Altered Motor Activity Patterns within 10-Minute Timescale Predict Incident Clinical Alzheimer's Disease

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Abstract.
Background: Fractal motor activity regulation (FMAR), characterized by self-similar temporal patterns in motor activity across timescales, is robust in healthy young humans but degrades with aging and in Alzheimer's disease (AD).
Objective: To determine the timescales where alterations of FMAR can best predict the clinical onset of AD.
Methods: FMAR was assessed from actigraphy at baseline in 1,077 participants who had annual follow-up clinical assessments for up to 15 years. Survival analysis combined with deep learning (DeepSurv) was used to examine how baseline FMAR at different timescales from 3 minutes up to 6 hours contributed differently to the risk for incident clinical AD.
Results: Clinical AD occurred in 270 participants during the follow-up. DeepSurv identified three potential regions of timescales in which FMAR alterations were significantly linked to the risk for clinical AD: <10, 20–40, and 100–200 minutes. Confirmed by the Cox and random survival forest models, the effect of FMAR alterations in the timescale of <10 minutes was the strongest, after adjusting for covariates.
Conclusions: Subtle changes in motor activity fluctuations predicted the clinical onset of AD, with the strongest association observed in activity fluctuations at timescales <10 minutes. These findings suggest that short actigraphy recordings may be used to assess the risk of AD.

Keywords: Actigraphy, Alzheimer's disease, deep learning, motor activity

INTRODUCTION

The pathology of Alzheimer's disease (AD) can progress silently for decades before the clinical diagnosis of the disease, and this long preclinical phase is believed to provide a window for effective interventions [1]. Thus, understanding physiological changes in preclinical AD and identifying people at risk for developing AD at earlier stages are of great clinical relevance.

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Using concepts and methods derived from non-linear dynamics, previous studies in healthy young humans identified fractal motor activity regulation (FMAR) that manifests as robust self-similar patterns in spontaneous motor activity fluctuations with similar temporal correlations across a wide range of timescales from seconds to hours [2–7]. Using the Memory and Aging Project (MAP) dataset at Rush University AD Center [8], we previously showed that FMAR degrades with aging, leading to more random movements (i.e., reduced temporal activity correlations), and the degradation accelerated after the onset of mild cognitive impairment and dementia [9]. In addition, after adjusting for other risk factors for dementia (e.g., age, education, physical activity, sleep fragmentation, and daily activity rhythm), more random activity fluctuations predicted a faster cognitive decline and increased risk of incident AD in older people years before any sign of cognitive impairment [10]. Furthermore, our recent study showed a link between FMAR and AD pathology in preclinical AD [11].

However, despite the established links between FMAR and AD, the timescale where FMAR is the most sensitive to risk of clinical AD is unknown. In prior studies, average behaviors and changes in FMAR were commonly examined in two wide timescales: shorter and longer than 90 min [9, 10, 12–15]. Although there is strong evidence that changes in these two wide timescales have been linked to the effect of aging and the risk for dementia, they are overly coarse, and no study has examined the changes in FMAR across finer time scales. Clarifying the alterations of FMAR at finer timescales during the development/progression of AD is important for the mechanistic understanding of the impacts of AD on physiological processes/functions related to motor control, which can facilitate better design of biomarkers for early detection of AD.

Here, we test whether alterations in the temporal correlations of motor activity at different timescales have different contributions to the risk for clinical AD. We followed the participants with no dementia at baseline for up to 15 years. Using motor activity recordings (actigraphy) collected from these participants at baseline, we examined the temporal correlations in activity fluctuations across a wide range of timescales from 3 min to 6 h. We used deep learning survival analysis to identify the timescale region(s) significantly associated with incident clinical AD. The identified candidate timescale regions were then validated by examining the association

between the FMAR in these regions and incident clinical AD with traditional survival analysis approaches, including Cox Proportional Hazard model and random survival forest.

MATERIALS AND METHODS

Participants

Participants were from the Rush Memory and Aging Project (MAP), a longitudinal cohort study at the Rush University Medical Center (RUMC). All participants signed an informed consent for participation and a repository consent to allow data to be re-purposed. MAP was approved by the Intuitional Review Board of the RUMC. The current study was approved by the Mass General Brigham Intuitional Review Board. The inclusion criteria were 1) valid motor activity assessment (actigraphy) and 2) valid cognitive assessment at baseline. Until the end of 2018, 1,401 participants met these inclusion criteria. The exclusion criteria were: 1) poor data quality (see the following subsection); 2) no follow-up clinical assessment until 2020; and 3) presence of any type of dementia at baseline due to AD, Parkinson's disease, Lewy body disease, stroke, depression, or frontotemporal degeneration. Note that patients with other neurological diseases but without dementia were included. Based on the flowchart in Fig. 1, we finally had 1,077 participants.

