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Interaction between the progression of Alzheimer's disease and fractal degradation

Peng Li [a,b,*], Lei Yu [c], Jingyun Yang [c], Men-Tzung Lo [d], Chelsea Hu [a], Aron S. Buchman [c], David A. Bennett [c], Kun Hu [a,b,**]

[a] Division of Sleep and Circadian Disorders, Departments of Medicine and Neurology, Brigham and Women's Hospital, Boston, MA, USA
[b] Division of Sleep Medicine, Department of Medicine, Harvard Medical School, Boston, MA, USA
[c] Rush Alzheimer's Disease Center, Rush University Medical Center, Chicago, IL, USA
[d] Institute of Translational and Interdisciplinary Medicine and Department of Biomedical Sciences and Engineering, National Central University, Taoyuan, Taiwan

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ABSTRACT

Many outputs from healthy neurophysiological systems including motor activity display nonrandom fluctuations with fractal scaling behavior as characterized by similar temporal fluctuation patterns across a range of time scales. Degraded fractal regulation predicts adverse consequences including Alzheimer's dementia. We examined longitudinal changes in the scaling behavior of motor activity fluctuations during the progression of Alzheimer's disease (AD) in 1068 participants in the Rush Memory and Aging Project. Motor activity of up to 10 days was recorded annually for up to 13 years. Cognitive assessments and clinical diagnoses were administered annually in the same participants. We found that fractal regulation gradually degraded over time ($p < 0.0001$) even during the stage with no cognitive impairment. The degradation rate was more than doubled after the diagnosis of mild cognitive impairment and more than doubled further after the diagnosis of Alzheimer's dementia (p's ≤ 0.0005). Besides, the longitudinal degradation of fractal regulation significantly correlated with the decline in cognitive performance throughout the progression from no cognitive impairment to mild cognitive impairment, and to AD ($p < 0.001$). All effects remained the same in subsequent sensitivity analyses that included only 255 decedents with autopsy-confirmed Alzheimer's pathology. These results indicate that the progression of AD accelerates fractal degradation and that fractal degradation may be an integral part of the process of AD.

1. Introduction

Many neurophysiological outputs, such as the heart rate and motor activity, exhibit fractal or self-similar fluctuations that are characterized by similar fluctuation patterns or statistical properties over a wide range of time scales (Goldberger et al., 2002; Pittman-Polletta et al., 2013). Such a scale-invariant behavior or fractal/self-similar patterns persist without environmental influences, suggesting an intrinsic fractal regulation (FR) in physiological systems (Hu et al., 2004; Nunes Amaral et al., 2001). Numerous studies provide evidence for the physiological importance of FR. For example, the fractal scaling behavior in cardiac dynamics and motor activity are altered or broken down (i.e., loss of self-similarity) in elders and under various pathological conditions including stroke and myocardial infarction (Amaral et al., 2004; Hu et al., 2009; Peng et al., 1995); and altered fractal patterns in cardiac dynamics can better predict survival rate than traditional cardiovascular parameters (Huikuri et al., 2000; Mäkikallio et al., 2004, 2001; Stein et al., 2005). Based on these findings, it is believed that FR imparts essential physiological advantages in terms of system integrity and adaptability, and that FR degradations indicate loss of functional resilience and increased vulnerability to catastrophic events as occurred with aging and in diseases (Bassingthwaighte et al., 1994; Goldberger et al., 2002; Pittman-Polletta et al., 2013; West, 2010).

Consistent with the adaptability theory of fractal physiological regulation, our cross-sectional study has shown that FR in motor

* Corresponding author at: 221 Longwood Avenue, Suite BL035M, Boston, MA 02115, USA. Tel.: 617-278-0061; fax: 617-732-7337.
** Corresponding author at: 221 Longwood Avenue, Suite BLI40, Boston, MA 02115, USA. Tel.: 617-525-8694; fax: 617-732-7337.
E-mail addresses: pli9@bwh.harvard.edu (P. Li), khu@bics.bwh.harvard.edu (K. Hu).

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activity is degraded in elders and is more degraded in those with Alzheimer's dementia (Hu et al., 2009). In addition, the degree of FR degradation is strongly associated with cognitive performance in very old adults with dementia (Hu et al., 2016). In a human postmortem study of patients with dementia, we found a strong association of FR degradation before death with the loss of neurotransmitters in the master circadian clock (suprachiasmatic nucleus [SCN]) and with amyloid-β plaque density in the occipital cortex (an estimate of the severity of Alzheimer's disease [AD]) (Hu et al., 2013). Our recent longitudinal study further showed that degraded fractal activity regulation at baseline can predict the risk of Alzheimer's dementia (Li et al., 2018). These results strongly suggest a mechanistic link between FR degradation and AD. However, no study has examined the longitudinal change of FR in cognitively healthy subjects and how the process interacts with the course of AD progression.

We hypothesize that FR degrades over time and that the degradation accelerates with the progression of AD. To test the hypotheses, we analyzed longitudinal data of 1068 subjects participating in the Rush Memory and Aging Project (MAP) (Bennett et al., 2012a) who have been followed for up to 13 years at the time of our analysis (4/17/2018) with annual clinical diagnoses. Motor activity data were collected annually and were used to assess longitudinal changes in FR.

