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ORIGINAL COMMUNICATION

Free-living ambulatory physical activity and cognitive function in multiple sclerosis: the significance of step rate vs. step volume

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Abstract

Background Physical activity (PA) represents a promising behavioral approach for managing cognitive dysfunction in multiple sclerosis (MS). However, there is a lack of information on the pattern of free-living PA intensity (e.g., step rate) and its unique association with cognition. Such information is essential for informing clinical trials in MS.

Objective We examined associations among PA volume and intensity with cognitive function in persons with MS, and intensity was derived from steps-based metrics (peak 30-min cadence [Peak-30_{CAD}], and time spent in incremental cadence bands).

Methods We included data from 147 persons with MS who underwent assessments of cognitive function (via Brief International Cognitive Assessment in MS) and wore an ActiGraph GT3X + accelerometer for 7 days. We performed bivariate and partial correlations and regression analyses examining associations among PA metrics and cognitive outcomes.

Results Higher Peak-30_{CAD} was significantly associated with better performance in cognitive processing speed and verbal learning and memory ($r_s = 0.19$–0.38), and the associations remained significant when controlling for daily steps, age, sex, and years of education ($p < 0.05$). By comparison, daily steps was only correlated with cognitive processing speed ($r_s = 0.26$), and the association was non-significant when controlling for Peak-30_{CAD} and covariates. There were stronger correlations among time spent in higher intensity cadence bands with cognitive performance ($r_s = 0.18$–0.38).

Conclusion Our results highlight the important role of PA intensity for cognition in MS, and may inform future development of focal PA interventions that focusing on step rate patterns for improving cognition in persons with MS.

Keywords Step-based metric · Peak cadence · Walking · Processing speed · Learning and memory

Introduction

Multiple sclerosis (MS) is an immune-mediated, neurogenerative disease of the central nervous system (CNS) with a prevalence of one million adults in the United States [1]. This disease is characterized by demyelination and transection of axons and subsequent loss of neurons (i.e., neurodegeneration) in the CNS [2]. Cognitive dysfunction is a prevalent and poorly managed consequence of MS that has deleterious effects on the lives of those with the disease [3]. An estimated 67% of persons with MS demonstrate cognitive impairment based on neuropsychological testing, including slowed processing speed and impaired learning and memory [4, 5]. Cognitive dysfunction may further erode independence and compromise quality of life among the MS population [6]. To date, there are no FDA-approved pharmacological treatments for managing MS-related cognitive dysfunction [7]. This underscores the importance of considering alternative approaches for treating cognitive impairment in persons with MS.

Physical activity (PA) represents a promising behavioral approach for improving cognition in MS [8]. There is cross-sectional and prospective evidence that higher levels of device-measured free-living PA are associated with better cognitive performance in MS, primarily faster processing speed [9–11]. Such evidence provides the basis for potential PA recommendations for cognition in persons with MS. However, the role of intensity, an important component

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of PA, and its association with cognition in MS (e.g., dose–response relationship) has been insufficiently defined [5, 12]; this limits our ability to develop targeted and focal PA interventions for preventing and/or managing cognitive dysfunction in MS. To date, researchers have primarily applied free-living PA outcomes such as daily steps or activity counts, and time spent in a priori defined intensity categories (e.g., sedentary behavior, light-intensity PA [LPA], moderate-to-vigorous physical activity [MVPA]) based on corresponding activity count cut-points via accelerometry [13, 14]. These outcomes encapsulate the accumulated PA amount (time or counts) over the monitored period, but do not reflect specific intensity values that describe continuous, natural effort during daily ambulatory behavior. Those predefined intensity categories tend to be reductionist to depict the nuances of intensity levels (e.g., continuous, full spectrum) for PA assessment and prescription, particularly for individuals with MS who may experience functional declines and engage in less MVPA [15]. There is a need for identifying novel, applicable metrics that comprehensively evaluate free-living PA intensity in MS and further examining association with cognition. Such knowledge is essential for developing efficacious interventions and the eventual prescription of PA within clinical settings for treating cognitive impairment in the MS population.

Step-based metrics (e.g., daily steps [steps/day], cadence [steps/min]) have been increasingly applied in the general population and MS as measures of PA [13, 16], given that walking is a highly prevalent form of activities of daily living [17]. Such PA outcomes are easily tractable from wearable sensors and understandable by the general public. Peak cadence has emerged as a promising indicator of natural effort during ambulatory activity in population-based PA research [18, 19]. Peak 30-min cadence (Peak-30_{CAD}; the average of the 30 highest cadence values in a day) has been included as a proxy for PA intensity [20] and is associated with mortality, cardiometabolic risk, and other health outcomes in the general population [21–23]. One recent study involved peak cadence in MS and reported a strong association between Peak-30_{CAD} and laboratory-assessed walking performance among 147 persons with MS [24]. That study further utilized incremental cadence bands and identified distinct patterns of LPA in MS (e.g., accumulated more incidental movement [1–19 steps/min]) compared with healthy controls. Such preliminary evidence supports the use of step-based metrics in MS and presents a viable avenue for examining potential association between PA intensity and cognition.

