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Protocol for a systematically-developed, phase I/II, single-blind randomized controlled trial of treadmill walking exercise training effects on cognition and brain function in persons with multiple sclerosis

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ABSTRACT

Slowed cognitive processing speed (CPS) is a common and debilitating consequence of multiple sclerosis (MS) that is notoriously difficult to treat. As such, we undertook a systematic line of research that indicated that supervised, progressive treadmill walking exercise (TMWX) training might improve CPS and brain functioning among fully-ambulatory persons with MS. The current study will be the first adequately-powered, single-blind randomized controlled trial (RCT) that examines the efficacy of 12-weeks of TMWX training compared with an active control condition on CPS, thalamocortical brain connectivity (based on resting-state fMRI), and exploratory functional outcomes in 88 fully-ambulatory persons with MS who present with slowed CPS. The intervention condition involves supervised, progressive TMWX training 3 times/week over 12-weeks; this initially involves 15-min of light-to-moderate intensity TMWX that progresses up to 40-min of vigorous intensity TMWX. The active control condition involves supervised, minimal intensity, stretching-and-resistance exercise that will be delivered on the same frequency as the intervention condition. The primary study outcomes involve Symbol Digit Modalities Test performance (i.e., CPS) and fMRI-based measures of thalamocortical resting-state functional connectivity. Exploratory study outcomes involve measures of community participation, activities of daily living, quality of life, and functional mobility. All study outcomes will be administered before and after the 12-week study period by treatment-blinded assessors. If successful, the current study will provide the first Class I evidence for the effects of TMWX training as an approach for improving CPS and its neural correlate, and possibly mitigating the impact of slowed CPS on functional outcomes in MS.

1. Introduction

Cognitive impairment is prevalent, impactful, and poorly-managed in multiple sclerosis (MS). Upwards of 67% of patients demonstrate cognitive impairment based on neuropsychological testing [1]. Such cognitive impairment primarily manifests as slowed cognitive processing speed (CPS), as well as impaired learning and memory, and executive dysfunction, but less so as impairment in intellectual functions and language skills [1]. Of note, MS-related impairments in learning and memory and executive functioning may be a by-product of a fundamental deficit in CPS [2]. MS-related CPS impairment contributes to reduced community participation, ability to perform activities of daily living, quality of life (QOL), and functional mobility [1]. There are no FDA-approved pharmacological treatments (i.e., disease modifying therapies (DMT)/symptomatic treatments) for CPS impairment in MS. Cognitive rehabilitation represents a promising approach to improve some cognitive domains in MS, but there is a lack of evidence supporting cognitive rehabilitation for directly targeting CPS in persons with MS who have objective CPS impairment [3,4]. This collectively underscores the critical importance of identifying new approaches for managing CPS impairment in MS, particularly those that can result in secondary health and functional benefits. One particularly promising

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approach is exercise training [5,6].

There is an exceptionally strong and consistent body of literature supporting exercise training effects on cognition across the lifespan (i.e., healthy children through older adults) [7]. By comparison, there have been several RCTs of exercise training and cognition in MS, and the results of those studies have been equivocal [8–18]. This may be based on methodological flaws (e.g., lack of inclusion of a physical fitness outcome measure as a manipulation check for documenting the success of an exercise training intervention); lack of inclusion of cognitively-impaired samples; and inconsistent focus on cognition as a primary outcome [4,19]. Relatedly, none of the exercise training RCTs in MS included a systematically developed exercise stimulus designed for improving cognition nor considered the role of brain systems subserving exercise training effects on CPS.

The current study will be the first adequately-powered RCT that examines the efficacy of 12-weeks of treadmill walking exercise (TMWX) training compared with an active control condition on CPS and brain function based on thalamocortical resting-state functional connectivity (RSFC) in fully-ambulatory persons with MS who present with slowed CPS. The current study will examine a potential mechanism based on neuroplasticity for progressive TMWX training effects (i.e., increased thalamocortical RSFC) on CPS. The present study further will explore the potential impact of progressive TMWX training on community participation, ability to perform activities of daily living, QOL, and functional mobility. Such a RCT builds upon extensive and systematic pilot testing for a direct examination of the efficacy and possible mechanisms of TMWX training for improving CPS, its neural correlate, and functional consequences in persons with MS who most need such an intervention.

2. Methods

2.1. Systematic development of current RCT

We have spent the past several years systematically delineating an optimal exercise training intervention for improving cognition in persons with MS. This involved a stepwise process of identifying (a) the optimal domain(s) of fitness (i.e., cardiorespiratory fitness (CRF) or muscular strength) for improving cognition; (b) the cognitive domain(s) that would be most sensitive to exercise; (c) MS subsamples who would be likely to demonstrate cognitive benefits with exercise; and (d) the optimal exercise stimulus itself (i.e., modality [type] and intensity) for improving cognition [20–27]. Collectively, the results from our rigorous, systematic line of research indicated that an optimal exercise training intervention involves progressive (i.e., both intensity and duration) TMWX for improving CPS, in particular, among fully-ambulatory persons with MS.

Consequently, the aforementioned systematic line of cross-sectional and non-RCT research led to the initial testing of such an intervention in a pilot RCT of progressive TMWX training and its effects on CPS and brain function in 10 fully-ambulatory females with MS (median EDSS = 3.0) [28,29]. Of note, half of the sample demonstrated slowed CPS at entry based on initial Symbol Digit Modalities Test (SDMT) scores 1 *SD* below the regression-based normative score for healthy controls [30]. Participants were randomly assigned into either (a) 12-weeks of supervised TMWX training that progressed from 15 min of light intensity TMWX up to 40 min of vigorous intensity TMWX that took place 3 times per week based on American College of Sports Medicine (ACSM) guidelines [31] (see Table 1) or (b) waitlist control conditions. All participants were asked not to undertake additional exercise training (i.e., joining a new gym) for the duration of the RCT. Participants underwent measurement of CPS (SDMT) and brain function (thalamocortical resting-state functional connectivity (RSFC) based on fMRI) before and after the 12-week study period; all baseline and follow-up assessments were performed by treatment-blinded assessors. We further included a measure of CRF (i.e., VO_{2peak} based on a graded exercise test (GXT) on a treadmill) as a manipulation check for documenting the success of the intervention.