2. Material and methods

2.1. Participants

Participants were from the MAP, a community-based, longitudinal cohort study of aging that began in 1997. In 2005, a watch-like device was introduced to record participants' daily motor activity or actigraphy (see Section 2.2) (Bennett et al., 2012a). At the time of analysis, 1068 participants finished their baseline actigraphy assessments and had at least one follow-up actigraphy visit. Besides, among the 1068 participants, 434 died with 255 diagnosed with AD at autopsy. Written informed consent was obtained from all participants, and participants signed an Anatomical Gift Act for brain donation. The study was approved by the institutional review boards of Rush University Medical Center and the Partners Healthcare, Inc and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

2.2. Data collection and preprocessing

In each annual assessment, daily motor activity data were collected continuously for up to 10 days (Fig. 1) when subjects wore a watch-like activity monitor (Actical, Philips Respironics, Bend, OR) on their nondominant wrists. The device predominantly measures acceleration in a direction parallel to the face of the device with a continuous sampling frequency of 32 Hz. Raw acceleration data were integrated into proprietary counts in 15-second epochs. The activity count recordings were subject to signal quality screenings with the assistance of a self-designed MATLAB GUI program (Ver. R2015a, the MathWorks Inc, Natick, MA, USA) to identify (1) isolated huge spikes with amplitude going beyond 10 standard deviations (SDs) away from the individual global mean levels and (2) sequences of zeros with duration >60 minutes during the daytime (e.g., as occurred when subjects took the device off). The identified data points or segments were marked as gaps and were excluded from the FR analysis (Hu et al., 2001).

2.3. Cognition tests and clinical diagnoses

Cognitive function was assessed with a battery of 21 neuropsychological tests across a range of cognitive abilities administered each year. Of them, 19 tests were used to construct measures of 5 cognitive domains (Bennett et al., 2012a): (1) episodic memory (Logical Memory Ia, Logical Memory IIa, Immediate story recall, Delayed story recall, Word List Memory, Word List Recall, Word List Recognition); (2) working memory (Digit Span Forward, Digit Span Backward, Digit Ordering); (3) semantic memory (Boston Naming Test, Category Fluency, National Adult Reading test); (4) perceptual speed (Symbol Digit Modalities Test, Number Comparison, Stroop word reading, Stroop color naming); and (5) visuospatial abilities (Judgment of Line Orientation, Standard Progressive Matrices). To obtain domain-specific measures, individual tests within each domain were first z-scored based on the corresponding baseline means and SDs of all subjects in the cohort and then averaged across the tests. In addition, a global composite cognitive measure was obtained by averaging the 19 z-scored cognitive tests. For each of these normalized cognitive measures, larger positive scores indicate better cognitive

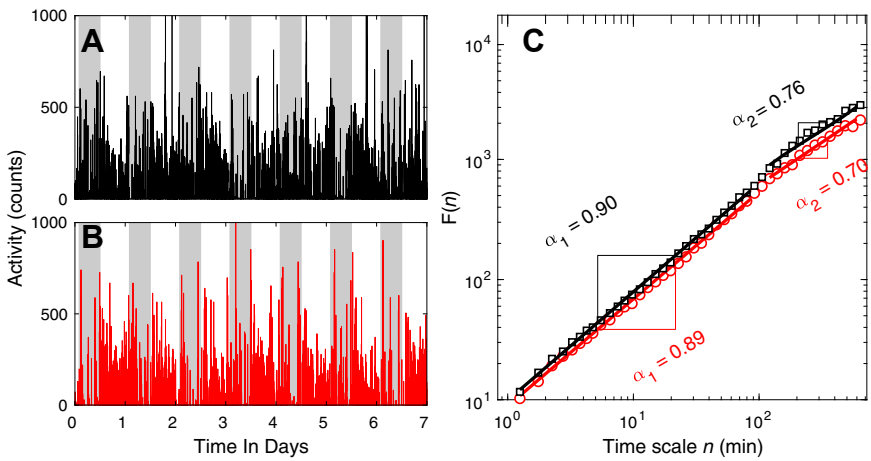

Fig. 1. Fractal correlations in motor activity. Shown on panels A and B are 2 activity recordings collected from the same female participant when she was 84 (upper panel) and 89 (lower panel) years old. Gray-shaded areas indicate the common sleep time (9 PM–7 AM). Shown on panel C are the corresponding fluctuation functions plotted versus time scale *n* on a log-log scale. The motor activity recording and its corresponding fluctuation function for the 84-year-old female participant are shown in black and those for the 89-year-old female participant are in red. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

performance with 0 representing the mean and 1 representing 1 SD of the baseline raw score of all MAP participants.

