MS diagnosis, medical history, and current medications. Participants meeting basic inclusionary criteria were then invited to the Clinical Neuroscience Laboratory at the Ohio State for their first behavioral session. During this session, we administered the Mini-Mental Status Examination to rule out severe cognitive impairment. We also administered a battery of neuropsychological tests (see section 2.5.1) to establish the baseline cognitive profile of each participant. In this session, participants also signed the Health Information Portability and Accountability Act form to provide consent for study personnel to acquire protected health information from their MS neurologist to confirm the participant's RRMS diagnosis, disease duration, MS medications, and EDSS score. All participants meeting the inclusionary criteria from the first assessment session were then asked to track their physical activity using an accelerometer (Actigraph GT3X+) and water consumption using the H_20 Pal Smart Water Bottle Hydration Tracker during the seven-day period between the first behavioral session and the second neuroimaging session. Participants were asked to wear the accelerometers on their left help using an adjustable belt. All participants were requested to bring the accelerometer and their H_20 Pal bottle to the neuroimaging session where the study coordinator calculated their baseline levels of physical activity and water intake. The neuroimaging session took place at the Center for Cognitive and Behavioral Brain Imaging housed in the Department of Psychology at Ohio State (detailed MRI components are included under section 2.5.4). Participants were fully informed of the nature of the study, its procedures, and the required commitment.

Table 1
List of primary recruitment sources employed for the study.

Category	Recruitment Strategy
Clinic Recruitment	Study coordinator shadowed patient visits at an MS Clinic with the study's MS neurologist and presented the study to patients. Study coordinator worked with local neurologists to recruit at Ohio State Care Point clinics.
Outreach Activities	Lab staff attended yearly Columbus MS Walk events and staffed a booth with information about our laboratory and research. NMSS-sponsored MS Breakthrough events in Columbus and Cincinnati. US Defense Logistics Agency Resilience Fair in Columbus. Lab hosted yearly MS Wellness Day events (March 2018 and March 2019) aimed at providing the latest evidence-based research on various approaches to psychosocial wellness. Attended and gave presentations at local MS support groups.
Online Recruitment	Research Match (an online recruitment tool with a database of participants). Study Search (a database of active studies at the Ohio State). Media advertisements (Facebook, Columbus Dispatch, Ohio State's OnCampus newspapers). Worked with the Wexner Medical Center to recruit patients via messages sent through MyChart.
Other	Flyers were displayed in doctor's offices, coffee shops, community centers, libraries, and fitness locations throughout Ohio. Flyers were also dispersed to MS support groups in Ohio and surrounding states.

At the end of the neuroimaging session, all eligible and consenting participants were randomized to one of two groups: the Step-track group or the Water-track group. A permuted-block design (blocks of 4) was employed, and randomization was stratified by sex and EDSS [EDSS ($\leq$3.5 vs. $>$ 3.5)]. Participants were informed of their group assignment through a closed envelope method without being told that physical activity was the key factor being tested. The PI prepared the randomization sequence, and the study coordinator was responsible for randomizing the eligible participants. The study coordinator and research assistants in charge of weekly data collection were the only members of the research team aware of group assignments. All research associates performing the pre, midpoint, and post-intervention assessments remained blind to the participants' group assignments. Furthermore, participants were requested to keep their group assignment confidential during midpoint and post-intervention assessments and refrain from using study materials during these assessment sessions (including the use of Fitbit trackers and H_20 Pal water bottles). Participants were asked to engage in health behavior tracking for a six-month period using our in-house, mobile application (TRAC-MS; section 2.4.3 for more information). Assessments were conducted at midpoint and after the six-month intervention period.

2.4. Intervention

2.4.1. Step-track

Participants randomized to the Step-track group were provided with a FitBit Alta, a lightweight pedometer (29 g), to track their daily steps. Participants were asked to wear their device all day, except while showering or swimming, for at least 10 h each day. The 10-h minimum was based on previous literature indicating that this was the minimum daily time needed to ensure that accelerometer recordings were valid and reliable [28]. Daily step goals were increased by 500 steps each week until achieving a total daily step count in the next activity category according to pedometer indices for public health and/or 12,500 steps