Exposure: Fractal motor activity regulation and its alterations

First, motor activity during the baseline visit was recorded using an actigraphy device (Actical, Philips Respironics, Bend, OR, US) worn on participants'
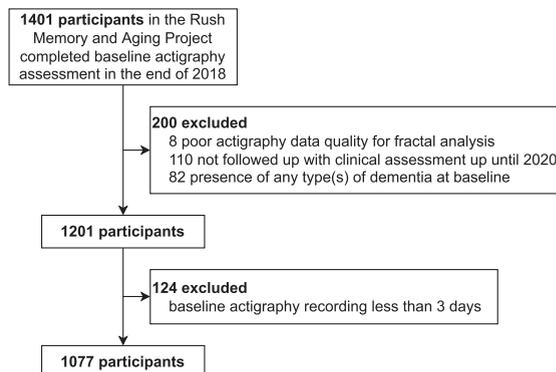

Fig. 1. The flowchart for inclusion/exclusion of study participants.

non-dominant wrist continuously for 10 days on average (max 14 days, standard deviation 1 day) [8]. Raw accelerometer data were integrated into proprietary counts (activity counts) in 15-s epochs. All activity count recordings were subject to signal quality screening [9, 10, 14], and low quality (defined as long segments with continuous zeros during daytime or spikes with amplitude 10 standard deviations higher than individual recording means [10]) were marked as gaps and excluded from subsequent data analysis. Those recordings that were shorter than 3 days [10] or had ≥50% gaps were also excluded (Fig. 1).

Next, to assess FMAR, detrended fluctuation analysis (DFA) [16] was performed to obtain a fluctuation amplitude F(n) as a function of timescales n from 3 min up to 6 h (see details in the Supplementary Methods and Supplementary Figure 1). For fractal fluctuations within a region of time scales, F(n) should be a power-law function (i.e., $F(n) = n^\alpha$), where the scaling exponent, α, estimates the temporal correlation in the fluctuations within the timescale region [17]. Note that all the participants in this study were old (59 to 100 years) and at risk for many diseases. Thus, it is expected that activity fluctuations in these participants may have altered temporal fluctuations. The altered temporal fluctuations can cause deviation from the power-law, hence different scaling exponents (α's) at different timescales. To identify the timescales where altered FMAR was associated with the risk for clinical AD, we obtained the local scaling exponent "$\alpha(n)$" at each timescale n by performing the power-law fit of 5 consecutive points (two points at both sides plus one middle point) of the function centered at timescale n (Supplementary Figure 2). The choice of 5 points is a trade-off between estimation reliability and locality, with Pearson's R^2 of the local estimation more than 0.5 for 98% of $\alpha(n)$'s. The result of using different numbers of points to evaluate the local $\alpha(n)$ is in Supplementary Figure 3. Note, compared to other analyses to assess FMAR, such as the Hurst analysis and the auto-correlation analysis, the DFA can better quantify positive temporal correlations embedded in non-stationary biological/physiological fluctuations including motor activity fluctuations.

Outcome: Onset of clinical Alzheimer's disease

To determine the clinical onset of AD, the 1984 National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria [18] were used since the Rush MAP started on 1997. The diagnosis of dementia due to AD was based on comprehensive clinical assessment according to the following four steps in the Rush MAP [19]. Step 1: History of cognitive decline was based on a structured interview with participants. Step 2: Cognitive impairment ratings of eleven tests were assessed covering five areas of cognition: orientation, attention, memory, language, and visuospatial ability. Step 3: A neuropsychologist rendered a clinical judgment: Impairment in one or two areas was consistent with single- or multiple-domain mild cognitive impairment, and impairment in three to five areas was consistent with dementia. When two areas of impairment were present, the neuropsychologist rendered an opinion regarding the presence of dementia. Step 4: A clinician entered all the information (i.e., history of cognitive decline, the number of impaired domains, the presence of memory impairment, and a clinical judgment regarding meaningful cognitive decline) to a decision tree, which generated a clinical diagnosis of dementia and AD based on the NINCDS-ADRDA criteria. The clinician was then offered an opportunity to override the decision. Note that "Alzheimer's dementia" was used in the Rush MAP to describe the above multi-domain clinical dementia symptom of AD.

Other types of dementia were also identified in the Rush MAP using other criteria, including dementia related to vascular (NINDS-AIREN [20]), Parkinson's or Lewy bodies (CAPIT [21]), depression (DSM-III-R criteria supported by the Hamilton rating scale for depression [22]), and frontotemporal degeneration (strict clinical judgment [19]).

Death is a competing risk. Here we assigned the primary outcome, clinical AD, as censored (unknown) for participants who died before the clinical diagnosis of AD.

