Fragmentation, circadian amplitude, and fractal pattern of daily-living physical activity in people with multiple sclerosis: is there relevant information beyond the total amount of physical activity?

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Declaration of Interest

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ABSTRACT

Background. Physical activity is lower in people with multiple sclerosis (pwMS) compared to healthy controls. Previous work focused on studying activity levels or activity volume, but studies of daily-living rest-activity fragmentation patterns, circadian rhythms, and fractal regulation in pwMS are limited. Based on findings in other cohorts, one could suggest that these aspects of daily-living physical activity will provide additional information about the health and well-being of pwMS. Therefore, here, we aimed to (1) identify which fragmentation, fractal, and circadian amplitude measures differ between pwMS and healthy controls, (2) evaluate the relationship between fragmentation, fractal, and circadian amplitude measures and disease severity, and (3) begin to evaluate the added value of those measures, as compared to more conventional measures of physical activity (e.g., mean signal vector magnitude (SVM). a global measure of the overall volume of physical activity).

Methods. 132 people with relapsing-remitting MS (47±11 yrs, 69.7% female, Expanded Disability Status Scale, EDSS, median (IQR): 3(2-4)) and 90 healthy controls (46±11 yrs, 47.8 %female) were asked to wear a 3D accelerometer on their lower back for 7 days. Rest-activity fragmentation, circadian amplitude, fractal regulation, and mean SVM metrics were extracted. PwMS and healthy controls were compared using independent samples t-tests and linear regression, including comparisons adjusted for mean SVM to control for the effect of physical activity volume. Spearman correlations between measures and logistic regressions were used to identify the clinical condition based on the measures that differed significantly after adjusting for SVM. All analyses included adjustments for demographic and clinical parameters (e.g., age, sex).

Results. Multiple measures of activity fragmentation significantly differed between pwMS and healthy controls, reflecting a more fragmented active behavior in pwMS. PwMS had a lower circadian rhythm amplitude, indicating a smaller amplitude in the circadian changes of daily activity, and weaker temporal correlations as based on the fractal analysis. When taking into account physical activity volume, one circadian amplitude measure and one fractal measure remained significantly different in pwMS and controls. Fragmentation measures and circadian amplitude measures were significantly associated with disability level as measured by the EDSS; the association with circadian amplitude remained significant, even after adjusting for the mean SVM.

Conclusion. The physical activity patterns of pwMS differ from those of healthy individuals in rest-activity fragmentation, the amplitude of the circadian rhythm, and fractal regulation. Measures describing these aspects of activity provide information that is not captured in the total volume of physical activity and could, perhaps, augment the monitoring of disease progression and evaluation of the response to interventions.

KEYWORDS Multiple sclerosis; Daily living; Accelerometer; Activity fragmentation; Fractal regulation; Circadian amplitude

1. INTRODUCTION

People with multiple sclerosis (pwMS) are less physically active compared to healthy individuals [1][2][3][4][5][6]. While early work documented these changes via self-report, in recent years, wearable sensors have been used to quantify daily-living activity and mobility outcomes in pwMS [7][8][9]. These efforts have produced valuable insights into the effects of MS on the quality of life of patients and on the association of physical activity levels with disease severity and disability level [4], [5][6]. However, most of the work quantifying and studying physical activity in free-living environments has focused on the amount of activity, rather than the patterns of activity and active-sedentary behavior throughout the day.

The fragmentation of rest and activity patterns is altered in a wide variety of clinical conditions. For example, rest-activity patterns are altered in preclinical Alzheimer's disease [10], Parkinson's disease [11], and older adults with cognitive impairments [12] and with fatigability [13]. Activity fragmentation was also previously associated with mortality rates in older adults [14][15][16]. Together, these studies suggest that there is clinically relevant information that can be gleaned from investigating how physical activity changes during the day and that fragmentation provides a measure that is, at least theoretically, independent of the total volume of activity (e.g., see Figure 1 in the supplementary material, SM).