Table 1
Exercise prescription and progression over the 12-week period for treadmill walking exercise training condition based on pilot work and American College of sports medicine guidelines.

Week	Sessions	Exercise intensity	Exercise duration	Training stage
Baseline testing				
1	1–3	40–50% VO_2R/HRR	15–20 min	Initiation
2	4–6	40–50% VO_2R/HRR	20–25 min	Initiation
3	7–9	50–60% VO_2R/HRR	20–25 min	Improvement
4	10–12	50–60% VO_2R/HRR	25–30 min	Improvement
5–6	13–18	60–70% VO_2R/HRR	25–30 min	Improvement
7–8	19–24	60–70% VO_2R/HRR	30–35 min	Improvement
9–10	25–30	70–80% VO_2R/HRR	30–35 min	Maintenance
11–12	31–36	70–80% VO_2R/HRR	35–40 min	Maintenance
Follow-up testing				

Note: VO_2R = oxygen consumption reserve; HRR = heart rate reserve.

The 12-week period of TMWX training was well-tolerated, with all 5 participants attending at least 83% of the training sessions. There further were no adverse events and all 5 participants (100%) complied with the exercise prescription. This was not unexpected considering that we included principles based on social cognitive theory (SCT [32]) for maximizing attendance and compliance. There were large, non-statistically significant intervention effects on SDMT performance (Cohen's $d = 0.95$) whereby persons who underwent TMWX training demonstrated a 3-point increase in SDMT scores; those who underwent the waitlist control condition demonstrated a clinically-meaningful [33], ~4-point decrease in SDMT scores [28]. There were large effects on VO_{2peak} ($d = 1.08$) such that persons who underwent TMWX demonstrated a 14% improvement in CRF, whereas there was minimal change (i.e., 1% decrease) for those in the control condition. There were large intervention effects on RSFC between the thalamus and right superior frontal gyrus (SFG) ($d = 1.92$) and left medial frontal gyrus (MFG) ($d = 1.70$), respectively, such that persons who underwent TMWX training demonstrated increases in thalamocortical RSFC whereas those who underwent the waitlist control condition demonstrated decreased thalamocortical RSFC [29]. The change in VO_{2peak} was moderately associated with change in SDMT scores ($\rho = 0.60$), RSFC between the thalamus and right SFG ($\rho = 0.48$), and RSFC between the thalamus and left MFG ($\rho = 0.54$). The change in SDMT performance was moderately associated with changes in RSFC between the thalamus and right SFG ($\rho = 0.42$) and RSFC between the thalamus and left MFG ($\rho = 0.53$) [29]. This pattern of preliminary results supports a potential adaptive compensatory mechanism [34] whereby progressive TMWX training improves CPS through increased thalamocortical RSFC.

The progressive TMWX training intervention is highly promising for improving CPS based on systematic preliminary data and pilot testing, but it has not yet been delivered in an adequately-powered sample of persons with MS who have slowed CPS. This is the critical next step for research on exercise and cognition in MS, as no prior RCTs of exercise have specifically recruited persons with MS-related cognitive impairment *a priori* [19]. This methodological aspect is especially noteworthy, as the current study will be the first examination of exercise training as a potential *treatment* for slowed CPS in fully-ambulatory persons with MS [19]. We further highlight that our pilot RCT did not include an active control condition that accounted for attention and social contact, nor outcomes associated with functional consequences of MS-related CPS impairment [28,29]. The current RCT overcomes those limitations and could substantially advance the current line of research towards causation, and perhaps most importantly, provide a rigorous examination of the efficacy of TMWX as a possible *treatment* for MS-related CPS impairment (i.e., Class I evidence).

2.2. Experimental overview and hypotheses

The study protocol has been approved by the University of Alabama at Birmingham (UAB) Institutional Review Board (IRB) and further is registered at clinicaltrials.gov: NCT03677440. All potential protocol modifications will be approved by the UAB IRB and will be reported at clinicaltrials.gov. The current study, data collection, and intervention will take place at UAB in Birmingham, AL, USA. This study involves a single-blind, Phase I/II RCT on the effects of supervised TMWX training compared with an active control condition (i.e., minimal intensity stretching-and-resistance exercise) on CPS, thalamocortical RSFC, and downstream functional outcomes (i.e., community participation, activities of daily living, QOL, and functional mobility) in 88 fully-ambulatory (i.e., Expanded Disability Status Scale (EDSS) $\leq$ 4.0) persons with MS who have objective impairment in CPS. The primary study outcomes involve the SDMT as a neuropsychological measure of CPS and neuroimaging measures of thalamocortical RSFC. The secondary study outcomes involve measures of community participation, activities of daily living, QOL, and functional mobility. CRF outcomes will be included as a manipulation check for documenting the success of the intervention for improving aerobic power.

During baseline, eligible participants who demonstrate scores on the SDMT $\geq$1 SD below the regression-based normative mean will first complete a battery of neuropsychological tests addressing CPS; a maximal, GXT on a motor-driven treadmill to measure CRF; an MRI scan for measurement of thalamocortical RSFC; and a battery of self-report and objective measurements of community participation, ability to perform activities of daily living, QOL, and functional mobility. Those outcomes will be measured by assessors who are uninvolved in the exercise training (i.e., treatment blinded assessors). After baseline testing, participants will be randomly assigned to either the intervention or active control conditions using concealed allocation (i.e., opaque, sealed envelopes). Participants further will be masked to condition (i.e., unaware that the TMWX training condition represents the intervention condition and the minimal intensity stretching-and-resistance exercise condition represents the active control condition) and these are undertaken in isolated locations within the research facility.