The current study involved a cross-sectional analysis of associations among accelerometer-measured PA volume and intensity with cognitive function in persons with MS, with a focus on using step-based metrics (daily steps, peak cadence, and time spent in cadence bands). We hypothesized that higher levels of PA volume and intensity would both be associated with better cognitive performance, and PA intensity (Peak-30_{CAD}) would be independently associated with cognitive performance while controlling for daily steps and other covariates. Based on the PRocessing, Integration of Multisensory Exercise-Related Stimuli (PRIMERS) framework whereby stimuli involving greater activation of CNS pathways (e.g., higher intensity movement) may result in greater neural adaptations [25], we further hypothesized that more time spent in higher intensity cadence bands might exhibit a stronger association with better cognitive performance. Our results may provide unique insights into dose–response relationship of PA and inform future development of focal interventions and clinical prescriptions of PA that optimize cognitive benefits within the MS population.

Method

Participants

The study represents a secondary analysis of data from a cross-sectional study that examined the effects of age and MS on physical function and cognition [24, 26]. The methods for this study were approved by a university institutional review board (IRB). Participants were recruited through flyers posted in the community, mailing lists of persons with MS from the local MS clinics, therapeutic recreation facility, and advertisements through the National MS Society and regional MS Society chapters. Persons with MS were screened based on the following inclusion criteria: (1) MS diagnosis; (2) no relapse within the last 30 days; (3) age between 20–79 years old; (4) able to walk with or without assistive devices; and (5) willingness to complete the testing procedures. Individuals who did not meet those criteria were excluded from participation.

Measures

Cognitive function Cognitive function was measured using the Brief International Cognitive Assessment for MS (BICAMS) neuropsychological battery [27, 28]. The BICAMS includes the Symbol Digit Modalities Test (SDMT), the California Verbal Learning Test-II (CVLT-II), and the Brief Visuospatial Memory Test-Revised (BVMT-R) as measures of cognitive processing speed, verbal learning and memory, and visuospatial learning and memory, respectively. All tests were administered and scored according to standardized procedures [27], and the primary outcomes were the raw scores per assessment [29]. We further calculated *z*-scores that accounted for age, sex, and education to determine cognitive impairment in the current sample classified based on *z*-scores of at least 1.5 SD units below the

regression-based normative score for each assessment [30, 31].

Free-living physical activity Free-living PA was measured using waist-worn ActiGraph GT3X + accelerometers (ActiGraph Corporation, Pensacola, FL, USA). Participants wore the accelerometer on an elastic belt around the waist over the non-dominant hip during waking hours of a 7-day period except for water-based activities (e.g., showering), and further recorded wear time in a log for compliance. The accelerometer was initialized to collect data at a sampling rate of 100 Hz. We downloaded the raw data in 60-s epochs using ActiLife software and applied the Troiano algorithm to identify non-wear time [32]. Days consisting ≥ 10 h of wear time (i.e., ≥ 600 min) were considered valid and individuals with ≥ 1 valid day were included in the analyses [33]; this was confirmed using the self-reported wear time log. Minute-level data were further processed using custom R scripts to generate step-based metrics [34]. Daily steps (steps/day) were calculated by averaging step counts across all valid days. Peak-30_{CAD} (step/min) was generated by: (1) first rank-ordering an individual's steps/min values within each valid day; (2) calculating the mean of the highest 30 non-consecutive values within each day; and (3) finally taking the average of the resulting cadence values across all valid days. A graphic representation for generating daily peak cadence is displayed in Fig. 1. PA was further classified using time spent in established cadence bands across valid days: non-movement (0 steps/min), incidental movement (1–19 steps/min), sporadic movement (20–39 steps/min), purposeful movement (40–59 steps/min), slow walking (60–79 steps/min), medium walking (80–99 steps/min), brisk/moderate walking (100–119 steps/min), and faster walking (≥ 120 steps/min) [18]. We further generated time spent (min/day) in LPA and MVPA using MS-specific cut-points [35] to