Due to the impaired mobility of pwMS, which potentially affects the ability to sustain physical activity for long periods, one can speculate that the fragmentation patterns are altered in pwMS. In their pilot study, Blikman et al. reported differences in the active-sedentary patterns of fatigued pwMS compared to healthy controls [3]. Although the study was limited to severely fatigued patients, these findings hint at the possibility of extracting potentially valuable information from outcomes related to rest-activity fragmentation in pwMS.

Fractal analysis of human motor activity provides an alternative means of examining the changes in physical activity during the day. This approach evaluates correlations in the temporal fluctuations of the activity signal over varying time scales [17][18]. When applied to recorded accelerometer data, measures based on fractal analysis predict frailty, disability, and mortality [19] as well as cognitive decline and Alzheimer's disease [20] in older adults. Li et al. found that the degradation of motor fractal regulation, which occurs in association with aging [21][22][23][24], is accelerated in Alzheimer's disease, and that acceleration worsens after diagnosis of cognitive impairment and worsens further after the clinical onset of Alzheimer’s dementia [25]. In a pilot study, differences in the scaling exponent derived from the fractal analysis were observed between groups of patients with different self-reported disability level and ambulatory status, and an association with patient-rated walking impairment measures were also observed, with a lower scaling exponent being linked to greater impairment [26]. These preliminary results suggest that fluctuations in physical activity during the day are not simply noise; rather, they may provide important information about MS-related physical activity patterns.

The circadian rhythm amplitude (the maximum range of daily activity) decreases with aging [27] and was associated with an increased risk of developing Parkinson's and Alzheimer's disease [28][29]. There is, however, little information about circadian amplitude metrics in pwMS. Nonetheless, due to the general decrease in physical activity that is associated with disease progression among pwMS, a relationship similar to what is seen in older adults might emerge in pwMS. Preliminary evidence of a negative relationship between circadian

amplitude and disability level, as assessed by the Expanded Disability Status Scale (EDSS) [30] provides some initial support for this possibility. Together, these findings, along with those related to aging and Parkinson's disease, suggest that measures of circadian activity amplitude could potentially be valuable in the study of pwMS.

To explore these largely unaddressed questions in the context of MS, we evaluated daily-living activity patterns in pwMS and healthy controls. We aimed to (1) identify which fragmentation, fractal, and circadian amplitude measures differ between pwMS and healthy controls, (2) evaluate the relationship between fragmentation, fractal, and circadian amplitude measures and disease severity, and (3) begin to assess the added value of those measures compared to more conventional volume-based measures of physical activity (e.g., signal vector magnitude (SVM)).

2. METHODS

2.1 Participants

The analysis was based on the baseline data of patients with relapsing-remitting MS (n=132) and healthy controls (n=90) who were recruited as part of three studies. 41 pwMS and 30 controls participated in an observational study. The data of the other 91 MS patients were collected from the baseline assessment of a multi-center intervention designed to ameliorate motor-cognitive interactions in MS patients using virtual-reality (NCT02427997). For all pwMS, the inclusion criteria were: relapsing-remitting type of MS according to McDonald criteria 2010 [31], ages 18-65 years, free of relapse in the past 30 days, mild to moderate disability (i.e., Expanded Disability Status scale (EDSS) score of 0 to 6). PwMS were excluded if they had neurological, orthopedic, or psychiatric disorders that are likely to affect gait. The rest of the control subjects (n=60) participated in a study that was designed to evaluate Parkinson's disease. Controls were included if they had no neurological, orthopedic, or psychiatric disorders that may affect gait and no substantial cognitive impairment (Montreal Cognitive Assessment score > 21). All subjects provided informed written consent, as approved by local human studies, before participation.

2.2 Assessment of demographics and disease severity

Age, sex, and other demographic characteristics were collected. Disease severity among the pwMS was assessed using the Expanded Disability Status Scale (EDSS)[32].

2.3 Collection of free-living physical activity data

Subjects wore a small, body-fixed, water-proof tri-axial accelerometer (Axivity AX3 or AX6, York, UK; about 23.0×32.5×7.6 mm; weight: 11 g; 100 Hz sampling rate) on their lower back (lumbar vertebrae 4–5), as previously described [33]. The device recorded 3D accelerations in a free-living setting for a continuous period of seven days. The subjects were asked to carry on with their daily activities while wearing the device and send it back to the study site at the end of the seven days.