The intervention condition will include 12-weeks of supervised, progressive light, moderate, and vigorous intensity TMWX, and will be based on ACSM guidelines for exercise prescription [31] and pilot work [23,25,28,29]. The exercise training itself will take place 3 times per week over 12-weeks, and will be facilitated by certified exercise leaders. The exercise prescription will initially consist of 15–20 min of light-to-moderate intensity TMWX and eventually progress to 35–40 min of vigorous intensity exercise by week 12 (Table 1). We note that this exercise stimulus is identical to that of our pilot RCT [28,29]. The active control condition will involve minimal intensity stretching-and-resistance exercise that will be delivered using the same frequency and duration of the TMWX condition and facilitated by certified exercise leaders. This is a methodological improvement over our pilot RCT that involved a waitlist (i.e., passive) control condition [28,29]. We further note that the intervention and active control conditions are identical to those of a separate, ongoing study of the effects of TMWX training on learning and memory, and hippocampal volume/connectivity outcomes in persons with MS who have impairments in learning new information [35]. Regardless of the assigned condition, all participants will be asked to not undertake additional exercise (i.e., not join a gym and begin exercising) over the duration of the study. The CPS, RSFC, functional, and CRF outcomes will be assessed again following the 12-week study period by treatment blinded assessors.

The primary hypothesis is that those who undergo TMWX training will demonstrate larger improvements in CPS and larger (adaptive) increases in thalamocortical RSFC than those who undergo the active control condition of minimal intensity stretching-and-resistance exercise. We further hypothesize those who are randomly assigned to the TMWX training condition will demonstrate improvements in community participation, ability to perform activities of daily living, QOL, and functional mobility relative to those in the control condition.

2.3. Participants

2.3.1. Sample size

We plan to enroll 88 fully-ambulatory persons with MS (i.e., 44 per condition) who have objective impairment in CPS; this is based on a power analysis and presumed 25% attrition. The minimal sample size of 66 persons with MS (i.e., 33 per condition) was determined based on power analysis using previous effect sizes from our preliminary RCT of TMWX training on CPS outcomes (i.e., $\eta_p^2 = 0.11$) and standard assumptions of Type I error (0.05) and power (0.80) based on analysis of covariance (ANCOVA) on follow-up SDMT scores, controlling for baseline SDMT score [28]. We note that this rate of attrition exceeds that of the overall average of exercise training studies among persons with MS based on a systematic review [36] making our calculations conservative.

2.3.2. Recruitment

Prospective participants will be recruited directly through the UAB MS Center, the Alabama-Mississippi Chapter of the National MS Society (NMSS), and our laboratory database of previous participants with MS who have inquired about participating in exercise studies. Advertisements for the study will be distributed through the UAB MS Center, facilitators of local MS support groups, *MS Connection* publications, and e-mail distributions. As a backup plan, we may recruit prospective participants with MS through the North American Research Committee on Multiple Sclerosis (NARCOMS) patient registry or iConquerMS if enrollment is slow.

2.3.3. Inclusion/exclusion criteria

All participants will be between the ages of 18–59, have a neurologist-verified, clinically definite MS diagnosis based on established criteria [i.e., [37]] and be fully-ambulatory based on EDSS scores between 0 and 4.0. All participants will demonstrate objective impairment in CPS based on scores from an alternate version of the SDMT at least 1.0 *SD* below the regression-based normative score for healthy controls that accounts for age, sex, and education [30]. Participants will be relapse-free for at least 30 days (i.e., relative neurologic stability), and will not have a history of schizophrenia, bipolar disorder I or II, major depressive disorder, or substance-abuse disorders. Participants further will not be taking medications that can affect cognition (e.g., antipsychotics, benzodiazepines), and all participants will be on a stable FDA-approved disease-modifying therapy (e.g., interferon beta-1a; interferon beta-1b; glatiramer acetate; natalizumab; dimethyl fumarate, etc.) regimen for at least 6 months. Participants will have corrected vision better than 20/80, be right-handed (to control for organization of the brain), and will not have known/diagnosed cardiovascular, metabolic or renal disease based on ACSM exercise preparticipation health screening recommendations [38]. Persons who have known/diagnosed cardiovascular, metabolic, or renal disease who are asymptomatic will be included only with a physician's approval. Participants further will have a low risk for contraindications for MRI based on: (a) not having metal (e.g., non-MRI compatible aneurysm clips, metal shards in the body or eyes, or recently placed surgical hardware) or electronic devices (e.g., pacemaker, cochlear implant) within the body. Participants will not be meeting public health guidelines for participating in physical activity (i.e., at least 150 min per week of moderate-to-vigorous aerobic activity) based on the Godin Leisure-Time Exercise Questionnaire [39] in order to minimize potential ceiling effects of the TMWX training intervention on CRF. Participants will not be actively engaging in cognitive rehabilitation over the course of the study.

2.4. Outcome measures

All outcome measures will be assessed by treatment-blinded assessors who have undergone extensive training in the collection of neuropsychological, mobility, and exercise data among persons with MS. The outcome assessments further will occur in a separate room than the intervention or control conditions to prevent possible experimental bias.

2.4.1. CPS

The primary study outcome for measuring CPS involves the oral version of the SDMT [40]. This test has emerged as the best predictor of future cognitive decline in persons with MS, and is often considered the best-characterized neuropsychological measure of generalized cognitive impairment in this population [41]. Briefly, the SDMT involves a key that pairs 9 single-digit numbers with 9 abstract geometric symbols. Participants are presented with an array of 110 geometric symbols, and are asked to voice the correct numbers that correspond to each symbol as quickly as possible. The primary SDMT outcome is the total number of correctly provided symbol-digit pairs in 90 s (i.e., raw score).

The current study includes other exploratory neuropsychological measures involving CPS. We note that many of those measures are not pure measures of CPS per se, but rather are speeded neuropsychological tests that involve a large CPS component. Those measures include the 3″ and 2" Paced Auditory Serial Addition Test (PASAT; [42]), modified flanker task [43], Pattern & Letter Comparison Tests [44], Delis-Kaplan Executive Function System (DKEFS) Trail-Making & Color-Word Interference Tests [45]. Those measures will be included to examine the generalizability of the effects of TMWX training on the overall construct of CPS. All neuropsychological testing will occur in a quiet, sound-dampened room in the Exercise Neuroscience Research Laboratory (ENRL) at UAB.

