Within-person changes in objectively measured activity levels as a predictor of brain atrophy in multiple sclerosis

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Running head: Changes in patterns of activity and brain atrophy in multiple sclerosis

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Abstract (250 words)

Objective. The evaluate the association between changes in accelerometry-derived activity patterns and brain atrophy in people with multiple sclerosis (PwMS).

Methods: We included PwMS aged ≥40 years with approximately annual brain MRI who wore GT9X Actigraph accelerometers every three months over two years. Functional principal components analysis (fPCA) summarized overall activity and timing. Additional indices included total and 2-hour specific activity, sedentary time, and circadian rhythm parameters. Whole brain segmentation used SLANT-CRUISE. Generalized estimating equations quantifying between- and within-person effects modeled associations between accelerometry changes and MRI outcomes, adjusting for demographic and clinical factors.

Results: We included 233 PwMS (mean age: 54.4 years, SD: 8.6, 30% male) who wore accelerometers an average of 6.3 times over 58 days across two years. fPCA showed within-person increases in the first fPC, representing low nighttime and high morning activity, were associated with slower brain atrophy (per 1 SD increase: 0.24%; 95% CI: 0.10, 0.40; p=0.0009). Similarly, a 10% increase in 8:00–10:00 AM activity was associated with 0.49% higher whole brain volume (95% CI: 0.19, 0.79; p=0.001) over time, while increased nighttime activity (0:00–2:00) was linked to -0.28% brain volume loss (95% CI: -0.48, -0.08; p=0.007). Higher moderate-to-vigorous activity and daytime activity were associated with greater brain volume preservation longitudinally.

Interpretation: Changes in activity patterns, particularly increased nighttime activity and reduced morning activity, are linked to brain atrophy in PwMS. Accelerometry offers a scalable, sensitive method for tracking MS progression and may be beneficial as a recruitment or outcome measure in trials.

Introduction

Multiple sclerosis (MS) is the most common cause of non-traumatic disability in young adults and affects millions of people worldwide.[1,2] Most people with MS are initially diagnosed with relapsing-remitting MS (RRMS), in which immune-mediated demyelinating attacks are common. Approximately half of people with RRMS will transition to a progressive phase of the disease, typically around age 45, where disability accumulation becomes more apparent with a gradual worsening of physical and cognitive functioning.[3] A small percentage of PwMS (~10%) have progressive-onset disease, in which steady deterioration of function is apparent from diagnosis.[2,3] Notably, while current disease modifying MS therapies are effective in reducing immune-mediated attacks, they do not meaningfully slow insidious progression of MS, thought to be occurring as a result of underlying neurodegeneration.[4,5] These processes likely begin years prior to the manifestation of clinical symptoms. Thus, there remains a critical need to develop therapies that can effectively target this phase of the disease.

One current roadblock in the path to advancing progressive MS therapies remains a lack of accurate measures of clinical disease progression.[6] The Expanded Disability Status Scale (EDSS), widely used in clinical trials, has significant limitations due to its semi-quantitative and non-linear nature, which affects its reliability and responsiveness.[7,8] These drawbacks translate to larger sample sizes and longer follow-ups in clinical trials, increasing costs and complicating drug development. Additionally, the EDSS may fail to identify individuals in early progressive stages, particularly those with suspected clinical worsening that cannot be confirmed over short intervals, leaving them classified as having RRMS and ineligible to participate in progressive MS trials. Improved methods to track progression are essential to overcome these challenges.

Wearable technologies, such as accelerometry, provide an opportunity to better detect and monitor disability progression possibly by better measuring underlying contributing neurodegeneration.[9-12] Accelerometry offers objective, real-world data on physical activity, circadian rhythms, and sleep patterns and is relatively cheap and accessible.[13,14] Short-term, continuous monitoring allows for insight into variation in activity within a 24-hour period or over the course of several days indicative of disease progression that may be missed during a traditional clinical visit.[10] Furthermore, as the use of telemedicine continues to grow, real-world activity data from accelerometers could help supplement virtual care; patients with concerning activity patterns could be prioritized for in-person visits, while stable individuals could continue with hybrid care models.[15,16] By integrating accelerometry into routine

care and clinical trials, MS monitoring and management could become more accurate, efficient, and likely equitable.

However, to date, most wearable studies in MS have been cross-sectional and have primarily focused on the correlation of total step count with symptoms or disability outcomes like the EDSS.[9,11,12,17,18] Few studies have included potentially more sensitive outcomes like those derived from brain MRI (e.g., total brain or gray matter volume) or have incorporated changes in activity as predictors of such outcomes in PwMS. For example, findings linking sensitive measures of activity (or changes therein) over the course of the day to gray matter loss are particularly significant, as such atrophy is strongly predictive of worse long-term disability in PwMS.[19] Here, we evaluated whether within-person changes in accelerometry measures, including at specific times of the day and overall activity patterns, are associated with brain compartment atrophy.

