PHYSIOLOGY

More random motor activity fluctuations predict incident frailty, disability, and mortality

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Mobile healthcare increasingly relies on analytical tools that can extract meaningful information from ambulatory physiological recordings. We tested whether a nonlinear tool of fractal physiology could predict long-term health consequences in a large, elderly cohort. Fractal physiology is an emerging field that aims to study how fractal temporal structures in physiological fluctuations generated by complex physiological networks can provide important information about system adaptability. We assessed fractal temporal correlations in the spontaneous fluctuations of ambulatory motor activity of 1275 older participants at baseline, with a follow-up period of up to 13 years. We found that people with reduced temporal correlations (more random activity fluctuations) at baseline had increased risk of frailty, disability, and all-cause death during follow-up. Specifically, for 1-SD decrease in the temporal activity correlations of this studied cohort, the risk of frailty increased by 31%, the risk of disability increased by 15 to 25%, and the risk of death increased by 26%. These incidences occurred on average 4.7 years (frailty), 3 to 4.2 years (disability), and 5.8 years (death) after baseline. These observations were independent of age, sex, education, chronic health conditions, depressive symptoms, cognition, motor function, and total daily activity. The temporal structures in daily motor activity fluctuations may contain unique prognostic information regarding wellness and health in the elderly population.

INTRODUCTION

Advances in wearable technologies in the last decade have made it possible to monitor physiological function unobtrusively for long periods of time (1, 2). One of the most commonly collected types of physiological data is motor activity. Several watch-like actimetry sensors, worn on the wrist or ankle, have been developed to enable monitoring of motor activity (namely, actigraphy—noninvasive monitoring of movement amplitude to assess rest versus active periods) continuously for days and months. Actigraphy has widely been used to objectively estimate physical activity (3), daily/circadian activity rhythms, and sleep (4, 5), leading to many original physiological findings related to health and diseases. Despite the potential application of wearable devices in healthcare, harnessing the wealth of data from these devices is still a contemporary challenge. One of the main barriers is that uncontrolled daily schedules and environmental conditions may affect traditional physiological measures and complicate interpretation of results. New biomarkers that can reflect intrinsic properties of physiological systems while being resilient to external influences are desirable.

In parallel, the last 20 years have witnessed an exponential growth of an interdisciplinary field in physiology, namely, "fractal physiology," which is focused on understanding complex physiologic networks. One key finding in this field is that many physiological outputs such as motor activity and cardiac activity exhibit fractal fluctuations (similar temporal, structural, and statistical properties of the fluctuations at a wide range of time scales) (6–11). One advantage of fractal fluctuations is that they appear to be stable within the same individuals and sensitive to pathological conditions. For instance, fractal patterns in motor activity of healthy young humans persist under different envi-

ronmental conditions (free running or highly controlled in-laboratory conditions) despite large variations in mean physical activity (6); fractal fluctuations of human movement degrade with aging and in pathological states (12–15); and degraded fractal motor activity patterns in patients with dementia can better predict neurodegenerations in the circadian master clock of these patients as compared to traditional circadian measures (circadian amplitude and intradaily variability) (16). In addition, restoration or optimization of fractal patterns is considered a potential promising target of neurologic physical therapy (17–20). Supporting this concept, some pilot studies showed that sleep and memory can be enhanced with acoustic stimulations during specific sleep stage using pink noise—a sound with similar fractal temporal correlations as observed in many physiological signals such as motor activity, heartbeat, and brain activity (21, 22).

As a hallmark of healthy physiology, fractal regulation is believed to represent the system adaptability and to reflect the complexity of physiological networks in which regulatory processes function interactively over a wide range of time scales (23–26). Consistently, our recent study further showed that the degraded fractal motor activity regulation is associated with cognitive impairment and predicts the risk of developing Alzheimer's dementia in elderly individuals many years before the clinical onset of dementia (27). However, its value for predicting other adverse health consequences has not been fully explored. Here, we tested the hypothesis that fractal regulation in motor activities predicts frailty, disability, and all-cause mortality in a large community-based elderly cohort. Frailty and disability affect overall health and quality of life, particularly in older individuals, and there is evidence showing that both frailty and disability are linked to increased mortality (28–31). Thus, we also explored whether the effect of fractal regulation on all-cause death is independent of frailty and disability.

RESULTS

At the time of analysis, 1398 participants finished their baseline actigraphy assessments. Among them, 8 participants were screened out during preprocessing because of poor signal quality and 115 participants were

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excluded because of lack of follow-up clinical examinations (67 died before follow-up, 43 were not yet eligible for follow-up, and 5 withdrew from further participation). Thus, a total of 1275 participants were included in this study. Detrended fluctuation analysis (DFA) was used to extract two metrics that quantify the temporal correlations of motor activity recordings in two time scale regions: α_1 at time scales <1.5 hours and α_2 at time scales >2 hours (up to 10 hours). Examples of motor activity recordings and the corresponding DFA plots are shown in Fig. 1. In five participants, the maximal time scale when performing the DFA was <8 hours such that the metric α_2 could not be obtained reliably.