Covariates

We considered the following categories of covariates at baseline: 1) Demographics: age, sex, years of education; 2) Cognition: Scores of 19 neuropsychological tests were z-transformed based on the means and standard deviations of the cohort, and then averaged to obtain a global composite cognitive measure (higher scores indicate better cognitive performance); 3) motor function assessed by a composite score covering 10 motor performance tests [23]; 4) chronic

health conditions assessed by the number (ranging from 0 to 3) of present vascular risk factors (hypertension, diabetes, and smoking) and the number (ranging from 0 to 4) of present vascular diseases (myocardial infarction, congestive heart failure, claudication, and stroke) [24]; 5) physical activity assessed by total activity counts per day [25]; 6) the probability of the transition from activity to resting (kar) [26] that likely represents the fragmentation of daytime active period, and the probability of transition from resting to activity after a long (about 5 min) period of rest (kra) that represents sleep fragmentation [26]; 7) Interdaily stability, a measure of the stability of 24-h activity rhythms (ranging between 0–1 with low values for higher day-to-day variations); and 8) Intradaily variability, a measure of fragmentation of the rest-activity rhythms [27]. The collinearity structure among these covariates plus some scaling exponents is shown in Supplementary Figure 4 in the Supplementary Material. 1.6% of the covariates are missing. We imputed them using the K-nearest neighbor model with $K = 10$.

We also explored the potential interaction effect of altered FMAR and genetic risk on the clinical onset of AD. We considered the *APOE* $\varepsilon4$ allele that increases the risk of late-onset AD and predicts cognitive decline with aging [28]. *APOE* genotyping in the Rush MAP was performed by Polymorphic DNA Technologies (Alameda, CA). DNA was extracted from peripheral blood mononuclear cells, and the *APOE* haplotypes were determined by the two polymorphisms of rs7412 (codon 158) and rs429358 (codon 112) at exon 4 of the *APOE* gene. *APOE* $\varepsilon4$ genotype status was dichotomized as *APOE* $\varepsilon4$ carrier (heterozygote or homozygote, including *APOE* $\varepsilon2/\varepsilon4$, $\varepsilon3/\varepsilon4$, and $\varepsilon4/\varepsilon4$) or noncarrier.

Survival analysis with DeepSurv

We used DeepSurv [29], a deep learning approach of survival analysis, using convolutional neural network (CNN) as its hazard function. The rationale of using DeepSurv is that it takes all $\alpha(n)$'s as input and let us inspect the importance of $\alpha(n)$. The inputs to DeepSurv were the covariates at the baseline visit and the local scaling exponents $\alpha(n)$ at different timescales. $\alpha(n)$ went through two convolution blocks, where each block contained a convolution layer (see the learned kernels of the first convolutional layer in Supplementary Figure 5), batch normalization, ReLU activation, max-pooling (downsampling the inputs 4 times), and dropout. The

outputs were then concatenated with the baseline covariates defined above and fed to a fully connected layer with sigmoid activation. The model was trained using Adam's optimizer with 0.001 learning rate (a common choice). The learning rate was reduced to its 10% to allow for annealing when the loss on the validation set did not decrease in 5 consecutive scans of the training dataset. The training was early stopped when the loss on the validation set did not decrease in 10 consecutive scans.

Determining the important timescales for AD risk

To obtain candidate timescales, we first computed the gradient of the DeepSurv-predicted AD hazard with respect to the local DFA scaling exponents $\alpha(n)$ at each timescale n. Since every participant has different gradient, we took the average of the gradients across all participants. We further smoothed the gradient across timescales using Savitzky-Golay filter with window length of 21 points and polynomial order of 2. The importance of $\alpha(n)$ was defined as the gradient. The candidate important timescales were identified as those with significant importance at 95% level (95% confidence interval does not include 0). The confidence interval was constructed as follows. First, assume the gradients follow normal distribution at each timescale, with mean equals to the mean across all participants, standard deviation equal to the standard error across all participants. Second, we used Bonferroni correction to control for family-wise error rate, therefore the lower bound is the value with cumulative probability at 2.5%/number of timescales in the normal distribution; and the upper bound is the value with cumulative probability at 100% – (2.5%/number of timescales in the normal distribution). The conserveness is good for our case of no *a priori* hypothesis over certain timescale. Note that we did not do variable selection since it is often affected by collinearity among predictors.

To validate candidate timescales found by DeepSurv, we performed analyses using two other survival analysis models: the Cox proportional hazards model with ElasticNet penalty (Cox), and random survival forests (RSF) [30]. The inputs to these two models were the DFA scaling exponent in the important timescales identified by the gradient of DeepSurv, adjusted by age, sex, education, and *APOE* $\varepsilon4$. Note that DeepSurv, Cox, and RSF models were trained with nested 5-fold cross validation (see Supplementary Methods). Since the results can be affected by the collinearity among the $\alpha(n)$ at different timescales

n, we also investigated the univariate importance of each $\alpha(n)$, by fitting a Cox model to each $\alpha(n)$ while adjusting for the covariates.