All participants underwent a uniform, structured, clinical evaluation each year. A clinician, after examining the participant and reviewing all the data, rendered a clinical diagnostic classification of no cognitive impairment (NCI), mild cognitive impairment (MCI), Alzheimer's dementia, or other dementia. The clinical diagnosis of Alzheimer's dementia was based on the criteria of the joint working group of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (McKhann et al., 1984). Diagnosis of MCI was rendered when a subject had cognitive impairment but did not meet criteria for dementia (Bennett et al., 2002). The cases without dementia and MCI were categorized as having NCI. Based on the clinical evaluations, we tagged the activity data with 3 different pathophysiological stages: (1) NCI stage; (2) MCI stage; and (3) Alzheimer's dementia stage.

2.4. Assessment of postmortem Alzheimer's disease pathology

Brain autopsy was performed following a standard protocol at death (Bennett et al., 2003, 2006). The brains were removed, hemisected, cut into 1-cm slabs, and fixed in 4% paraformaldehyde. To quantify AD pathology, 6-μm paraffin-embedded sections from the midfrontal gyrus, middle temporal gyrus, inferior parietal gyrus, entorhinal cortex, and hippocampus were stained with a modified Bielschowsky silver stain. Neurofibrillary tangles, diffuse plaques, and neuritic plaques were counted in the region that appeared to have the maximum density of each pathological index (Bennett et al., 2006). The modified NIA-Reagan diagnosis criteria of AD were followed to determine the likelihood of AD (Bennett et al., 2006). Participants were determined to have developed AD pathology provided that the postmortem examinations rendered a high or intermediate likelihood of AD.

2.5. Assessment of FR degradation

The detrended fluctuation analysis (DFA) was performed to assess the scaling behavior in motor activity fluctuations over a range of time scales from ~1 minute up to 10 hours. DFA examines the multiscale correlations of activity fluctuations at multiple time scales. It provides a fluctuation amplitude $F(n)$ as a function of time scales n (Hu et al., 2001; Peng et al., 1994). Specifically, DFA includes the following steps:

(i) removing the global mean and integrating the time series of a signal, that is, $X_t = \sum_{i=1}^{t} (x_i - \bar{x})$ where $\bar{x}$ denotes the mean value of the time series x_i;
(ii) dividing the integrated signal into nonoverlapping windows of the same chosen size n;
(iii) detrending the integrated signal in each window using polynomial functions to obtain residuals, that is, $\widehat{X}_t = X_t - Y_t$ where Y_t denotes the trend obtained by polynomial fit and $\widehat{X}_t$ the integrated time series after detrending;
(iv) calculating the root mean square of residuals in all windows as detrended fluctuation amplitude $F(n)$, that is, $F(n) = \sqrt{\frac{1}{N}\sum_{t=1}^{N} \widehat{X}_t^{\,2}}$.

The same 4 steps are repeated for different time scales n. The second order of polynomial function was used to detrend data (in step iii) to eliminate the effect of possible linear trends in original data (Hu et al., 2001). A power-law form of $F(n)$, that is, $F(n) \sim n^{\alpha}$, indicates a fractal structure in the fluctuations (Fig. 1). The parameter α, called the scaling exponent, quantifies the multiscale 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). Different from the autocorrelation coefficient, the scaling exponent provides complementary information about the temporal structure of the fluctuations at multiple time scales. Our previous simulation studies have shown that this method (especially the second-order DFA) has much better performances than other analyses for assessment of multiscale correlations in nonstationary and noisy signals (Chen et al., 2002; Hu et al., 2001). Mathematically, α can range between 0 and 3 for the second-order DFA. α Values that are close to 1.0 have been observed in many physiological outputs under healthy conditions (Hausdorff et al., 1997; Hu et al., 2004; Peng et al., 2002, 1995), indicating the most complex underlying control mechanisms.

Previous studies showed that degraded FR, as occurred in elders and in dementia, lead to distinguished behaviors of $F(n)$ with different α's over 2 time scale regions with the boundary at ~1.5–2 hours (Hu et al., 2013, 2016; 2009). We thus calculated the scaling exponent α in the 2 regions (i.e., α_1 at < 90 minutes, and α_2 from 2 hours up to 10 hours), respectively, omitting the transitional region of time scales between 1.5 and 2 hours (Fig. 1). In other words, we assessed FR degradation from the changes in the scaling of fluctuation amplitude $F(n)$ that can be quantified by the 2 scaling exponents (α_1 and α_2). To ensure reliable estimation of $F(n)$ at a time scale n, at least 6 segments without gaps of size n are required. Otherwise $F(n)$ at and beyond that time scale will not be estimated. The time scale n sequence starts from 1.5 minutes (i.e., 6 data points with epoch length = 15 seconds) and ends at a maximal time scale that was determined by the length and gaps of the signals. The selected time scales were uniformly distributed with 8 points in each $\log_2$ interval. For all activity recordings, the maximal time scale was greater than 90 minutes such that there were no missing data for α_1. To obtain reliable α_2, we also required a reliable estimation of $F(n)$ between time scales $n = 2$ hours to at least 8 hours. In 13 recordings, the maximal time scale was < 8 hours such that α_2 could not be obtained.