Demographic, actigraphical, and clinical characteristics of participants at baseline are summarized in Table 1. α_1 ranged from 0.63 to 1.21 (mean, 0.92; median, 0.92; SD, 0.06), and α_2 ranged from 0.51 to 1.32 (mean, 0.82; median, 0.81; SD, 0.10), suggesting positive temporal correlations in the activity fluctuations ($\alpha > 0.5$) in motor activity in both time scale regions and in all participants. α_1 was weakly correlated with α_2 (Pearson $r = 0.07$, $P = 0.008$). Both α_1 and α_2 were negatively correlated with age (α_1: $r = -0.10$, $P = 0.004$; α_2: $r = -0.18$, $P < 0.0001$). α_1 was positively correlated with years of education ($r = 0.07$, $P = 0.009$), but α_2 was not ($P = 0.7$). There were no sex differences in either α_1 or α_2 (both $P > 0.05$).

Perturbed fractal motor activity regulation predicts incident physical frailty

There were 936 participants (73.4% of 1275; female/male, 712/224) who were not frail (number of frailty components <2) at baseline. Over a mean of 4.7 (SD, 2.8; range, 0.7 to 12.2) years of follow-up, incident frailty was rendered for 291 (31.1% of 936; female/male, 263/28) participants. To assess the relationship between α_1/α_2 and frailty, we performed Cox proportional hazards models of incident frailty with α_1, and separately α_2, adjusted for age, sex, and education. A lower level of α_1 was associated with an increased risk of frailty: For 1-SD decrease in α_1, the hazard ratio (HR) was 1.31 [95% confidence interval (CI), 1.16 to 1.48; Table 2], which is equivalent to being 3.3 years older at baseline (table S1). Figure 2A shows the predicted probability of being not frail as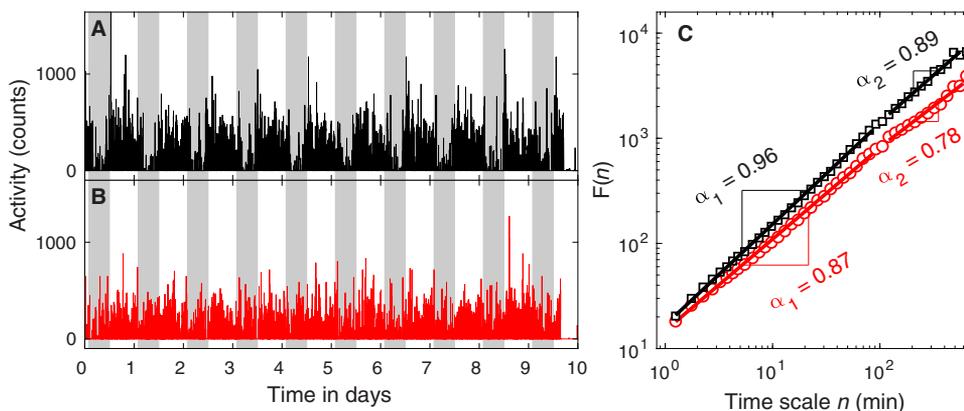 a function of time for different values of α_1. The participants with $\alpha_1 = 0.85$ (the 10th percentile) had an overall 1.7-fold increased hazard of frailty compared to the participant with $\alpha_1 = 0.98$ (the 90th percentile). The association between α_1 and frailty remained after adjusting separately for multiple potential covariates such as chronic health conditions, depressive symptoms, cognitive function, motor function, and physical activity (table S1). We did not observe a significant association ($P > 0.2$) between α_2 and incident frailty as shown in Fig. 2B and Table 2.

Perturbed fractal motor activity regulation predicts incident disability

There were 1073 participants (84.2% of 1275; female/male, 813/260) who reported no disability on basic activities of daily living (ADL). Over a mean of 4.2 (SD, 2.8; range, 0.6 to 12.3) years of follow-up, 529 (49.3% of 1073; female/male, 419/110) developed ADL disability. Cox proportional hazards models of incident ADL disability with α_1, and separately α_2, adjusted for age, sex, and education were performed. A lower level of α_1 was associated with an increased risk of ADL disability: For 1-SD decrease in α_1, the HR is 1.25 (95% CI, 1.14 to 1.36; Table 2), which is equivalent to being 2.3 years older at baseline (table S2). Figure 3A shows the predicted probability of being not disabled as a function of time for different values of α_1. The participants with $\alpha_1 = 0.85$ (the 10th percentile) had an overall 1.6-fold increased hazard of disability compared to the participant with $\alpha_1 = 0.98$ (the 90th percentile). The association between α_1 and disability remained after adjusting separately for all tested covariates (table S2). Similarly, a lower level of α_2 was also associated with an increased risk of ADL disability: HR was 1.11 (95% CI, 1.01 to 1.22; Table 2) for 1-SD decrease in α_2, which is equivalent to being about 1.1 years older at baseline (table S3). As shown in Fig. 3D, the participant with lower α_2 ($\alpha_2 = 0.70$, the 10th percentile) had an overall 1.2-fold increased hazard of disability compared to the participant with higher α_2 ($\alpha_2 = 0.94$, the 90th percentile). The association between α_2 and disability remained significant after controlling separately for the other risk factors except for total daily activity level (table S3).