Metrics for performance evaluation

To evaluate the performance of all models, we obtained two metrics: 1) concordance index (C-index) that measures how concordant the ranking of time to the clinical onset of AD is compared to the ranking of individual risks at the end of 15 years of follow-up; and 2) the average 3-to-9 years cumulative/dynamic AUC that measures the discrimination between the cases of clinical AD until a given time and the cases without the clinical onset at or after the given time. The range of 3-to-9 years was used to ensure enough participants for each point of time to the onset such that AUC was less subject to random noise.

All confidence intervals were obtained from bootstrapping the dataset 1000 times. The 2.5% and 97.5% percentiles were taken as the lower and upper bounds respectively to form 95% percentile confidence interval.

RESULTS

Participants characteristics

As shown in Table 1, 1,077 participants (age at baseline: 59 to 100 years old, 23% males) were included in this study. Until 15 years after baseline, 270 out of 1,077 participants were diagnosed with clinical AD. The median time to the clinical onset of AD was 6 years (1st and 3rd quartiles 3 and 8 years). The Kaplan-Meier survival curve in Fig. 2 shows that, about 30% participants had the clinical onset of AD at 10 years after baseline and about 46% at 15 years after baseline.

Candidate timescales associated with incident clinical AD

Between groups with different risk for clinical AD, the local scaling exponents $\alpha(n)$ showed the greatest and consistent difference at timescales $n < 10$ min (Fig. 3A). This observation was confirmed by the importance of $\alpha(n)$ from the DeepSurv model (Fig. 3B). The importance was significant at 0.05 level in three timescale regions: 1) <10 min, importance <0 such that larger $\alpha(n)$ was associated with a lower risk for clinical AD; 2) Between 20 to 40 min, importance >0 such that larger $\alpha(n)$ was associated with a higher risk; 3) Between 100 to 200 min, importance >0 such that larger $\alpha(n)$ was associated with a higher risk.

To examine the potential effects of the collinearity among the $\alpha(n)$'s at different timescales on the result in Fig. 3B, the univariate hazard ratio of each $\alpha(n)$ after adjusting for covariates was examined, which are not affected by the collinearity but noisier since being univariate (Supplementary Figure 6). The shape of the univariate hazard ratio as a function of n was similar to the shape of DeepSurv-derived importance in Fig. 3B, i.e., both their zero-crossing point were around 13 to 14 min and both the directionality of being harmful and beneficial to AD risk were the same. On the other hand, the univariate hazard

Table 1
Participant characteristics

Variable	Value
Number of participants	1,077
Time to the clinical onset of AD (y) (median, 1st and 3rd quartiles)	6 (3, 8)
Age at baseline visit (y) (mean, stdev)	80.9 (7.3)
Male sex (*n*, %)	247, 23%
Years of education (y) (mean, stdev)	15 (3)
APOE ε4 carrier (*n*, %)	226, 21%
Cognition score at baseline visit (normalized, a.u.) (mean, stdev)	0.15 (0.53)
Interdaily stability (mean, stdev) [is]*	0.53 (0.12)
Intradaily variability (mean, stdev) [iv]*	0.72 (0.19)
Motor function (mean, stdev)	1.02 (0.23)
Daily activity level (mean, stdev)	2.75 (1.54)
Transition probability from activity to resting (median, 1st, 3rd quartiles) [kar]*	0.06 (0.05, 0.08)
Transition probability from resting to activity (median, 1st, 3rd quartiles) [kra]*	0.03 (0.02, 0.03)
Vascular disease burden+ (median, 1st and 3rd quartiles)	0 (0, 1)
Vascular disease risk factor^ (median, 1st and 3rd quartiles)	1 (1, 2)