2.6. Statistical analysis

To examine how FR changes longitudinally and how this longitudinal change varies with the progression of AD, we performed linear mixed-effects models with 2 change points anchored at the diagnoses of MCI and Alzheimer's dementia. In these models, the scaling exponents (i.e., α_1 and α_2) were the longitudinal outcomes, and time in years since baseline was a predictor. The first change point was set at MCI diagnosis, and time in years since this change point was included to estimate additional changes in FR after MCI diagnosis. The second change point was set at the diagnosis of Alzheimer's dementia and time in years because this change point was included to estimate additional changes after the diagnosis of Alzheimer's dementia. These analyses were performed using MATLAB Statistics and Machine Learning Toolbox (Ver. R2018a, The MathWorks Inc, Natick, MA, USA). Next, we examined whether the longitudinal change in FR is correlated with the change in cognition. Bivariate linear mixed models were used to examine the simultaneous changes in the scaling exponent α_1 and global cognition, and separately, in the scaling exponent α_2 and global cognition (Buchman et al., 2014). The correlations between the changes in the scaling exponents and cognition are captured by the covariance structure of the random effects, such that a significant and positive/negative covariance between the random slopes of the scaling

exponents and cognition would indicate that both FR and cognition change in the same/opposite direction over time. These analyses were performed using SAS/STAT software (Ver. 9.4 of the SAS System for Linux, SAS Institute Inc, Cary, NC, USA). All the models were adjusted for baseline age, sex, and years of education, and a statistically significant level of 0.05 was used. We finally repeated all aforementioned analyses in 255 decedents who were confirmed to have AD pathology at autopsy.

3. Results

3.1. Demographic and actigraphic characteristics of participants

Fig. 2 summarizes the numbers of participants available in each follow-up year by the time of analysis and disaggregated data for each category at baseline as well as converters (i.e., NCI to MCI, MCI to Alzheimer's dementia) during follow-up assessments. The demographic and actigraphic characteristics of all participants are summarized in Table 1. At baseline, α_1 ranges from 0.63 to 1.21 and α_2 ranges from 0.51 to 1.32, suggesting positive multiscale correlations ($\alpha > 0.5$) in motor activity in both time scale regions and in all participants. Baseline α_1 is weakly correlated with baseline α_2 (Pearson $r = 0.07$, $p = 0.03$). Both baseline α_1 and baseline α_2 are negatively correlated with age (α_1: $r = -0.09$, $p = 0.004$; α_2: $r = -0.15$, $p < 0.0001$). Neither baseline α_1 nor baseline α_2 is correlated with years of education (both p's > 0.1). There are no sex differences in either baseline α_1 or baseline α_2 (both p's > 0.2).

Participants had an average of 5 repeated actigraphy assessments (range, 2–13) (Fig. 2). For those who were NCI at baseline, 339 developed MCI (Fig 2; Table 1) at averagely ~3.4 years after baseline. For those who developed Alzheimer's dementia during follow-up assessments, the average time interval between MCI onset and the diagnosis of Alzheimer's dementia was about 4 years, and they were further followed on average ~2.5 years after the diagnosis of Alzheimer's dementia.

3.2. FR gradually degrades with aging and the degradation accelerates with the progression of Alzheimer's dementia

During the NCI stage, both α_1 and α_2 decreased over time with an annual decline of 0.002 ± 0.0005 (mean ± SE unless otherwise indicated) for α_1 ($p < 0.0001$) and of 0.006 ± 0.0007 for α_2 ($p < 0.0001$) (Table 2; Fig. 3), suggesting that activity fluctuations in both time scale regions became more random with aging. These degradations did not differ between females and males or by years of education (all p's > 0.1) (Table 2) except that higher years of education was associated with slower decline rate in α_2 ($p = 0.045$). The decline in α_1 was faster in older individuals ($p < 0.0001$) (Table 2). On the other hand, we did not observe a significant association of baseline age with decline rate in α_2 ($p = 0.5$) (Table 2).

After MCI diagnosis, α_1 declined much faster and the decline rate was increased by 150% (estimate of increase: 0.003 ± 0.001; $p = 0.0003$) (Table 2). Similarly, α_2 also declined faster after MCI diagnosis, that is, the rate increased by ~133% after the diagnosis (estimate of increase: 0.008 ± 0.001 $p < 0.0001$) (Table 2; Fig. 3).

After the clinical onset of Alzheimer's dementia, the declines in α_1 and α_2 were further accelerated with an increase of 0.017 ± 0.003 for α_1 (4.4 times of the rate at MCI, $p < 0.0001$) and an increase of 0.016 ± 0.005 for α_2 (2.1 times of the rate at MCI, $p = 0.0005$), respectively (Table 2; Fig. 3).