There were 641 participants (50.3% of 1275; female/male, 459/182) who reported independence in instrumental ADL (IADL) at baseline. Over a mean of 3.0 (SD, 2.3; range, 0.6 to 11.1) years of follow-up, 442 (70.0% of 641; female/male, 320/122) developed IADL disability. Cox proportional hazards models of incident IADL disability with α_1, and separately α_2, adjusted for age, sex, and education were performed. A lower level of α_1 was associated with an increased risk of IADL disability: For 1-SD decrease in α_1, HR is 1.15 (95% CI, 1.04 to 1.26; Table 2), which is equivalent to being 1.9 years older at baseline (table S4). Figure 3B shows the predicted probability of being not disabled as a function of time for different values of α_1. The participants with $\alpha_1 = 0.85$ (the 10th percentile) had an overall 1.3-fold increased hazard of disability compared to the participant with $\alpha_1 = 0.98$ (the 90th percentile). The association between α_1 and disability remained after adjusting separately for the possible confounders (table S4). We did not observe

Fig. 1. Fractal patterns of daily motor activity fluctuations. (**A** and **B**) Representative motor activity recordings of two ~81-year-old female participants. The participant whose activity is shown in (A) survived after the follow-up of 9 years; the participant whose activity is shown in (B) was deceased 7 years after baseline. Gray shaded area indicates 9 p.m. to 7 a.m. (**C**) DFA results of the signals in (A) and (B). The fluctuation functions F(n) at different time scale n are plotted in log-log scale. F(n) is fitted using power-law functions in two regions: 1.25 to 90 min and 120 to 600 min. The slopes of the fitting lines in the two regions are denoted by α_1 and α_2, respectively. For better visualization and comparison between the two signals, F(n) of signal (B) has been vertically shifted.

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Table 1. Demographical, actigraphical, and clinical characteristics at baseline. ADL, activities of daily living; IADL, instrumental activities of daily living; IQR, interquartile range.

Variable	All ($n = 1275$) Mean (SD), median [IQR], or n (%)	Not frail ($n = 936$) Mean (SD), median [IQR], or n (%)	Not ADL disabled ($n = 1073$) Mean (SD), median [IQR], or n (%)	Not IADL disabled ($n = 641$) Mean (SD), median [IQR], or n (%)	Not mobility disabled ($n = 684$) Mean (SD), median [IQR], or n (%)
Demographics					
Age at baseline (years)	81.2 (7.3)	81.7 (7.1)	80.6 (7.1)	78.9 (7.1)	79.3 (7.2)
Sex (female)	974 (76.4%)	712 (76.1%)	813 (75.8%)	459 (71.6%)	490 (71.6%)
Education (years)	15.0 (3.0)	14.9 (2.9)	15.2 (3.0)	15.7 (3.0)	15.6 (3.0)
Actigraphical					
Total daily activity ($\times 10^5$)	1.75 (1.75)	1.75 (1.34)	1.85 (1.83)	2.01 (2.11)	1.94 (1.41)
α_1	0.92 (0.06)	0.92 (0.06)	0.92 (0.05)	0.93 (0.05)	0.93 (0.05)
α_2	0.82 (0.10)	0.82 (0.10)	0.83 (0.09)	0.84 (0.10)	0.84 (0.09)
Clinical					
Vascular risk factor*	1 [1]	1 [1]	1 [1]	1 [2]	1 [2]
Vascular diseases†	0 [1]	0 [1]	0 [0]	0 [0]	0 [0]
Depressive symptoms‡	0 [2]	0 [1]	0 [1]	0 [1]	0 [1]
Global cognition§	0.07 (0.65)	0.05 (0.64)	0.12 (0.61)	0.27 (0.51)	0.20 (0.57)
Motor function‖	1.00 (0.23)	0.99 (0.22)	1.03 (0.22)	1.11 (0.20)	1.11 (0.20)

*A composite measure of vascular risk burden considering three self-reported factors (hypertension, diabetes, and smoking history).   †A composite measure of vascular disease burden considering four self-reported diseases (myocardial infarction, congestive heart failure, claudication, and stroke).   ‡Assessed with a modified 10-item version of the Center for Epidemiologic Studies Depression scale.   §A composite score for overall cognitive function based on a battery of 19 cognitive tests.   ‖A composite measure of global motor function covering 10 motor performance tests.

a significant association ($P > 0.5$) between α_2 and incident IADL disability as shown in Table 2 and Fig. 3E.

There were 684 participants (53.6% of 1275; female/male, 490/194) who reported no mobility disability on the Rosow-Breslau scale at baseline. Over a mean of 3.1 (SD, 2.3; range, 0.6 to 12.1) years of follow-up, 443 (64.8% of 684; female/male, 331/112) developed mobility disability. Cox proportional hazards models of incident mobility disability with α_1, and separately α_2, adjusted for age, sex, and education were performed. A lower level of α_1 was associated with an increased risk of mobility disability: HR was 1.19 (95% CI, 1.08 to 1.32; Table 2) for 1-SD decrease in α_1, which is equivalent to being 2.6 years older at baseline (table S5). Figure 3C shows the predicted probability of being not disabled as a function of time for different values of α_1. The participants with $\alpha_1 = 0.85$ (the 10th percentile) have an overall 1.4-fold increased hazard of disability compared to the participant with $\alpha_1 = 0.98$ (the 90th percentile). The association between α_1 and disability remained after adjusting separately for all tested confounders (table S5). We did not observe a significant association between α_2 and incident mobility disability as shown in Table 2 and Fig. 3F ($P > 0.5$).