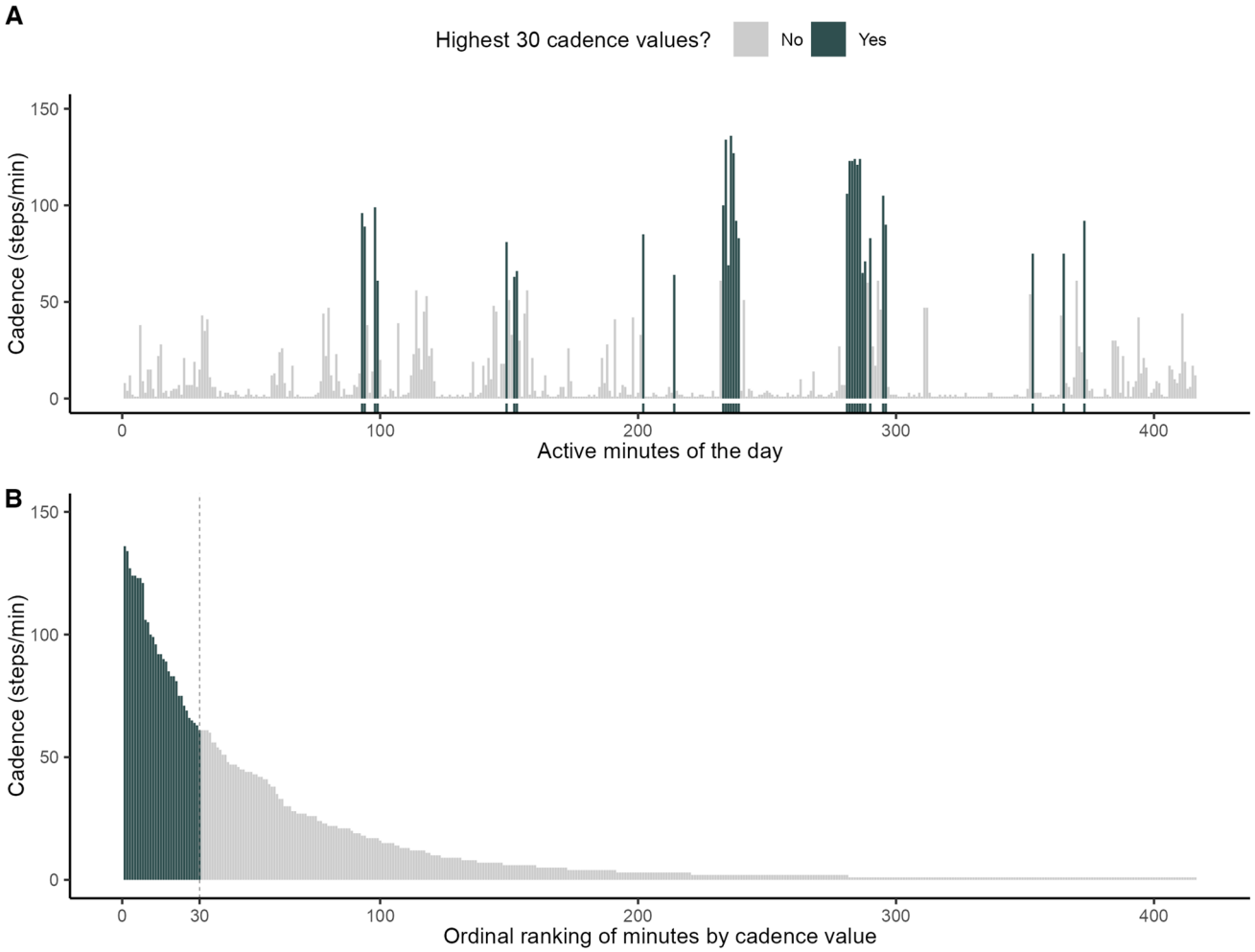

Fig. 1 Visual description of peak 30-min cadence (Peak-30_{CAD}) calculation. Figure illustrates data processing steps performed to calculate Peak-30_{CAD} using one day of data from an individual (962 min of total wear time; 416 min of active minutes [i.e., cadence above zero]). **A** Displays cadence values across active minutes within a day; **B** first rank orders the 30 highest cadence values within a day and identifies the highest 30 (not necessarily consecutive) values (highlighted); and the average of these cadence values is the Peak-30_{CAD} of the day

facilitate a comparison between step-based PA metrics and conventional intensity categories.

Other outcomes Participants self-reported MS type and disease duration and completed questionnaires regarding demographic information (age, sex, race/ethnicity, and years of education) and disability status via the Patient Determined Disease Steps (PDDS). The PDDS is a valid measure of self-reported ambulatory disability status in MS, with scores ranging between 0 (Normal) and 8 (Bedridden); higher scores reflected greater levels of perceived disability in persons with MS [36].

Procedures

The study protocol was approved by a University Institutional Review Board. All participants provided written informed consent before data collection. Participants completed questionnaires regarding demographic and clinical information, disability status, and underwent cognitive function assessment during a single visit to the laboratory. Participants were then provided with an accelerometer, elastic waist band, and wear time log along with instructions for wearing the device for 7 days. Upon completion of the 7-day period, participants mailed the device back through United States Postal Service in a prepaid, pre-addressed envelope.

Data analysis

The data were analyzed using R (version 4.3.1) with the α level set at 0.05. Descriptive statistics were calculated and presented as mean (standard deviation), median (interquartile range), and range (min–max), where appropriate. We initially examined the bivariate correlations among steps-based PA metrics (daily steps, Peak-30_{CAD}, and time spent in incremental cadence bands), time spent in LPA and MVPA, and cognitive performance scores using Spearman (r_s) correlation coefficients, and then performed partial correlations (pr_s) between Peak-30_{CAD} and cognitive performance while controlling for daily steps (i.e., collinearity between PA volume and intensity). We further performed partial correlations between PA and cognitive outcomes while adjusting for age, sex, and years of education as those variables are jointly associated with PA and cognition in MS [15, 26, 35]. The magnitude of correlation coefficients was interpreted as weak (0.1), moderate (0.3), and strong (0.5) [37]. To examine the independent association between PA intensity and cognition in MS, we further performed multiple linear regression analyses. We regressed cognitive performance scores on single and combined PA outcomes (both daily steps and Peak-30_{CAD}), while controlling for covariates (age, sex, and years of education) and accounting for the interaction between daily steps and Peak-30_{CAD}.

Results

Demographic and clinical characteristics of the sample are provided in Table 1. The sample of 147 persons with MS was primary female (77.6%) and had a mean age of 50.2 years. Participants were diagnosed with MS for an average of 13.4 years, and the majority had relapsing–remitting MS (87.8%) and mild disability based on the median PDDS score of 1.0.

