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Research paper

# Age and asymmetry of corticospinal excitability, but not cardiorespiratory fitness, predict cognitive impairments in multiple sclerosis

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ABSTRACT

*Background:* Cognitive impairment is a disabling and underestimated consequence of multiple sclerosis (MS), with multiple determinants that are poorly understood.
*Objectives:* We explored predictors of MS-related processing speed impairment (PSI) and age-related mild cognitive impairment (MCI) and hypothesized that cardiorespiratory fitness and corticospinal excitability would predict these impairments.
*Methods:* We screened 73 adults with MS (53 females; median [range]: Age 48 [21–70] years, EDSS 2.0 [0.0–6.5]) for PSI and MCI using the Symbol Digit Modalities Test and Montréal Cognitive Assessment, respectively. We identified six persons with PSI (No PSI, $n = 67$) and 13 with MCI (No MCI, $n = 60$). We obtained clinical data from medical records and self-reports; used transcranial magnetic stimulation to test corticospinal excitability; and assessed cardiorespiratory fitness using a graded maximal exercise test. We used receiver operator characteristic (ROC) curves to discern predictors of PSI and MCI.
*Results:* Interhemispheric asymmetry of corticospinal excitability was specific for PSI, while age was both sensitive and specific for MCI. MS-related PSI was also associated with statin prescriptions, while age-related MCI was related to progressive MS and GABA agonist prescriptions. Cardiorespiratory fitness was associated with neither PSI nor MCI.
*Discussion:* Corticospinal excitability is a potential marker of neurodegeneration in MS-related PSI, independent of age-related effects on global cognitive function. Age is a key predictor of mild global cognitive impairment. Cardiorespiratory fitness did not predict cognitive impairments in this clinic-based sample of persons with MS.

## 1. Introduction

Cognitive impairment in multiple sclerosis (MS) is a common yet overlooked disease complication that negatively affects physical functioning, quality of life, social participation, and self-efficacy (Lakin et al., 2021). Despite the 28–70 % prevalence of cognitive impairment in MS (Hoffmann et al., 2007; Kalb et al., 2018; Sumowski et al., 2018), its invisible nature makes true morbidity difficult to estimate (Lakin et al., 2021). It is therefore important to identify predictors of MS-related cognitive deficits (Sumowski et al., 2018).

Relative to age-matched controls, persons with MS-related cognitive impairments have deficits in cognitive processing speed, episodic memory, attention (Oreja-Guevara et al., 2019; Sumowski et al., 2018), and sometimes visuospatial, executive, and language functions (Benedict et al., 2020). In neuroimaging studies, the degree of cognitive impairment is related in part to the extent of subcortical white matter and cortical gray matter lesions; atrophy of cortical and deep gray matter; and aberrant neural network functional connectivity (Benedict et al., 2020; Sumowski et al., 2018). Thalamic atrophy, in particular, is an important marker of cognitive impairment and disability in MS (Amin and Ontaneda, 2020; Houtchens et al., 2007).

Recent work has also shown that transcranial magnetic stimulation (TMS)-based markers of corticospinal excitability are significantly different between individuals with and without MS-related cognitive impairments (Di Lazzaro et al., 2021; Lanza et al., 2022). Our group previously found statistically significant associations between interhemispheric asymmetry of corticospinal excitability and processing speed impairment (PSI) (Chaves et al., 2019), which were best explained by lower corticospinal excitability in the brain hemisphere corresponding to the clinically weaker upper extremity (Chaves et al., 2021b). It was hypothesized that a shift from a hyperexcitable neuroinflammatory, to hypoexcitable neurodegenerative, disease phenotype

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may explain this association (Dutta and Trapp, 2014).

MS-related PSI is a unique condition that should be distinguished from age-related mild cognitive impairment (MCI). Problems related to PSI are identifiable early in the disease course, predict future disability and functional impairments, and in some individuals can necessitate escalation of disease-modifying therapy (Benedict et al., 2020; DeLuca et al., 2020; Sumowski et al., 2018). Whereas persons with PSI have disabling cognitive complaints as early as their 30s (Staff et al., 2009), age-related MCI follows a more indolent course and usually affects individuals in their 50s or later (Benedict et al., 2020). A recent review of the literature suggested that, compared to age-related MCI, MS-related impairments involve reduced processing speed but superior memory, executive, and language functions (Chiang et al., 2022). In terms of neuroimaging findings, persons with age-related MCI in MS have a similar pattern of atherosclerotic cerebral small vessel disease to persons with MCI but without MS (DeLuca et al., 2015). Distinguishing these cognitive phenotypes is important for management and prognostication (Benedict et al., 2020; DeLuca et al., 2020; Sumowski et al., 2018).

As noted above, MS-related cognitive impairments are due in part to neuroinflammation, demyelination, and neurodegeneration (Barros and Fernandes, 2021; DeLuca et al., 2015), making therapeutic strategies that target these processes of interest (Pierson and Griffith, 2006). Cardiovascular exercise is one intervention that has been promoted as a critical component of cognitive rehabilitation in MS, and which may have disease-modifying potential (Motl and Sandroff, 2018; Motl et al., 2017; Ploughman, 2008). However, the effects of exercise interventions on attention, memory, executive function, and processing speed are small and inconsistent (Sandroff et al., 2016), due in part to heterogeneous and small samples, brief interventions, and poorly defined outcomes (Motl et al., 2017; Sandroff et al., 2022a,b). One proposed means to elucidate true effects of exercise interventions is to better characterize participants' baseline cognitive phenotype, cardiorespiratory fitness, and physical activity level (Motl and Sandroff, 2018; Motl et al., 2017; Ploughman, 2008). Likewise, while the literature supports cardiorespiratory fitness as protective against age-related MCI (Davenport et al., 2012), a meta-analysis of exercise interventions shows that novel exercise prescription imparts only a small beneficial effect on cognitive function, and that other unknown factors may moderate the fitness-cognition relationship (Ciria et al., 2023).

In terms of physical activity and cardiorespiratory fitness, the literature highlights relationships with both MCI and PSI. In a systematic review of studies in MS, both cardiorespiratory fitness (peak oxygen uptake [$VO_{2peak}$]) and physical activity level (accelerometry) were associated with cognitive processing speed but not executive function, memory, or attention (Sandroff et al., 2016). A more recent cross-sectional study found that cardiorespiratory fitness was related to processing speed only, but not visuospatial function, memory, language, or attention (Langeskov-Christensen et al., 2018). Other work showed that cardiorespiratory fitness and cognitive processing speed were only correlated in persons with objective PSI, but not those without impairments (Sandroff et al., 2017). The fitness-processing speed relationship is associated with greater gray matter volume in midline cortical structures and enhanced white manner microstructural integrity in sensorimotor-related regions and tracts (Prakash et al., 2010), including preserved structure of the thalamus and thalamic radiations (Prakash et al., 2010; Sandroff et al., 2022a,b). In age-related MCI, physical activity level is related to memory and executive, visuospatial, and language functions, but not processing speed (Chang, 2020). Overall, fitness effects on age-related MCI are putatively mediated by cerebrovascular health (Davenport et al., 2012), which is distinct from MS-related pathology that is driven in part by inflammatory lesions of gray and white matter, demyelination, oxidative stress, and Wallerian degeneration (Houtchens et al., 2007).

We conducted a cross-sectional study to explore predictors of cognitive impairments in MS. In a clinic-based sample of community-dwelling adults with MS, we aimed to: (1) identify and characterize cognitive deficits using validated screening tools for PSI and MCI; (2) examine differences in cognition, demographic and disease characteristics, lifestyle factors, cardiorespiratory fitness, and corticospinal excitability in MS participants with and without cognitive impairments; and (3) determine what factors best predict PSI and MCI. We hypothesized that cardiorespiratory fitness and corticospinal excitability would predict PSI and MCI.