*Abbreviation. +Including four vascular diseases: myocardial infarction, congestive heart failure, claudication, and stroke, ranges from 0 to 4. ^Including three risk factors: hypertension, diabetes, and smoking, ranges from 0 to 3.
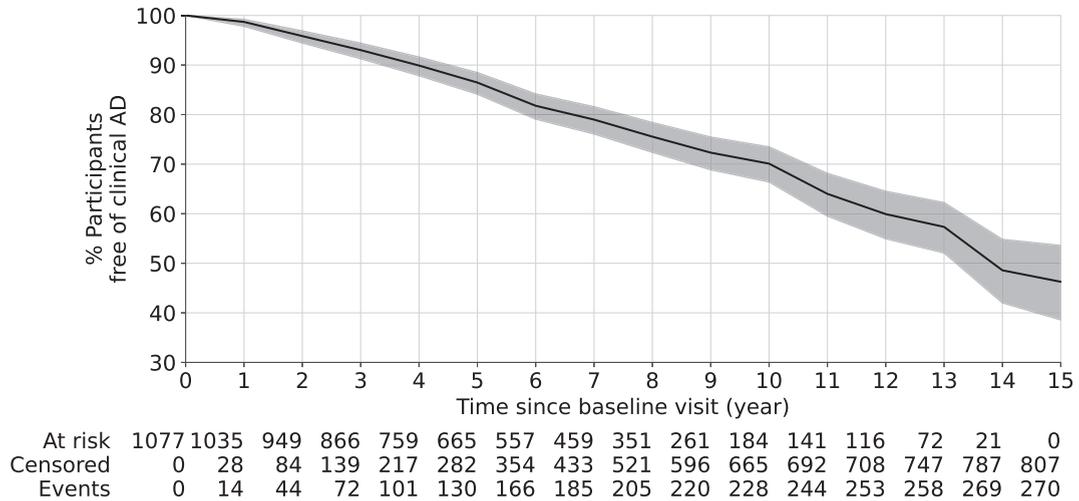
Fig. 2. Overall survival curve using Kaplan-Meier estimator. The shaded area represents the 95% confidence interval. The risk table at the bottom shows the number of participants at risk (who has not developed clinical AD) at different years after baseline visit. Here, at risk is defined as participants who have not developed clinical AD yet; censored is defined as participants lost-to-follow up due to any reason; and event is defined as being diagnosed of clinical AD.
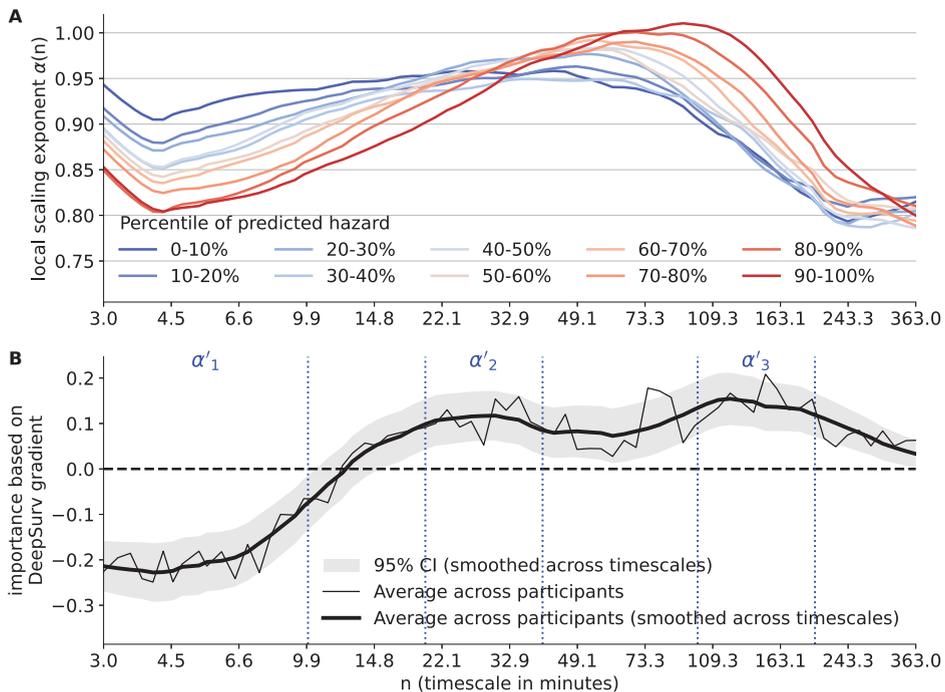

Fig. 3. Results of deep learning for survival analysis. A) The average local scaling exponents $\alpha(n)$ of participants stratified by percentile of predicted hazards. The predicted hazards are obtained after adjusting for the covariates. The x-axis represents timescale n (in min). B) The importance based on the DeepSurv gradients for each local scaling exponent. The data were the averages of all participants. Both the raw (thin solid line) and smoothed curves (thick solid line) are shown. The horizontal dashed line indicates importance of 0, i.e., no effect. The vertical dashed lines indicate the borders of the three candidate timescales represented by α'_1, α'_2, and α'_3.

ratios of $\alpha(n)$ had wider confidence interval compared to that in Fig. 3B, likely due to lower predictability of using only one local $\alpha(n)$. Overall, these results indicated that the identified timescale regions relevant to clinical AD risk (Fig. 3B) were reliable, not significantly affected by collinearity.