The descriptive statistics for cognitive and PA outcomes are too provided in Table 1. The mean SDMT, CVLT-II, and BVMT-R scores were 49.7, 46.0, and 21.8, respectively; these values were similar with the BICAMS test scores from other samples of persons with MS [30, 38, 39], and were above the cut-off scores for cognitive impairment in MS [40]. Based on the adjusted z-scores, 32.0% of the sample demonstrated impaired cognitive processing speed (SDMT), 32.2% had impaired verbal learning and memory (CVLT-II), and 22.6% had impaired visuospatial learning and memory (BVMT-R). The sample had mean daily steps of 5161 steps/day and mean Peak-30_{CAD} of 53.3 steps/min. Those values were lower than published normative data from the US population (9676 steps/day and 71.1 steps/min) [20, 41]. Using a step-defined index of < 5000 steps/day [42], 78 out of 147 participants (53%) were classified as physically inactive. Compared with the normative values, the MS sample spent more time in non-movement to sporadic movement (cadence bands: 0 to 39 steps/min), and accumulated less time in higher intensity cadence bands (≥ 40 steps/min) [18].

Correlations among step-based metrics and cognitive performance scores in MS are provided in Table 2, and scatterplots with fitted lines for linear associations among daily steps, Peak-30_{CAD}, cognitive performance are displayed in Fig. 2. Daily steps (volume) was significantly correlated with SDMT score ($r_s = 0.26$), but not with other test scores ($p > 0.05$). Peak-30_{CAD} (intensity) was correlated with all cognitive performance scores ($r_s = 0.19$ to 0.38), and these correlations were slightly attenuated in magnitude, but remained significant after controlling for daily steps ($pr_s = 0.18$ to 0.29; $p < 0.05$). When jointly adjusting for aged, sex, and education, the partial correlations between Peak-30_{CAD} with SDMT and CVLT-II scores remained significant ($p > 0.05$), whereas there were no significant partial correlations between BVMT-R score with all PA outcomes.

When classifying PA using cadence bands, there were significant correlations between greater time spent in sporadic movement to faster locomotion (from 20 to 39 steps/min to ≥ 120 steps/min) and higher SDMT score ($r_s = 0.22$–0.38); and such correlations became stronger ($r_s = 0.32$–0.38) at higher intensity cadence bands (60–79

Table 1 Sample characteristics and descriptive statistics of PA and cognitive outcomes

	Mean (SD)	Range (min–max)
Age, year	50.2 (13.5)	22.0–76.0
Sex, % female	114 (77.6%)	–
Education, year	16.5 (2.3)	9.0–21.0
Race, *n* (%)		
Caucasian	96 (65.3%)	–
African American	43 (29.3%)	–
Other	8 (5.4%)	–
MS type, *n* (%)		
Relapsing–remitting	129 (87.8%)	–
Progressive	14 (9.5%)	–
Unknown	4 (2.7%)	–
Disease duration, years	13.4 (9.8)	1.0–48.0
PDDS, median (IQR)	1.0 (3.0)	0.0–6.0
Cognitive tests		
SDMT raw score	49.7 (12.5)	6.0–84.0
SDMT *z*-score	− 1.0 (1.09)	− 4.0–1.1
CVLT-II raw score	46.0 (12.5)	26.0–73.0
CVLT-II *z*-score	− 1.2 (0.9)	− 3.0–0.9
BVMT-R raw score	21.8 (6.9)	0.0–34.0
BVMT-R *z*-score	− 0.6 (1.2)	− 4.1–1.2
Physical activity outcomes		
Valid days (# days)	5.9 (1.5)	4.0–9.0
Wear time (min/day)	819.1 (89.9)	644.4–1228.3
LPA (min/day)	302.9 (85.3)	76.0–607.8
MVPA (min/day)	61.3 (35.5)	0.2–177.0
Daily steps (steps/day)	5161 (2374)	299–13,670
Peak-30_{CAD} (steps/min)	53.3 (22.8)	5.4–119.1
Time spent in cadence bands (min/day)		
Non-movement (0 steps/min)	1017.8 (104.3)	672.3–1310.7
Incidental movement (1–19 steps/min)	343.2 (87.2)	128.9–698.2
Sporadic movement (20–39 steps/min)	51.9 (27.1)	0.4–140.6
Purposeful steps (40–59 steps/min)	14.3 (11.5)	0.0–81.4
Slow walking (60–79 steps/min)	5.4 (5.4)	0.0–31.0
Medium walking (80–99 steps/min)	3.2 (3.6)	0.0–17.0
Brisk walking (100–119 steps/min)	3.4 (7.2)	0.0–65.4
Faster locomotion (≥ 120 steps/min)	0.7 (2.1)	0.0–17.0

Data were presented as means and standard deviations (SDs) unless otherwise noted

MS multiple sclerosis, *PDDS* patient determined disease steps, *IQR* interquartile range, *SDMT* Symbol Digit Modalities Test, *CVLT-II* California Verbal Learning Test-II, *BVMT-R* Brief Visuospatial Memory Test-Revised, *Peak-30_{CAD}* peak 30-min cadence, *LPA* light-intensity physical activity, *MVPA* moderate-to-vigorous intensity physical activity

steps/min and above). There were significant correlations between greater time spent in medium walking, brisk walking, and faster locomotion (from 80–99 steps/min to ≥ 120 steps/min) and higher CVLT-II score ($r_s = 0.20$–0.29), while higher BVMT-R score was only correlated with greater time spent in faster locomotion ($r_s = 0.18$), but not with other cadence bands ($p > 0.05$). After controlling for age, sex, and education, the partial correlations between SDMT scores and cadence bands remained significant ($p < 0.05$), whereas CVLT-II scores only correlated with faster locomotion ($pr_s = 0.19$, $p < 0.05$), and the correlation between BVMT-R scores and faster locomotion became non-significant after controlling for covariates ($p > 0.05$). In addition, there was no significant bivariate or partial correlations between cognitive performance scores and time spent in LPA and MVPA (all $p > 0.05$).