## 2. Materials and methods

### 2.1. Participants

The local research ethics board approved the study (Ref#: 15.103). One-hundred-ten outpatients from a local MS clinic provided informed consent per the Declaration of Helsinki. Volunteers were $\geq$ 18 years old, diagnosed using 2010 or 2017 McDonald Criteria (Polman et al., 2011; Thompson et al., 2018), had Expanded Disability Status Scale (EDSS) scores $\leq$ 6.5 (Kurtzke, 1983), and had inactive and relapse-free disease for $\geq$ 3 months. All participants were English-speaking. We excluded participants with contraindications to exercise (Bredin et al., 2013) or TMS (Rossi et al., 2021), or who could not complete the entire study. We estimated sample size using G*Power 3 (Faul et al., 2007). We considered studies of cardiorespiratory fitness and corticospinal excitability in MS-related PSI and age-related MCI (Alagona et al., 2004; Sandroff et al., 2016), as well as studies of predictors of PSI in MS (Sandroff et al., 2013; Sandroff et al., 2017; Sandroff et al., 2015; Sandroff et al., 2019). From comparison studies, we estimated effect sizes (Cohen's *d*) (Cohen, 1988) of 0.7 and 4.1, respectively, for differences in cardiorespiratory fitness and corticospinal excitability. From prediction studies, we estimated a target effect size (Cohen's $f^2$) of 1.17. Using alpha = 0.05 and power = 0.80, we estimated a target sample size of 48–56 participants ($n$ = 24–28 per group).

### 2.2. Design and setting

This cross-sectional study took place on a single occasion at a neurorehabilitation research laboratory in a rehabilitation hospital. We gathered data from MS clinic charts and participants' self-reports. In the lab, participants underwent TMS testing and completed a graded maximal exercise test. Participants completed the study within 3 h. We blinded experimenters to group allocation.

### 2.3. Demographic, disease, and lifestyle characteristics

We gathered age, sex, MS type, disease duration, disability status (EDSS), comorbidities, and medications from clinic charts. In the lab, we measured height, body mass, and body mass index (Health O Meter®, McCook, IL, USA). We asked participants to self-report daily physical activity, including frequency, intensity, duration, and type (Wadden et al., 2018), which we used to calculate metabolic equivalent of task (MET)-hours per week of moderate- to vigorous-intensity physical activity (MVPA) (Ainsworth et al., 2011; Ploughman et al., 2015). Participants reported nutritional supplementation, recreational drug use (tobacco, alcohol, cannabis), and level of education (secondary, post-graduate, graduate).

### 2.4. Cognition and processing speed

To assess cognitive processing speed, we asked participants to complete the written Symbol Digit Modalities Test (SDMT) (Smith, 1982). The SDMT is a clinically meaningful, valid, and reliable test in MS, whose sensitivity and specificity for information processing deficits have been well established (Benedict et al., 2017; Drake et al., 2010). To determine whether participants had PSI, we compared written SDMT scores to written test norms based on age, sex, and education, from a large sample of English-speaking participants (Kiely et al., 2014). Scores

≤ 1.5 standard deviations (SD) below their respective norms indicated PSI (Parmenter et al., 2007).

To screen for age-related MCI, a trained rater administered the Montréal Cognitive Assessment (MoCA) (Nasreddine et al., 2005). The MoCA is valid and reliable in MS research for detecting MCI (Rosca and Simu, 2020). This test is sensitive but not specific for MCI in persons with MS (Rosca and Simu, 2020). We used a threshold MoCA score < 26 to identify MCI (Nasreddine et al., 2005). To characterize cognitive deficits, we derived MoCA index scores for attention, executive function, language, memory, orientation, and visuospatial function (Julayanont et al., 2014).

### 2.5. Depression, anxiety, and MS-related symptoms

Because these symptoms moderate cognitive impairment in MS (Ayache and Chalah, 2017), we asked participants to rate depression and anxiety using the Hospital Anxiety and Depression Scale (HADS) (Honarmand and Feinstein, 2009; Snaith, 2003; Zigmond and Snaith, 1983), and fatigue, pain, and heat sensitivity using 100 mm visual analog scales (Ploughman et al., 2010).

### 2.6. Neurophysiology

We examined corticospinal excitability of the stronger and weaker first dorsal interossei (FDI) using single-pulse TMS. This method is useful for characterizing the neurophysiology of MS-related impairments (Chaves et al., 2021b; Snow et al., 2019). We determined stronger and weaker hands using a calibrated dynamometer (Lafayette Instrument Corp., Lafayette, IN, USA) (Chaves et al., 2021b). A BiStim $200^2$ stimulator (Magstim Co., Whitland, UK), connected to a 70 mm figure-of-eight coil, delivered monophasic magnetic pulses. Experimenters held the coil tangential to the scalp with the handle oriented posterolateral to the midsagittal line at 45°, resulting in a posterior-anterior current (Rossini et al., 2015). We obtained the hotspot, maintained coil location, and recorded electromyographic (EMG) activity (2500 V/V amplification, 3 kHz sampling rate, 600 V/V gain, 5–550 Hz bandwidth) using the Brainsight interface (Rogue Research, Montréal, QC, Canada) (Chaves et al., 2021b). We sampled EMG activity 100 ms pre- to 800 ms post-stimulus. The hotspot was the area with the greatest motor evoked potential (MEP) amplitude in FDI, during a series of suprathreshold stimulations, while participants maintained a 10 % maximal tonic contraction. We processed TMS data offline using Signal v6.04 software (Cambridge Electronic Design, Cambridge, UK). We inspected MEPs for pre-stimulus artefact exceeding 100 μV and omitted < 1 % of trials.

We defined active motor threshold (AMT) as the minimum TMS intensity (percent maximal stimulator output [% MSO]) to elicit MEPs with a peak-to-peak amplitude of ≥ 200 μV in ≥ five of 10 trials during a 10 % maximal tonic contraction of FDI (Rossini et al., 2015). AMT assesses glutamate-mediated excitability of low-threshold neurons and reflects the bias level, or intrinsic excitability, of the motor cortical representation (hotspot) (Groppa et al., 2012; Rossini et al., 2015). In MS, reduced AMT reflects both demyelination and axonal damage (Snow et al., 2019).

During a 10 % maximal tonic contraction of FDI, we elicited MEPs using stimulation intensities between 105 % and 155 % AMT. We delivered six stimulations each in randomized blocks of 10 % AMT (36 trials total), using a randomized 4–10-second inter-trial interval, allowing participants a brief rest between blocks. We produced excitatory (eREC) and inhibitory (iREC) MEP recruitment curves, based on MEP amplitude (μV) and corticospinal silent period (CSP normalized to MEP amplitude, ms/μV) versus stimulation intensity (% AMT), respectively. MEP recruitment curves characterize input-output properties of corticospinal pyramidal neurons and inhibitory interneurons (Groppa et al., 2012; Rossini et al., 2015). We calculated the area under the eREC and iREC to characterize overall corticospinal outputs (Potter-Baker et al., 2016). MEP amplitude reflects voltage-gated ion channel and glutamatergic (facilitatory) activity, whereas CSP indexes GABAergic (inhibitory) activity (Rossini et al., 2015). In MS, these outcomes index axonal damage and excitotoxicity (Snow et al., 2019).

We also examined MEP latency as a proxy of corticomotoneuronal conduction (Groppa et al., 2012; Rossini et al., 2015; Snow et al., 2019). MEP latency was the height-normalized time (ms/cm) from TMS pulse to MEP onset (EMG amplitude > 2 standard deviations [SD] of mean background activity) (Groppa et al., 2012; Rossini et al., 2015). Increased MEP latency reflects demyelination causing reduced corticospinal conduction velocity (Snow et al., 2019).