Validation of timescales associated with incident clinical AD

We next used the Cox and RSF models to validate the feature importance of the scaling exponents within the three candidate timescale regions identified by DeepSurv (<10 min: α'_1; 20–40 min: α'_2; 100–200 min: α'_3). Note that α'_1, α'_2, and α'_3 were not computed by averaging $\alpha(n)$, but by fitting a line to the timescale region. As shown in Table 2, both Cox and RSF models confirmed that α'_1 among all scaling exponents contributed the most to the prediction of clinical AD. The direction of the impact of α'_1 on hazard was also consistent with that observed in DeepSurv, i.e., larger α'_1 for lower risk. For the impacts of α'_2 and α'_3, the impact directions in Cox and RSF models appeared to be consistent with those in DeepSurv but the effects did not reach the significance level (*p* values > 0.05).

Contributions of FMAR alterations after adjusting for APOE ε4

To examine the effects of α'_1, *APOE ε4* status (1 for homozygous or heterozygous carrier and 0 otherwise), and their interaction, the Cox model was used while adjusting for age, sex, and education. Other covariates such as motor function and cognition based on clinical tests at baseline were not included because these covariates were linked to FMAR as reported previously and the current study was not focused on whether or how FMAR alterations predict the risk of AD via or independent of motor function and cognition. The hazard ratio for *APOE ε4* carriers compared to non-carriers was 2.17 (95% CI: 1.65–2.84, *p* < 0.0001). The hazard ratio for α'_1 remained statistically significant: for one standard deviation increase in α'_1, the hazard ratio was 0.79 (95% CI: 0.70–0.91, *p* = 0.0013). The interaction

between α'_1 and APOE ε4 carrier was not statistically significant (*p* = 0.4).

Comparison to previous FMAR measure

We tested whether α'_1 contributed to the risk for clinical AD, similar to or differently from the previously used scaling exponent at <90 min (α_1). We performed analyses using Cox model, where we only adjust for age, sex, years of education, and *APOE ε4* (Table 3). We selected Cox model because the model was used in a previous study to demonstrate the effect of α_1 on the risk of clinical AD, and the Cox model had an equivalent performance compared to RSF and DeepSurv (next subsection).

When including α_1 (<90 min) and α'_1 (<10 min) in separate models (α_1 in Model A and α'_1 in Model B), we found that both were significantly associated with the risk of clinical AD (both *p* < 0.001). Consistently, α'_1 and α_1 were highly correlated (Spearman's correlation 0.76, *p* < 0.001) (Supplementary Figure 4). When both α_1 and α'_1 were included in the same model (Model C), the contribution of α'_1 remained significant (HR = 0.77, *p* = 0.009) while the contribution of α_1 became not significant (*p* > 0.6). In Model D, the effects of α'_2 and α'_3 did not reach significance level.

Survival analysis performance

The C-index at 15 years of follow-up (averaged from the five testing sets) was similar in the Cox model and RSF models (Cox: 0.84, 95% confidence interval [0.81–0.87]; RSF: 0.82 [0.78–0.84]; *p* > 0.05 compared to Cox). The C-index was slightly but significantly lower in the DeepSurv (0.80 [0.78–0.81]). To confirm the importance of <10-min timescale, we repeated DeepSurv without <10-min timescale and obtained a C-index of 0.74 [0.72–0.76], which

Table 2
Feature importance of candidate scaling exponents based on Cox and RSF

Model	Feature	Hazard ratio 15 years after baseline when increased 1 stdev
Cox	α'_1: <10 min (stdev = 0.08)	0.76 [0.66–0.87]*
	α'_2: 20 to 40 min (stdev = 0.09)	0.98 [0.86–1.12]
	α'_3: 100 to 200 min (stdev = 0.13)	1.07 [0.95–1.20]

Model	Feature	RSF feature importance (Reduction in Gini impurity)
RSF	α'_1: <10 min	9.8 [6.8–12.8]
	α'_2: 20 to 40 min	0.1 [−0.9–1.2]
	α'_3: 100 to 200 min	2.0 [0.9–3.1]

Table 3
Hazard ratios and *p*-values of scaling exponents for prediction of clinical AD using Cox model

Variable	Basic Model: Covariates only		Model A: Covariates + α_1		Model B: Covariates + α'_1		Model C: Covariates + α_1, α'_1		Model D: Covariates + $\alpha'_1, \alpha'_2, \alpha'_3$	
	HR	p	HR	p	HR	p	HR	p	HR	p
Age	2.48	0.0**	2.43	0.0**	2.36	0.0**	2.37	0.0**	2.35	0.0**
Male sex	1.06	0.37	1.05	0.42	1.03	0.66	1.03	0.60	1.03	0.67
Education	0.83	0.004*	0.83	0.004*	0.83	0.004*	0.83	0.004*	0.83	0.006*
APOE ε4	2.25	0.0**	2.22	0.0**	2.13	0.0**	2.16	0.0**	2.10	0.0**
α_1 (<90 min)	/	/	0.79	0.0**	/	/	0.91	0.34	/	/
α'_1 (<10 min)	/	/	/	/	0.76	0.0**	0.82	0.04*	0.76	0.0**
α'_2 (20–40 min)	/	/	/	/	/	/	/	/	0.98	0.76
α'_3 (100–200 min)	/	/	/	/	/	/	/	/	1.07	0.28