Perturbed fractal motor activity regulation predicts increased all-cause mortality

Among all 1275 participants, there were 535 deaths (42% of cohort; female/male, 388/147) after a mean of 5.8 (SD, 2.9; range, 0.6 to

12.7) years. Older age, being a male, or fewer years of education was associated with higher risk of death (tables S6 and S7). Cox proportional hazards models with α_1, and separately α_2, as a predictor adjusted for age, sex, and education were performed to examine the survival of participants. A lower level of α_1 was associated with an increased risk of death: For 1-SD decrease in α_1, HR was 1.26 (95% CI, 1.17 to 1.37; Table 2), which is equivalent to being 2 years older at baseline (table S6). Figure 4A shows the predicted probability of survival as a function of time for different values of α_1. The participants with $\alpha_1 = 0.85$ (the 10th percentile) have an overall 1.6-fold increased risk of death compared to the participant with $\alpha_1 = 0.98$ (the 90th percentile). The association between α_1 and death remained after adjusting separately for all tested covariates, as well as after adjusting separately for the disability status at baseline (table S6). Similarly, a lower level of α_2 was also associated with an increased risk of death, with an HR of 1.12 (95% CI, 1.02 to 1.23; Table 2) for 1-SD decrease in α_2, which is equivalent to being 1 year older at baseline (table S7). As shown in Fig. 4B, the participant with lower α_2 ($\alpha_2 = 0.70$, the 10th percentile) had an overall 1.3-fold increased risk of death compared to the participant with higher α_2 ($\alpha_2 = 0.94$, the 90th percentile). The association between α_2 and death remained significant after controlling separately for all tested risk factors except for motor function and the three disability measures (all $P < 0.05$; table S7). Of note, post hoc χ^2 tests suggest potential violation of the proportional hazard assumption for both α_1 and α_2 ($P < 0.05$), suggesting

Table 2. Fractal regulation in motor activity, potential confounders, and risk of frailty, disability, and death. Results are presented as HR (95% CI), P value, FDR-corrected P value.

Outcome	α_1*	α_2*
Frailty	1.31 (1.16–1.48), <0.0001, <0.0001	1.09 (0.95–1.24), 0.2, >0.2
ADL disability	1.25 (1.14–1.36), <0.0001, <0.0001	1.11 (1.01–1.22), 0.02, 0.03
IADL disability	1.15 (1.04–1.26), 0.01, 0.02	1.03 (0.94–1.13), 0.6, >0.6
Mobility disability	1.19 (1.08–1.32), 0.0004, 0.001	1.02 (0.93–1.13), 0.6, >0.6
All-cause death	1.26 (1.17–1.37), <0.0001, <0.0001	1.12 (1.02–1.23), 0.01, 0.02

*Results for 1-SD decrease.

Fig. 2. Predicted survival curves from Cox proportional hazards models. The predicted probabilities of being not frail for two representative participants whose fractal metrics (**A**) α_1 or (**B**) α_2 were in the 90th (dashed lines) or 10th percentiles (solid lines). Shading in (B) indicates not statistically significant association between α_2 and incident frailty.

that the association with mortality may not be constant over time. Therefore, we augmented the core model for α_1, and separately the core model for α_2, by including an interaction term with time to death (32). The results showed that the associations of both α's with mortality were attenuated in participants with longer survival time (table S8). Briefly, for a representative female participant of mean age and having mean years of education, the HR for 1-SD decrease in α_1 was attenuated by 0.06 with every one additional year of survival. Similarly, the HR for 1-SD decrease in α_2 was reduced by 0.05 with every one additional year of survival.

DISCUSSION

By following a cohort of 1275 older persons for up to 13 years, we found that degraded fractal regulation in ambulatory motor activity predicted a higher risk of incident frailty, incident disability, and death. Specifically, a higher risk for frailty was observed in participants who had more random motor activity fluctuations at time scales between ~1 and 90 min (as indicated by smaller values of the fractal activity metric α_1). Similarly, a higher risk for ADL, IADL, and mobility disability was observed in these participants with smaller α_1. A higher risk for ADL disability was also associated with more random activity fluctuations at time scales >2 hours (as indicated by smaller values of the fractal activity metric α_2). A higher risk for mortality was associated with more random motor activity fluctuations in both time scale regions (smaller α_1 and α_2). These associations remained after accounting for other factors associated to risk of frailty, disability, or decreased life expectancy including age, sex, education, chronic health conditions, depressive symptoms, cognition, motor function, and total daily activity. These findings indicate that spontaneous fluctuations in daily motor activity contain useful information about wellness and health, and that nonlinear dynamic analysis can serve as a powerful tool to extract such information.

Frailty is believed to reflect declines in physiological reserve across multiorgan systems, thus increasing vulnerability to stressors. Our results showed that degraded fractal motor activity regulation precedes and predicts frailty; within those without frailty at baseline, frailty occurred ~4.7 years on average after motor activity monitoring. This finding supports the theory that fractal regulation reflects the complexity of physiological control. Conversely, the degradation suggests a reduced complexity in the system; thus, the system becomes less adaptive to perturbations and more vulnerable to catastrophic events (26, 33).