Those decedents with confirmed AD pathology ($N = 255$) showed similar patterns of longitudinal changes in both scaling exponents, that is, α_1 and α_2 declined over time at the NCI stage, the decline accelerated after MCI onset, and further accelerated after the diagnosis of dementia (Table 3; Fig. 3). To explore the possible

Table 1
Demographic, clinical, and actigraphic characteristics of the participant

Characteristics	Values expressed as N (female/male) or mean (standard deviation)	
	All	Pathological Alzheimer's disease subset
N (female/male)		
Total at baseline	1068 (809/259)	255 (194/61)
NCI at baseline	810 (628/182)	156 (126/30)
Converted to MCI	339 (257/82)	114 (89/25)
Converted to dementia	121 (95/26)	58 (47/11)
MCI at baseline	208 (150/58)	69 (48/21)
Converted to dementia	91 (70/21)	46 (37/9)
Dementia at baseline	43 (26/17)	27 (18/9)
Age at baseline (y)	80.9 (7.2)	85.7 (5.5)
Education (y)	15.1 (3.0)	14.4 (2.9)
Cognition		
MMSE	27.8 (2.6)	26.7 (3.6)
Global cognition	0.12 (0.58)	−0.20 (0.61)
Episodic memory	0.18 (0.74)	−0.17 (0.87)
Working memory	0.04 (0.74)	−0.21 (0.75)
Semantic memory	0.16 (0.64)	−0.08 (0.66)
Perceptual speed	0.08 (0.79)	−0.38 (0.76)
Visuospatial abilities	0.11 (0.84)	−0.15 (0.88)
Fractal regulation		
α_1	0.92 (0.06)	0.91 (0.06)
α_2	0.82 (0.10)	0.82 (0.09)

Key: dementia, Alzheimer's dementia; MCI, mild cognitive impairment; MMSE, mini–mental state examination; NCI, no cognitive impairment.

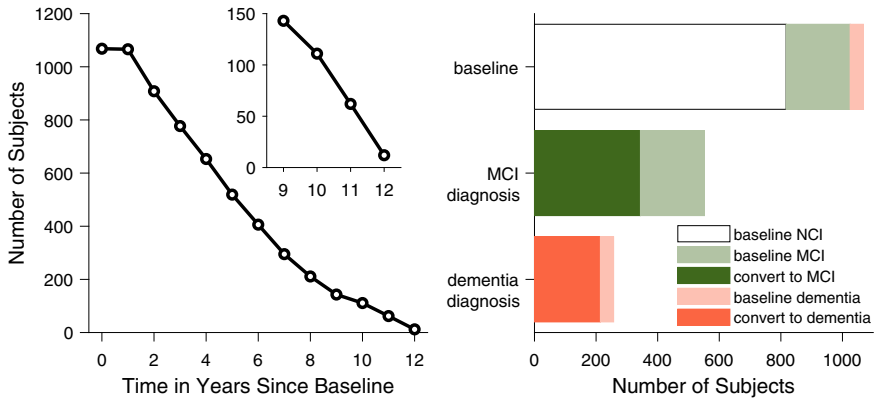

Fig. 2. Number of participants. Left panel shows number of participants in each follow-up year (with a roomed portion shown on the top-right corner). Right panel illustrates the number of participants in each category (i.e., NCI, MCI, and Alzheimer's dementia) at baseline, at MCI diagnosis, and at Alzheimer's dementia diagnosis, respectively. Abbreviations: NCI, no cognitive impairment; MCI, mild cognitive impairment.

Table 2
Longitudinal changes of the scaling exponents α_1 and α_2 with respect to the progression of Alzheimer's dementia

Term	α_1		α_2	
	Estimate (SE)	p	Estimate (SE)	p
Intercept	0.917 (0.002)	0	0.824 (0.003)	0
Time since baseline	−0.002 (0.0005)	<0.0001	−0.006 (0.0007)	<0.0001
Age at baseline	−0.0006 (0.0002)	0.004	−0.002 (0.0004)	<0.0001
Age at baseline * time since baseline	−0.0004 (5e−5)	<0.0001	5e−5 (8e−5)	0.5
Sex (male)	−0.006 (0.004)	0.1	−0.002 (0.006)	0.8
Sex (male) * time since baseline	0.001 (0.0009)	0.3	0.0005 (0.001)	0.8
Years of education	0.001 (0.0005)	0.017	−5e−5 (0.0009)	>0.9
Years of education * Time since baseline	7e−5 (0.0001)	0.6	0.0004 (0.0002)	0.045
Time since MCI	−0.003 (0.0008)	0.0003	−0.008 (0.001)	<0.0001
Age at baseline * time since MCI	−0.0002 (0.0001)	0.1	−0.0003 (0.0001)	0.07
Sex * time since MCI	0.0007 (0.002)	0.7	−0.002 (0.002)	0.4
Years of education * time since MCI	2e−5 (0.0002)	0.9	−0.0002 (0.0003)	0.6
Time since dementia	−0.017 (0.003)	<0.0001	−0.016 (0.005)	0.0005
Age at baseline * time since dementia	0.0002 (0.0003)	0.5	0.0009 (0.0005)	0.1
Sex * time since dementia	0.004 (0.005)	0.5	0.006 (0.008)	0.5
Years of education * time since dementia	6e−5 (0.0007)	0.9	−0.002 (0.001)	0.1

Key: dementia, Alzheimer's dementia; MCI, mild cognitive impairment.