Results from regression analyses are presented in Table 3. No significant interaction effects were detected between

Table 2 Associations among physical activity outcomes and cognitive performance in persons with multiple sclerosis

	SDMT		CVLT-II		BVMT-R	
	r_s	pr_s	r_s	pr_s	r_s	pr_s
LPA (min/day)	−0.07	0.04	−0.03	0.08	−0.07	0.03
MVPA (min/day)	0.13	0.11	0.12	0.14	0.15	0.10
Daily steps	0.26**	0.25**	0.11	0.13	0.11	0.05
Peak-30_{CAD}	0.38**	0.28**	0.22**	0.18*	0.19*	0.05
Peak-30_{CAD} (controlled for daily steps)	0.29**	0.17*	0.25**	0.16*	0.18*	0.04
Time spent in cadence bands						
Non-movement (0 steps/min)	−0.02	−0.06	0.03	−0.04	0.02	−0.01
Incidental movement (1–19 steps/min)	−0.10	−0.05	−0.05	0.02	−0.06	0.00
Sporadic movement (20–39 steps/min)	0.22**	0.23**	0.08	0.10	0.13	0.09
Purposeful steps (40–59 steps/min)	0.27**	0.24**	0.11	0.11	0.15	0.08
Slow walking (60–79 steps/min)	0.38**	0.32**	0.15	0.10	0.16	0.04
Medium walking (80–99 steps/min)	0.36**	0.27**	0.20*	0.16	0.16	0.03
Brisk walking (100–119 steps/min)	0.36**	0.25**	0.22**	0.13	0.13	−0.02
Faster locomotion (≥ 120 steps/min)	0.32**	0.16*	0.29**	0.19*	0.18*	0.00

Spearman's bivariate (r_s) and partial (pr_s) correlations were reported

SDMT Symbol Digit Modalities Test, *CVLT-II* California Verbal Learning Test-II, *BVMT-R* Brief Visuospatial Memory Test-Revised, *LPA* light-intensity physical activity, *MVPA* moderate-to-vigorous intensity physical activity, *Peak-30_{CAD}* peak 30-min cadence

*$p < 0.05$, **$p < 0.01$

daily steps and Peak-30_{CAD} when including both outcomes in Models 3, 6 and 9 ($p > 0.05$). We observed that greater daily steps was associated with higher SDMT score (Model 1; $\beta = 0.11$, $p = 0.004$), but this association was attenuated and non-significant after including Peak-30_{CAD} (Model 3; $p = 0.06$). Daily steps was not significantly associated with CVLT-II or BVMT-R ($p > 0.05$), whereas greater Peak-30_{CAD} was associated with higher CVLT-II score (Models 5 and 6: $\beta = 0.08$ and 0.21, $p = 0.03$ and 0.02, respectively) but not with BVMT-R score (Models 8 and 9: $p = 0.55$ and 0.07, respectively). Overall, the regression analyses consistently demonstrated independent associations between Peak-30_{CAD} with SDMT and CVLT-II scores after adjusting for daily steps and covariates (Models 3 and 6, $p < 0.05$). Compared with daily steps alone (Models 1 and 4), the inclusion of Peak-30_{CAD} (solely or jointly) resulted in elevated adjusted R^2 values in Models 2, 3, 5 and 6, indicating an improved model performance in explaining the variance of associated cognitive outcomes.

Discussion

The present study provided the first examination of associations between free-living PA and cognitive function in persons with MS with the use of step-based metrics of PA volume and intensity. The primary novel result indicated a significant and independent association between PA intensity (Peak-30_{CAD}) with cognitive performance (processing speed, verbal learning and memory) in MS, even while controlling for daily steps and covariates (age, sex, and years of education). Daily steps (PA volume) was only associated with cognitive processing speed (SDMT), but this association was attenuated and became non-significant when including Peak-30_{CAD}. These results suggest a stronger association between PA intensity (peak effort) and cognition than for daily PA volume in MS. The significance of PA intensity was further supported by correlation analyses involving incremental cadence bands. Persons with MS accumulated most time in non-movement and incidental movement (0–19 steps/min), but there was a notable trend where time spent in higher intensity PA (ranging from sporadic movement to faster locomotion) exhibited stronger associations with cognitive performance. Yet, the PA-cognition relationship was not detected using conventional intensity categories (LPA and MVPA) in the current MS sample. Collectively, our findings support the use of step-based PA outcomes in MS and highlight the important role of PA intensity for cognitive function in persons with MS.