Methods

Study population

We included participants from the Home-based Evaluation of Actigraphy to predict Longitudinal Function in MS (HEAL-MS) cohort, as described previously. Briefly, HEAL-MS participants were recruited from the Johns Hopkins MS Precision Medicine Center of Excellence between January 2021 and March 2023 and were aged 40 years or older, did not have known significant comorbidities that could impair physical activity (e.g., heart failure, end-stage renal disease), did not have a MS relapse within the six months prior to enrollment, and had a baseline EDSS score of 6.5 or lower. We developed these criteria to enroll people with relapsing remitting MS (RRMS) who (1) age-wise are at an elevated risk for transitioning to the progressive phase of MS; (2) to ensure that changes in accelerometry were likely to be related to changes in MS rather than other conditions; and (3) to avoid confounding for baseline scores that were impacted by recovery from a relatively recent relapse. We categorized individuals into three groups. One group included people with stable MS who had no evidence of suspected or confirmed progression. Another group included people with confirmed disability worsening on EDSS. The final group included people with RRMS who were suspected of clinical progression but did not have sustained disability worsening. Here, confirmed disability worsening was defined as an EDSS increase of at least 1.0 points for individuals with baseline EDSS ≤ 5.5 or an increase of at least 0.5 points for individuals with baseline EDSS at least 6 that was sustained at least 24 weeks later. A neurologist specializing in MS reviewed electronic healthcare records (EHR) to confirm eligibility for each participant

and to assign PwMS to individual groups. The two RRMS groups were matched for age (± 2 years), sex at birth, race/ethnicity, and efficacy class of current DMT. We categorized DMT use into "first line injectable" (interferon-beta and glatiramer acetate), oral (teriflunomide, sphingosine-1-phosphate inhibitors, and fumaric acid esters), "infusion or immune reconstitution"' (anti-CD20 agents, natalizumab, alemtuzumab, and cladribine), "other", and "untreated".

Accelerometry measures

HEAL-MS participants wore GT9X Actigraph accelerometers that feature a built-in tri-axial accelerometer at pre-specified 3-month intervals throughout the course of the study. At each wear, individuals were instructed to wear the device on the wrist of their non-dominant hand continuously for 24 hours per day over a two-week period. Each device was configured such that it recorded three-dimensional acceleration at 30 Hz with a range of ±8 G. Raw acceleration data in .gt3x format were downloaded using ActiLife v6.134 Lite Edition,[20] and binary activity data were processed using the read.gt3x package in R, converted into activity count data with 60-second epochs, and formatted for analysis with 1440 minutes per day (midnight to 11:59 PM).[12] For each approximate 2-week wear-period, we defined non-wear time as an interval of at least 90 minutes in which all minute-level activity counts were equal to 0. As in previous analyses, a valid day during a given wear-period was defined as those in which wear-time exceeded 90% of the day (i.e., at least 1296/1440 minutes).[21] We excluded wear-periods in which an individual had at less than 3 valid wear-days (<1% of wear-times were removed).

For our primary analyses, we applied functional principal components analysis (fPCA) as a dimension reduction technique to help simultaneously summarize overall activity as well as the timing of activity in a unified approach.[22-24] fPCA is similar to PCA with the exception that it applies additional smoothing steps and has been applied extensively in the context of accelerometry data analyses. To provide additional intuition behind the fPCs, we also performed analyses examining log-transformed, 2-hour specific activity counts. For secondary analyses, we also calculated a series of measures summarizing different physical and circadian activity patterns. For physical activity, these included: (1) light intensity physical activity (LIPA); (2) moderate-to-vigorous physical activity (MVPA); (3) number of sedentary minutes; (4) measures of fragmentation including the sedentary to active transition probability (SATP) and (5) active to sedentary transition probability (ASTP).[25] For circadian measures, we included parametric and non-parametric indices. Parametric indices were using extended cosinor models and include: (1) amplitude- half the distance between the peak/trough of activity; (2) acrophase- maximal

activity point in cycle (3) mesor- mean value around which the cycle oscillates.[26] Non-parametric indices included diurnal landmarks such as (1) M10- most active 10-hours of a 24-hour period; (2) L5- least active 5-hours of a 24-hour period; (3) daytime activity ratio (DARE), defined as activity from 8:00-20:00 divided by the total activity from 0:00-23:59; (4) relative amplitude defined as (M10-L5)/(M10+L5); (5) inter-daily stability (IS) in a 24-hour period; and inter-daily variability (IV) in a 24-hour period.[27,28] For each wear-time, we averaged values across all days for each candidate measures.

Outcomes

MRI

Research MRIs obtained on a 3T Siemens scanner were acquired as a part of the HEAL-MS protocol at baseline and at the conclusion of Year 2. Interim MRIs collected under an identical protocol obtained as a part of clinical care were also included, when available. Our MRI processing pipeline was developed for a large-scale, multi-site MS clinical trial in which clinically acquired scans are analyzed that allowed us to increase power and better characterize longitudinal trajectories by including interim MRI scans obtained on multiple scanners. It was designed to handle various image sources, including T1-weighted, T2-weighted, PD-weighted, and T2-FLAIR imaging for processing, and images before and after contrast are usable (and a subset of contrasts can be missing).[29,30] Multi-slice image volumes undergo deep learning-based super-resolution with SMORE (Synthetic Multi-Orientation Resolution Enhancement),[31-33] followed by alignment of the super-resolved and 3D-acquired images using a longitudinal registration system. This system, using the advanced normalization tools (ANTs) software package, is optimized to manage diverse longitudinal data. The alignment process involves three main steps: (1) aligning each subject to a reference atlas; (2) adjusting images across different time points; and (3) aligning images within each time point. Rigid transformations are employed to maintain anatomical integrity. Applying Harmonization with Attention-based Contrast, Anatomy, and Artifact Awareness (HACA3), three contrast targets at each time point are generated: 3D T1-weighted MPRAGE, 3D T2-FLAIR, and multi-slice T2-weighted images, all of which attempt to adhere to standardized protocol from the Johns Hopkins MS on a single Siemens 3T scanner.[34,35] The HACA3-harmonized images serve as inputs for white matter lesion segmentation using a 3D U-Net architecture. T1-weighted images, with any lesions filled, are segmented using Spatially Localized Atlas Network Tiles (SLANT), which segments the brain into 133 distinct regions of interest.[36,37] After segmentation, the surface is reconstructed using Cortical Reconstruction Using Implicit Surface Evolution (CRUISE) to refine SLANT segmentation boundaries and

measure cortical thickness.[38,39] A U-Net-based algorithm is used to calculate the total intracranial volume as a surrogate for head size, and all MRI volumes are normalized for head size.