2.4.2. Thalamocortical RSFC

Participants will undergo neuroimaging, which will include structural imaging as well as a resting-state functional scan. The MR instrument that will be used is an FDA-approved Siemens MAGNETOM Prisma 3 T clinical imager housed in the Civitan International Neuroimaging Research Center at UAB. Each scan session will begin with the acquisition of high-resolution T1-weighted axial anatomical images (MP-RAGE). This 3D isotropic sequence will be acquired sagittally (TR = 2100 ms, TE = 3.41 ms, flip angle = 9°, effective TI = 900 ms, 256 × 256 matrix, FOV = 256 mm, NEX = 1, 176 slices, 1.00 mm slice thickness, 0 mm skip). Total imaging time for this sequence is 4 min 53 s. In addition, an inversion-recovery sequence will be acquired axially (TR = 9000 ms, TE = 91 ms, flip angle = 150°, 256 × 256 matrix, FOV = 256 mm, NEX = 1, 50 slices, 3 mm slice thickness, 0 mm skip). Together, these scans will be used for volumetric analyses and for image segmentation and normalization of the resting-state fMRI scan. Functional imaging will consist of multi-slice gradient echo, T2*-weighted images acquired with echoplanar imaging (EPI) methods (TE = 30 ms; TR = 2000 ms; FOV = 220 mm; flip angle = 90°; slice thickness = 3 mm contiguous, matrix = 64 × 64, in-plane resolution = 2.50 mm^2). In order to provide coverage of the entire brain, a total of 32 images will be acquired in the axial plane. For the resting-state scan, 180 volumes will be acquired.

Preprocessing of the RSFC data will be performed using AFNI software (http://afni.nimh.nih.gov/afni/). The first three volumes will be removed in order to control for saturation effects. Preprocessing steps include slice timing correction, realignment to an image exactly halfway through the acquisition run using affine transformation, co-registration to the T1 MPRAGE image for localization of activated areas, smoothing (6 mm FWHM) to minimize anatomical differences and increase the signal to noise ratio, scaling each voxel to the grand mean intensity of that voxel (across the acquisition run), high-pass filtering (150 s), and normalization using a nonlinear approach (3dQwarp) to a standardized T1 template from the Montreal Neurological Institute (MNI). In all cases, the data will be checked for excessive motion (a shift of $>$ 3.5 mm, or 1° of angular motion) and for spikes (using the Root Mean Squared Error [RMSE] of each volume relative to a reference volume [which will be the volume half-way through the acquisition run]). Data acquisition runs with excessive motion will be discarded. Individual acquisitions with a RMSE amplitude that exceeds the 75th percentile plus the value of 150% of the interquartile range of RMSE for all volumes in a given run will be excluded from further analysis using the 'censorTR' function in 3dDeconvolve. The motion parameters from the realignment step will be used as regressors of no interest in the deconvolution, and the residuals will be saved.

Using a seed-based analytical approach, a seed (radius = 3 mm) will be placed in the thalamus (i.e., bilateral ventroposterior lateral nuclei). Time series from those seeds will be correlated with time series from every voxel in the brain. We will then *z*-transform the correlation coefficients (Fisher's *z*), and the resulting statistical maps will be used in the group-level analyses. We will use the MNI atlas that is part of the AFNI distribution to create a mask that will be applied to each subject's data after it has been warped into standard MNI space. We will use these ROIs to guide subsequent voxel-wise analyses. These procedures have been successfully used for documenting changes in thalamocortical RSFC in our pilot RCT of TMWX training on cognition in persons with MS [29]. Importantly, all MRI processing and analyses will be performed by an off-site co-investigator (GRW at Kessler Foundation) who will be blinded to condition. To our knowledge, this is among the first exercise RCTs in any population to include this additional level of rigor to enhance the proposed trial's reproducibility.

2.4.3. Functional outcomes

Functional outcomes include measures of community participation, ability to perform activities of daily living, QOL, and functional mobility. To measure community participation, we will administer the Community Integration Questionnaire (CIQ; [46]). This measure is particularly sensitive to the effects of MS-related CPS impairment [47]. We will administer the Lawton-Brody Instrumental Activities of Daily Living (IADL) scale [48] as a measure of ability to perform activities of daily living; worse IADL performance has been associated with lower SDMT scores in persons with MS [49]. We will administer the Multiple Sclerosis Impact Scale-29 (MSIS-29; [50]) as a self-report measure of MS-specific QOL; scores on this questionnaire have been strongly associated with performance on the SDMT [51]. Lastly, we will measure functional mobility using the six-minute walk (6 MW), Timed 25-Foot Walk (T25FW) test, and Life-Space Mobility Assessment (LSMA). The 6 MW is a measure of walking endurance that has been consistently associated with CPS based on SDMT scores among persons with MS [22,28,52]. The T25FW is considered the best-characterized measure of MS-related mobility and has been associated with MS-related cognitive impairment [53]. The LSMA is a measure of real-world mobility that is a well-validated, composite measure of a person's frequency of movement in geographically defined life-space zones [54].

2.4.4. CRF

CRF will be measured as peak oxygen consumption (VO_{2peak}), using a maximal, GXT undertaken on a motor-driven treadmill (Trackmaster TMX428CP, Lawrence, KS) with an open-circuit spirometry system (ParvoMedics True One 2400, Sandy, UT) for analyzing expired gases based on a modified Balke protocol in the ENRL at UAB. This protocol was successfully used in our pilot RCT [28,29] and is consistent with the ACSM guidelines for exercise testing of MS patients [31]. The test will be preceded by a 3-min warm up. The initial work rate for the GXT will be at a brisk, but submaximal pace (derived from the baseline 6 MW speed), and the grade will continuously increase at a rate of 2.0% every 2-min until the participant reaches volitional fatigue. Participants are asked not to use handrails unless it is absolutely necessary for safety reasons. Heart rate (HR) and rating of perceived exertion will be

recorded every minute during the test. VO_{2peak} will be expressed in $ml \cdot kg^{-1} \cdot min^{-1}$ based on highest recorded 20-s VO_2 value when two of four criteria are satisfied: (1) VO_2 plateau with increasing grade; (2) respiratory exchange ratio ≥ 1.10; (3) peak heart rate within 10 $beats \cdot minute^{-1}$ of age-predicted maximum (i.e., ~1 SD); or (4) peak rating of perceived exertion ≥17. The test will be followed by a 3-min cool-down period. Data from the GXT further will be used for prescribing TMWX training [28,31,35].