One common risk factor for frailty, disability, and mortality that can be derived from actigraphy is low physical activity. Health benefits of physical activity have long been acknowledged, and there is indisputable evidence for the association between higher physical activity and lower risk for disability and mortality (28, 34–37). Physical activity may also be beneficial for reducing the risk of frailty in the elderly (38), although the role of being physically active in preventing sedentary elderlies from being physically frail is still under debate (39). Here, we showed that, independent of total daily activity, fractal patterns in the spontaneous activity fluctuations provide distinct insights into frailty, disability, and mortality in the elderly. This may not be surprising because fractal motor activity regulation reflects the system integrity that is required for successful, repetitive execution of different motor tasks. Altered fractal fluctuations of motor activity may represent subclinical information stemming from disruptions to multiple physiological functions, including cognition, psychiatric stability, coordination, and physical conditioning. This interpretation is supported by our previous findings that fractal motor activity regulation was degraded in dementia and associated with cognitive impairment (13, 27, 40), and the finding in this study that the associations between α_1 and frailty/disability/mortality were slightly weakened (but still statistically significant) when the composite motor function measure (incorporating many tests that involve cognition) was included in the model. Together, these findings support that fractal motor activity regulation provides additional valuable information about physiological function beyond total daily activity.

It has been established that frailty and disability predict mortality (28–31). One logical hypothesis is that frailty and disability mediate the effect of degraded fractal motor activity regulation on death. This hypothesis is supported by the reduced effects of fractal activity metrics on mortality after controlling for baseline frailty or disability:

Fig. 3. Predicted survival curves from Cox proportional hazards models. The predicted probabilities of being not ADL disabled (A and D), not IADL disabled (B and E), and not mobility disabled (C and F) for two representative participants whose fractal metrics (A to C) α_1 or (D to F) α_2 were in the 90th (dashed lines) or 10th percentiles (solid lines). Shading in (E) and (F) indicates not statistically significant association between α_2 and the corresponding outcome.

HR for mortality corresponding to 1-SD decrease in α_1 was reduced from 1.26 to 1.20 after controlling for baseline frailty, and the association between α_2 and mortality became not significant after controlling for baseline disability. Because frailty and disability predict not only mortality but also neuropathological changes, such as Alzheimer's disease, our findings highlight the possibility that degraded fractal motor activity regulation may serve as an earlier sign or risk factor for pathological changes.

It is also worth noting that the association between α_1 and mortality persisted after accounting for baseline frailty/disability. This finding provides strong evidence that there should be additional pathways leading to increased mortality, independent of the tested frailty and disability measures, and that degraded fractal motor activity regulation provides information for the prediction of all-cause death.

Although both α_1 and α_2 showed significant associations with ADL disability and death, the effects of decreased α_1 on the two outcomes appeared to be stronger than those of decreased α_2. The associations between α_2 and these health outcomes became borderline or not significant after adjusting for motor function or total daily activity. On the other hand, our previous studies showed that α_2 seems more sensitive to night shifts, and it recovered more slowly after night shifts (41). These distinct responses or associations of α_1 and α_2 suggest that fractal fluctuations at different time scales involve different physiological or biological mechanisms, and their changes reflect different physiopathological alterations that contribute to disability and mortality.

Despite the current limited understanding of the neural network(s) responsible for fractal regulation, it is well established that the circadian control system is required to maintain fractal fluctuations in motor activity, especially at larger time scales (26). In rats, lesioning the suprachiasmatic nucleus (SCN)—the central circadian clock in mammals—led to completely random activity fluctuations at time scales >~4 hours (α_2 close to 0.5) (42), and lesioning the dorsomedial hypothalamic nucleus—one of the important neural nodes that relay the influences of the SCN on motor activity—also caused a significant reduction in α_2 (43). In humans, perturbed fractal motor activity regu-

lation in terms of the difference between α_1 and α_2 (more reduced α_2) was associated with greater loss of vasopressin and neurotensin neurons, two major neurotransmitters in the SCN (16). Thus, the observed effects of α_2 on risk of disability/mortality may be linked to circadian dysfunction.

Recent human studies showed that the degradation of the fractal motor activity regulation at time scales <2 hours (smaller α_1) was associated with dysregulations in higher brain activities including mood and cognitive function (40, 44–48), indicating that the decrease of α_1 could be an omen of accelerated cognitive degeneration. This hypothesis was supported by our recent study showing that α_1 reduction predicted faster cognitive decline and increased risk for dementia (27). This hypothesis was further supported by our observed association between smaller baseline α_1 and increased risk of IADL disability, considering that the decline in IADL is likely to represent a decline in cognitive function. On the other hand, we found that, even after controlling for cognition, α_1 still predicted frailty, ADL disability, and mobility disability that may be closely related and linked to physical problems. These findings indicate previously unidentified contributions of mobility control to fractal regulation. The neural circuitry of fractal activity regulation at small time scales may thus involve multiple physiological control mechanisms.