Statistical analysis

Initial analyses calculated descriptive statistics accelerometry measures over time using means or medians along with standard deviations or interquartile ranges across demographic or clinical characteristics.

We assessed whether changes in each accelerometry measure were associated with changes in brain atrophy measures (e.g., total brain and gray matter) by modeling within-person effects. To do so, we calculated an overall person-specific accelerometry mean (e.g., the average of given accelerometry measure for a person across all visits) and a within-person measure as the difference between the overall person-specific mean of a accelerometry measure and the person's accelerometry measure at each time point. We then fit a model using generalized estimating equations (GEE) to account for within-person correlation, in which we included a term for the overall mean of a given measure as well as the within-person difference.[40-42] Models were additionally adjusted for age, sex, race, body mass index (BMI, as kg/m^2), and baseline EDSS scores. Sensitivity analyses additionally adjusted for baseline HEAL-MS subgroup (e.g., stable RRMS, suspected-progression-RRMS, progressive MS). Each accelerometry measure (e.g., fPC1, …, fPC6, TAC, $TAC_{0:00\text{-}2:00,}$ ASTP, among others) was fit in a separate model for each outcome in which the overall person-specific mean as well as the time-point specific difference measure were included.

Results

We included 233 participants who on average were 54.4 years (standard deviation; SD: 8.6 years), approximately 30% were male, and 21% were non-white races. With respect to MS characteristics, participants had an average MS duration of 13.3 years (SD: 8.3 years) with mean baseline EDSS score 3.4 (SD: 1.6); 42% were receiving an infusion therapy, and 34% had progressive MS. Full descriptive characteristics across the initial HEAL-MS groupings are provided in **Table 1**.

Functional PCA

We found that the first 6 fPCs explained 54% of the variability in data across wears (**Supplemental Figure 1** and **Figure 1**). Individuals with high fPC1 (explaining 19.2% of the variability) values tend to have low activity in the night (e.g., 0:00-7:00) and then have a peak in activity levels occurring around 8:00, whereas individuals with low fPC1 values tend to have higher activity at night and very low activity

in early-to-mid morning (e.g., 6:00-10:00). For fPC1, individuals with low values tend to have lower overall daytime activity when compared to those with higher values, and fPC1 was correlated with overall activity levels (r=0.59; 95% CI: 0.55 to 0.62; p<0.0001; **Figure 1A**). While fPC2 was also correlated with overall activity levels similarly (r=0.59), correlations with 2-hour specific activity windows were distinct suggesting each was capturing different activity patterns in a 24-hour period. With respect to changes in MRI outcomes, within person change in fPC1 values were associated with whole brain and gray matter atrophy rates. A 1 SD within person increase in fPC1 (e.g., shifting from a blue-to-red activity pattern or a high-to-low nighttime and low-to-high early morning activity; **Figure 1B**) was associated with a 0.24% greater difference in whole brain volume over time (0.24; 95% CI: 0.10, 0.40; p=0.0009). Within-person increases in fPC4 (e.g., peak activity from 14:00-16:00 and higher night-time activity) were, in contrast, associated with lower whole brain volumes over time (per 2 SD increase in fPC4: -0.24; 95% CI: -0.48, -0.02; p=0.02). These findings were similar for gray matter volume changes. In mean (between-person) models, higher average fPC6 values (e.g., high levels of activity variability intraday) were associated with higher whole brain volumes; similar findings were not observed for gray matter volumes for fPC6.

These findings, particularly for fPC1, mirrored analyses of 2-hour specific activity windows. For example, a 10% within-person increase in activity from 8:00-10:00 was associated with a difference of 0.49% in whole brain volume over time, whereas a 10% increase in activity from 0:00-2:00 was associated with loss of -0.28% in whole brain volume over time (**Figure 2**; for 8:00-10:00: 0.49%; 95% CI: 0.19, 0.79; p=0.001; for 0:00-2:00: -0.28%; 95% CI: -0.48, -0.08; p=0.007). Findings were relatively consistent across 2-hour activity levels with respect to their relation to changes in whole brain and gray matter volumes for within-person models. For mean models, higher total 24-hour activity as well as higher mean activity levels from 12:00-2:00 and 16:00-18:00 were associated positively with gray matter volumes over time (**Figure 2**).

Other circadian and physical activity summaries

For other activity and circadian measures, a 1 SD within-person increase in acrophase (e.g., shifting peak activity to later times in the day) or L5 (e.g., lowest 5-hour activity) was associated with a respective loss of 0.26% and 0.18% in gray matter volume (**Table 3**; for acrophase: -0.26%, 95%CI: -0.50, -0.03; p=0.03; for L5: -0.18%, 95% CI: -0.36, 0.00; p=0.04). For mean/between person models, higher average MVPA levels over follow-up were associated with better brain and gray matter volumes over time (**Table 3**; per

1SD in average MVPA for whole brain volume: 0.69%; 95% CI: 0.11, 1.27; p=0.02; for gray matter volume: 0.65%; 95% CI: 0.04, 1.24; p=0.04). Likewise, higher mean M10 (e.g., highest 10-hour activity) was associated with higher gray matter volumes over time (0.56%; 95% CI: 0.02, 1.11; p=0.04). Other between-person and within-person accelerometry measures were not associated with MRI outcomes.