Last, we examined the onset latency of the ipsilateral silent period (iSP) to index transcallosal inhibition (Giovannelli et al., 2009). Participants maximally contracted FDI while we stimulated over the hemisphere ipsilateral to the hand at 180 % of resting motor threshold (% MSO to elicit 50 μV MEPs in ≥ five of 10 trials at rest) (Chaves et al., 2021b; Rossini et al., 2015). We completed four trials per side, separated by inter-trial intervals of 10–15 s. EMG data were full-wave rectified and averaged across all trials. Mean pre-stimulus EMG amplitude (100 ms pre-stimulus) defined baseline muscle activity (Fleming and Newham, 2017; Giovannelli et al., 2009; Schmierer et al., 2002). Onset latency was the time from TMS stimulus to iSP onset, where average EMG activity fell below mean pre-stimulus EMG for ≥ five data points (1.67 ms) (Fleming and Newham, 2017; Giovannelli et al., 2009; Schmierer et al., 2002). Abnormal iSP latency represents callosal conduction slowing due to demyelination (Jung et al., 2006).

For AMT, area under the eREC and iREC, MEP latency, and iSP latency, we calculated interhemispheric asymmetry ratios of the weaker/stronger hemisphere (Chaves et al., 2019; Potter-Baker et al., 2016). These variables are associated with select cognitive functions in MS (Chaves et al., 2021a,b; Chaves et al., 2019; Llufriu et al., 2012).

### 2.7. Cardiorespiratory fitness

The gold standard test of cardiorespiratory fitness involves graded maximal exercise testing and indirect calorimetry to measure maximal oxygen uptake ($VO_{2max}$) (American College of Sports Medicine, 2022; Beltz et al., 2016). In MS, $VO_{2max}$ is valid, reliable, and related to clinically meaningful outcomes (Langeskov-Christensen et al., 2015; Langeskov-Christensen et al., 2014). We performed $VO_{2max}$ testing using a total body recumbent stepper (NuStep, Ann Arbor, MI, USA) (Kelly et al., 2017). Participants wore a facemask with one-way air valve (Hans Rudolph, Shawnee, KS, USA) and a heart rate (HR) monitor with chest strap (H10, Polar Electro, Oy, Finland). We recorded metabolic data with a gas- and volume-calibrated indirect calorimetry system (AEI Technologies, Inc., Pittsburgh, PA, USA). Before testing, participants rested quietly for 5 min while we measured resting $VO_2$ and HR. During exercise, participants maintained a stepping rate of 80 strides/minute, and we increased the load level (standard scale of 1–10) by 20 Watts every 2 min, beginning at load level of 3/10 (20 Watts). If participants did not stop exercising by load level 10, stride rate increased by 10 strides/minute, every 2 min. We recorded HR, $VO_2$, power (Watts), and rating of perceived exertion (RPE; 10-point scale) (Borg, 1998) every 2 min. Criteria for test termination were: (1) volitional exhaustion; (2) no increase in HR or $VO_2$ despite increasing workload; (3) inability to maintain load level or stepping rate; or (4) excessive fatigue (Kelly et al., 2017). Because many participants did not achieve a true $VO_{2max}$ (Beltz et al., 2016), we instead extracted $VO_{2peak}$.

We reported HR reserve (HRR) and $VO_2$ reserve ($VO_2R$), defined as peak minus resting values. In addition to $VO_2R$ we reported aerobic reserve capacity, defined as $VO_{2peak}$ minus average $VO_2$ from the first stage of the graded maximal exercise test (Arnett et al., 2008; Feasel et al., 2021a) While HRR and aerobic reserve capacity are associated with cognitive function in MS (Feasel et al., 2021a; Morrison and Mayer, 2017), no such association has been explored using $VO_2R$. We also reported peak RPE, Watts, and time to exhaustion (TTE).

### 2.8. Statistical analysis

We used SPSS 28 (IBM Corp., Armonk, NY, USA) for data analysis, with two-tailed tests and a statistical significance threshold of $p < .05$. Because data were non-normally distributed based on statistically significant Shapiro-Wilk tests, we used nonparametric tests. We conducted analyses separately across participants with PSI (SDMT $\leq$ 1.5 SD below norms) versus No PSI, as well as MCI (MoCA score < 26) versus No MCI, using the Bonferroni correction to adjust for multiple comparisons. We reported Bonferroni corrected *p*-values only. To assess confounding effects of age, sex, or education we conducted separate binomial logistic regressions on PSI and MCI (yes/no) (Konstantopoulos et al., 2016; Strober et al., 2020).

We compared continuous and ordinal variables across groups (PSI versus No PSI, MCI versus No MCI) using Mann-Whitney *U*-tests, and categorical variables using Pearson Chi-square ($\chi^2$) tests. We examined associations with PSI and MCI (yes/no) using Kendall's Tau-b ($\tau$) tests. To avoid spurious associations, we only tested variables that were significantly different across groups with and without cognitive impairments. We aimed to conduct separate binomial logistic regressions to determine predictors of PSI and MCI (yes/no). However, due to small numbers of participants with PSI ($n = 6$) and MCI ($n = 13$), this low minimum number of events per variable (EPV) precluded regression analysis (Peduzzi et al., 1996). Instead, for the individual outcomes that were significantly correlated with PSI and MCI, we conducted separate receiver operator characteristic (ROC) curve analyses to determine which outcomes best classified PSI and MCI, as well as their sensitivity and specificity (Hanley and McNeil, 1982).

For descriptive statistics, we reported number of participants (%) or median (range). We also reported effect sizes with 95 % confidence intervals (95 % CI). For *U*-tests, effect sizes (*r*) were trivial if < 0.1, small if 0.1–0.3, medium if 0.3–0.5, and large if > 0.5 (Cohen, 1988). For $\chi^2$-tests, effect sizes (*h*) were trivial if < 0.2, small if 0.2–0.5, medium if 0.5–0.8, and large if > 0.8 (Cohen, 1988). Correlations ($\tau$) were trivial if < 0.1, weak if 0.1–0.3, moderate if 0.3–0.5, and strong if > 0.5 (Cohen, 1988). From ROC curves, we reported the optimal cut-point to classify PSI and MCI (Unal, 2017), sensitivity and specificity, and area under the ROC curve (AUC) (Hanley and McNeil, 1982). AUC had no value if < 0.5, was fair if 0.5–0.7, acceptable if 0.7–0.8, excellent if 0.8–0.9, and outstanding if > 0.9 (Mandrekar, 2010).

## 3. Results

### 3.1. Participants

We included 73 of 110 volunteers. Of the 37 excluded participants, 31 did not complete TMS and six did not complete questionnaires (Fig. 1). The sample was comprised of 53 females and 20 males, with a median (range) age of 48 (21−70) years. Median (range) EDSS was 2.0 (0.0–6.5). Sixty-six participants had relapsing MS, six secondary-progressive MS (SPMS), and one primary-progressive MS (PPMS). Based on SDMT scores, there were six participants (8 %) with PSI and 67 (92 %) with No PSI. Based on MoCA scores, there were 13 participants (18 %) with MCI and 60 (82 %) with No MCI.

### 3.2. Groupwise comparisons

There were no statistically significant confounding effects of age, sex, or education on PSI ($p > .05$; data not shown). Thirty-eight percent more participants with PSI were prescribed statin medications (PSI 50 % versus No PSI 12 %; $p = .01$, medium effect size; Table 1). Groups were not significantly different in terms of other participant characteristics, performance on the MoCA or its index scores (data not shown), anxiety, depression, fatigue, pain, or heat sensitivity ($p > .05$). Median AMT interhemispheric asymmetry ratio was 38% greater in persons with PSI (PSI 1.38 versus No PSI 1.00), meaning those with PSI had significantly lower corticospinal excitability in the weaker hand ($p = .02$, medium effect size; Fig. 2 A; Table 1). No other TMS or cardiorespiratory fitness outcomes were significantly different ($p > .05$).