differences in FR degradation between this subset and the other subjects in the cohort, we first performed additional linear mixed-effects models using the remained subset (i.e., full cohort excluding 255 autopsy-confirmed AD subjects). Based on the estimated decline rates and standard errors at the 3 different stages obtained from the 2 subsets, we calculated the t static and double-sided p values with the assumption of independence and unequal variances between the 2 subsets. The results suggested a significant group difference in the rate of α_1 decline at Alzheimer's dementia stage (α_1 declined faster in deceased subjects with autopsy-confirmed Alzheimer's pathology; $p = 0.04$). Besides, α_2 in the decedents with Alzheimer's pathology also declined significantly faster than that in the remained subset at Alzheimer's dementia stage ($p = 0.002$). In addition, the decline rates of α_1 at NCI and MCI stages in the decedents with Alzheimer's pathology were also higher than those in the remained subset, but the differences did not reach a statistical significance ($p = 0.07$ at NCI stage; $p = 0.09$ at MCI stage). No significant group differences were observed in the rates of α_2 decline at NCI and MCI stages (both p's > 0.2).

In addition, we also repeated these analyses using α_1 and α_2 obtained from motor activity segments during the common active time (i.e., 10 AM–9 PM). The aforementioned observations persisted. Specifically, (1) during the NCI stage, both α_1 and α_2 decreased over time with an annual decline of 0.002 ± 0.0005 for α_1 ($p < 0.0001$) and of 0.003 ± 0.0007 for α_2 ($p < 0.0001$). (2) After MCI diagnosis, α_1 declined much faster, and the decline rate was increased by 150% (estimate of increase: 0.003 ± 0.0009; $p = 0.0006$). Similarly, α_2 also declined faster after MCI diagnosis, that is, the rate increased by ~167% after the diagnosis (estimate of increase: 0.005 ± 0.002, $p = 0.002$). (3) After the clinical onset of AD, the declines in α_1 and α_2 were further accelerated with an increase of 0.018 ± 0.003 for α_1 (3.6 times of the rate at MCI, $p < 0.0001$) and an increase of 0.013 ± 0.005 for α_2 (1.6 times of the rate at MCI, $p = 0.01$), respectively.

3.3. Longitudinal degradation in FR correlates to the longitudinal decline in cognition

The bivariate linear mixed models confirmed the gradual decreases in both α_1 and α_2 with time (both p's < 0.0001), and gradual decline with time in global cognition ($p < 0.0001$ in both models). In addition, the longitudinal change in global cognition was positively correlated with the longitudinal changes in α_1 (correlation = 0.23, $p = 0.0009$) and in α_2 (correlation = 0.37, $p < 0.0001$) (Table 4). Subsequent sensitivity analysis within 255 decedents with AD pathology at autopsy further confirmed these observations (Table 5).

4. Discussion

Using a longitudinal, community-based cohort of over 1000 participants, we have documented, for the first time, the longitudinal degradation of FR in human motor activity for up to 13 years during the progression of AD. Specifically, FR was progressively degraded over time, leading to more random fluctuations in motor activity over a range of time scales from ~5 minutes to up to 8 hours. Moreover, with the progression of AD, we observed much faster degradation of FR over time after the diagnosis of MCI (i.e., 2.50 times faster for α_1 and 2.33 time faster for α_2) and further after

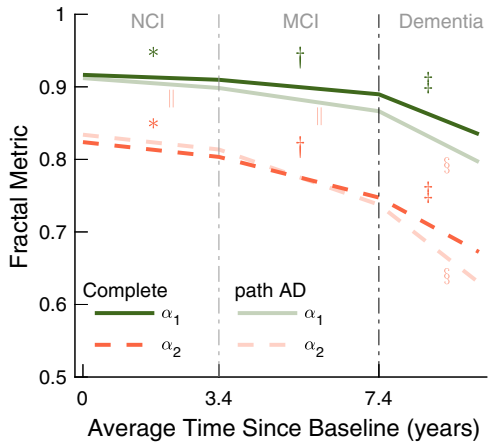

Fig. 3. Degradation of fractal activity regulation with the progression of Alzheimer's dementia. The durations of the NCI stage and MCI stage were based on the averaged time lags between baseline and MCI diagnosis (~3.4 years) and between MCI diagnosis and Alzheimer's dementia diagnosis (~4 years). The plotted α_1 (thick solid line) and α_2 (thick dashed line) were based on their mean values at baseline and their averaged annual declines during the 3 stages (e.g., NCI, MCI, and Alzheimer's dementia). * indicates a significant decline over time; † indicates a significant change in the rate of decline after MCI diagnosis; ‡ indicates a significant change in the rate of decline between MCI stage and dementia stage; § indicates a significant difference in the rate of change between the deceased subset with Alzheimer's disease pathology (path AD) and the remained subset; || indicates a borderline significant difference (i.e., $p < 0.1$) in the rate of change between the deceased subset with path AD and the remained portion. Abbreviations: AD, Alzheimer's disease; NCI, no cognitive impairment; MCI, mild cognitive impairment.