Findings were relatively consistent in analyses stratifying by HEAL-MS subgroup in that the observed associations between accelerometry measures (and within-person changes) were not modified in any of the categories.

Discussion

In this relatively large and well-characterized cohort of PwMS, including both longitudinal accelerometry and MRI outcomes, changes in activity timing in the 24-hour cycle were significantly associated with brain atrophy. Specifically, our findings suggest that pairing a within-person increase in night-time activity (i.e., increasing activity from 0:00-2:00) with reducing morning activity (i.e., reducing activity from 8:00-10:00) is associated with faster rates of whole brain and gray matter volume loss. These imaging results are highly meaningful, as gray matter volume loss, believed to reflect neurodegeneration, is a strong indicator of more severe long-term disability risk in individuals with MS. We also show that greater moderate to vigorous physical activity was associated with greater total and gray matter brain volume preservation longitudinally in between-person analyses. Notably, these associations were detectable over a relatively short period of time, indicating that it may be feasible within or between persons to detect thresholds for change in activity patterns that portend a loss of brain volume in a time frame corresponding to a Phase 2 clinical trial for progressive MS.

To date, accelerometry studies in MS have mostly been cross-sectional. A recent systematic review and meta-analysis focusing on differences in accelerometer-derived physical activity and sedentary time in PwMS versus healthy controls (HC) identified 21 prior studies focusing on this topic.[18] In general, cross-sectional studies show that (1) PwMS engage in less physical activity and have more sedentary time than age-matched healthy people, and (2) both physical activity and sedentary time correlate with disability levels, but in the opposite direction.[9-11,17,43] For example, in a comparably-sized population of PwMS, Motl et al. correlated accelerometer output with walking behavior parameters and EDSS-defined disability levels in a cross-sectional analysis. We have shown that after adjusting for relevant covariates, lower activity counts are cross-sectionally correlated with progressive versus relapsing MS. For example,

in a baseline analysis of the HEAL-MS cohort, we also found that lower overall activity as well as lower MVPA was correlated with disability levels Longitudinal studies in the field are sparse. Block et al., found that, in 95 PwMS, decreasing total step-count in a 1-year period was associated with worse clinic-based outcomes (timed 25-foot walk, timed-up-and-go, and patient-reported outcomes).[10] Our finding that between-person differences in overall physical activity are associated with lower brain volumes corresponds nicely to the results from this study.

In this relatively short duration study, the relevant changes in accelerometry patterns may reflect occult neurodegeneration that later manifests as a change in brain volume and, ultimately, as disability worsening. However, it is noteworthy that in prior epidemiological studies of later-onset neurodegenerative disorders such as Alzheimer's Disease, less physical activity and exercise in mid-life are associated with greater risk of later disease incidence.[44-46] Further, studies of aging have shown, using fairly standard accelerometry measures, that greater physical activity is associated longitudinally with brain volume preservation over several years.[47,48] Whether the activity patterns herein that appear relevant to brain atrophy might also be a treatment target, such as by enhancing exercise or improving sleep quality, is certainly of interest. Our finding that increasing activity in in the night with a reduction in morning activities (suggestive of circadian disruption) is linked with more brain atrophy is also consistent with observations of circadian disruption in people with other neurodegenerative diseases (e.g., Alzheimer's Disease, Parkinson's Disease) in which circadian disruption is commonly observed; research also suggests that these changes in patterns of activity manifest prior to the clinical manifestation or are potentially risk factors for each disease.[49-52] Lower circadian amplitude and phase advances (e.g., a later M10) are linked with greater cognitive decline in people with mild cognitive impairment.[53]

Strengths of this study include its novel design and inclusion of multiple accelerometry measures per person; each person contributed nearly 60 days of accelerometer wear-time. Other strengths include the inclusion of both overall activity and circadian patterns of activity, as many prior studies in MS have focused on total step count. We also considered a comprehensive set of circadian and physical activity measures that include both *a priori*-defined (e.g., MVPA or acrophase) and more data-driven approaches (e.g., fPCA) and obtained relatively consistent findings using either approach. Other strengths include the relatively large sample size (comparable to a Phase 2 trial in MS) compared with the existing longitudinal literature linking wearable devices in PwMS.

One limitation of this study includes the relatively short follow-up period, although if anything this would bias results toward the null, whereas we were able to detect significant loss of whole brain and gray matter volume loss during this period. We anticipate being able to link these measures with changes in disability status in future analyses that include greater follow-up time. Though hip-worn accelerometers, rather than wrist-worn for this cohort, may augment assessments of gait change, prior research in large-scale cohort studies (e.g., NHANES or UK Biobank) leveraged wrist-worn accelerometry. NHANES changed from hip-placed to wrist-worn devices to enhance participant adherence.[54] Further, aspects of activity beyond gait may be relevant to predicting MS worsening and likewise will be more inclusive of individuals with MS who are no longer ambulatory. Finally, while activity patterns herein were characterized using research-grade accelerometers, which enhances the reliability of their detection, using these devices at scale (or clinic-wide) may not be feasible.

In addition to confirming our results in an independent cohort, establishing clinically meaningful thresholds for change in the amount and timing of activity in relation to subsequent brain atrophy as well as confirming the association of these accelerometry measures with longer-term disability itself represent important next steps. Future research is also needed leveraging commercial activity monitoring devices, which will provide better scalability in assessing activity in PwMS and the ability to assess other digital biomarkers, such as heart rate, for their association with functional outcomes. Nonetheless, our findings demonstrate a compelling rationale for incorporating wearable accelerometers in MS clinical trials, particularly those focused on the prevention or reduction of MS disability.