There was a statistically significant confounding association between age and MCI ($p = .01$; data not shown), but not sex or education ($p > .05$). MCI participants were significantly older by a median difference of 7.5 years (MCI 54.0 years versus No MCI 46.5 years; $p = .004$, medium effect size; Table 2), with significantly longer median disease duration by 3 years ($p = .008$, small effect size). However, neither age at disease onset nor disease duration adjusted for age were significantly different ($p > .05$; data not shown), suggesting the difference in disease duration was driven by age. We therefore excluded disease duration from further analyses. The MCI group had 26 % more progressive MS participants (MCI 31 % versus No MCI 5 %; $p = .01$, small effect size; Table 2). Thirty-seven percent more MCI participants had prescriptions for the GABA agonist medication baclofen (MCI 39 % versus No MCI 2 %; $p = .00002$, medium effect size; Table 2). Other characteristics were not significantly different ($p > .05$). Persons with MCI group scored significantly lower on attention (13 % difference, $p = .001$, medium

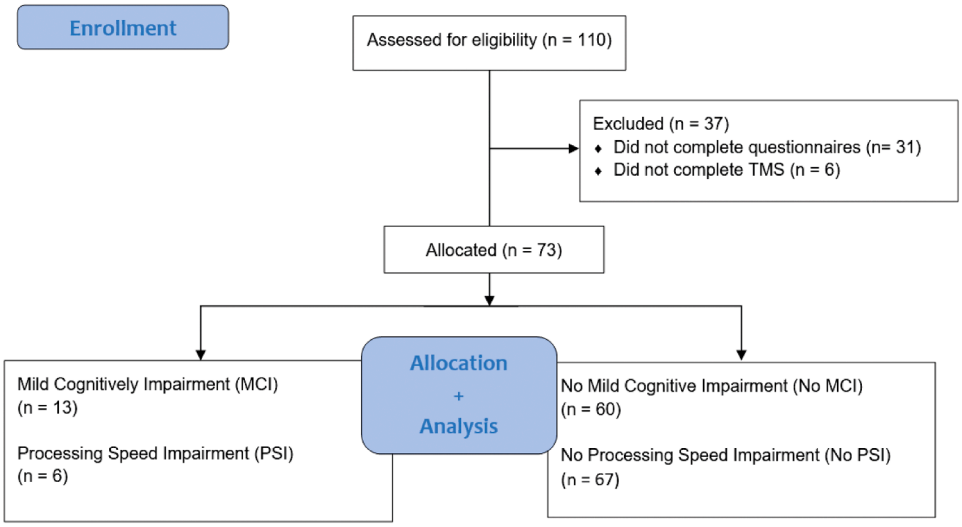


**Fig. 1.** Participant flow from recruitment to study completion.

**Table 1**
Participant characteristics, questionnaires, neurophysiology, and cardiorespiratory fitness in persons with processing speed impairment (PSI) versus No PSI.

| Variable | PSI ($n$ = 6) | No PSI ($n$ = 67) | $p$-value | Effect Size (95% CI) |
|---|---|---|---|---|
| **Participant Characteristics** | | | | |
| Age (years) | 50.5 (23.0–57.0) | 48.0 (21.0–70.0) | 1.0 | 0.01 (−0.22 to +−0.25) Trivial |
| Sex (female, male) | Female = 4 (67 %) Male = 2 (33 %) | Female = 49 (73 %) Male = 18 (27 %) | 1.0 | 0.07 (−0.42 to +0.55) Trivial |
| EDSS (0–10) | 3.75 (1.0–6.0) | 2.0 (0.0–6.5) | 0.30 | -0.17 (−0.40 to +0.07) Small |
| MS type (RMS, PrMS) | RMS = 4 (67 %) PrMS = 2 (33 %) | RMS = 66 (90 %) PrMS = 7 (10 %) | 0.08 | 0.24 (−0.20 to +0.67) Small |
| Disease duration (years) | 20.0 (1.0–28.0) | 15.0 (1.0–30.0) | 0.85 | -0.09 (−0.33 to +0.14) Trivial |
| MVPA (MET-hours/week) | 5.3 (0.0–10.9) | 5.5 (0.0–24.8) | 1.0 | 0.07 (−0.17 to +0.30) Trivial |
| Education (secondary, post-secondary) | Secondary = 0 (0 %) Post-secondary = 6 (100 %) | Secondary = 22 (30 %) Post-secondary = 51 (70 %) | 0.19 | -0.33 (−0.64 to +0.03) Small |
| Recreational drugs (no, yes) | No = 0 (0 %) Yes = 6 (100 %) | No = 19 (26 %) Yes = 54 (74 %) | 0.26 | -0.29 (−0.58 to +0.01) Small |
| Statin (no, yes) | No = 3 (50 %) Yes = 3 (50 %) | No = 64 (88 %) Yes = 9 (12 %) | 0.01 * | -0.75 (−0.89 to −0.61) Medium |
| **Questionnaires** | | | | |
| MoCA | 26.5 (20.0–29.0) | 27.0 (22.0–30.0) | 0.77 | 0.10 (−0.13 to +0.34) Small |
| Anxiety (HADS) | 5.0 (0.0–17.0) | 5.0 (0.0–14.0) | 1.0 | 0.01 (−0.23 to +0.24) Trivial |
| Depression (HADS) | 2.5 (1.0–6.0) | 2.0 (0.0–13.0) | 1.0 | 0.004 (−0.23 to +0.24) Trivial |
| Fatigue (mm) | 45.0 (25.0–72.0) | 31.0 (0.0–100.0) | 0.84 | -0.09 (−0.33 to +0.14) Trivial |
| Pain (mm) | 3.0 (0.0–49.0) | 8.0 (0.0–100.0) | 0.78 | 0.10 (−0.13 to +0.34) Small |
| Heat sensitivity (mm) | 53.5 (0.0–100.0) | 9.0 (0.0–96.0) | 0.13 | -0.22 (−0.45 to +0.02) Small |
| **Neurophysiology** | | | | |
| AMT ratio | 1.38 (0.91–1.59) | 1.00 (0.67–2.03) | 0.02 * | -0.30 (−0.53 to −0.07) Medium |
| MEP-L ratio | 1.08 (0.95–1.20) | 1.01 (0.83–1.24) | 0.08 | -0.24 (−0.47 to −0.01) Small |
| eREC ratio | 0.62 (0.31–1.10) | 0.93 (0.14–2.55) | 0.52 | 0.13 (−0.10 to +0.37) Small |
| iREC ratio | 1.50 (1.03–2.10) | 1.09 (0.49–2.56) | 0.10 | -0.23 (−0.47 to +0.004) Small |
| iSP-L ratio | 0.95 (0.65–1.27) | 0.95 (0.51–1.66) | 1.0 | 0.02 (−0.22 to +0.25) Trivial |
| **Cardiorespiratory fitness** | | | | |
| TTE (minutes) | 14.5 (10.0–18.7) | 15.4 (8.0–22.9) | 0.71 | 0.11 (−0.13 to +0.34) Small |
| HRR (bpm) | 96.5 (16.0–112.0) | 85.0 (25.0–123.0) | 1.0 | -0.07 (−0.31 to +0.16) Trivial |
| $VO_2R$ ($mL \bullet min^{-1} \bullet kg^{-1}$) | 26.6 (6.8–37.0) | 22.03 (5.58–43.24) | 1.0 | -0.06 (−0.30 to +0.17) Trivial |
| Aerobic reserve capacity ($mL \bullet min^{-1} \bullet kg^{-1}$) | 23.8 (6.4–35.2) | 20.20 (2.90–41.40) | 1.0 | -0.07 (−0.30 to + 0.17) Trivial |
| Peak RPE (0–10) | 9.0 (6.0–10.0) | 8.0 (4.0–10.0) | 1.0 | 0.03 (−0.21 to +0.26) Trivial |
| Peak power (Watts) | 153.0 (86.0–257.0) | 145.0 (55.0–316.0) | 1.0 | -0.05 (−0.28 to +0.19) Trivial |