This study indicates that multiscale characteristics derived from spontaneous daily movement can be useful for heath monitoring in older adults. As compared to the traditional clinical assessments of frailty, disability, and mortality, actigraphy-based methods have many advantages because the unobtrusive data collection is cost efficient and requires less effort from individuals and healthcare providers. To further establish the fractal motor activity regulation indices as a diagnostic tool, the following issues need to be addressed: (i) Replications using a separate, larger database are required to validate our findings. (ii) The optimal time scale regions in which the scaling behavior can better predict health outcomes are yet to be determined. (iii) The cohort used here consisted of relatively old participants. It is worth investigating whether the fractal indices can predict similar outcomes in middle-aged and younger adults. As the technique for motor activity monitoring is very mature, many large-cohort research or clinical studies such as the UK Biobank have included or have collected motor activity recordings. Analyzing the data in these studies is crucial not only for validating our findings but also for better application of wearable technologies in health monitoring.

In addition, it may become possible to apply the actigraphy-derived tools as a part of long-term home care monitoring, which may open up new avenues for clinical practice and healthcare research. Together with other clinical and physiological measures, the fractal regulation indices based on actigraphy may improve identification of older people at risk of frailty such that these individuals might benefit from early interventions. The advantages of the actigraphy-derived tools include noninvasiveness and cost efficiency as compared

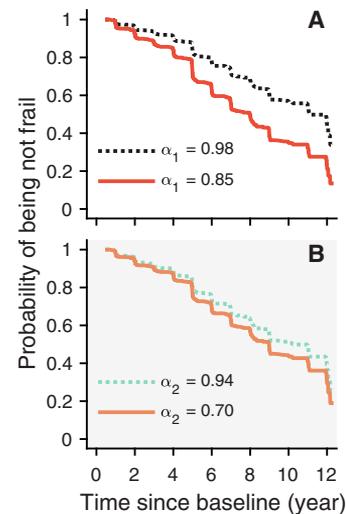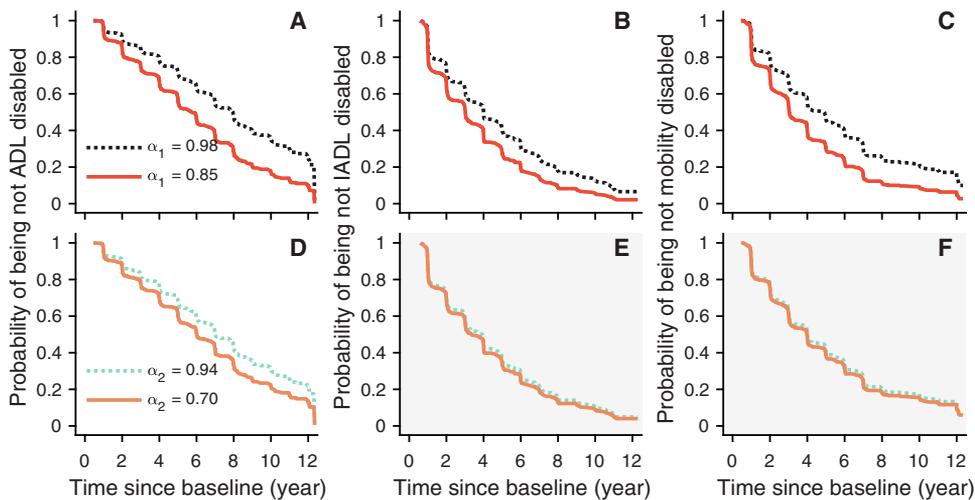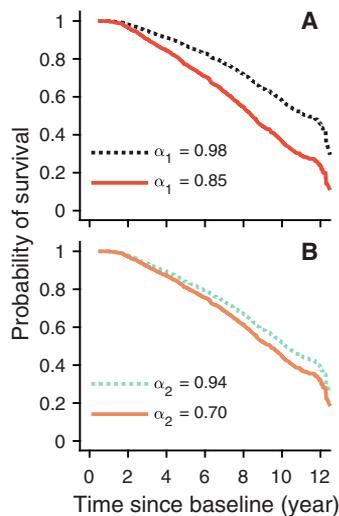**Fig. 4. Predicted survival curves from Cox proportional hazards models.** The predicted probabilities of survival for two representative participants whose fractal metrics (**A**) α_1 or (**B**) α_2 were in the 90th (dashed lines) or 10th percentiles (solid lines).

to the traditional clinical assessments. For instance, the motor score was also shown to be associated to outcomes, but it was derived from 10 motor performance tests (including Purdue Pegboard test, finger-tapping test, time to cover a distance of 8 feet, number of steps required to cover 8 feet, 360° turn time, number of steps to complete a 360° turn, leg stand, toe stand, grip strength, and pinch strength) (49), which require clinical visits and significant time/effort of those elder participants. Fractal motor activity patterns appear to be modifiable. For example, increased daily light exposure has been shown to diminish or even abolish the degradations of fractal motor activity regulation with aging in older persons with dementia (40). Studies on movement rehabilitation have implied the therapeutic milieu of promoting complexity of movement and restoring the optimal amount of movement variability to prevent motor system rigidity or instability (17–20). Further investigations are merited to determine whether fractal motor activity regulation can identify targets for interventions with the aim to improve physical well-being and longevity. One testable hypothesis is that improving fractal regulation in motor activity can help maintain physical well-being and increase life expectancy.