*$p < 0.05$; **$p < 0.001$. HR, Adjusted hazard ratio 15 years after baseline when increased by 1 standard deviation.

showed a statistically significant drop. Note that the 0.06 difference in C-index is considered numerically big because we obtained a C-index of 0.72 [0.70–0.74] by fitting another DeepSurv without age, a known important covariate, which corresponded to a 0.08 difference. The 3-to-9-year averaged cumulative/dynamic AUC was also similar in the Cox model and RSF (Cox: 0.88 [0.85–0.90]; RSF: 0.89 [0.86–0.90]; $p > 0.05$ compared to Cox) and was slightly lower in the DeepSurv (0.84 [0.83–0.86], $p < 0.05$ compared to both Cox and RSF). The cumulative/dynamic AUC showed a trend to decrease over the years since baseline, e.g., AUC in the DeepSurv = 0.86 after 3 years, 0.85 after 4 years, 0.85 after 5 years, 0.85 after 6 years, 0.84 after 7 years, 0.83 after 8 years, and 0.83 after 9 years. We also compared their survival curves of clinical AD during 15 years of follow-up in Supplementary Figure 7.

DISCUSSION

In this study, we systematically examined the temporal correlations of motor activity across a wide range of timescales (3 min to 6 h) and their associations with the clinical onset of AD ("Alzheimer's dementia" used in Rush MAP) in the cohort of the Rush Memory and Aging Project. We showed that temporal correlations in these participants varied dramatically at different timescales (Fig. 3 and Supplementary Figure 8), suggesting loss of the scale-invariance and degraded FMAR. Our results showed that reduced temporal correlations (indicating more random motor activity fluctuations) at <10 min timescale was associated with increased risk for clinical AD.

Potential application of motor activity assessment in healthcare

Wearable devices allow collection of motor activity at a high sampling rate. The short-term activity fluctuations (at small timescales <90 min) attract attentions due to recent findings of their associations with mood disorders [4, 15], faster cognitive decline and risk for dementia [10], AD pathology in preclinical AD [11], and many other health outcomes such as frailty and disability in the elderly [14]. Our new results indicated that the pathophysiological alterations in FMAR linked to the development or clinical onset of AD is within the timescale of <10 min. This interpretation was supported by other findings: 1) α_1 was correlated with both α'_1 and α'_2 (scaling exponent at timescales between 20–40 min) (α_1 versus α'_2: Spearman's correlation 0.68, $p < 0.001$) (Supplementary Figure 4), but α'_2 hardly predicted the clinical onset of AD (Table 2); and 2) the association between α_1 and the clinical onset of AD became not significant when α'_1 was included in the same model. In addition, we found that FMAR within 10 min estimated from one day was both reliable (Supplementary Figure 9) and enough for predicting onset of AD (Supplementary Figure 10). Thus, our findings support the potential of using actigraphy-based FMAR in continuous, long-term monitoring of the risk for dementia in older adults. One of the follow-up questions is how early altered FMAR can predict the risk for Alzheimer's dementia. Relatedly, the observed decrease of the cumulative AUC over the time (Year 3–9 after baseline) in the DeepSurv suggests that FMAR might have a better performance in predicting the risk of Alzheimer's dementia in a shorter term. Because AD-related neuropathology may progress silently for two decades before the onset

of cognitive symptoms, further studies with more participants during a longer follow-up period are required to systematically determine the reliability of FMAR in the prediction at early preclinical stages.

Possible mechanisms of FMAR and its links to clinical AD

As proposed by Buchman et al., "motor function is not a unitary process" and "complexity and novelty of motor tasks demand increasing cognitive and sensory information processing for the accuracy of successful movements" [31]. Based on this theory, subtle changes in motor control such as more random activity fluctuations may reflect the effects of AD pathology on cognitive and sensory information processing in preclinical AD, which may explain the observed association between altered FMAR at small timescales and AD risk.

Another possible mechanism is related to sleep disturbances. There is evidence that sleep quality is linked to the pathology of amyloid-β (Aβ) in preclinical AD [32]; deep sleep enhances the glymphatic system that helps clear Aβ [33]; and sleep deprivation increases Aβ [34]. In this cohort, we did not find significant association of an actigraphy-based sleep fragmentation measure (kra, see Supplementary Tables 1 and 2) with incident clinical AD after controlling for FMAR measures and other covariates. In addition, kra was not significantly associated with FMAR at <10 min (α'_1, Spearman's correlation 0.026, $p > 0.05$) or in the other timescale regions linked to AD risk (20–40 min: α'_2, Spearman's correlation 0.034, $p > 0.05$; 100 to 200 min: α'_3, Spearman's correlation 0.028, $p > 0.05$) (Supplementary Figure 4). To formally confirm or refute that sleep disturbances are linked to temporal activity correlations at small timescales and contribute the FMAR-AD association, better sleep assessments based on polysomnography should be used to quantify sleep in future studies.