Data presented as median (range) or number of participants (%). * , statistically significant at $p < .05$. 95 % CI, 95 % confidence interval; AMT, active motor threshold; EDSS, Expanded Disability Status Scale; eREC, excitatory motor evoked potential (MEP) recruitment curve; HADS, Hospital Anxiety and Depression Scale; HRR, heart rate reserve; iREC, inhibitory MEP recruitment curve; iSP-L, ipsilateral silent period latency; MEP-L, motor evoked potential latency; MET, metabolic equivalent of task; MoCA, Montréal Cognitive Assessment; MVPA, moderate- to vigorous-intensity physical activity; RMS, relapsing MS; RPE, rating of perceived exertion; PrMS, progressive MS; $VO_2R$, reserve volume of oxygen uptake.

effect size; data not shown), executive (9 % difference, $p = .01$, medium effect size), and language functions (17 % difference, $p = 02$, medium effect size). Visuospatial function, memory, orientation, and processing speed were not significantly different ($p > .05$; data not shown). There were no statistically significant differences ($p > .05$) in anxiety, depression, fatigue, pain, heat sensitivity, corticospinal excitability, or cardiorespiratory fitness (Table 2).

### 3.3. Predictors of PSI and MCI

Presence of PSI was moderately associated with statin prescription ($\tau = -0.34$, $p = .01$; Table 3) and weakly associated with greater AMT interhemispheric asymmetry ratio ($\tau = 0.25$, $p = .02$). AMT interhemispheric asymmetry ratio emerged as a statistically significant classifier of PSI, with an excellent ability to discriminate PSI (AUC = 0.82, $p = .02$; Fig. 2B; Table 4). An AMT asymmetry ratio of 1.23 (i.e., when CSE was 123 % lower in the weaker versus stronger side) was 67 % sensitive and 81 % specific for PSI. The AUC for statin prescription was nonsignificant ($p > .05$).

Presence of MCI was moderately associated with greater age ($\tau = 0.31, p = .01$; Table 3) and progressive MS ($\tau = 0.33, p = .01$). MCI was strongly associated with baclofen prescription ($\tau = 0.51$, $p = .00003$). Age emerged with a statistically significant and acceptable ability to classify MCI (AUC = 0.78, $p = .01$; Table 4). At 53.5 years of age, sensitivity and specificity for MCI were 77 % and 78 %, respectively. AUCs for progressive MS and baclofen prescription were nonsignificant ($p > .05$).

## 4. Discussion

We conducted a cross-sectional study to explore predictors of cognitive impairments in MS and hypothesized that cardiorespiratory fitness and corticospinal excitability would predict PSI and MCI. Overall, we found a low prevalence of both MS-related impairments in cognitive processing speed (PSI; 8%) and age-related mild cognitive impairment (MCI; 18%). PSI was best predicted by interhemispheric asymmetry of corticospinal excitability, whereas MCI was best predicted by age. Cardiorespiratory fitness and physical activity level predict neither PSI

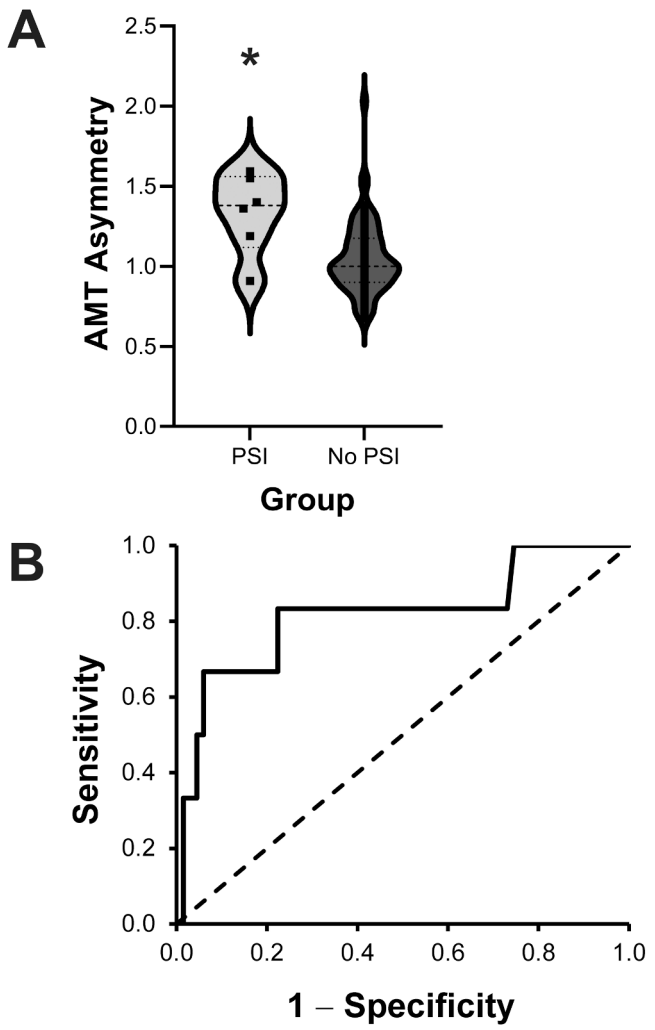


**Fig. 2.** (A) Violin plot depicting interhemispheric asymmetry ratio of active motor threshold (AMT Asymmetry) between persons with multiple sclerosis (MS)-related cognitive processing speed impairment (PSI, light gray; $n = 6$) versus No PSI (dark gray; $n = 67$). AMT asymmetry > 1.0 reflects higher AMT (i.e., lower corticospinal excitability) in the primary motor cortical representation of the clinically weaker upper extremity. Black squares represent individual data points, whereas the colored background represents the probability density of the data distribution. The dashed and dotted lines represent the median and first and third quartiles, respectively. Note that individual data points in the No PSI group overlap for visual clarity. * , statistically significant, $p < .05$. (B) Receiver operator characteristic (ROC) curve, plotting 1 minus specificity (false positives) × sensitivity (true positives). The plot depicts the ability of AMT asymmetry to correctly classify PSI versus No PSI. The diagonal line represents a 50% classification ability, below which cannot discriminate PSI better than chance. AMT Asymmetry emerged as a statistically significant classifier of PSI (area under ROC curve [95 % confidence interval] = 0.82 [0.61–1.00], $p = .010$). AMT Asymmetry of 1.23 (i.e., when CSE was 123 % lower in the weaker versus stronger side) was 67 % sensitive and 81 % specific for PSI.

nor MCI. Here, we show evidence to support that PSI and MCI are distinct clinical phenotypes that are associated with different clinical characteristics and neurophysiological markers.