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Conflicts of Interest

Kathryn Fitzgerald receives consulting fees from SetPoint Medical. Ellen Mowry serves as PI for investigator-initiated studies from Biogen and Genentech. She also receives royalties for editorial duties on UpToDate and consulting fees from BeCareLink, LLC.

Table 1. Demographic and clinical characteristics of included participants.

	Overall	HEAL-MS Group		
		RRMS (stable)	**RRMS** (suspected progression)	**Progressive**
N	233	77	76	80
N MRIs, mean (SD)	2.22 (1.01)	2.19 (0.92)	2.33 (1.09)	2.14 (1.03)
Follow-up time, mean (SD), years	1.17 (0.92)	1.12 (0.89)	1.21 (0.94)	1.18 (0.93)
Number of accelerometry wears, mean (SD)	6.33 (2.65)	6.01 (2.53)	6.33 (2.84)	6.62 (2.58)
Number of 24-hour periods (days) overall, mean (SD)	58.00 (26.59)	55.97 (25.66)	58.09 (28.48)	59.88 (25.79)
Number of days per wear, mean (SD)	9.03 (1.16)	9.15 (1.18)	8.99 (1.24)	8.95 (1.06)
log(TAC) across all days, mean (SD)	6.30 (0.15)	6.32 (0.11)	6.32 (0.13)	6.24 (0.18)
Age (SD), years	54.93 (8.61)	53.01 (7.62)	53.95 (8.38)	57.70 (9.12)
Male sex at birth, n (%)	69 (29.6)	24 (31.2)	19 (25.0)	26 (32.5)
Race, n (%)				
White	180 (77.3)	58 (75.3)	59 (77.6)	63 (78.8)
Black	41 (17.6)	17 (22.1)	12 (15.8)	12 (15.0)
Other races	7 (3.0)	0 (0.0)	2 (2.6)	5 (6.2)
Hispanic or Latinx ethnicity, n (%)	9 (4.1)	3 (4.1)	3 (4.3)	3 (3.9)
Years of education, mean (SD)	14.00 (1.91)	14.36 (1.34)	13.76 (2.10)	13.86 (2.16)
BMI, mean (SD), kg/m^2	28.50 (6.07)	29.04 (6.03)	28.35 (5.92)	28.13 (6.30)
MS symptom duration, mean (SD), years	13.32 (8.26)	11.84 (7.22)	13.86 (8.12)	14.19 (9.15)
MS DMT, n (%)				
Injectable	40 (17.2)	11 (14.3)	15 (19.7)	14 (17.5)
Oral	39 (16.7)	19 (24.7)	15 (19.7)	5 (6.2)
Infusion or immune reconstitution	99 (42.5)	31 (40.3)	37 (48.7)	31 (38.8)
None	55 (23.6)	16 (20.8)	9 (11.8)	30 (37.5)
EDSS, mean (SD)	3.43 (1.62)	2.42 (1.04)	3.07 (1.33)	4.75 (1.44)