2.4 Measures of physical activity behavior

For a detailed description of the measures and their extraction process, see supplementary material.

Mean SVM was used to quantify the amount of physical activity [34]. Fragmentation measures included an active fragmentation index, which is the number of active bouts divided by the total active time [3][35], the average bout duration for each state (sedentary/active), the Gini index, a measure of the distribution of the time spent in each state [14][36], the average hazard, an estimate of the hazard function in the context of transitioning between the states [14], and K_{AR} and K_{RA}, measures of the state transition probability [37]. The scaling exponent of the detrended fluctuation analysis (DFA) was used to quantify fractal regulation. It was estimated in two time scale ranges: α_1 in the range of 1.5-90 minutes, and α_2 in the range of 2-10 hours [25]. An un-normalized circadian amplitude (CA) measure and a relative amplitude (RA) measure were also extracted [37][38] [39].

2.5 Statistical Analysis

Details of the statistical analysis are reported in the SM. Briefly, when comparing the pwMS to the healthy controls, we used t-tests and linear regression models to adjust for age, sex, study site, and the number of valid days, and mean SVM. To assess associations between measures, nonparametric Spearman's correlations were used. Binary logistic regression models were used to assess the ability to classify the subject grouping. A Benjamini–Hochberg [40] correction was used to account for possible false-positives due to multiple comparisons, and significance was defined as $p<0.05$.

3. RESULTS

3.1 Subject characteristics

All characteristics except for sex were similar between the MS group and the control groups (Table 1). The percentage of female participants was higher in the MS group, as might be expected in a study of MS [41].

Table 1: Subject characteristics (entries presented as mean±SD unless stated otherwise)

Variable	pwMS (n=132)	HCs (n=90)	P-value
Age (yrs)	47.13±11.24	46.06±11.26	0.488
Sex (% female)	69.70	47.78	0.001*
Height (cm)	168.81±9.71	171.02±8.51	0.052
Weight (kg)	75.57±21.00	74.40±14.17	0.980
BMI (kg/m2)	26.21±6.95	25.07±4.96	0.798
EDSS	median(IQR): 3(2-4)	---	

EDSS: Expanded Disability Status scale Status scale
* p<0.05

3.2 Between-group differences in measures of physical activity behavior

Participants in the MS group wore the sensor for 6.0±1.2 valid days and controls for 6.4±1.0 (p=0.006) days. The differences in activity measures are described in Table 2. After adjusting for age, sex, and the number of valid days, pwMS had significantly higher active

fragmentation index values (p=0.048), indicating more fragmented active bouts. Their active periods were also characterized by a significantly lower Gini index (p=0.002), indicating that the time spent in an active state was distributed more equally and in shorter bouts. Their sedentary time showed a non-significant trend of being less equally distributed, and spread over fewer, longer bouts, as indicated by a higher sedentary Gini index (p=0.055). Additionally, patients had a higher active average hazard (p=0.013), supporting the idea of higher activity fragmentation, along with K_{AR}, which was also higher in the MS group (p=0.003). As for the circadian amplitude metrics, CA differed significantly between the groups (p<0.001), with patients showing a smaller amplitude of daily activity. The fractal analysis (see for example the analysis of two subjects in Figure 3 in the SM) showed positive temporal correlations for both groups (scaling exponent α>0.5), with significantly stronger correlations in the control group, both in the time scale range of 1 to 90 minutes (α_1, p=0.001), and 2-10 hours (α_2, p=0.002).

After adjusting for mean SVM (i.e., taking into account total activity volume), CA (p=0.003) and α_1 (p=0.014) remained significantly different in pwMS and controls. A significant difference appeared in the sedentary average hazard as well (p=0.045), with a slightly higher mean for the MS group.

Table 2: Between-group differences between pwMS and HCs in daily measures of fragmentation and activity distribution.