### 4.1. AMT asymmetry predicts PSI

We found that AMT interhemispheric asymmetry ratio was a specific, but not sensitive, predictor of MS-related PSI. Persons with PSI had significantly greater asymmetry of corticospinal excitability—characterized by diminished excitability in the hemisphere corresponding to

**Table 2**
Participant characteristics, questionnaires, neurophysiology, and cardiorespiratory fitness in persons with mild cognitive impairment (MCI) versus No MCI.

| Variable | MCI ($n = 13$) | No MCI ($n = 60$) | $p$-value | Effect Size (95% CI) |
|---|---|---|---|---|
| **Participant Characteristics** | | | | |
| Age (years) | 54.0 (43.0–70.0) | 46.5 (21.0–65.0) | 0.004 * | -0.37 (−0.60 to −0.13) Medium |
| Sex (female, male) | Female = 8 (61.5 %) Male = 5 (38.5 %) | Female = 45 (75 %) Male = 15 (25 %) | 0.64 | 0.14 (−0.35 to +0.63) Trivial |
| EDSS | 2.0 (0.0–6.0) | 2.0 (0.0–6.5) | 0.38 | -0.15 (−0.38 to +0.09) Small |
| MS type (RMS, PrMS) | RMS = 9 (69 %) PrMS = 4 (31 %) | RMS = 57 (95 %) PrMS = 3 (5 %) | 0.01 * | -0.49 (−1.38 to −0.40) Small |
| Disease duration (years) | 18.0 (6.0–30.0) | 15.0 (1.0–29.0) | 0.01 * | -0.28 (−0.51 to −0.04) Small |
| MVPA (MET-hours/week) | 6.2 (0.0–18.6) | 5.4 (0.0–24.8) | 1.0 | -0.04 (−0.27 to +0.20) Trivial |
| Education (secondary, post-secondary) | Secondary = 4 (31 %) Post-secondary = 9 (69 %) | Secondary = 18 (30 %) Post-secondary = 42 (70 %) | 1.0 | 0.01 (−0.48 to +0.49) Trivial |
| Recreational drugs (no, yes) | No = 5 (39 %) Yes = 8 (61 %) | No = 14 (23 %) Yes = 46 (77%) | 0.52 | 0.16 (−0.33 to +0.65) Trivial |
| Baclofen (no, yes) | No = 8 (61%) Yes = 5 (39 %) | No = 59 (98 %) Yes = 1 (2 %) | 0.00002 * | -0.73 (−1.78 to −0.33) Medium |
| **Questionnaires** | | | | |
| SDMT | 1.84 (0.56–2.91) | 2.38 (0.81–4.14) | 0.08 | 0.24 (0.00–0.47) Small |
| Anxiety (HADS) | 4.0 (0.0–13.0) | 5.0 (0.0–17.0) | 1.0 | -0.02 (−0.25 to +0.22) Trivial |
| Depression (HADS) | 4.0 (0.0–12.0) | 2.0 (0.0–13.0) | 0.58 | -0.12 (−0.36 to +0.11) Small |
| Fatigue (mm) | 53.0 (0.0–100.0) | 30.5 (0.0–100.0) | 0.27 | -0.17 (−0.41 to +0.06) Small |
| Pain (mm) | 11.0 (0.0–80.0) | 6.0 (0.0–100.0) | 1.0 | -0.07 (−0.30 to +0.17) Trivial |
| Heat sensitivity (mm) | 9.0 (0.0–60.0) | 11.5 (0.0–100.0) | 1.0 | 0.08 (−0.16 to +0.31) Trivial |
| **Neurophysiology** | | | | |
| AMT ratio | 1.04 (0.73–1.59) | 1.00 (0.67–2.03) | 1.0 | -0.04 (−0.28 to +0.19) Trivial |
| MEP-L ratio | 1.00 (0.85–1.20) | 1.01 (0.83–1.24) | 1.0 | 0.04 (−0.20 to +0.27) Trivial |
| eREC ratio | 0.75 (0.36–1.10) | 0.98 (0.14–2.55) | 0.36 | 0.16 (−0.08 to +0.39) Small |
| iREC ratio | 1.20 (0.49–2.10) | 1.11 (0.52–2.56) | 0.60 | -0.12 (−0.36 to +0.11) Small |
| iSP-L ratio | 0.95 (0.65–1.11) | 0.95 (0.51–1.66) | 0.98 | 0.08 (−0.15 to +0.31) Trivial |
| **Cardiorespiratory fitness** | | | | |
| TTE (minutes) | 15.2 (10.0–19.1) | 15.7 (8.0–22.9) | 0.43 | 0.15 (−0.09 to +0.38) Small |

(*continued on next page*)

**Table 2** (*continued*)

| Variable | MCI ($n = 13$) | No MCI ($n = 60$) | *p*-value | Effect Size (95% CI) |
|---|---|---|---|---|
| HRR (bpm) | 77.0 (16.0–102.0) | 87.5 (27.0–123.0) | 0.14 | 0.23 (−0.01 to +0.46) Small |
| $VO_2R$ ($mL \bullet min^{-1} \bullet kg^{-1}$) | 19.4 (6.8–35.0) | 22.4 (5.6–43.2) | 0.83 | 0.09 (−0.14 to +0.33) Trivial |
| Aerobic reserve capacity ($mL \bullet min^{-1} \bullet kg^{-1}$) | 18.8 (2.9–31.5) | 20.7 (3.7–41.4) | 0.57 | 0.12 (−0.11 to +0.36) Small |
| Peak RPE (0–10) | 9.0 (4.0–10.0) | 8.0 (4.0–10.0) | 1.0 | 0.04 (−0.19 to +0.28) Trivial |
| Peak power (Watts) | 117.0 (55.0–241.0) | 150.0 (73.0–316.0) | 0.18 | 0.20 (−0.04 to +0.43) Small |

Data presented as median (range) or number of participants (%). * , statistically significant at $p < .05$. 95 % CI, 95 % confidence interval; AMT, active motor threshold; EDSS, Expanded Disability Status Scale; eREC, excitatory motor evoked potential (MEP) recruitment curve; HADS, Hospital Anxiety and Depression Scale; HRR, heart rate reserve; iREC, inhibitory MEP recruitment curve; iSP, ipsilateral silent period latency; MEP-L, motor evoked potential latency; MET, metabolic equivalent of task; MS, multiple sclerosis; MVPA, moderate- to vigorous-intensity physical activity; RMS, relapsing MS; RPE, rating of perceived exertion; PrMS, progressive MS; SDMT, Symbol Digit Modalities Test, normalized to Nine Hole Peg Test; $VO_2R$, reserve volume of oxygen uptake.

**Table 3**
Correlations (Kendall's tau-b, τ) with processing speed impairment (PSI) and mild cognitive impairment (MCI).

| Variable | Correlation coefficient (95% CI) | *p*-value |
|---|---|---|
| **PSI** | | |
| AMT ratio | −0.25 (−0.39 to −0.10) Weak | 0.02* |
| Statin (no, yes) | −0.34 (−0.47 to −0.20) Moderate | 0.01* |
| **MCI** | | |
| Age (years) | −0.31 (−0.44 to −0.16) Moderate | 0.01* |
| MS type (RMS, PrMS) | −0.33 (−0.47 to −0.19) Moderate | 0.01* |
| Baclofen (no, yes) | −0.51 (−0.62 to −0.39) Strong | 0.00003* |

* statistically significant at $p < .05$. 95 % CI, 95 % confidence interval; AMT, active motor threshold; MS, multiple sclerosis; RMS, relapsing MS; PrMS, progressive MS.

**Table 4**
Receiver operator characteristic (ROC) curve analysis for classifiers of processing speed impairment (PSI) and mild cognitive impairment (MCI).

| Variable | Cut-point | Sn | Sp | AUC (95% CI) | *p*-value |
|---|---|---|---|---|---|
| **PSI** | | | | | |
| AMT ratio | 1.23 | 67% | 81% | 0.82 (0.61–1.00) Excellent | 0.02* |
| Statin (no, yes) | Yes | 50% | 91% | 0.71 (0.45–0.96) Acceptable | 0.20 |
| **MCI** | | | | | |
| Age (years) | 53.5 | 77% | 78% | 0.78 (0.66–0.90) Acceptable | 0.01* |
| MS type (RMS, PrMS) | PrMS | 31% | 95% | 0.63 (0.44–0.82) Fair | 0.44 |
| Baclofen (no, yes) | Yes | 39% | 98% | 0.68 (0.50–0.87) Fair | 0.12 |

* statistically significant at $p < .05$. 95% CI, 95% confidence interval; AMT, active motor threshold; AUC, area under the receiver operator characteristic (ROC) curve; MS, multiple sclerosis; RMS, relapsing MS; PrMS, progressive MS; Sn, sensitivity; Sp, specificity.

the weaker upper extremity—than those without PSI. AMT asymmetry was significantly correlated with presence of PSI and was 81 % specific for PSI, with an excellent area under the ROC curve. In other words, lower corticospinal excitability in the weaker extremity can help rule in the distinct phenotype of MS-related PSI, but lack of asymmetry cannot rule out PSI relative to impairments in other cognitive domains. AMT asymmetry was not associated with MCI, supporting a distinct neurophysiological basis underlying PSI and MCI.