Table 2. Functional PCs and change in MRI outcomes

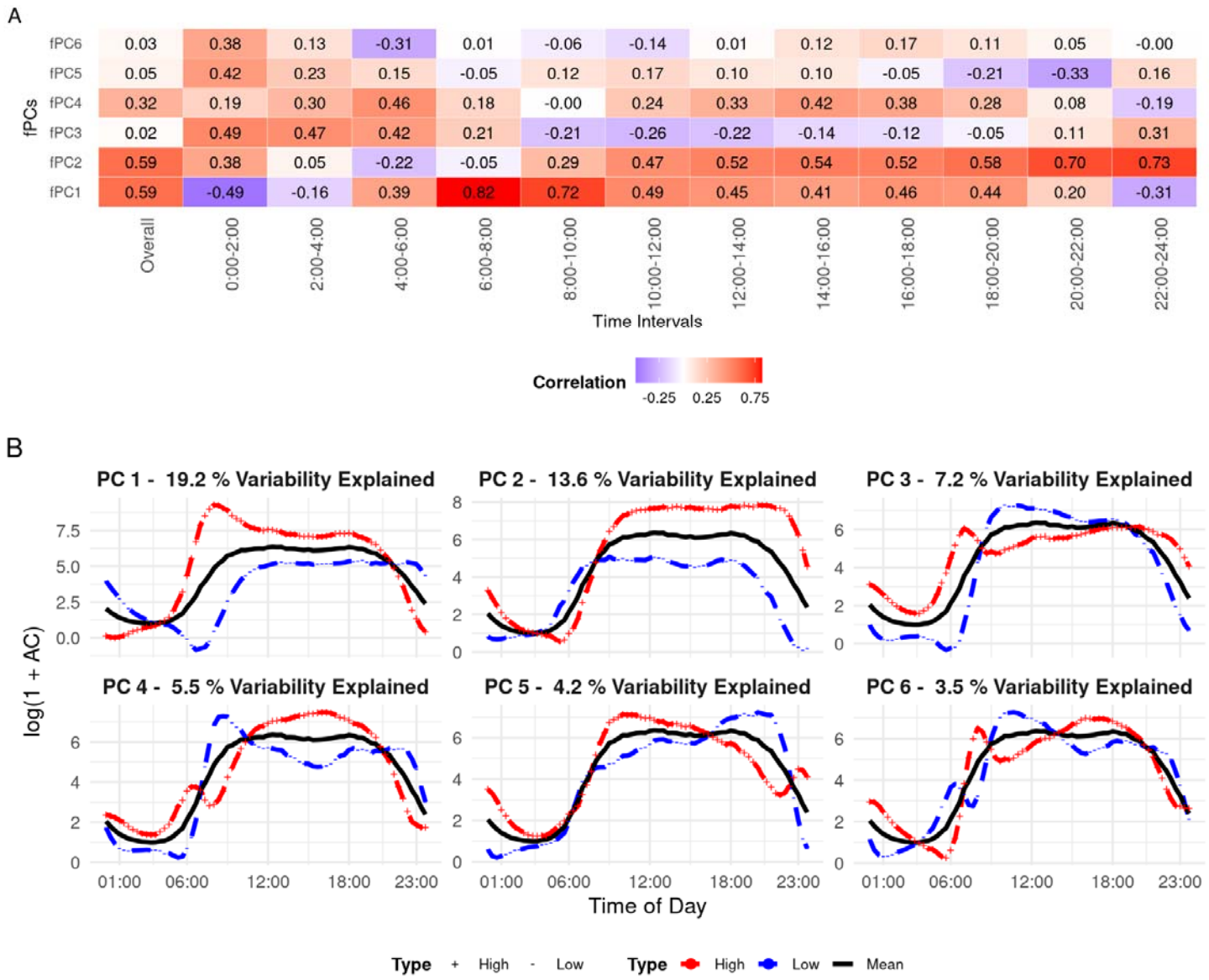
	Mean effect (Between-person)		Within-person effect	
%difference in WBV over time	**Effect (95% CI)**	**P value**	**Effect (95% CI)**	**P value**
fPC1	0.52 (-0.54, 1.58)	0.34	0.24 (0.10, 0.40)	0.0009
fPC2	0.52 (-0.46, 1.50)	0.29	-0.04 (-0.24, 0.14)	0.65
fPC3	-0.64 (-1.72, 0.46)	0.26	-0.06 (-0.26, 0.14)	0.54
fPC4	-0.54 (-1.54, 0.48)	0.30	-0.24 (-0.48, -0.02)	0.03
fPC5	0.50 (-0.46, 1.48)	0.30	0.12 (-0.10, 0.34)	0.31
fPC6	1.18 (0.18, 2.18)	0.02	0.02 (-0.20, 0.22)	0.92
%difference in GMV over time				
fPC1	0.42 (-0.58, 1.44)	0.41	0.46 (0.08, 0.84)	0.02
fPC2	0.72 (-0.18, 1.60)	0.11	-0.34 (-0.74, 0.08)	0.11
fPC3	-0.30 (-1.28, 0.70)	0.56	-0.36 (-0.76, 0.06)	0.09
fPC4	-0.40 (-1.36, 0.56)	0.41	-0.64 (-1.20, -0.08)	0.02
fPC5	0.34 (-0.56, 1.22)	0.47	-0.18 (-0.72, 0.36)	0.54
fPC6	0.92 (-0.04, 1.86)	0.06	0.24 (-0.26, 0.74)	0.34

Table 3. Other activity and circadian-based indices and longitudinal MRI outcomes

	Mean effect (Between-person)		Within-person effect	
%difference in WBV over time	**Effect (95% CI)**	**P value**	**Effect (95% CI)**	**P value**
Physical activity measures				
ASTP	-0.23 (-0.73, 0.26)	0.36	0.01 (-0.07, 0.08)	0.89
LIPA	0.03 (-0.50, 0.56)	0.91	0.05 (-0.05, 0.15)	0.30
MVPA	0.69 (0.11, 1.27)	0.02	-0.08 (-0.24, 0.07)	0.30
SATP	0.11 (-0.43, 0.66)	0.68	0.04 (-0.05, 0.13)	0.38
Sedentary activity	-0.26 (-0.81, 0.29)	0.35	-0.02 (-0.12, 0.08)	0.65
Circadian rhythm measures				
Acrophase	-0.20 (-0.57, 0.18)	0.30	-0.08 (-0.17, 0.02)	0.12
Amplitude	0.28 (-0.31, 0.86)	0.36	-0.11 (-0.26, 0.05)	0.18
DARE	0.23 (-0.33, 0.79)	0.42	0.05 (-0.05, 0.15)	0.35
IS	0.01 (-0.51, 0.53)	0.98	-0.02 (-0.16, 0.12)	0.77
IV	-0.29 (-0.82, 0.25)	0.30	0.00 (-0.09, 0.10)	0.94
L5	-0.14 (-0.64, 0.35)	0.58	-0.06 (-0.17, 0.05)	0.28
M10	0.54 (-0.04, 1.11)	0.07	-0.05 (-0.18, 0.07)	0.42
MESOR	0.28 (-0.33, 0.88)	0.37	-0.10 (-0.26, 0.05)	0.20
Relative amplitude	0.33 (-0.22, 0.88)	0.24	0.06 (-0.06, 0.19)	0.30
%difference in gray matter volume over time	**Effect (95% CI)**	**P value**	**Effect (95% CI)**	**P value**
Physical activity measures				
ASTP	-0.38 (-0.83, 0.07)	0.10	0.00 (-0.16, 0.16)	0.98
LIPA	0.09 (-0.38, 0.57)	0.70	-0.08 (-0.34, 0.17)	0.51
MVPA	0.65 (0.04, 1.26)	0.04	-0.17 (-0.44, 0.10)	0.21
SATP	0.11 (-0.38, 0.60)	0.66	-0.15 (-0.42, 0.11)	0.25
Sedentary activity	-0.30 (-0.81, 0.20)	0.24	0.12 (-0.13, 0.36)	0.35
Circadian rhythm measures				
Acrophase	-0.12 (-0.48, 0.23)	0.50	-0.26 (-0.50, -0.03)	0.03
Amplitude	0.41 (-0.12, 0.95)	0.13	-0.31 (-0.62, 0.01)	0.06
DARE	0.20 (-0.31, 0.71)	0.45	0.14 (-0.08, 0.37)	0.21
IS	-0.02 (-0.51, 0.47)	0.94	-0.07 (-0.35, 0.22)	0.65
IV	-0.47 (-0.96, 0.03)	0.06	-0.11 (-0.31, 0.09)	0.28
L5	-0.20 (-0.67, 0.27)	0.40	-0.18 (-0.36, -0.00)	0.04
M10	0.56 (0.02, 1.11)	0.04	-0.14 (-0.39, 0.11)	0.26
MESOR	0.36 (-0.17, 0.89)	0.19	-0.19 (-0.47, 0.08)	0.16
Relative amplitude	0.37 (-0.13, 0.88)	0.14	0.16 (-0.06, 0.38)	0.16