This research provides unique insights into existing literature with a particular focus on free-living PA intensity via accelerometry, given that much of the prior work in MS only involved accumulative measures of PA volume (e.g., time, activity counts, or steps per day). We first applied the novel peak cadence in MS to explore the dose–response relationship among both PA volume and intensity with cognitive function in MS. When compared with daily steps, Peak-30_{CAD} exhibited overall significant and stronger

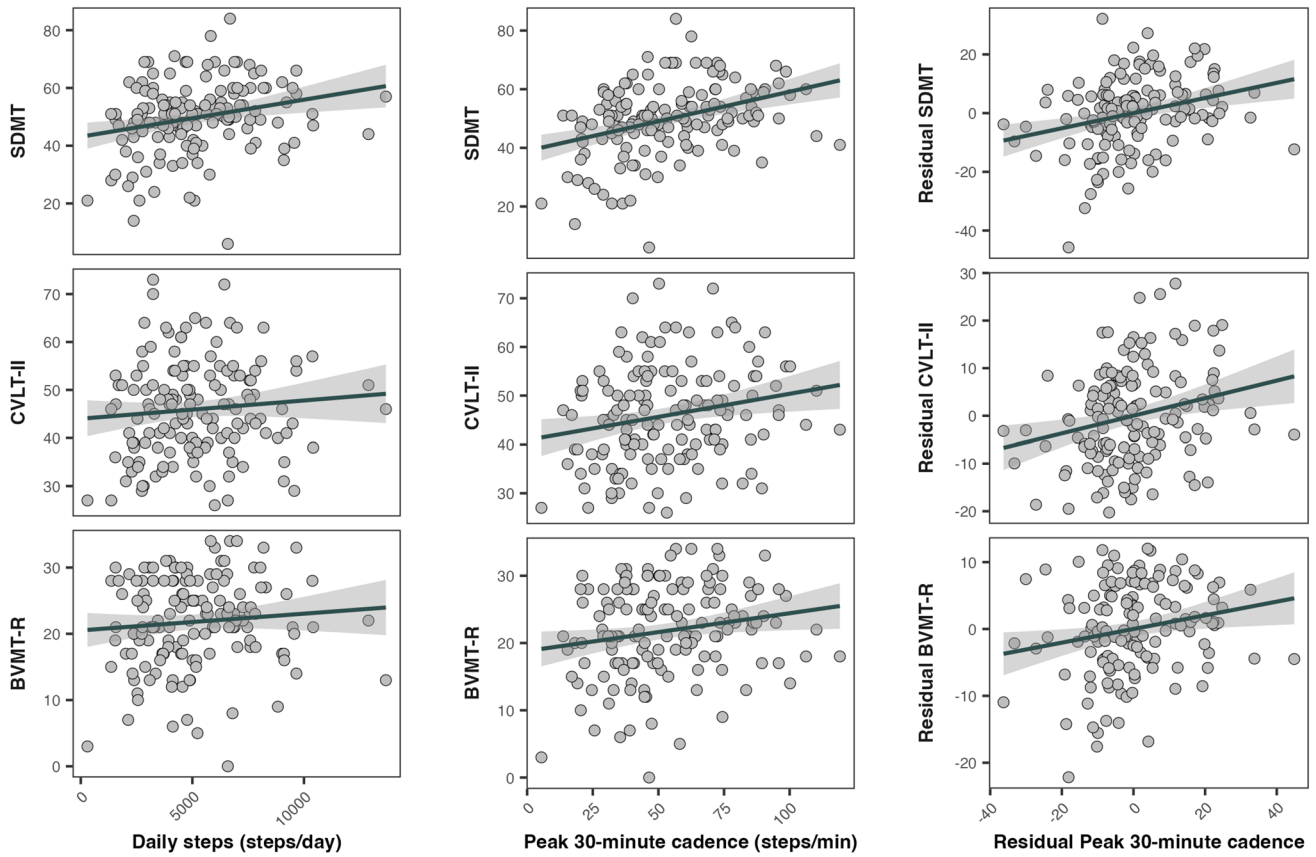

Fig. 2 Scatter plots for associations among daily steps (left), peak 30-min cadence (middle and right), and cognitive performance in persons with multiple sclerosis, along with lines of best fit and 95% confidence intervals (shaded areas). The partial residual plot (right) displayed the partial correlations among peak 30-min cadence and cognitive test scores while controlling for daily step. *SDMT* Symbol Digit Modalities Test, *CVLT-II* California Verbal Learning Test-II, *BVMT-R* Brief Visuospatial Memory Test-Revised