There are also limitations that are worth noting. First, the co-morbidity and other health-related data were self-reported, which potentially limits the validity of the study. Second, the frailty and disability are questionnaire-based surrogate endpoints. The associations of fractal motor regulation with objective health outcomes such as falls, fractures, hospitalization, and care consumption are yet to be determined. Third, the regions of time scales for the two fractal regulation metrics were determined empirically on the basis of previous studies of aging and dementia. They are not necessarily optimal for predicting different outcomes. Further works are warranted to finely tune time scale region(s) to better define outcome-specific metrics. Last, the DFA approach assesses temporal fractal structure by examining the scaling behavior. There might be properties that are not be captured by DFA. The use of different methods, including other fractal or nonlinear dynamic analyses, to extract more health-related information from spontaneous fluctuations of motor activity should be encouraged.

MATERIALS AND METHODS
Study design
We reported results from an on-going prospective, observational co-hort study, namely, the Rush Memory and Aging Project (MAP) that is conducted at the Rush Alzheimer's Disease Center, Rush University Medical Center. This current study focused on the use of noninvasive and unobtrusive activity monitoring to identify predictors of adverse health outcomes (including frailty, disability, and mortality) in an aging population of human participants. The results were reported in accordance with the guidelines for reporting observational studies—the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement. The MAP project began in 1997. In 2005, a watch-like device was introduced to record daily movement or motor activity, which was the specific baseline for the current study (see the next section) (50). By mid-2018, motor activity recordings were col-lected from 1398 participants (age at baseline, 56 to 100 years old; fe-male, 1065). Participants without follow-up clinical examinations were excluded from this study ($n = 115$); the remaining participants were followed annually for up to 13 years (range, 1 to 13; mean, 6; SD, 3). The protocol of the parent MAP study was approved by the Institu-tional Review Board of Rush University Medical Center. Written informed consent was obtained from all participants, and all partici-pants signed a repository consent to allow their data to be repurposed. More information regarding the data can be found at www.radc. rush.edu. The protocol for this current study was approved by the Institutional Review Board of Partners Healthcare Inc.

Data collection and preprocessing
Motor activity (Fig. 1 and fig. S1) was collected continuously for up to 10 days at baseline using an activity monitor (Actical, Philips Respironics) worn on the nondominant wrist. The device pre-dominantly measures acceleration in a direction parallel to the face of the device with a continuous sampling frequency of 32 Hz. By built-in data processor, the raw acceleration data were integrated into proprietary counts in 15-s epochs (actigraphy data) that essentially re-flect the movement amplitude. The activity recordings were subjected to signal quality screenings with the assistance of a self-designed MATLAB GUI program (version R2015a, the MathWorks Inc.) to identify the following: (i) isolated huge spikes with amplitude going beyond 10 SDs away from the individual global mean levels and (ii) sequences of zeros with duration of >60 min during the daytime (as occurred when participants took the device off). The identified data points or segments were marked as gaps (51). Recordings of <4 days or with identified gaps >60% of data were excluded before subse-quent analysis.

Assessment of fractal regulation
To assess the fractal regulation of motor activity, DFA was per-formed to examine the temporal correlations of motor activity fluc-tuations at different time scales (51, 52). The method calculates the fluctuation amplitude, $F(n)$, as a function of time scale n. Specifically, for a time series $\{x_i \mid i = 1, 2, \ldots, N\}$, DFA performs the following processes (see figs. S2 and S3 for demonstrations) (6, 51):

1) Removing the global mean and integrating the time series by $X_t = \Sigma_{i=1}^{t}(x_i - \bar{x})$, where $\bar{x}$ denotes the mean value of the time series x_i;

2) Dividing the integrated signal X_t into nonoverlapping windows of the same chosen size n;

3) Detrending the integrated signal X_t in each window using polynomial functions to obtain residuals by $\hat{X}_t = X_t - Y_t$, where

Y_t denotes the trend obtained by polynomial fit and $\hat{X}_t$ denotes the integrated time series after detrending;

4) Calculating the root mean square of residuals in all windows as detrended fluctuation amplitude using $F(n) = \sqrt{\frac{1}{N}\sum_{t=1}^{N}\hat{X}_t^2}$.

The same four steps are repeated for different time scales (n). The second order of polynomial function was used to detrend data in step 3 to eliminate the effect of possible linear trends in original data (6). A power-law form of $F(n)$, where $F(n) \sim n^\alpha$, indicates a fractal structure in the fluctuations (Fig. 1). The parameter α, called the scaling exponent, quantifies the temporal correlation as follows: If $\alpha = 0.5$, there is no correlation in the fluctuations ("white noise"); if $\alpha > 0.5$, there are positive correlations, where large values are more likely to be followed by large values (and vice versa); if $\alpha < 0.5$, there are negative correlations, where large values are more likely to be followed by small values (and vice versa). For many physiological outputs under healthy conditions, α values are close to 1.0 (6, 53–55), indicating the most complex underlying control mechanisms. To ensure reliable estimation of $F(n)$ at a time scale n, at least six segments without gaps of size n are required. Otherwise, $F(n)$ at and beyond that time scale will not be estimated. We have implemented the DFA using computer programs written in MATLAB, which are openly available at Zenodo (56).