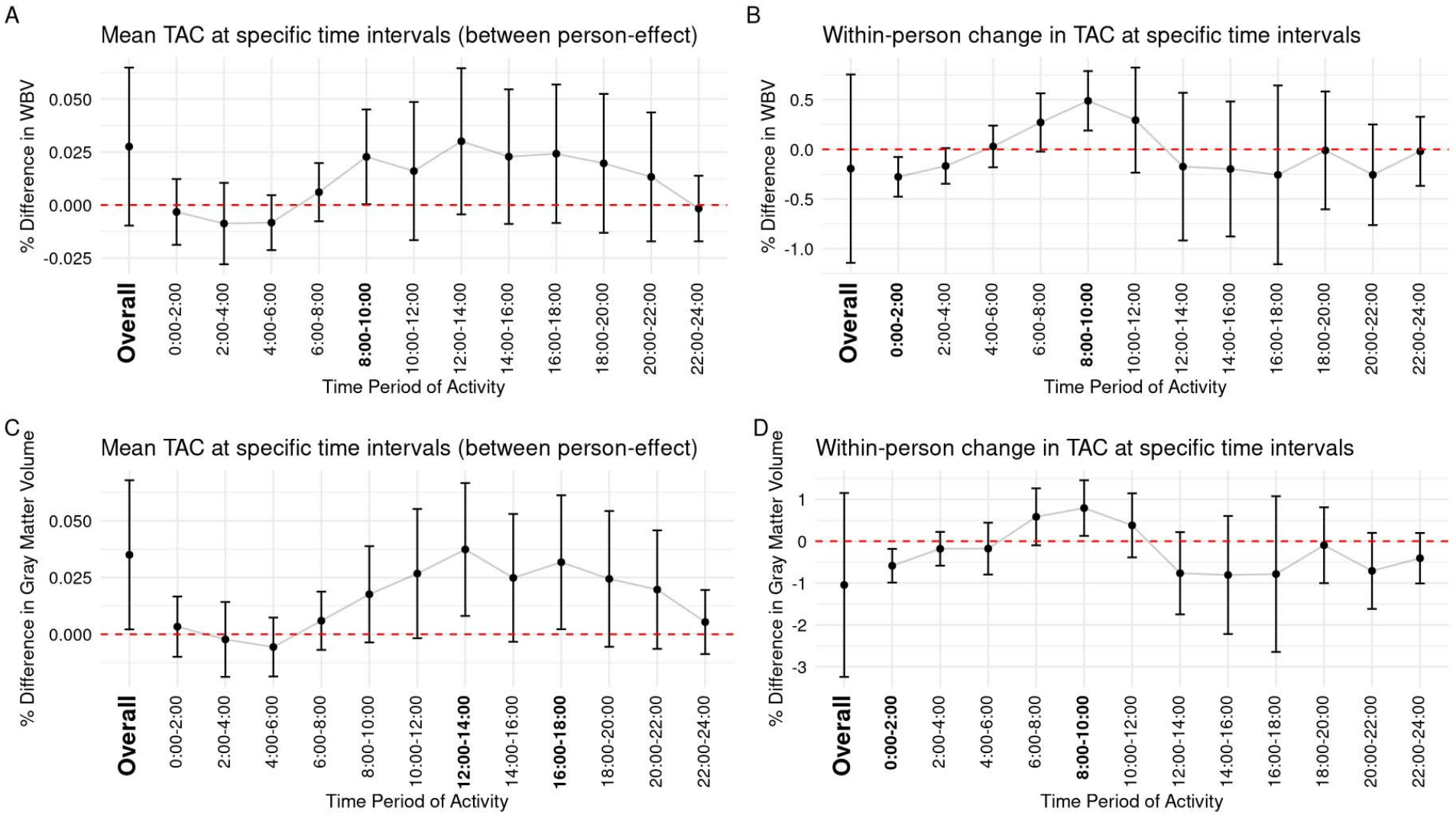
ASTP: active to sedentary transition probability.
LIPA: low intensity physical activity
MVPA: moderate-to-vigorous physical activity
SATP: sedentary to active transition probability
DARE: daytime activity ratio
IS: interdaily stability
IV: interdaily variability
L5: Average activity during least 5h activity period
M10: Average activity during most 10h activity period
Relative amplitude is the normalized difference between the L5 and M10

Figure 1. Functional Principal Components summarizing activity patterns in a 24-hour period.