Fig. 2. Screenshots of TRAC-MS study-specific mobile application. Employing social cognitive theory that centralizes self-monitoring techniques as essential for promoting health behaviors, our application was designed to encourage individuals to monitor their respective health behavior in pursuit of improving that respective behavior. Panels A and B show the dashboards for the Water-track and Step-track groups, respectively. Panel C displays the weekly progress towards the step goals for a participant in the Step-track group, and Panel D is a screenshot presenting the timeline of the study to the participants.

per day [39]. These recommendations are designed to result in an estimated average increase of 2,500 steps/day by the end of the intervention. A change of 2,500 steps/day is feasible for PwMS based on previous physical activity interventions and would also represent a clinically meaningful change by moving the participant from the "sedentary" to the "low active" category or higher [38,39].

2.4.2. Water-track

PwMS randomized to the Water-track group were provided an H20 Pal Smart Water Bottle to track daily water intake. This bottle has built-in Bluetooth connectivity with an accompanying mobile application that monitors water consumption, provides feedback, and automatically resets after 24 h. We employed an idiographic approach to increase participants' water intake by considering their baseline hydration levels. Daily water consumption goals were increased by an incremental amount (8 oz/day) to reach dietary recommendations per day and by sex [42]. Female participants were given the goal of reaching/maintaining a total intake of 64 oz/day, and male participants were encouraged to reach/maintain a total intake of 87.5 oz/day.

2.4.3. TRAC-MS application

Following randomization and before the start of the intervention, participants were requested to download our in-house, cross-platform mobile application: TRAC-MS. Fig. 2 presents screenshots of our TRAC-MS application. Employing social cognitive theory which posits that self-monitoring techniques are essential for promoting health behaviors, our application was designed to encourage individuals to monitor their health behavior to improve the respective health behavior. The study team designed the TRAC-MS application to interface with both the Fitbit and H20 Pal applications and provide enrolled participants with daily, weekly, and monthly step count and water intake data, respectively. The TRAC-MS application was also designed to deliver regular motivational materials for goal attainment and intervention adherence. Based on Bandura's social cognitive theory for promoting health behaviors, the motivational materials were designed to empower participants to reach their personalized physical activity or waterintake goals. These were designed to allow participants to develop a toolbox of personally effective self-regulation strategies to promote regular adherence to their respective health behavior based on a view of the individual as both an agent for change and respondent to change [46]. The materials were tailored for PwMS through increased emphasis on benefits and expectancies related to increased physical activity and water intake, safety tips, and value-based exercise engagement designed to increase long-term adherence (Kangasniemi, 2015) [47]. These group-specific materials were delivered at regularly scheduled intervals: once a week for the first month, twice a week for the following three months, and once a month for the last two months. Motivational materials covered the following content areas: self-regulation, safety, goal setting, self-efficacy, value-based action, health behavior enjoyment, personalization, social support, expectation management, and relapse prevention. Careful attention was given to ensure that individuals in both the intervention and control groups received the same number of motivational materials with topics and content matched across the two groups.

2.4.4. Assessing and maximizing adherence

Given the longitudinal nature of the study, when adherence was deemed low, participants were sent a message or phoned by the study clinician (H.R.M). Contact was made according to a study flowchart if the app was unopened, motivational materials were not reviewed, or 80% of their current goal was unmet for consecutive days. Motivational interviewing was used to scaffold reflection on perceived benefits and solutions to barriers, support participants' self-efficacy, and reinforce positive change talk. Motivational interviewing phone contacts were supervised by the licensed clinical psychologist and study principal investigator (R.S.P).

2.5. Assessments

2.5.1. Neuropsychological assessment

As individual measures of neuropsychological functioning are often considered inadequate to assess their respective cognitive domains, we administered multiple measures of cognitive functioning to create sample-specific composite scores for the various cognitive domains. Specifically, participants were administered the Minimal Assessment of Cognitive Functioning in Multiple Sclerosis (MACFIMS) battery [48], the NIH Toolbox Cognition Battery (NIHTB-CB), and the processing speed and working memory measures from the Wechsler Adult Intelligence Scale (WAIS-IV) [49]. Details about the specific tests comprising the three batteries can be found in the Supplementary Materials. We also administered secondary measures assessing depression (Beck Depression Inventory) [50], anxiety (Penn State Worry Questionnaire) [51], perceived stress (Perceived Stress Scale) [52], quality of life (Satisfaction with Life Scale and the World Health Organization Quality of Life Scale) [53,54], fatigue (Modified Fatigue Impact Scale) [55], and sleep (Pittsburgh Sleep Quality Index) [56].