	PwMS (mean±SD)	**Healthy Controls (mean±SD)**	**T-test (P-value)**	**Adjusted for age, sex, no. of valid days, and study site (P-value)**	**Adjusted for age, sex, no. of valid days, study site, and mean SVM (P-value)**
Active fragmentation index (Hz)	0.018±0.003	0.016±0.003	0.009*	0.048*	0.371
Active average bout duration (s)	38.009±5.660	37.238±5.148	0.328	0.554	0.221
Sedentary average bout duration (s)	73.738±28.567	65.302±17.267	0.067	0.096	0.208
Active Gini index (nu)	0.426±0.045	0.451±0.045	<0.001*	0.002*	0.252
Sedentary Gini index (nu)	0.699±0.068	0.673±0.061	0.009*	0.055	0.251
Active average hazard (nu)	0.298±0.057	0.272±0.044	0.001*	0.013*	0.402
Sedentary average hazard (nu)	0.142±0.014	0.142±0.014	0.853	0.823	0.080
K_{AR} (nu)	0.212±0.068	0.178±0.057	<0.001*	0.003*	0.603
K_{RA} (nu)	0.043±0.010	0.047±0.010	0.013*	0.135	0.211
RA (nu)	0.247±0.070	0.270±0.060	0.016*	0.508	0.056
CA (mg)	6257.279±2320.801	9613.411±4613.367	<0.001*	<0.001*	0.015*

α_1 (nu)	0.982±0.081	1.046±0.092	<0.001*	0.001*	0.044*
α_2 (nu)	0.805±0.110	0.850±0.135	0.016*	0.002*	0.066

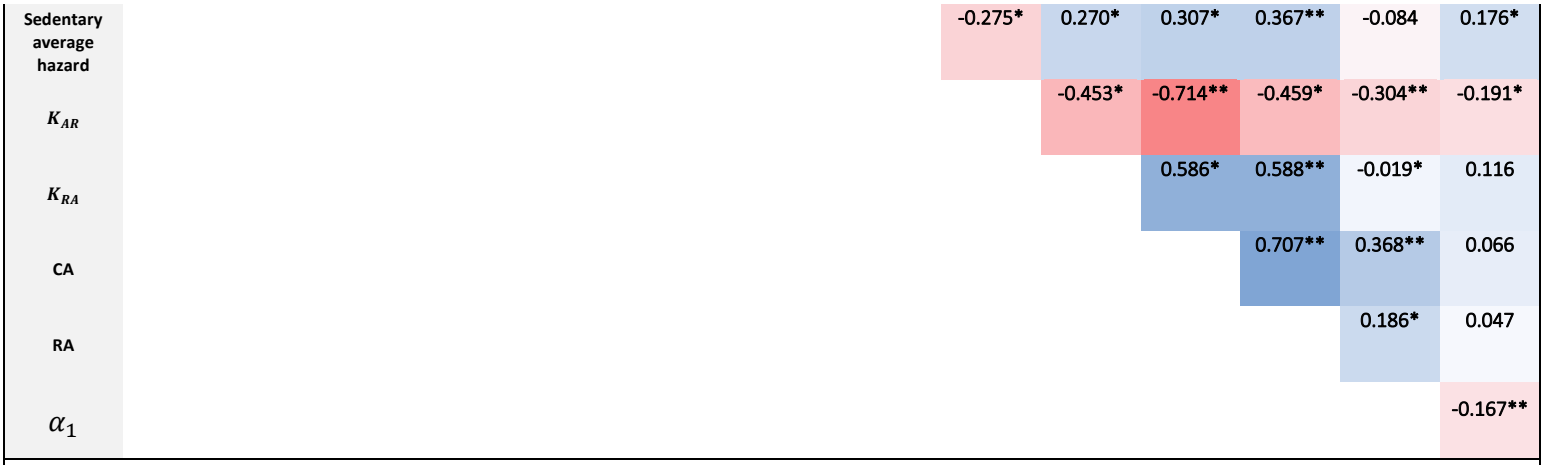
SVM: Signal vector magnitude; CA: Circadian amplitude; RA: Relative amplitude
* p<0.05 after adjusting for multiple comparisons

3.3 Correlations between measures of activity fragmentation, activity distribution, activity level and disability level in pwMS

Correlations between measures of physical activity and disability level among the pwMS are presented in Figure 1. Among the fragmentation-related measures, all measures excluding active average bout duration were significantly associated (p<0.05) with EDSS. Among the circadian amplitude and fractal measures, CA (rho: -0.439, p<0.001) and RA (rho=-0.358, p<0.001) were significantly associated with EDSS. Measures indicating a more fragmented pattern in the active state were positively correlated with EDSS, while the measure indicating a less fragmented activity pattern (active Gini index) was negatively correlated with EDSS. An opposite trend was seen in the measures describing the sedentary state. The circadian amplitude measures were both negatively correlated with disability level. After adjusting for mean SVM, only CA remained significantly associated with EDSS.