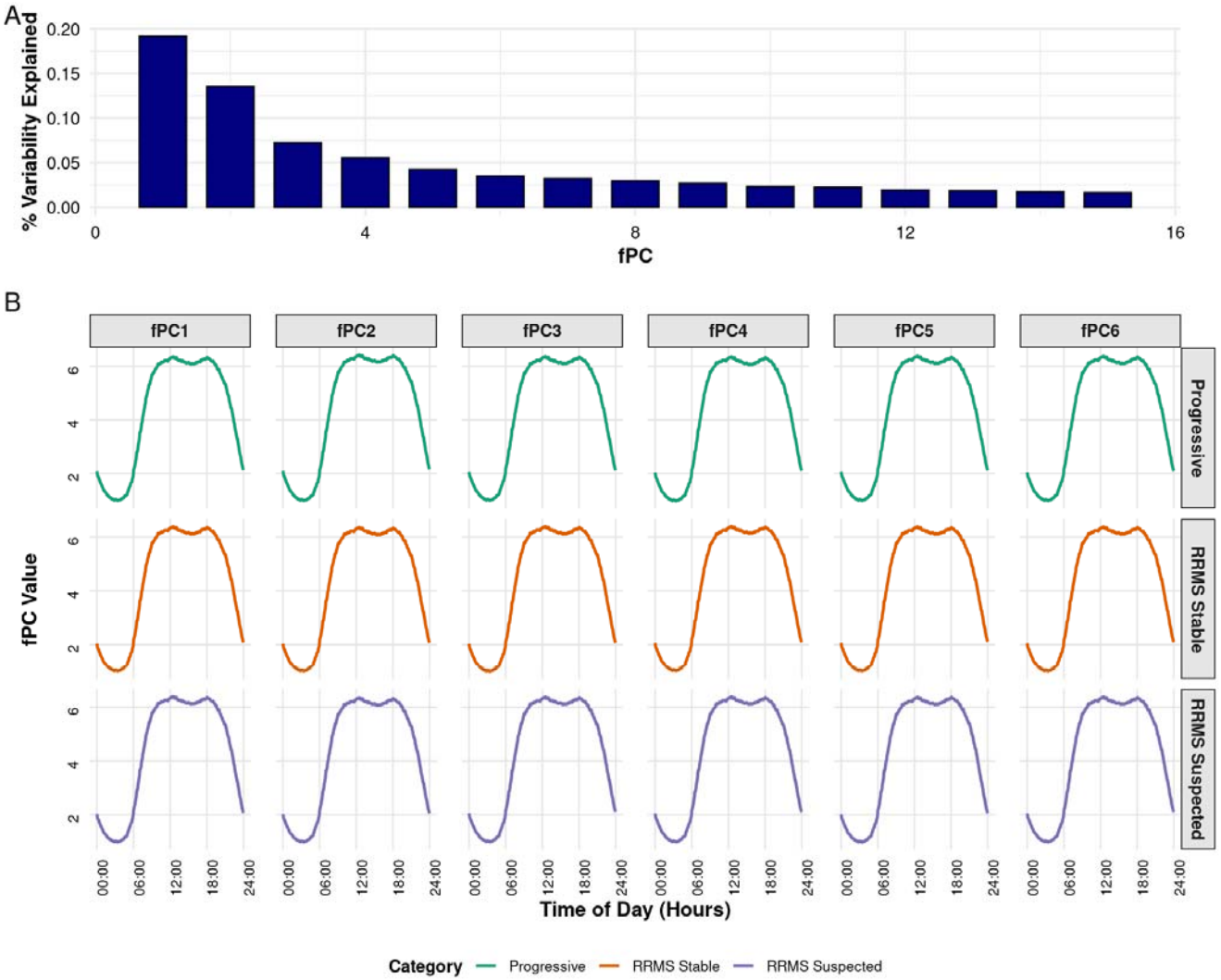
A. Correlation between overall time-specific activity log(activity counts) and fPC values. Values displayed in each of the boxes denote Pearson correlation coefficients. The darker blue values denote correlations closer to -1 whereas darker red values denote correlations closer to 1. **B**. The first 6 functional PCs (fPCs) explain 53% of the variability in the dataset. The blue lines denote individual activity patterns in a 24-hour period who have low mean values for a given fPC (e.g., those with <2 SD below the mean for a given fPC). The red line denotes individual activity patterns in a 24-hour period who have high mean values for a given fPC (e.g., those with <2 SD above the mean for a given fPC). fPCs were derived including all wear-times for all individuals.

Figure 2. Activity patterns overall and over the course of a 24-hour period and changes in whole brain volume (WBV) and gray matter volume.



The mean effect reflects the between-person effect comparing TAC across individuals in relation to changes in WBV (A) and (B) and gray matter volume (C) and (D). Effect estimates for mean reflect a 1 SD increase in mean TAC in a specific time-period or overall for WBV (A) and gray matter (C) volume over time. The effect estimates for the within-person models reflect a 10% increase in within person TAC in a specific time window for WBV (B) and gray matter volume (D). The overall measure in each plot reflects the total activity over the course of the day (e.g., the sum of TAC from 0:00 to 23:59). Estimates are adjusted for age, sex, race, BMI, and baseline EDSS score. Bolded labels denote those which are statistically significant ($p<0.05$)

Supplemental Figure 1. fPCA plots describing components and variability across baseline HEAL-MS category.



A. Percentage of variability explained by each of the fPCs. **B**. fPC values across different baseline HEAL-MS categories for the top 6 fPC

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