In support of this finding, our group's past work similarly found that lower excitability of the weaker side was significantly associated with, and predicted a significant degree of variance in, slower cognitive processing speed (SDMT) but not increased generalized cognitive impairment (MoCA) (Chaves et al., 2019). When accounting for MS type, disease duration, disease-modifying therapy, and handedness, asymmetry of corticospinal excitability was also associated with greater disability (EDSS), fine motor (Nine Hole Peg Test) and gross motor impairment (walking speed), fatigue, heat sensitivity, and other physical and psychological disease-related complaints (Multiple Sclerosis Impact Scale) (Chaves et al., 2019). This finding reflected the fact that individuals with slower processing speed and greater AMT asymmetry were more clinically impaired, with more progressive or later-stage disease (Chaves et al., 2019). It was hypothesized that a shift from a hyperexcitable neuroinflammatory state, characteristic of active relapsing MS, to a hypoexcitable neurodegenerative state, more typical for inactive secondary-progressive MS, may explain the above association (Dutta and Trapp, 2014).

Neuroimaging investigations of PSI in MS suggest the degree of impairment is related to the extent of subcortical white matter and cortical gray matter lesions; atrophy in cortical and deep gray matter structures; and aberrant neural network functional connectivity (Benedict et al., 2020; Sumowski et al., 2018). Thalamic atrophy appears to impart a substantial negative impact on cognitive function in MS (Swartz et al., 2008), and is an important marker of PSI, disability, and motor signs, irrespective of age and above other imaging findings (Amin and Ontaneda, 2020; Houtchens et al., 2007). Low corticospinal excitability could serve as an indirect marker of thalamic atrophy or global neurodegeneration.

The thalami have extensive cortical, subcortical, brainstem, and cerebellar projections, and are ubiquitous in the processing and integration of afferent and efferent information (Power and Looi, 2015). Connections with the thalamus are critical for sensorimotor integration, whereby ascending sensory information offers critical feedback to modify motor planning and output online (Edwards et al., 2019; Moreno-Lopez et al., 2016). Thalamocortical connections are involved in TMS interactions with the motor system, when pulses are delivered over the primary motor cortex and motor association cortices (Esser et al., 2005). In MS participants with thalamic atrophy and cognitive impairment, there is evidence of abnormal functional connectivity of thalamocortical and corticocortical networks (Tewarie et al., 2015). Due to their widespread projections, damage to the thalami in MS contributes to various deficits in cortical functioning, including cognitive, motor, and sensory domains (Power and Looi, 2015).

Thalamic atrophy is common across MS (Amin and Ontaneda, 2020; Houtchens et al., 2007), healthy aging (Choi et al., 2022), neurodegenerative dementias (Power and Looi, 2015), and schizophrenia (Huang et al., 2020), and is correlated with impairments in several cognitive domains, including processing speed. By measuring blood oxygen level-dependent (BOLD) signal activation with functional magnetic resonance imaging (fMRI), Peters et al. (2020) showed that the bilateral thalami are activated as part of a greater motor functional brain network following subthreshold single-pulse TMS over the dorsal premotor cortex (Peters et al., 2020). In participants with schizophrenia-related cognitive impairment, Guller et al. (2012a,b) found deficient thalamic BOLD signal activation in response to single-pulse TMS of the primary motor cortex, despite normal motor network connectivity (Guller et al., 2012a,b). In studies of thalamic infarction there is reduced corticospinal excitability on the lesioned side in persons with greater lesion size and more substantial clinical deficits (Faig and Busse, 1996; Inoue et al., 2012; Liepert et al., 2005), whereas

deep brain stimulation targeting the thalamus increases corticospinal excitability in persons with essential tremor (Molnar et al., 2005). Although speculative, deficient corticospinal excitability could indirectly probe structural or functional thalamic abnormalities in relation to PSI. This putative association should be explored in future investigations.

### 4.2. Association between statin use and PSI

Sample-wide, 12% of participants were prescribed statin medications. Fifty percent of people with PSI were prescribed statins, compared to only 12% without PSI. Statin prescription was moderately correlated with PSI. Statins, or β-hydroxy-β-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, are key for the prevention of cardiovascular disease and stroke, and are among the most commonly prescribed medications in North America (Gauthier and Massicotte, 2015; Koch, 2012; Schultz et al., 2018). Statin therapy is relevant because persons with MS, independent of disease-related factors, have a greater level of vascular risk compared to controls (Albuquerque et al., 2021; Etemadifar et al., 2022) and are susceptible to atherosclerotic cerebral small vessel disease and vascular cognitive impairment (DeLuca et al., 2015). Statins reduce vascular risk by inhibiting the rate-limiting step in hepatic cholesterol synthesis, upregulating hepatic low-density lipoprotein (LDL) receptors, improving vascular endothelial function, and stabilizing atherosclerotic plaques (Koch, 2012).

Interestingly, despite their putative neurovascular protective role (Wood et al., 2010), statins are associated with detrimental cognitive effects (Schultz et al., 2018). There is evidence of short-term reversible cognitive impairment from safety testing and post-marketing data of statins (Schultz et al., 2018). Statin use is associated with dose-dependent impairments in attention, working and short-term memory, and processing speed, which improve upon drug discontinuation, recur with reintroduction of the drug, and are absent in participants taking placebo (Schultz et al., 2018). Statins can cross the blood-brain barrier and decrease central nervous system cholesterol and coenzyme Q10 levels (Schultz et al., 2018; Wood et al., 2010). The downstream effects are impaired myelin formation, decreased steroid hormone production, reduced neurotransmitter and receptor levels, and mitochondrial dysfunction and oxidative stress (Schultz et al., 2018; Wood et al., 2010). Statin use could also be an indirect marker of increased baseline cerebrovascular disease, or vascular cognitive impairment, in participants with PSI (Hamilton et al., 2021).

### 4.3. Age-related MCI in MS

Presently, 18 % of participants screened positive for age-related MSI using a cutoff MoCA score $< 26$. These individuals demonstrated deficits in attention, executive function, and language domains, independent of visuospatial function, memory, processing speed, fatigue, or psychological disturbances. Of all factors considered, age, progressive MS, and prescriptions for the GABA agonist baclofen were associated with age-related MCI in MS. However, only age emerged as a statistically significant predictor that was sensitive and specific.

MCI participants were significantly older and with relatively more progressive MS than those without MCI. Age and secondary-progressive MS cluster together, wherein older individuals progress from relapsing disease and have greater neurodegeneration, leading to more disability and functional impairment (Correale et al., 2017). Our finding that age is a key predictor of MCI in MS aligns with previous work. For example, Tremblay et al. (2020) found, in a large sample of persons with MS, that advanced age, but not disease duration, significantly predicted memory and attention, after controlling for disease type, comorbidities, fatigue, quality of life, and depression (Tremblay et al., 2020). In another large study, greater age was associated with a significant increase in the odds of MCI in MS (Amato et al., 2019). The authors suggested the combined effect of age and MS confers greater negative effects on cognitive function compared to age alone, and may relate to cortical and deep gray matter degeneration that occurs with later, secondary-progressive disease (Amato et al., 2019; Tremblay et al., 2020). As above, increased age could also be associated with a higher prevalence of age-related small-vessel cerebrovascular disease (Hamilton et al., 2021). While others have not commented on the age of MCI onset in MS, 50 years is the approximate average age of secondary-progressive MS diagnosis (Tremlett and Zhao, 2017), which coincides with the current study's findings.