Figure 1: Correlations between different measures of physical activity and disability level measured by EDSS in pwMS. Values presented are Spearman's rho values in correlations adjusted for age, sex, no. of valid days and study site.

	Mean SVM	Active fragmentation index	Active average bout duration	Sedentary average bout duration	Active Gini index	Sedentary Gini index	Active average hazard	Sedentary average hazard	K_{AR}	K_{RA}	CA	RA	α_1	α_2
EDSS	-0.390*	0.252*	0.008	0.189*	-0.256*	0.242*	0.325*	-0.228*	0.310*	-0.188*	-0.439**	-0.358*	-0.055	0.031
Mean SVM		-0.607*	0.099	-0.736*	0.462*	-0.787*	-0.750*	0.337*	-0.706*	0.703*	0.871*	0.653*	0.202*	0.162
Active fragmentation index			-0.401**	0.292**	-0.856**	0.255**	0.901**	-0.284*	0.775**	-0.200**	-0.592*	-0.306*	-0.172	-0.208*
Active average bout duration				0.018	0.375**	0.074**	-0.333**	0.144	-0.103	-0.103**	0.073	0.081	-0.282**	-0.006
Sedentary average bout duration					-0.115**	0.890**	0.492*	-0.485**	0.463*	-0.766**	-0.629*	-0.644**	-0.006**	-0.168
Active Gini index						-0.132**	-0.794**	0.172	-0.755**	0.130**	0.503**	0.275*	0.294**	0.123
Sedentary Gini index							0.495**	-0.291*	0.480*	-0.854**	-0.684*	-0.658**	-0.060	-0.125
Active average hazard								-0.325*	0.907**	-0.445*	-0.722**	-0.492*	-0.195*	-0.185*



SVM: Signal vector magnitude; CA: Circadian amplitude; RA: Relative amplitude; EDSS: Expanded disability status scale
* p<0.05 after adjusting for age, sex, no. of valid days and study site ** p<0.05 after adjusting for age, sex, no. of valid days, study site and mean SVM.

Some of the measures showed associations with each other (see Figure 1). Among the fragmentation measures, active fragmentation index was strongly associated with the active Gini index and active average hazard. The sedentary Gini index was also strongly correlated with K_{RA} and active average hazard with K_{AR}. Other measures were not as strongly correlated with each other, excluding CA, which, being a measure of un-normalized activity amplitude, had a strong association with mean SVM.

3.4 Classification of clinical condition based on measures with significant differences between patients and controls after adjusting for mean SVM

The classification success of the logistic regression models is summarized in Table 3. CA and α_1 (in addition to the adjustment parameters) showed slightly better performances compared to the other models.

Table 3: Classification of patients groups

	Model 1			Model 2			Model 3			Model 4		
	Acc.	**Sens.**	**Spec.**	**Acc.**	**Sens.**	**Spec.**	**Acc.**	**Sens.**	**Spec.**	**Acc.**	**Sens.**	**Spec.**
pwMS vs health controls	0.679	0.727	0.607	0.777	0.833	0.693	0.751	0.780	0.708	0.786	0.848	0.693
pwMS with EDSS<4* vs controls	0.750	0.529	0.966	0.783	0.701	0.864	0.739	0.621	0.854	0.777	0.690	0.864
pwMS with EDSS≥4 **vs controls	0.813	0.467	0.989	0.880	0.778	0.932	0.843	0.711	0.910	0.895	0.822	0.932
pwMS with EDSS<4 vs EDSS≥4	0.705	0.267	0.931	0.780	0.600	0.874	0.750	0.511	0.874	0.750	0.533	0.862