2.4.5. Disability status

Participants will undergo a neurological examination for generating a baseline EDSS score; this is not a study end-point, but rather for characterizing the sample. All participants will be fully-ambulatory (i.e., EDSS scores ≤4.0).

2.5. Intervention condition

The intervention condition will include 12-weeks of supervised, progressive light, moderate, and vigorous intensity TMWX training based on ACSM guidelines for maximizing adaptations with exercise training. This will occur in a laboratory setting within the ENRL that is separate from the location of the active control condition to minimize the possibility of contamination. Full details on the TMWX training condition are presented elsewhere [35]. Briefly, the exact TMWX prescription is presented in Table 1 and further represents the identical stimulus that was included in our pilot RCT that demonstrated improvements in CPS, thalamocortical RSFC, and CRF in persons with MS [28,29]. The TMWX training itself will be led by certified exercise leaders who are not involved in the collection of outcome assessments. At the outset of each session, participants will be fitted with a Polar HR Monitor (Oy, Finland), and HR will be monitored continuously throughout each session. Each session will begin with a 5 min warm-up, followed by the exercise; the target TMWX intensity (i.e., based on heart rate reserve/oxygen consumption reserve (HRR/VO_2R) ranges) will be maintained for as long as possible during each exercise period. This will be followed by a 5 min cool-down. We will define compliance (i.e., within-session adherence) as exercising within the prescribed HRR/VO_2R range for at least 90% of each exercise session. Compliance will be monitored and recorded in real-time by the certified exercise leaders. Further, we will apply highly developed principles and techniques associated with SCT to maximize adherence (i.e., attendance) and compliance with the intervention, as has been done in previous RCTs from our laboratory [22,55–57]. This will involve certified exercise leaders delivering topics for enhancing adherence and compliance (i.e., self-efficacy, goal setting, overcoming barriers to exercise, monitoring of performance feedback, promotion of realistic outcome expectations, importance of social support) during actual exercise training sessions via the supervision of a co-investigator (RWM). Participants will complete an exercise log at the conclusion of each session for better characterizing the experience with the intervention. Log data will include ratings of perceived exertion, well-being, enjoyment, and mental/physical fatigue. Throughout each session, we further will collect data on treadmill speed and grade for improving the rigor and reproducibility of the intervention [35].

2.6. Active control condition

The active control condition will involve supervised, minimal intensity stretching-and-resistance exercise involving muscle groups of the upper and lower extremities in order to control for the effects of social contact and attention. The active control condition will be delivered using the same frequency and duration of the TMWX training condition. As is the case for the TMWX training condition, stretching-and-resistance exercise sessions will be led by certified exercise leaders who are not involved in the collection of outcome assessments. Full details on the minimal intensity stretching-and-resistance exercise condition are presented elsewhere [35]. Briefly, throughout each session, participants will wear a HR monitor, and we will collect data on HR and ratings of perceived exertion to ensure that this condition occurs at a low intensity. As is the case for the intervention condition, participants will complete an exercise log at the conclusion of each session that includes data on ratings of well-being, enjoyment, and mental/physical fatigue. This stimulus has been included as a control comparison condition in a recent exercise training RCT in persons with MS and did not result in cognitive improvements and was well-received with no increase in drop-out compared with progressive exercise training [58]. Further, we will apply the same principles and techniques associated with SCT for the active control condition at the same frequency as the intervention condition to maximize adherence and compliance. Regardless of the assigned condition, all participants will be asked to not undertake additional exercise (i.e., not join a gym and begin exercising) during this trial. In the event where a participant might be unable to attend a given TMWX/stretching-and-resistance exercise session, a make-up session will be scheduled as soon as possible.

2.7. Procedure

Participant flow through the study is presented in Fig. 1. Participant recruitment, contact, and screening will be undertaken via telephone and/or email by an ENRL project coordinator. If a participant satisfies initial inclusion/exclusion criteria, the project coordinator will request written verification from the participant's neurologist of a definite MS diagnosis and confirmation that the participant has been on a stable DMT regimen for at least 6-months. Upon receipt of those materials from the participant's neurologist, the project coordinator will schedule the participant for an in-person screening session (i.e., administration of SDMT, visual acuity, EDSS). If the participant satisfies in-person inclusion criteria, they will be eligible to complete baseline testing immediately following the in-person screening. Baseline testing will be led by assessors who are blinded to condition and assessments will be split over 2, non-consecutive days to minimize cognitive and physical fatigue. On the first day, participants will initially provide written informed consent followed by administration of the neuropsychological battery of CPS tests. Participants will then undertake objectively-measured functional outcome measurements (i.e., 6 MW, T25FW) followed by a 15-min rest period (to minimize physical fatigue), and then the GXT for measurement of CRF; the 6 MW informs the speed for the GXT. The second day of baseline testing will involve completion of the self-report functional outcome measures (i.e., CIQ, Lawton-Brody IADL, MSIS-29, LSMA) and the MRI protocol. Participants will be remunerated $100 for completing the baseline assessments.

After baseline testing, participants will be randomly assigned to either the TMWX training or active control conditions using concealment (i.e., opaque, sealed envelopes) and computerization by the study biostatistician (i.e., GRC) [35]. Participants further will be masked to the intent of the condition (i.e., unaware that the TMWX training condition represents the experimental condition and the stretching-and-toning exercise condition represents the active control condition). To do this, the study is advertised as a comparison of two different exercise programs on CPS in persons with MS. We note that it is not possible for participants or certified exercise leaders to be blinded to the actual condition (i.e., participating in TMWX or stretching-and-resistance exercise activities).