Table 3
Longitudinal changes of the scaling exponents α_1 and α_2 with respect to the progression of Alzheimer's dementia in decedents with Alzheimer's disease pathology

Term	α_1		$\alpha 2$	
	Estimate (SE)	p	Estimate (SE)	p
Intercept	0.912 (0.005)	0	0.834 (0.008)	0
Time since baseline	−0.004 (0.001)	0.01	−0.006 (0.002)	0.006
Age at baseline	−0.0007 (0.0006)	0.2	−0.003 (0.001)	0.006
Age at baseline * time since baseline	−0.0002 (0.0002)	0.9	0.0005 (0.0003)	0.1
Sex (male)	−0.011 (0.008)	0.2	−0.02 (0.01)	0.2
Sex (male) * time since baseline	−0.002 (0.003)	0.4	0.004 (0.004)	0.3
Years of education	−0.00 (0.001)	0.4	−0.004 (0.002)	0.02
Years of education * time since baseline	−0.0003 (0.0004)	0.4	0.001 (0.001)	0.06
Time since MCI	−0.004 (0.002)	0.03	−0.012 (0.003)	<0.0001
Age at baseline * time since MCI	−0.0002 (0.0002)	0.5	−0.0004 (0.0004)	0.3
Sex * time since MCI	0.003 (0.003)	0.3	0.005 (0.005)	0.3
Years of education * time since MCI	0.0003 (0.0004)	0.5	−0.0002 (0.0007)	0.7
Time since dementia	−0.020 (0.004)	<0.0001	−0.024 (0.005)	<0.0001
Age at baseline * time since dementia	0.0009 (0.0004)	0.03	0.001 (0.001)	0.02
Sex * time since dementia	0.001 (0.006)	0.8	0.01 (0.01)	0.2
Years of education * time since dementia	0.0004 (0.0007)	0.6	−0.001 (0.001)	0.2

Key: dementia = Alzheimer's dementia, MCI, mild cognitive impairment.

the diagnosis of Alzheimer's dementia (i.e., 4.40 times faster for α_1 and 2.10 time faster for α_2). Furthermore, we also found that the longitudinal change of FR was strongly associated with decline of cognitive function throughout the disease progression during different clinical stages from NCI to MCI and to Alzheimer's dementia. Importantly, we confirmed the same effects in a portion of participants who had AD confirmed at autopsy.

4.1. Neural mechanisms of FR in physiology

Fractals in physiology are believed to result from a complex neurophysiological network with interactive regulatory processes functioning over a wide range of time scales (Bassingthwaighte et al., 1994; Goldberger et al., 2002; Pittman-Polletta et al., 2013; West, 2010). Although the neural circuitry of FR is still elusive, solid evidence has linked the endogenous circadian system with FR: (1) In rats, lesioning the central circadian clock—the SCN—caused a breakdown of fractal patterns in the motor activity (Hu et al., 2007). Specifically, the scaling exponent α at larger time scales (>∼4 hours) reduced to close to 0.5 indicating a complete loss of multiscale correlations. (2) In rats, lesioning the dorsomedial hypothalamic nuclei—a neural node that conveys the SCN influences to locomotor activity through its output to the orexin-contained lateral hypothalamic area—also caused a significant reduction in the scaling exponent (i.e., more random activity fluctuations) at time scales >∼4 hours (Lo et al., 2016). (3) In humans, we found strong associations between the reduction of the scaling exponent and reducing SCN neurotransmitters (e.g., vasopressin and neurotensin) (Hu et al., 2013). (4) Disrupted circadian regulation, as occurred during night shift, caused perturbed scaling behavior in both rats and humans (Hsieh et al., 2014; Li et al., 2017a) as characterized by more random activity patterns, especially at time scales >∼2–4 hours. Thus, the observed decrease in α_2 (large time scales >2 hours) over time in this study may reflect the degradation of the circadian control.

In addition, the scaling patterns at smaller time scales (<90 minutes) appear to be more resilient to circadian disruptions as compared with those at large time scales, for example, being less affected by lesioning the SCN activity and night shifts in rats (Hsieh et al., 2014; Hu et al., 2007) and recovering more quickly in human chronic shift workers after night shifts (Li et al., 2017a). Our recent studies showed that the scaling exponent at <90 minutes was strongly associated with higher level brain functions such as cognition and mood (Hu et al., 2016) and appeared to better predict the risk for dementia in the elders (Li et al., 2018). Consistently, the present study showed a longitudinal association between α_1 and cognition during the progression of AD. However, it is yet to be determined what neural nodes are responsible for the scaling behavior at small time scales. To fill the knowledge gap, follow-up studies should be designed to examine how fractal degradations are associated with neuropathologic changes in different brain regions using brain imaging data and/or postmortem brain histopathologic data.