associations with the two cognitive domains in the current MS sample, regardless of age, sex, education, and even daily steps. In other words, when maintaining similar PA volume, individuals with MS who accumulated PA at higher intensity levels might have better cognitive processing speed and verbal learning and memory. Further, our findings are intriguing and distinct from previous research in MS that mostly reported positive relationships among measures of PA volume and cognitive processing speed, with limited yet null results on other cognitive domains (e.g., learning and memory) [9, 25, 43]. Indeed, a prior study observed that PA (steps/day) was correlated with processing speed (composite score of SDMT and Paced Auditory Serial Addition Test) but not learning and memory (composite score of BVMT-R and Selective Reminding Test) with or without controlling for age, sex, and education ($r = 0.39$ and 0.28, $pr = 0.02$ and 0.20, respectively) in 33 persons with MS [44]. Another study involved a cognitively impaired MS sample ($n = 60$) and reported moderate associations among MVPA (min/day) and daily steps with SDMT only ($pr_s = 0.36$ and 0.31, respectively) but not with CVLT-II or BVMT-R when adjusting for age, sex, education, and disability [9]. The lack of associations among those PA outcomes and performance on learning and memory were surprising, given the favorable benefits of PA interventions on these cognitive domains in MS [45, 46] and other populations [47]. Importantly, our results indicated that better performance in verbal and visuospatial learning and memory (CVLT-II and BVMT-R) was more associated with higher sustained PA intensity or peak effort, rather than LPA or volume-based PA outcomes in MS. This notion gains additional support from our data in cadence bands wherein these two cognitive scores were only associated with time spent in medium to brisk walking (≥ 80 steps/min) and/or faster locomotion (≥ 120 steps/min).

There is limited understanding of neural mechanisms concerning PA-related effects on cognitive domains in MS. The differential patterns of associations among PA and cognitive outcomes were previously outlined in the PRIMERS conceptual framework for central nervous system plasticity with PA in MS [25]. The PRIMERS model proposes that adaptations in central nervous system occur via activity-dependent neuroplasticity based on the integrative processing of

Table 3 Regression analysis examining the association between step-based PA outcomes and cognitive function in MS

	Age		Sex[a]		Education		Daily steps (per 100 steps/day)[b]		Peak-30_{CAD}		Adjusted R^2
	β	SE	β	SE	β	SE	β	SE	β	SE	
SDMT											
Model 1	−0.29**	0.06	3.37	2.05	2.02**	0.37	0.11**	0.04	–	–	0.32
Model 2	−0.27**	0.06	3.82	2.02	1.78**	0.37	–	–	0.14**	0.04	0.34
Model 3[c]	−0.25**	0.06	4.17*	2.00	1.85**	0.38	0.20	0.11	0.32**	0.10	0.36
CVLT-II											
Model 4	−0.08	0.06	4.72**	1.80	1.67**	0.32	0.04	0.03	–	–	0.20
Model 5	−0.07	0.06	5.08**	1.80	1.55**	0.32	–	–	0.08*	0.03	0.22
Model 6[c]	−0.05	0.06	5.30**	1.80	1.53**	0.33	0.08	0.09	0.21*	0.09	0.22
BVMT-R											
Model 7	−0.17**	0.04	−0.68	1.19	1.11**	0.21	0.01	0.02	–	–	0.26
Model 8	−0.17**	0.04	−0.62	1.19	1.11**	0.21	–	–	0.01	0.02	0.26
Model 9[c]	−0.15**	0.04	−0.47	1.19	1.14**	0.22	0.09	0.06	0.10	0.06	0.27

Models 1, 4 and 7 include age, sex, years of education, and daily steps; Models 2, 5 and 8 include age, sex, years of education, and Peak-30_{CAD}; Models 3, 6 and 9 include age, sex, years of education, daily steps, Peak-30_{CAD}, and an interaction term between daily steps and Peak-30_{CAD}

SE standard error, *MS* multiple sclerosis, *SDMT* Symbol Digit Modalities Test, *CVLT-II* California Verbal Learning Test-II, *BVMT-R* Brief Visuospatial Memory Test-Revised, *Peak-30_{CAD}* peak 30-min cadence

*$p<0.05$, **$p<0.01$

[a]Sex as categorical with male as the reference group

[b]The beta coefficient of daily steps was scaled by 100 for ease of interpretation; for example, a change of 100 steps/day in daily steps is associated with a 0.10 unit change in SDMT score, while holding other variables constant

[c]The beta coefficients for the interaction term (daily steps and Peak-30_{CAD}) in Models 3, 6 and 9 were −0.003, −0.002, and −0.002, respectively, all $p>0.05$

multisensory input and associated complex motor output required for the physiological regulation of exercise. In particular, the efficient communication within thalamocortical networks is among the most important processes for regulating exercise behavior, and such improved neural connectivity over time may explain the selective improvements/benefits in speed-related cognitive outcomes, given the role of the thalamus as the brain's relay station [25]. Our results aligned with this potential mechanism, wherein cognitive processing speed via SDMT emerged as a more sensitive outcome in relation to PA metrics, i.e., daily steps, Peak-30_{CAD}, and time spent in all cadence bands except for low intensity movement (0 ~ 19 steps/min). By contrast, the hippocampus may be involved in spatial navigation processes during exercise (e.g., free-living aerobic walking), leading to repetitive stimulation of specific neural networks and upregulation of neurotrophic factors for hippocampal neurogenesis. These changes eventually result in improved hippocampal connectivity and downstream behavioral adaptations, including hippocampal-dependent learning and memory [25, 43]. Combined with our results, we speculated that achieving higher intensity (e.g., ≥ 80 steps/min) during habitual ambulatory behavior may be necessary to elicit neural adaptations that contribute to cumulative benefits in learning and memory among persons with MS. Such an assertion is consistent with previous data on improvements in learning and memory and hippocampal neuroimaging outcomes in response to aerobic walking exercise training among persons with MS [48]. Additionally, our regression analyses further indicated potential effects of age and education on the association between Peak-30_{CAD} and BVMT-R in comparison with the significant correlation results. Such differential associations among PA and cognitive outcomes warrant further investigations in both cross-sectional and longitudinal studies for designing precise PA guidelines and prescriptions for cognitive benefits in the MS population.