2.5.2. Factor analysis of baseline neuropsychological data

To examine the latent structure of the various cognitive domains in the current sample, we first conducted a factor analysis on the baseline data. The specific measures employed in the factor analysis are also provided in the Supplementary Materials. Eighty-three participants with complete data on all sixteen measures were included in the exploratory factor analysis, which was based on the Pearson correlation matrix and used maximum likelihood estimation and oblique rotation. The number of factors was chosen via a parallel analysis [57]. An item was assigned to a factor if the primary loading was >0.32 and the item did not cross-load (loading was <0.32 for other factors) [58]. Factor scores were created using the item loadings to create weighted sums. Factor analysis was conducted in R [59] using the *psych* package [60].

2.5.3. Analysis of primary outcome variable

The primary aim of the current study will be examined by assessing the impact of the step-tracking intervention for the identified latent variable of working memory/processing speed. All data will first be tested for normality, outliers, and errors. We will then compute summary statistics and conduct statistical comparisons with the full sample to identify any baseline differences between groups in demographic or clinical characteristics. Intention-to-treat conventions will be followed for all statistical analyses conducted as part of the trial. To examine intervention effects, we will use a linear mixed model to account for the within-subject correlation arising from measuring each subject at three timepoints. Group (Step-track; Water-track), Time (pre-, mid-, post-intervention), and the Group $\times$ Time interaction will be defined as fixed effects, and when applicable, covariates will be included as fixed effects. Each participant's intercept will be included as a random effect.

2.5.4. Neuroimaging measures

A secondary goal of the study is to examine the effect of the step-tracking intervention in strengthening the neural circuitry supporting working memory. Interventions designed to improve cognitive functioning, like physical activity training, mindfulness meditation, and cognitive rehabilitation, have sought to identify concomitant changes in brain features—structural metrics, functional metrics, or combined structural and functional metrics—as a result of the respective training. However, the training literature has lacked reliable and valid brain-based signatures that clearly highlight the patterns of brain activity or connectivity that support better cognition. As such, it is increasingly important to identify neuromarkers—brain-based signatures that reliably predict variance in specific cognitive domains—and rigorously test them using independent samples. Our prior work has established the validity of a working memory neuromarker in predicting working memory performance in PwMS [61]. Specifically, using

connectome-based predictive modeling [62,63], we recently validated a neuromarker of working memory derived from 502 participants from the Human Connectome Project [64] to predict working memory in two independent samples of PwMS [61]. Fig. 3 shows the anatomical distribution of the neuromarker across the canonical networks. The neuromarker of working memory demonstrated an expected pattern of intranetwork (i.e. segregation) and internetwork (i.e. integration) connections with a greater segregation of the frontoparietal network being associated with better performance (high working memory network; Fig. 3A) and a greater integration of the default mode network with other brain regions predicting poor performance (low working memory network; Fig. 3B). In this study, we will examine if changes in network strength of this working memory neuromarker mediates the effect of the step-tracking intervention on cognitive functioning.

2.5.4.1. Working memory task. We have employed a minimally modified version of the Human Connectome Project's N-back task as our working memory measure for the MRI assessment. In this task, participants determine whether the current stimulus is the same as the target stimulus. In the 0-back condition, a target stimulus is presented at the beginning of the block. In the 2-back condition, the target is always the stimulus presented two trials prior to the current trial in that block. Four stimulus types (body parts, places, faces, and tools) and two conditions (0-back and 2-back) combine to create eight blocks. Participants complete two runs, each with eight total alternating blocks (four 0-back, four 2-back), and 10 trials per block for a total task duration of ~15 min.