In humans, aging and dementia lead to breakdown in the multi-scale patterns in motor activity that can be characterized by different correlations (indicated by different α) over two distinct time scale regions with the boundary at ~1.5 to 2 hours (13, 16, 40). Thus, two scaling exponents of $F(n)$ were calculated in this study: α_1 at <90 min and α_2 from 2 hours up to 10 hours (Fig. 1). Note that the transitional region of time scales between 1.5 and 2 hours was omitted. To ensure a reliable estimation of α_1, $F(n)$ must be available for up to at least $n = 5$ min. To ensure a reliable estimation of α_2, $F(n)$ must be available between time scales $n = 2$ hours to at least 8 hours.

Annual assessment of frailty
Physical frailty was assessed annually on the basis of five components (57): (i) Gait speed was based on time to walk 8 feet; (ii) grip strength is measured using the Jamar hydraulic hand dynamometer (Lafayette Instruments) and is the average of four trials (two per hand); (iii) body mass index (BMI) was calculated as weight (kilograms)/height (square meters); (iv) fatigue was assessed using two questions derived from a modified version of the Center for Epidemiologic Studies Depression scale; and (v) self-reported physical activity was based on the number of hours per week that participants engage in five types of activities including walking, gardening, calisthenics, bicycle riding, and swimming. We dichotomized each of the five components used to construct a categorical composite measure of physical frailty similar to other investigators (58). The lowest quintile of grip, gait, BMI, and physical activity were defined as frail, and any reports of fatigue were considered consistent with frailty. Because of level differences between men and women on performance measures, sex-specific quintiles were used for grip, gait, and physical activity. Similar to Fried *et al.* (58), frailty was present in participants with three or more frail components.

Annual assessment of disability
Disability was annually assessed using three tests including basic ADL, IADL, and mobility disability. ADL was assessed using a modified version of the Katz measure (34, 59). IADL was assessed using items adapted from the Duke Older Americans Resources and Services project (34, 60). The Rosow-Breslau scale was used to assess mobility disability (61). These assessments resulted in three composite measures, separately, for ADL (ranging between zero and six), IADL (zero and eight), or mobility disability (zero and three) with the values indicating the numbers of items required help/assistance reported by the participants. For each composite measure, the participants who had nonzero values were classified as having disability.

Other covariates
To test whether the multiscale indices predict incident frailty, incident disability, and mortality independent of known risk factors, we also consider the following covariates at baseline: chronic health conditions assessed by a composite measure of three vascular risk factors (hypertension, diabetes, and smoking) and a cumulative score for four vascular diseases (myocardial infarction, congestive heart failure, claudication, and stroke) (35); depressive symptoms assessed by the modified 10-item Center for Epidemiologic Studies Depression scale (62, 63); cognitive performance assessed by a composite score of cognition based on performances on 19 neuropsychological tests (64); motor function assessed by a composite score covering 10 motor performance tests (49); and total daily activity assessed in terms of counts per day estimated on the basis of actigraphy (3, 35, 65).

Statistical analysis
A series of Cox proportional hazards models were used to assess the associations of fractal indices with incident frailty, incident disabilities, and all-cause mortality. Results are reported as HR and 95% CI. For each outcome (frailty, ADL, IADL, mobility disability, and all-cause mortality), we performed two core models that included α_1 (model A1) or separately α_2 (model A2) as a predictor while controlling for age, sex, and education. As secondary analysis, we augmented the two core models by further adjusting for chronic health conditions (models B1 and B2), depressive symptoms (models C1 and C2), cognitive performance (models D1 and D2), motor function (models E1 and E2), and physical activity (models F1 and F2).

For the core models for mortality, we also adjusted for baseline frailty and disability measure (models G1/2, H1/2, I1/2, and J1/2) to test whether frailty or disability could mediate the associations between α_1/α_2 and death. These statistical analyses were done using JMP Pro (version 13, SAS Institute). The proportional hazards assumption was assessed using a global χ^2 test in R (66). Statistical significance was determined a priori at nominal level of $\alpha = 0.05$ (two-sided). Considering that our hypothesis testing involves two predictors (α_1 and α_2) and five incident events (frailty, ADL, IADL, mobility disability, and all-cause mortality), we reexamined the association after correction for multiple comparisons using false discovery rate (FDR) (67), and the results were unchanged (Table 2).

SUPPLEMENTARY MATERIALS

Table S8. Augmented models showing the associations of fractal regulation metrics with risk of death attenuate with longer survival time.

View/request a protocol for this paper from *Bio-protocol*.

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More random motor activity fluctuations predict incident frailty, disability, and mortality

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Predictive patterns

Fractals are self-similar patterns that exist across different conditions; in medicine, changes in fractal fluctuations can indicate disease, such as degraded fractal movement fluctuations seen with dementia. Using wrist-worn activity monitors, Li *et al.* analyzed daily motor activity of a large cohort of elderly subjects. They found that more random fluctuations over two time scales (1 to 90 min and greater than 2 hours) predicted increased risk of frailty, disability, and death years later —independent of age, sex, chronic health conditions, and total motor activity. Results suggest that fractal analyses can help predict health outcomes in the absence of overt symptoms and support the utility of passive monitoring.

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