The current study extends previous research on association between free-living PA and cognition in MS by involving peak cadence as a novel measure of intensity. Five previous studies involved device-measured PA and reported moderate to strong correlations ($r_s = 0.35$ to 0.53) between daily steps and cognitive processing speed (SDMT) in several MS samples and this association remained significant when adjusting for covariates including age, sex, education, or disability ($pr_s = 0.25$–0.35) [9–11, 44, 49]. Our finding was consistent with previous results but exhibited a

relatively weaker correlation between daily steps and SDMT ($r_s = 0.26$). This is likely attributed to less disability (median PDDS = 1.0) and overall better cognitive status in the current sample compared with those studies [40, 50]. Indeed, the associations among PA and cognitive outcomes appeared to be stronger (magnitude and significance) in subsamples with greater disability levels or cognitive impairment based on subgroup analyses (provided in the supplementary material); yet such results should be interpreted with caution given the unbalanced sample sizes within subgroups. Of note, none of previous cross-sectional studies focused on PA intensity and its independent association with cognition in MS. Only one study involved accelerometer-measured LPA and MVPA within a cognitively impaired MS sample ($n = 60$) and demonstrated that MVPA was significantly associated with SDMT but not CVLT-II or BVMT-R ($p > 0.05$) after controlling for covariates, while LPA only had significant bivariate correlation with SDMT ($r_s = 0.44$) [9]. However, we did not observe such correlations between LPA or MVPA with cognitive performance in the current sample. As previously stated, categorizing PA into the two intensity levels based on activity cut-points was insufficient for capturing specific intensity levels across the entire spectrum [24]. The current study expanded upon those findings and first reported small-to-moderate correlations between PA intensity (peak effort) and performance on cognitive processing speed, learning and memory, independent of age, sex, education, and daily PA volume in persons with MS. Further, the application of step-based metrics in MS also provides an avenue for comprehensive evaluation of free-living PA and examination of PA intensity on various health outcomes relevant to MS [24].

The current results may have implications for the development of PA interventions for managing cognitive dysfunction in persons with MS. There are few published clinical trials of PA interventions involving moderate-intensity walking (e.g., cadence ≥ 100 steps/min) as a form of aerobic exercise for several MS populations, with the primary outcomes on walking performance, MS symptoms, and quality of life [51–53]. Indeed, walking is the most common and accessible form of PA and requires little facility and low cost, making it an ideal choice for promoting PA levels in daily living [17, 54]. The current data support the potential of modulating the intensity of walking exercise for cognitive remediation, with the prospect of designing individually-tailored and personalized intervention programs. For example, PA interventions that target learning and memory might emphasize achieving a higher intensity (e.g., walking above 80 steps/min), while those focus on cognitive processing speed may expect some favorable results with accumulating sufficient daily PA [55]. Furthermore, compared to cognitive rehabilitation in MS, interventions incorporating PA within everyday living seem to have better ecological validity and are more advantageous in yielding physical health benefits beyond cognition [5]. Future studies are needed to explore the dose–response effects of PA volume and intensity on cognition in MS, as well as to design randomized controlled trials and examine the feasibility and efficacy of PA interventions using step-based metrics via accelerometry in the MS population.

Study strengths include the use of a relatively large and age-balanced MS sample as well as the rigorous standardization of outcome assessment methodologies. With the adjustment of age, sex, and education in regression analyses, our results on PA intensity and cognition might be generalizable for both men and women across different ages. However, several limitations should be acknowledged. First, this study represents an analysis of a parent cross-sectional study that examined the effects of age and MS on physical function and was not designed to specifically address correlations among PA and cognitive performance. Second, the current analyses were cross-sectional and precluded causal inferences. Future randomized controlled trials may provide such an opportunity for investigating acute or chronic effects of PA volume or intensity on different cognitive domains in MS. Lastly, we had a relatively heterogenous sample (e.g., less cognitively impaired and mild disability) and did not control for other factors (e.g., race/ethnicity, disease modifying treatment, presence of other neurological conditions) that might influence PA or cognitive performance. Our results should be interpreted with caution when applied to other samples with different disability levels or those who have cognitive impairment. By extension, future studies may control for potential factors that may intervene the association between PA and cognition, such as physical fitness [6].

Conclusion

Higher accelerometer-measured PA intensity (Peak-30_{CAD}) was significantly associated with better cognitive processing speed and verbal learning and memory in persons with MS, and these associations were independent of PA volume (daily steps), age, sex, and education. By comparison, daily steps was only correlated with cognitive processing speed, but this association was attenuated and became non-significant when controlling for Peak-30_{CAD}. Results in incremental cadence bands further indicated stronger associations between higher intensity PA and cognitive performance in MS. Our findings highlight the important role of PA intensity and may inform future development of targeted and effective PA interventions for improving cognitive function in persons with MS.

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Data availability The data that support the findings of the current study are available from the corresponding author upon reasonable request.

Declarations

Conflicts of interest The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethics approval The study protocol was approved by the Institutional Review Board of the University of Alabama at Birmingham (IRB-161108001). The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

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