2.5.4.2. Individual and group-level analyses to examine the impact of the intervention on network strength. Quality checks and preprocessing of fMRI data will be conducted using pipelines employed previously in the lab [65,66]. Details have been provided in the Supplementary section. After preprocessing and motion correction, we will employ the Shen atlas [63] to parcellate the 4D fMRI data for each participant into 268 contiguous, functionally-defined regions covering the cortex, subcortex, and cerebellum. We will then compute the connections between each of these regions, referred to as a functional edge, by cross-correlating the timecourse of activity between these regions. The resulting matrix will be comprised of 71,824 connections, and each cell of the matrix will represent the magnitude of the correlation between the respective functional regions. Using network masks validated in our prior work [61], we will then derive the network strength of the marker at pre-intervention and post-intervention. To examine whether changes in the network strength of the working memory connectome mediates the effect of the intervention on working memory we will construct three linear mixed models: 1) the impact of Group X Time on the primary outcome (see section 2.5.3); 2) the impact of Group on the slope of change in network scores; and 3) the impact of the network score slope in mediating the effect of Group on the dependent variable of interest. A mediation would be indicated by significant *F*-statistics for the Time × slope interaction along with a reduced *F*-statistic for the Group × Time interaction in model 3. We hypothesize that the pedometer-tracking intervention will strengthen connections in the working memory neuromarker and changes in this connectome-wide mask will mediate the impact of pedometer-tracking on working memory and processing speed performance. This will be the first study to examine whether changes in an independently derived and validated, whole-brain marker of working memory explains the prophylactic effect of step-tracking on improvements in cognitive functioning.

2.6. Patient and public involvement

The research questions posed in this study emanate directly from the authors interactions with individuals with MS in their clinic as well as through outreach events hosted by the study team. However, patients or the public were not directly involved in the design, conduct, reporting, or dissemination plans of our research.

2.7. Ethics and Dissemination

The Ohio State Institutional Review Board approved the study, and all recruited participants provided written informed consent.

3. Results

3.1. Baseline demographics of the randomized sample

Table 2 presents descriptive statistics for demographic, clinical, and tertiary variables of the randomized sample. The sample had a mean age

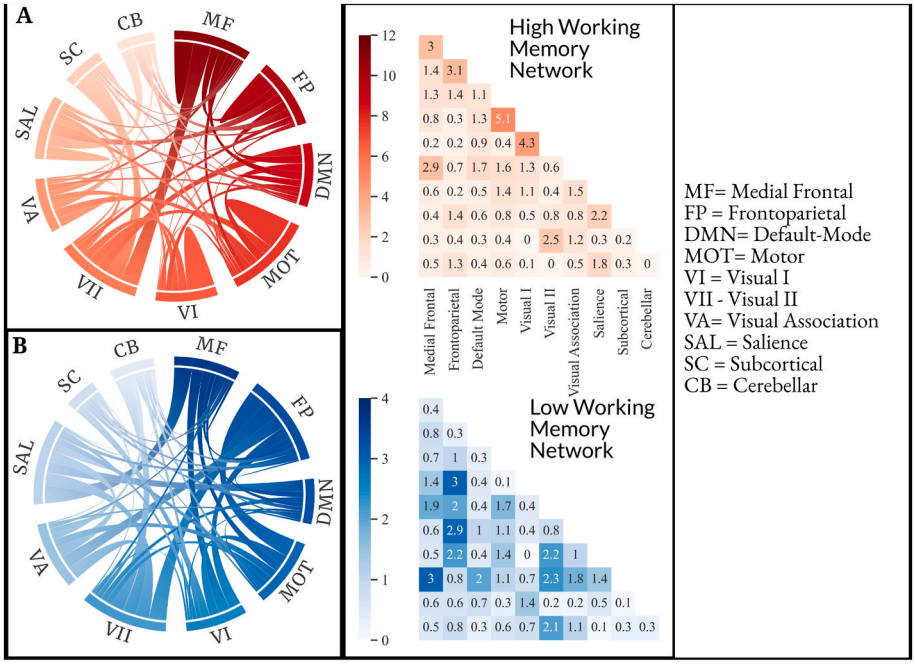

Fig. 3. Presents the intra-network and inter-network connections of the working memory neuromarker derived in Avery et al. (2019) and validated in Manglani et al. (2021). Panel A shows connections in the high WM network and Panel B shows connections in the low working memory network. The neuromarker combines both networks in one model. Matrices show the contributions of each canonical network with the diagonal representing intra-network connections. Values > 1 suggest a critical contribution of the canonical network.

Table 2
Demographic and clinical characteristics of the baseline sample.