Participants will undertake the intervention or active control conditions as described above over a 12-week period. Participants will be remunerated $5 per TMWX/stretching-and-resistance exercise visit attended (i.e., up to $180 total) for travel expenses. Following the completion of the 12-week study period, participants will again undergo assessments of CPS, thalamocortical RSFC, functional outcomes, and CRF using the same procedures as baseline testing (i.e., follow-up testing). Follow-up measures, using alternate forms where possible, will

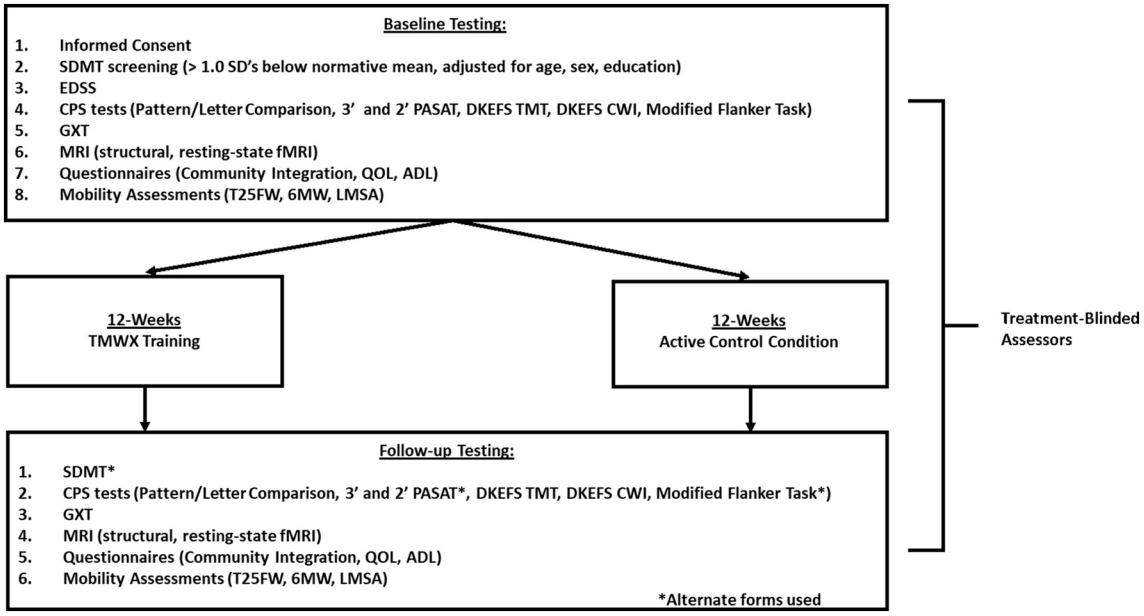

Fig. 1. Participant flow throughout the randomized controlled trial of the effects of treadmill walking exercise training compared with an active control condition on cognitive processing speed, brain function, and exploratory functional outcomes in fully-ambulatory persons with MS who demonstrate objective impairments in cognitive processing speed.
Note: 6 MW = six-minute walk; ADL = activities of daily living; CPS = cognitive processing speed; CWI = Color-Word Interference Test; DKEFS = Delis-Kaplan Executive Function System; EDSS = Expanded Disability Status Scale; fMRI = functional magnetic resonance imaging; GXT = graded exercise test; LSMA = Life-Space Mobility Assessment; MRI = magnetic resonance imaging; PASAT = Paced Auditory Serial Addition Test; QOL = quality of life; SD = standard deviation; SDMT = Symbol Digit Modalities Test; T25FW = timed 25-ft walk; TMT = Trail-Making Test; TMWX = treadmill walking exercise.

be administered by treatment blinded assessors. Participants will be remunerated $100 for completing the follow-up assessments.

2.8. Data integrity

All data will be entered, checked, and double-checked by UAB ENRL personnel under the direct supervision of the ENRL project coordinator (MDD) and study principal investigator (BMS). All ENRL personnel have undergone extensive training in good clinical practice and laboratory procedures. Given that the current study is not a multi-site, NIH-defined Phase III RCT, we do not include a formal data monitoring committee. In the event of an MS relapse or other adverse event, decisions on safety of continued participation will be made on a patient-by-patient basis, with the consultation of the study neurologist (JRR), and documented for reporting along with the main trial outcomes.

For both the TMWX and stretching-and-resistance exercise conditions, manuals of operating procedures were created for the certified exercise leaders, outlining the relative exercise prescriptions (i.e., frequencies, durations, intensities) as well as structured plans and contingencies for ensuring participant compliance. After several weeks of reviewing the manuals of operating procedures, the certified exercise leaders completed several acute TMWX/stretching-and-resistance sessions with both the study principal investigator (BMS) and project coordinator (MDD). Upon satisfactory completion of those sessions, the certified exercise leader was approved for training an actual participant. Further, the first time an exercise leader led a session with a participant was observed by the principal investigator to ensure appropriate delivery. Following that observation, the exercise leader is able to lead sessions independently. For both the TMWX and stretching-and-resistance conditions, fidelity is assessed based on random observations of training sessions by the principal investigator and study coordinator that occur on an approximate biweekly basis. The principal investigator and study coordinator make notations of errors, items that require improvement, and/or any other issues that need remediation in order to assure treatment integrity within and between subjects, as well as adherence to the exercise/stretching-and-toning protocols. The exercise leader is given verbal feedback following all random observations.

2.9. Statistical analysis

The data analyses will be overseen by a biostatistician (i.e., GRC) and follow intent-to-treat principles (i.e., include all persons once randomized regardless of adherence and/or compliance). In the case of a drop-out, missing data will be imputed by carrying the last observed value forward. We further will perform exploratory data analyses in only those who completed follow-up testing (i.e., completer's or per protocol analysis) and in those who demonstrated good adherence (i.e., attended at least 83% of sessions) and compliance [59]. The analytic plan will account for several potential confounders of the effects of progressive TMWX training on the outcome measures; these confounders include MS duration, BMI, age, sex, T_2-lesion volume, and relapse rate, if those variables differ between groups. Further, all study data are entered and analyzed in SPSS version 25 (IBM Inc., Armonk, NY).