APOE ε4 status

The other important finding in the study was that the association between α'_1 and the clinical onset of AD remains after adjusting for *APOE ε4* status. It is important to note that genetics cannot fully explain the risk of developing AD and related dementias. The estimated heritability for AD is about 60% to 80% in a twin study [35]. The alternative risk factors for AD can be environmental conditions, lifestyle and sched-

uled daily activities such as smoking, air pollution, and shift work [36–38]. In addition, although *APOE* gene is the major genetic risk factor for AD, studies have continued to identify other risk loci [39], providing evidence for AD as a polygenic disorder. Thus, it is not surprising that the effect of fractal activity measures contributed to the risk for AD, after adjusting for *APOE ε4* status. Consistently, our recent study showed that changes in fractal activity patterns were linked to AD pathology in preclinical AD, and the association was significant after adjusting for *APOE ε4* status [11]. Changes in other non-cognitive physiological functions such as circadian variables have also been found to be linked to AD pathology, after adjusting for *APOE ε4* status [40].

Limitations

Due to the historical reason (i.e., the Rush MAP was first launched in 1997), the NINCDS-ADRDA criteria established in 1984 was still the key criteria to determine the clinical onset of AD in the Rush MAP. Meanwhile, the 2011 NIA-AA guideline introduced the new criteria for clinical diagnosis of dementia due to AD [41], and the 2018 NIA-AA Research Framework further recommended certain changes in the criteria or terminology related to diagnosis of AD and related dementia [42]. This limitation may lead to certain misdiagnosis of AD based on clinical symptoms without pathological biomarkers. However, the potential effects on this and other studies in the Rush MAP should be minimized with the following two considerations: 1) The onset of dementia due to AD was based on the comprehensive cognitive assessments according to Rush MAP's 4-step procedure (see details in the Methods Section). 2) Other types of dementia were also evaluated using other relevant criteria such that the diagnosis of dementia related to AD was not treated as a stand-alone evaluation. Thus, the cases of misdiagnosis related to other types of dementias should be rare.

The mechanisms underlying the temporal activity correlations within 10 min are yet to be determined. Observational/retrospective studies are inherently limited to addressing all questions comprehensively. Future prospective and mechanistic studies should be designed to examine the patterns during specific, relatively short task events using approaches such as video or other modalities to test whether the suggested timescales of fractal motor regulation can genuinely enhance the diagnosis of AD without significantly increasing the clinical burden.

This is a community-based cohort, reflecting the local demographics of participants, which may not be generalizable to a broader population. The other source of selection bias can come from recruitment, where some individuals might be more or less likely to be enrolled into the study than others (healthy cohort effect). The prospective nature of the Rush MAP helped alleviate this bias because the outcome was unknown at time of enrollment, making it less prone to selection bias.

Conclusion

The fluctuation pattern in motor activity varied dramatically at different timescales. More random fluctuations in motor activity at timescales within 10 min were associated with increased risk for incident clinical AD. The finding implies the potential of using a short actigraphy in identifying individuals at risk of AD. Future work is needed to study the longitudinal change of FMAR within 10 min over the course of the follow-up, the circadian influence over FMAR within 10 min, and the robustness against more survival analysis models.

AUTHOR CONTRIBUTIONS

Kun Hu (Conceptualization; Funding acquisition; Methodology; Resources; Supervision; Writing – review & editing); Haoqi Sun (Data curation; Formal analysis; Investigation; Methodology; Validation; Visualization; Writing – original draft; Writing – review & editing); Peng Li (Data curation; Formal analysis; Methodology; Writing – original draft; Writing – review & editing); Lei Gao (Data curation; Investigation; Methodology; Writing – review & editing); Jingyun Yang (Data curation; Writing – review & editing); Lei Yu (Data curation; Writing – review & editing); Aron S. Buchman (Data curation; Writing – review & editing); David A. Bennett (Data curation; Writing – review & editing); M. Brandon Westover (Conceptualization; Funding acquisition; Supervision; Writing – review & editing).

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CONFLICT OF INTEREST

Dr. Westover is a co-founder of Beacon Biosignal. The work presented here is not relevant to it.

DATA AVAILABILITY

The data supporting the findings of this study are available on request from the corresponding author or from the Memory and Aging Project at the Rush University Medical Center (RUMC) at https://www.radc.rush.edu.

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: https://dx.doi.org/10.3233/JAD-230928.

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