With reference to GABA agonist prescriptions, 39 % of participants with MCI versus 2 % without MCI were prescribed baclofen, and this was significantly correlated with MCI. Baclofen (β-[4-chlorophenyl]-GABA), is an agonist for $GABA_B$ receptors on mono- and polysynaptic neurons in the brain and spinal cord, and is commonly used for the management of spasticity (Ghanavatian and Derian, 2022). Baclofen is thought to reduce presynaptic glutamate release and induce prolonged post-synaptic inhibition by activating inwardly-rectifying potassium channels, inactivating voltage-gated calcium channels, and inhibiting adenylate cyclase (Ghanavatian and Derian, 2022; Terunuma, 2018). Baclofen is also suspected to have anticholinergic properties (McCartney, 2015). The use of GABAergic and anticholinergic drugs is common in MS—especially progressive MS—for management of spasticity, pain, and neurogenic bladder (Al Dandan et al., 2020; Beal and Wallace, 2016; Kale et al., 2009). In MS, long-term intrathecal baclofen is reported to cause reversible cognitive impairment, which improves with dose reduction, and is suspected to be mediated by sedating effects of the medication (Rekand and Gronning, 2011). Others have shown that baclofen produces reversible impairments in memory and executive function (Hinderer and Liberty, 1996; Sandyk and Gillman, 1985). Thus, increased baclofen use may have contributed to MCI in the current work.

Conversely, it is possible that higher baclofen prescription is an indirect indicator of the greater prevalence of secondary-progressive MS, and therefore chronic symptom burden, in persons with age-related MCI. It should also be noted that individuals with secondary-progressive MS are older than those with relapsing disease on average; therefore, the high rate of these prescriptions may simply be reflective of the advanced age and higher rate of secondary-progressive MS in these participants.

### 4.4. On cardiorespiratory fitness and physical activity levels

High-quality cross-sectional evidence demonstrates positive associations between cardiorespiratory fitness, physical activity level, and cognitive processing speed, but not other cognitive domains (Langeskov-Christensen et al., 2018; Sandroff et al., 2016; Sandroff et al., 2017). Contrary to our hypothesis, neither cardiorespiratory fitness nor physical activity level were predictive of PSI or MCI. In general, our sample was primarily comprised of poor fitness individuals who achieved under 7 weekly MET-hours of MVPA. Indeed, only 25 % of participants achieved the US Department of Health and Human Services' recommended 500 weekly MET-minutes of MVPA (ACSM, 2019, US Department of Health and Human Services, 2018), and just 18 % achieved $VO_{2peak}$ at or above the American College of Sports Medicine (ACSM)'s 50th percentile for age and sex (American College of Sports Medicine, 2022). These data align with recent meta-analyses that show significantly lower levels of both cardiorespiratory fitness and physical activity in persons with MS compared to matched controls (Langeskov-Christensen et al., 2015; Macdonald et al., 2023). While there was a low proportion of both active and fit individuals enrolled in this study, there was likewise a low prevalence of cognitive impairment. Across the literature, the prevalence of PSI is 34–65 %, compared to 8 % in the current study (Benedict et al., 2020). Rates of MCI in MS range between 25 % and 58 %, relative to our 18 % (Rosca and Simu, 2020). This likely reflects the fact that participants in this study primarily had mild relapsing disease that was well-controlled using disease-modifying therapy, and were not representative of the entire clinical spectrum of

individuals with MS.

Expert opinion suggests that exercise is a critical disease-modifying intervention in MS (Dalgas et al., 2019, 2022; Motl and Sandroff, 2022). Riemenschneider et al. highlight that exercise should be delivered early in the disease course, where there may be a limited "window of opportunity" for disease-modifying effects (Riemenschneider et al., 2018). In a recent study of persons with mostly progressive MS, there were no significant associations between physical activity, fitness, or processing speed (Sandroff et al., 2021). The authors suggested their observation was moderated by participants' high disability level, which prevented engaging in sufficient activity to benefit either fitness or cognition (Sandroff et al., 2021). They noted that the restricted range of high disability, poor cognition, and low fitness may have omitted relevant associations that could be present in participants with higher functional status (Sandroff et al., 2021). We now show, to the contrary, that relatively non-disabled participants with inactive, relapse-free disease and high cognitive function have low activity and fitness levels, similar to persons with advanced disease and significant disability. It is possible that the present sample is earlier in the natural history of their disease than the participants of Sandroff et al. (2021). Accordingly, in the present group, the potential accumulation of physical disability and cognitive impairment has not yet occurred , despite low activity and fitness levels. Without early intervention, these participants may go on to develop physical disability and cognitive impairment. We therefore posit that these individuals would be ideal candidates for behaviour-modification interventions that promote increased physical activity and cardiorespiratory fitness, to potentially protect against further impairments.

### 4.5. Limitations

As highlighted above, this study was limited first by a low prevalence of cognitive impairment. Given the relatively homogeneous sample of persons with generally mild and inactive relapsing MS, few participants exhibited either PSI or MCI. This cohort is under-representative of the MS population at large (Podda et al., 2021), and may be a result of selection bias or volunteer bias, whereby higher-functioning individuals with lower disease severity were willing to participate in rigorous testing such as maximal exercise and TMS. Second, our study was powered for 24–28 participants per group, whereas the final sample was comprised of six PSI and 13 MCI participants. Low power may have caused us to falsely support the null hypothesis. Conversely, the lack of association between physical activity level, cardiorespiratory fitness, and cognitive impairment could represent MS patients with mild symptoms early in the natural history of their disease. Despite a lower prevalence of cognitive impairments relative to persons with more established disease, these individuals could be at risk for future declines in physical and cognitive functioning, and thus may benefit from exercise interventions.

## 5. Conclusion

This cross-sectional study explored predictors of MS-related cognitive impairments in a clinic-based sample of community-dwelling adults with MS. We hypothesized that cardiorespiratory fitness and corticospinal excitability would predict cognitive impairments. Contrary to our hypothesis, neither cardiorespiratory fitness nor physical activity level predicted MS-related PSI or age-related MCI. However, we found that interhemispheric asymmetry of corticospinal excitability was a specific predictor for PSI, while MCI was best predicted by age. We speculated that abnormal corticospinal excitability could be an indirect marker of global neurodegeneration or thalamic atrophy that mediates impairments in processing speed. PSI was also associated with greater prescriptions for statin medications, which may have reflected detrimental cognitive effects of these drugs or a higher prevalence of cerebrovascular disease in persons with PSI. Age-related MCI was also correlated with increased prevalence of progressive MS and baclofen prescriptions, suggesting an intersection between age, secondary-progressive MS, and increased symptom burden necessitating treatment that potentially caused reversible cognitive impairment. Our observations came from a relatively small and homogenous sample of highly educated persons with inactive relapsing MS and low disability level. This resulted in a low prevalence of both PSI and MCI, increasing risk of Type-II error. However, these inactive but high-functioning individuals could benefit from exercise interventions to prevent future cognitive and functional declines. Future work should examine predictors of cognitive impairments in a larger sample of more diverse participants.

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## CRediT authorship contribution statement

**NJS:** Conceptualization, Methodology, Formal Analysis, Investigation, Data Curation, Writing–Original Draft, Writing–Review & Editing, Visualization. **JL**: Conceptualization, Methodology, Writing–Review & Editing. **ARC**: Conceptualization, Methodology, Investigation, Data Curation, Writing–Review & Editing. **MP**: Conceptualization, Methodology, Resources, Writing–Review & Editing, Supervision, Project Administration, Funding Acquisition.

## Declaration of Competing Interest

We have no competing interests to declare.

## Data availability

All data are available at reasonable request to the corresponding author.

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### *Institutional Review Board Statement*

This work was approved by the Memorial University Human Research Ethics Board (HREB; File #: 20161208, Reference #: 15.103).

### *Informed Consent Statement*

All participants gave written informed consent under the Declaration of Helsinki.

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