Characteristic	Mean (SD) or N (%)		Range
Sex			
Female	69	(79%)	
Male	18	(21%)	
Race			
White	72	(83%)	
American Indian/Alaskan	1	(1.1%)	
Asian	–	–	
Black	9	(10.3%)	
More than One Race	2	(2.3%)	
Other	3	(3.4%)	
Ethnicity			
Non-Hispanic/Latinx	84	(96.5%)	
Hispanic/Latinx	1	(1.1%)	
Other	1	(1.1%)	
Prefer not to Answer	1	(1.1%)	
Age (years)	47.3	(7.93)	31 to 59
Education (years)	16.3	(2.648)	11 to 23
Disease Duration (years)[a]	10.4	(6.51)	.25 to 25
Expanded Disability Status Scale (EDSS)	3.96	(0.94)	0 to 5.5

[a] Disease duration data not available for one participant.

of 47.3 years and a mean education level of 16.3 years. 79.3% of the sample was female and 83% of the sample identified as non-Hispanic White.

3.2. Factor analyses of the cognitive measures

The resulting scree plot from the exploratory factor analysis indicated three factors: a working memory/processing speed factor, a visual episodic memory factor, and a verbal episodic memory factor. Table 3 presents the factor loading of the various measures on the three factors.

Table 3
Results of the exploratory factor analysis conducted on sixteen measures derived from the three neuropsychological batteries. Panel A presents the factor loadings from the exploratory factor analysis final solution. Panel B presents the summary of factor scores and correlations among the three factors.

Table 3A

	Working Memory/ Processing Speed	Visual Episodic Memory	Verbal Episodic Memory
Number of Items	6	2	3
Mean (SD)	297.6 (29.5)	140.4 (26.0)	99.5 (20.8)
Range	216.7–379.1	73.5–206.2	57.8–138.4
Correlation (*p*-value) with:			
Working Memory/ Processing Speed		.38 (<.001)	.14 (.208)
Visual Episodic Memory			.22 (.048)

Table 3B

Battery	Measure	Factor 1	Factor 2	Factor 3
MACFIMS	COWAT	**.37**	−.11	−.03
	JLO	.27	.23	−.07
	CVLT_Total_Learning	.08	.10	**.71**
	CVLT_Delayed_Recall	.11	.26	**.68**
	BVMTR_Total_Learning	.03	**.75**	.01
	BVMTR_Delayed_Recall	−.05	**.89**	.09
	SDMT	**.50**	.27	−.02
	DKEFS_Sorts	.25	.06	.03
	PASAT_avg_std	**.48**	.08	.02
WAIS	PSI	**.54**	.20	−.19
	WMI	**.45**	−.01	.10
NIHTB	FLANKER	.27	.29	**−.38**
	LIST_SORT	**.70**	−.26	.21
	DIM_CHANGE_CARD	.27	.34	−.43
	PATT_COMP	.42	.20	−.38
	PIC_SEQ	.34	.40	.30

Note: Bolded loadings were included in creating factor scores.

The working memory and processing speed factor are comprised of the following measures: the Controlled Oral Word Association Test, the Symbol Digit Modalities Test, the average accuracy of the 2s and 3s PASAT measure, the Processing Speed Index and the Working Memory Index from the WAIS-IV, and the List Sorting Test from the NIHTB-CB. Working memory and processing speed are two core cognitive deficits in individuals with MS, with multiple gold-standard measures in the MS literature, such as the PASAT, assessing both working memory and processing speed abilities. Using the factor loadings in Table 3A, we created a composite score for this latent factor of working memory and processing speed abilities. The slope of the change in this composite score from baseline, to mid-intervention, to post-intervention will be the primary outcome variable for this study.

The second and third factors in the factor analysis consisted of measures assessing visual and verbal episodic memory functioning, respectively. Factor 2—visual learning and memory—was comprised of the immediate and delayed recall metrics of the Brief Visuospatial Memory Test, whereas Factor 3—verbal learning and memory—was comprised of the immediate and delayed metrics from the California Verbal Learning Test (CVLT-II). Difficulties in new learning and memory are other hallmark cognitive sequelae of PwMS that impact work performance, social/vocational activities, and everyday functioning. In a set of exploratory analyses, we will examine the impact of our step-tracking intervention on the slope of change for the latent factors of visual and verbal episodic memory. Table 3B presents the mean, range, and *SD* of the three factors. The resulting cognitive composites were weakly correlated with each other showing correlations ranging from 0.14 to 0.32.