*87 pwMS had EDSS <4
**45 pwMS had EDSS ≥4
CA: Circadian amplitude; EDSS: Expanded disability status scale; Acc.: Accuracy; Sens.: Sensitivity; Spec.: Specificity
Model 1: Predictors were age, sex, no. of valid days, and study site
Model 2: Predictors were age, sex, no. of valid days, study site, CA, and α_1
Model 3: Predictors were age, sex, no. of valid days and study site, and mean SVM.
Model 4: Predictors were age, sex, no. of valid days, study site, CA, α_1, and mean SVM

4. DISCUSSION

The results of the present study revealed differences in the rest-activity fragmentation, the amplitude of the circadian rhythm, and the fractal regulation of pwMS, compared to healthy controls. Multiple measures reflecting active-state fragmentation were altered in the pwMS after adjusting for demographic parameters. The differences indicate higher activity fragmentation in pwMS, as well as a smaller variability in the active bout length. No measures of sedentary period distribution showed significant differences between pwMS and controls, suggesting that examining the active period distribution might provide more valuable information. In addition, lower CA in pwMS suggests a smaller amplitude (difference between the ten most active and five least active hours of the day) of daily activity in pwMS. A lower scaling exponent of the detrended fluctuation amplitude provides evidence that the fractal regulation of motor activity was degraded in pwMS.

When examining associations between the fragmentation measures, we found that some measures were strongly related to each other and may be assumed to reflect similar features of the activity pattern. Regarding relationships with disease progression, it appears that SVM is a strong predictor, making the associations between EDSS and the other measures (excluding CA) insignificant after adjustment. Although α_1 and α_2 were different between patients and controls, unlike measures of fragmentation and circadian amplitude, they were not associated with EDSS. This suggests that they reflect other MS factors not related to disability level.

Although various outcomes describing the rest-activity patterns of pwMS were different compared to the controls, when taking into account the effect of total activity volume by further adjusting for mean SVM, the differences in fragmentation were generally attenuated. Nonetheless, CA and α_1 remained significantly different in pwMS and controls. Based on these results, it appears that total activity volume is a strong marker of the disease when compared to activity fragmentation measures. Circadian amplitude and DFA, however, seem to contain important, independent information on the rest-activity patterns of pwMS and remain valuable as possible motor measures even when compared to physical activity levels. A regression-based model combining CA and α_1 (Table 3) resulted in slightly better performances in terms of classification accuracy than a model based on mean SVM, when trying to differentiate between patients and controls, or between controls and patients with both high and low EDSS scores. While α_1 is not correlated with mean SVM, CA and mean SVM are highly correlated, due to CA being a measure of the daily activity amplitude. However, it should be noted that while mean SVM quantifies the average total activity per day, CA is more indicative of the daily range between the amount of activity during the most active part of the day and that during the least active part (normally, the sleeping hours). From a theoretical standpoint, range and totals do not necessarily reflect the same properties (recall Figure 1 in the supplementary material).

The differences in the fragmentation measures that we observed are consistent with the findings of Blikman et al. They suggested that fatigued pwMS tend to have a more fragmented activity pattern [3]. Here we expand those findings and show that pwMS who are not necessarily severely fatigued also have alterations in their fragmentation. The differences in CA and RA are consistent with the association between a smaller RA and a higher disability level among pwMS reported previously [30]. These measures indicate that

not only is the total volume of activity affected by MS, but circadian rhythm characteristics are abnormal. Still, further exploration is needed to determine whether the differences in both activity fragmentation and circadian characteristics are mediated by direct disease-related factors like fatigue or motor impairment, by "external", habitual behavior that is indirectly affected, or both [42]. Blikman *et al.* [3] also found a less fragmented rest pattern in fatigued pwMS, a finding that generally does not correspond with the results of the present study – and could potentially indicate that rest patterns are related mainly to fatigue, while activity bout distribution is different. Further analyses including fatigue data or other demographic parameters (such as occupational status) are needed to explore these questions.