The primary analysis will involve a statistically efficient, hierarchical step-down testing approach using ANCOVA models to examine differences in post-test outcomes of CPS and thalamocortical RSFC (i.e., examining group differences in follow-up outcomes, adjusting for baseline as covariate). The hierarchical step-down approach presents a series of conditional hypothesis tests after the primary hypothesis is assessed. This *a priori* specifies the importance and order of the testing so that each hypothesis is tested in order, until the first non-significant result occurs. Once a null-hypothesis is not rejected, all formal testing will stop, and all subsequent results will be reported as *post-hoc* and/or descriptive. This protects against Type I error as it assumes that the outcomes are correlated, and the overall *p*-value is protected by reporting the largest *p*-value for all the tests. As the primary study outcome involves CPS based on SDMT scores, we will first perform an ANCOVA model on follow-up SDMT score, with group (intervention or

control) as a between-subjects factor and baseline SDMT score as the covariate. If statistically significant (i.e., $p < .05$), we will then assess the effects of the intervention on the general construct of CPS using MANCOVA and on the individual CPS tests using separate, univariate ANCOVA models.

Regarding thalamocortical RSFC, the next set of analyses will involve performing ANCOVA models on follow-up RSFC between the thalamus and frontal cortical areas (e.g., SFG, MFG [29]), respectively, with group (intervention or control) as a between-subjects factor and baseline RSFC between the thalamus and frontal cortical areas, as the covariates. We will require an alpha of 0.05 (corrected for multiple comparisons) for significance for thalamocortical RSFC outcomes. The correction for multiple comparisons will be achieved by establishing a suitable voxel cluster-level threshold through Monte Carlo simulations (using the 3dClustSim program, part of the AFNI suite of image analysis programs). Based on our pilot work [28,29], we expect significant group differences in SDMT score and RSFC between the thalamus and frontal cortical areas, respectively, at follow-up after controlling for baseline scores, whereby participants who are randomly assigned to the intervention group will demonstrate greater SDMT scores and stronger thalamocortical RSFC at follow-up compared with those who are randomly assigned to the control group.

As there are multiple, interrelated functional outcomes that are included as exploratory study outcomes, we will perform a multivariate analysis of covariance (MANCOVA) on follow-up scores for the functional outcomes controlling for baseline values as an approach for examining the consistency of the potential intervention effects (i.e., intervention vs. control as the between-subjects factor) on this overall construct (i.e., how functional consequences of CPS impairment may change together with TMWX training). This will involve clustering outcomes into like sets of variables. We further will explore the effects of the intervention on the individual outcomes using separate exploratory, descriptive, univariate ANCOVA models on follow-up CIQ scores (i.e., community participation), Lawton-Brody IADL scores (i.e., ability to perform activities of daily living), MSIS-29 scores (i.e., QOL), 6 MW, T25FW, and LSMA performance (i.e., functional mobility), respectively, with group (intervention or control) as a between-subjects factor and baseline CIQ, Lawton-Brody IADL, MSIS-29, 6 MW, T25FW, and LSMA scores, respectively, as the covariates. We expect significant and consistent group differences in those functional outcomes at follow-up after controlling for baseline scores, whereby participants who are randomly assigned to the intervention condition will demonstrate better follow-up scores on functional outcomes compared with those who are randomly assigned to the control condition.

As a manipulation check, we will perform similar ANCOVA models to examine differences in post-test CRF [VO_{2peak}] (i.e., examining group differences in follow-up VO_{2peak}, adjusting for baseline as covariate). We expect statistically significant group differences in VO_{2peak} at follow-up, after controlling for baseline VO_{2peak}, such that those who underwent the TMWX training intervention will have greater CRF relative to those who underwent the active control condition.

Effect sizes will primarily be expressed as partial eta-squared (η_p^2) [60]. Effect sizes further will be reported as Cohen's d in order to characterize the standardized mean difference of the effects of TMWX training on the outcomes [60] and for ease of inclusion in subsequent meta-analyses [60]. The effect sizes from the interaction terms from the ANCOVAs on CPS, thalamocortical RSFC, functional outcomes, and CRF will serve as effect sizes for the subsequent power analyses required for informing the development of a multi-site, Phase II/III RCT.

2.10. Trial status

The trial was successfully registered on clinicaltrials.gov on September 14, 2018, and the UAB Institutional Review Board approved the study on October 1, 2018. Recruitment for the first wave of participants began on February 6, 2019. The final outcome assessments for all participants are planned for August 1, 2022.

3. Discussion

The current Phase I/II RCT represents the first adequately-powered, systematically-developed exercise training intervention for improving CPS (i.e., the most common MS-related cognitive deficit) and thalamocortical RSFC in fully-ambulatory persons with MS who have impaired CPS. This approach was developed based on several pilot studies and uniquely overcomes several key methodological limitations associated with existing exercise RCTs on cognition in MS [19]. Importantly, this study is the first RCT of exercise training to selectively recruit persons with slowed (i.e., impaired) CPS. This is a critical methodological study component, as potential treatment effects (i.e., beyond simply improving cognitive performance) of exercise on MS-related cognitive dysfunction can only be assessed if participants demonstrate objective cognitive impairment. This further overcomes a major problem in MS exercise research, whereby the participants do not generally demonstrate deficits in the outcome being studied [61]. Thus, the current proposal will provide the first Class I evidence for the efficacy of TMWX training as a potential rehabilitative approach to treat MS-related CPS impairment.