4. Discussion

The current study advances the existent MS literature by examining potential neuropsychological gains resulting from increased physical activity. By employing a well-validated intervention strategy of step-tracking, the current study will determine the efficacy of this low-cost intervention, in comparison to an active control group, for fostering cognitive and neural functioning gains in a sample of PwMS. In comparison to the costs associated with laboratory-based RCTs examining the efficacy of moderate-intensity aerobic exercise, pedometer-tracking interventions present a low-cost alternative that requires little input on the part of the clinician. Meta-analytic reviews of laboratory-based trials fail to support the cardiovascular fitness hypotheses that attribute physical activity-induced improvements in cognitive and brain functioning to increased aerobic fitness capacity [67,68]. This provides further credibility to the examination of low-intensity physical activity interventions in reducing cognitive impairment. Large-scale epidemiological studies additionally provide critical evidence for low-to-moderate intensity physical activity measured via accelerometry in reducing the risk of cognitive decline [69], protecting against the development of Alzheimer's disease [70], and guarding against age-related decline in brain atrophy [71,72]. By incorporating elements of behavioral feedback and accountability [73], pedometer-tracking leads to similarly efficacious changes in physical activity as those observed in lab-based clinical trials while maintaining greater ecological validity and translational value in the lives of participants and clinicians.

An important strength of our study is the creation of latent factors to examine the effects of the intervention for domains of cognitive functioning. We administered a broad battery of cognitive tests to implement latent variable modeling to identify common variances across individuals that are "core" to the constituent cognitive domain. One of the key methodological advantages of employing latent variable modeling is that it creates weighted composites by identifying covariance in performance across tasks—thus yielding factors with measures that are strongly correlated with one another. This reduces biases due to measurement error, any test-specific effects that may influence performance, or other external factors that may influence test performance [74,75].

Our exploratory factor analysis, which included 16 different metrics across various domains of functioning, yielded three latent factors. Our primary outcome variable of the study—a combined working memory/processing speed factor—included performance from tasks that have been traditionally conceptualized as "pure" measures of working memory and processing speed, respectively. However, within this sample of individuals with MS, these measures loaded on the same factor, and this corroborates with previous studies highlighting the centrality of both of these domains in the cognitive sequelae of MS [10,76]. Our intervention study, examining the impact of step-tracking on this latent factor of working memory and processing speed, will causally establish the efficacy of this intervention for improving functioning in the combined domain of working memory and processing speed. Furthermore, by employing advanced connectomic methodologies, we will be able to examine the mechanistic pathway through which increased physical activity may improve cognitive functioning, specifically working memory functioning in PwMS. By employing a previously derived and validated neuromarker of working memory functioning, our study will be the first to leverage the computational advances in neurocognitive whole-brain modeling to better understand the effect of lifestyle intervention.

The proposed research is innovative and relevant for MS because it represents a substantial deviation from the status quo. This study will determine whether, and to what extent, a lifestyle change (one that is easily accessible for PwMS and translatable to evidence-based clinical practices) causally improves cognitive function and the neural mechanisms of these gains. Additionally, the identification of a mechanism causally linking physical activity with improved cognition bolsters the field of cognitive rehabilitation in MS by setting a potential benchmark for future interventions upon which to build.

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Contributorship statement

R.S.P. designed the study, wrote the protocol paper, and incorporated edits from co-authors, H.R.M., E.J.D., and A.J. designed the study, acquired the data, and provided edits to the manuscript, A.S., M.E.F., L. C. acquired the data and provided edits to the manuscript, R.P., J.N. designed the study and provided edits to the manuscript, R.A. conducted the analysis and provided edits to the manuscript.

Data availability statement

Data supporting the findings of this study will be shared upon request.

Declaration of competing interest

R.S.P. has received speaking honoraria from Sanofi Genzyme. H.R. M., E.J.D., A.S., M.E.F., A.J., L.C., R.P., R.A. report no conflicts of interest. J.A.N. has received research grants from Biogen Idec, Genzyme, Novartis, PCORI, ADAMAS and Alexion. She has received consulting fees and honoraria from Biogen, Genentech, GW Pharmaceuticals, EMD Serono, Bristol Myers Squib, Novartis, Alexion, Viela Bio and the American Academy of Neurology.

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Appendix A. Supplementary data

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