The fractal analysis of the physical activity of pwMS suggests a stronger effect of the disease on the correlations in the time scales of 1.5 to 90 minutes, and less on those in the range of 2 to 10 hours. This implies different underlying mechanisms of regulation for "short-term" and "long term" self-similarity. In their longitudinal study on fractal fluctuations in the activity of older adults, Li et al. [19] evaluated α_1 and α_2 in similar time scale ranges, and hypothesized that the degradation of fractal correlations in the longer time scale ranges might be related to circadian dysfunction, citing evidence of lesions in circuits related to the suprachiasmatic nucleus (SCN) in rat studies and loss of SCN neurotransmitters in humans being linked to a reduction in α_2. They also suggested that the regulation in the smaller time scales degrades with cognitive decline – based on associations with higher brain function decline and dementia – although other mechanisms might also be in play. Li et al. [25] suggested similar underpinnings α_1 and α_2. Several studies suggest that circadian regulation is involved in the fractal regulation of physical activity [19][20][23][24][25]; these studies suggest that either circadian rhythm regulation or a more complex integration of regulatory processes are responsible for the fractal motor patterns. The present study shows an association between circadian amplitude and a higher α_1, but not α_2. To better understand the relationship between circadian rhythm and the fractal measure, it may be helpful to evaluate other measures of circadian regulation, such as acrophase (time of peak activity), and the interdaily stability and intradaily variability of the activity rhythm [29].

There is little work regarding the fractal regulation of activity in pwMS. As noted above, Sosnoff et al. link the observed changes to disability and motor impairment [26]. The results presented here support the value of fractal analysis of physical activity patterns in MS. Although the present study does not offer further explanations regarding the process of fractal degradation, it is possible that MS accelerates the natural degradation process that occurs with aging, similar to what is seen in Alzheimer's disease [25], resulting in the observed differences in the scaling exponents between pwMS and controls. It is important to note that the present cross-sectional study limits our ability to interpret cause and effect and changes over time. Long-term, prospective studies might offer additional insight into the degradation of fractal patterns in MS, similar to the work by Li et al. in Alzheimer's disease.

As noted in the Introduction, prospective studies in different cohorts point to a possible long-term relationship between the circadian amplitude and the worsening of neurodegenerative symptoms, and even a predictive ability of the amplitude and other activity outcomes related to circadian rhythms. Rogers-Soeder et al [43], for instance, found that a lower circadian amplitude was associated with greater cognitive decline in older men. Further, a lower circadian amplitude was associated with an increased risk of developing Parkinson's disease and Alzheimer's disease [28][29]. In future studies, it would be

interesting to test the hypothesis that the circadian activity amplitude can predict the risk of cognitive decline and changes in disease severity among pwMS.

This work has several limitations. The analysis was performed on daytime data that was selected using a sleep-detection algorithm [44] based on the detection of lying periods. The algorithm uses a fixed threshold and makes certain assumptions (i.e. regarding minimal lying time for detecting sleep). The fragmentation analysis is based on a binary definition of active versus sedentary periods, with a pre-defined SVM threshold. It might be helpful to construct a more adaptive method to set the activity threshold, for example by adjusting the threshold based on clinical condition or per subject. In addition, the present work does not separate the analysis of weekdays and weekends. In the future, separate analyses that account for the differences in activity during weekdays and weekends might produce a more specific and accurate characterization of the daily activity patterns of pwMS. As mentioned above, this study was cross-sectional and as such, does not offer information regarding the causal nature of the relationships between the different measures. There are numerous directions in which the work presented here can be expanded using longitudinal analyses, as previously discussed. In addition, in the future, it might also be interesting to examine the potential utility of combining multiple measures in different ways (e.g., machine learning) to further enhance the ability to assess group differences and changes over time in disease severity.

5. CONCLUSIONS

Daily-living physical activity patterns in pwMS differ from those of healthy controls in multiple measures of fragmentation, circadian amplitude, and fractal analysis. Those measures may help to enhance the monitoring of disease progression and in the evaluation of the response to interventions. The present work suggests that some of these measures provide added value even when taking into account total physical activity, while others do not. Additional work should further explore the analytic approaches described here and their potential for augmenting the objective assessment of pwMS. The present study sets the stage for that work.

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