This efficacy study utilizes an exercise prescription that has previously demonstrated improvements in CPS [28], thalamocortical RSFC [29], and CRF outcomes among fully-ambulatory persons with MS. However, the next step for demonstrating efficacy of such an intervention involves the inclusion of an active, minimal-exercise control condition to account for the effects of attention and social contact associated with supervised exercise training. This is an advantageous methodological feature given that our pilot trial included a passive, waitlist control condition [28,29]. The inclusion of such an active control condition provides an opportunity to more directly attribute potential CPS, thalamocortical RSFC, and functional benefits to TMWX training. Across both conditions, we integrate well-established techniques based on SCT [32] for maximizing adherence and compliance, and minimizing attrition [35,55–57]. This is advantageous given many persons with MS have difficulty adopting physical activity behavior, despite the many benefits of supervised exercise training [61]. The current trial further includes CRF outcomes as a manipulation check for documenting the success of the TMWX intervention (i.e., demonstrating specificity of adaptations to TMWX training). We note that the inclusion of CRF outcomes is generally lacking in studies of exercise and cognition in MS [62].

One significant advance in research on exercise and cognition across the lifespan has been the focus on neuroimaging outcomes [7], yet no published RCTs of exercise training and cognition in MS have included neuroimaging approaches for measuring specific changes in brain function based on empirical preliminary data. The inclusion of functional neuroimaging outcomes, particularly thalamocortical RSFC, is critical for providing information on the potential neural mechanism(s) of exercise-related improvements in cognition in MS (e.g., [6,63]). This is primarily supported by preliminary data from our pilot RCT [29], as well as other evidence that thalamic dysfunction is consistently linked with MS-related CPS-impairment [64,65]. This too is consistent with preliminary cross-sectional data that suggest that frontal (i.e., right SFG, left MFG [66]) and thalamic [67] areas might be important regions of interest for examining aerobic exercise effects on the brain in this population. We further note that TMWX behavior requires selective communication between the thalamus and frontal cortex, and connectivity within this neural network is important for maximizing the speed of information processing when modifying behavior during changing environmental demands based on multisensory input [63]. Walking is a behavior that has been hypothesized not to become automatic over time, and progressive TMWX training might repeatedly activate the circuitry between the thalamus and frontal cortex, thereby resulting in improved thalamocortical RSFC over time (i.e., activity-

dependent neuroplasticity) [63]. This may result in a neural substrate explaining improved CPS with exercise training. The above mechanistic approach has not been directly tested in any population [68], but it is highly consistent with several general hypotheses for how exercise training might affect cognition at the brain-systems level (e.g., [6,68]), including a recent conceptual framework for integrative CNS plasticity among persons with MS [63]. This is consistent with recent studies of cognitive rehabilitation (i.e., repetitive, progressive cognitive training) in persons with MS that have reported improvements in cognition and concomitant increases in RSFC (e.g., [69,70]). Indeed, the present study is the first adequately-powered RCT of exercise training on cognition in MS to include targeted functional neuroimaging outcomes with direct relevance for brain adaptation with multisensory exercise input and behavioral regulation (i.e., thalamocortical RSFC), as a potential neural mechanism founded in a strong theoretical framework for the effects of TMWX training on CPS [63].

Importantly, impaired CPS is a major influence of functional outcomes in MS [1]. There is a paucity of data on functional consequences of exercise-related CPS improvement in this population, and we further include exploratory functional outcomes for examining the broader impacts of potential exercise-related CPS improvement. Those outcomes include measures of community participation, ability to perform activities of daily living, QOL, and functional mobility. This is important for better evaluating the efficacy of TMWX for managing MS-related cognitive impairment, given the focus on functional outcomes reflecting daily living that further are associated with CPS in this population [22,47,49,51,53]. The inclusion of exploratory functional outcomes set the stage for the development of larger, effectiveness trials of walking exercise for managing MS-related cognitive impairment in community-based settings.

Collectively, such methodological features are critical for reducing threats to internal validity (i.e., Type I error) and providing efficacy evidence for chronic TMWX as a behavioral approach for managing slowed CPS and its consequences in persons with MS who have the most need. This is consistent with recent recommendations for optimally positioning behavioral treatments for MS-related cognitive impairments towards implementation as a true standard-of-care [4]. If successful, the current study will provide the first Class I evidence for the effects of TMWX training as a rehabilitative approach to improve CPS, its neural correlate (i.e., thalamocortical RSFC), and possibly mitigate the impact of slowed CPS on functional outcomes in MS. This will ultimately inform the development of a multi-site, Phase III RCT for evaluating the effectiveness of such an approach that could eventually provide clinicians and MS patients with evidence and guidelines for using chronic exercise training as an approach for improving cognition and brain health.

Although the current proposal addresses a critical problem by applying a highly novel, systematically-developed exercise training intervention for improving CPS, thalamocortical RSFC, and functional outcomes among persons with MS who present with slowed CPS, there are several noteworthy limitations. First, the current proposal involves a relatively short intervention period and no long-term follow-up. Given that our small pilot RCT directly supports the feasibility and preliminary efficacy of 12-weeks of TMWX training on CPS and thalamocortical RSFC, the current adequately-powered proposal seeks to rigorously examine the potential treatment effects of that exact intervention on CPS, its potential neural correlate(s), and functional consequences. We believe this to be a necessary step prior to investigating the durability and sustainability of progressive TMWX training effects on those outcomes in subsequent large-scale studies. To that end, the present study will not examine the effectiveness of TMWX training on immediate and sustained changes in the primary outcomes in a large, national sample of persons with MS. Rather, the proposed study will advance our systematic and rigorous line of research by providing critical efficacy data prior to the development of a subsequent RCT for examining the effectiveness of the intervention for eventual translation into a community-based program. Another limitation is that the study sample will not involve persons with MS who present with substantial ambulatory disability. Rather, this proposal only focuses on persons with MS who are fully-ambulatory based on pilot data and safety concerns associated with TMWX training. Thus, the results of the current proposal might not be generalizable among all persons with MS, particularly those with severe ambulatory impairment. Finally, the present study will not directly compare the effects of TMWX training with cognitive rehabilitation as a control comparison condition on CPS. Instead, the proposed study includes an active, non-aerobic exercise training control condition in order to control for the potential effects of attention and social contact normally associated with supervised exercise training for testing the primary study hypothesis.

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