4.2. Fractal patterns and rhythmicity

It is important to note that fractal and rhythmicity are distinguished properties of temporal fluctuations. Changing one rhythm at a specific time scale may not affect fractal patterns. For instance, our simulation study demonstrated that artificially induced 24-hour rhythmicity to motor activity almost had no identifiable effects on fractal activity patterns (see Fig. 4 in [Hu et al., 2013]) and a 24-h rhythm of food availability enhanced the daily rhythms of motor activity in the rats with lesioned SCN but could not improve

Table 4
Covariance structure and correlation of baseline and longitudinal changes in FR and cognition (results are shown by [covariance, correlation] p value)

Variable	Baseline α_1	Change in cognition	Change in α_1	Variable	Baseline α_2	Change in cognition	Change in α_2
Baseline cognition	(0.003, 0.14) 0.0004	(0.015, 0.36) < 0.0001	(0.001, 0.27) < 0.0001	Baseline cognition	(0.0004, 0.01) 0.8	(0.014, 0.36) < 0.0001	(0.001, 0.13) 0.03
Baseline α_1	-	(0.001, 0.15) 0.002	(−0.0001, −0.31) < 0.0001	Baseline α_2	-	(−0.0003, −0.04) 0.4	(−0.0003, −0.37) < 0.0001
Change in cognition	-	-	(0.0001, 0.23) 0.0009	Change in cognition	-	-	(0.0003, 0.37) < 0.0001

Key: FR, fractal regulation.

Table 5
Covariance structure and correlation of baseline and longitudinal changes in FR and cognition in decedents with Alzheimer's disease pathology (results are shown by [covariance, correlation] p value)

Variable	Baseline α_1	Change in cognition	Change in α_1	Variable	Baseline α_2	Change in cognition	Change in α_2
Baseline cognition	(0.002, 0.12) 0.16	(0.027, 0.42) < 0.0001	(0.002, 0.33) 0.003	Baseline cognition	(0.004, 0.09) 0.3	(0.026, 0.41) < 0.0001	(0.0005, 0.06) 0.6
Baseline α_1	-	(0.0004, 0.09) 0.4	(−0.0002, −0.35) 0.02	Baseline α_2	-	(0.0004, 0.06) 0.6	(−0.0003, −0.27) 0.05
Change in cognition	-	-	(0.0003, 0.29) 0.03	Change in cognition	-	-	(0.0008, 0.48) 0.0005

Key: FR, fractal regulation.

perturbed fractal regulation (Li et al., 2017b). Besides, circadian rhythms may persist while fractal patterns are completely abolished, as observed in the in vitro SCN neural activity (Hu et al., 2012). These results are not unexpected because fractal requires the coupling of multiple processes with rhythms that function at different time scales. Except for the circadian rhythm, one of the possible physiological processes involved in fractal regulation is basic rest-activity cycle or ultradian rhythm (Kleitman, 1963). Since the observation of the 90-minute sleep-stage cycle, ultradian rhythms between 2 and 6 hours have been identified in many neurophysiological processes including behavior and hormone secretion even during wakefulness (Kleitman, 1982; Prendergast and Zucker, 2016). Although the neural circuitry of ultradian rhythmicity is still elusive, it is believed that ultradian rhythms are integrated with the circadian rhythm (Bourguignon and Storch, 2017). Based on the theory of fractal physiology, it is tempting to speculate that the ultradian-circadian interaction is one of the possible mechanisms generating fractal patterns in motor activity fluctuations from ~2 hours up to 24 hours. Further studies are warranted to test this speculation and to illustrate its relevance to neurodegenerative progression in AD.

Besides, another advantage of the scaling analysis over traditional rhythmicity or moment approaches is that the scaling behavior seems more resilient to many direct masking effects on actigraphy, for example, the effects of housing, nursing home schedules for feeding and sleep, and interactions between patients and caregivers (Hu et al., 2004). In a previous study, we also showed that degraded fractal activity regulation in patients at late dementia can better predict neuron loss in the SCN than the combined predictive power of 3 rhythmicity measures (i.e., 24-hour amplitude of core body temperature, 24-hour amplitude of motor activity, and intradaily variability of motor activity) (Hu et al., 2013).

Timed light exposure can promote circadian control that in turn offers benefit to cognition (Forbes et al., 2014) and many other physiological functions (Baron and Reid, 2014). In addition to its benefits to sleep and cognition, light treatment of up to 3.5 years appeared to decelerate or halt the aging effect on fractal regulation in older humans (Hu et al., 2016). In the present study, we do not have the data for daily light exposure or activity outside. Further studies are therefore warranted to test whether the effect of long-term daytime light exposure on circadian health underlie the association between the changes in fractal regulation and cognition.

4.3. Effects of aging on FR at different time scales

Previous studies showed that healthy and young subjects (i.e., 20–40 year old) have stable FR over a wide range of time scales (from minutes to 24 hours) as indicated by the similar values (~0.9) of scaling exponents α_1 and α_2 (Hu et al., 2004; Pittman-Polletta et al., 2013). In this study, we showed that these scaling exponents were gradually decreasing with aging even in those who remained cognitively normal throughout the study period. This may not be surprising because aging leads to many neuroanatomic changes in the brain, likely perturbing the neural network of FR. For instance, circadian disruptions commonly occur with aging (Harper et al., 2005; Musiek et al., 2018) and cognition starts to progressively decline with aging even before dementia onset (Bennett et al., 2012b; Wilson et al., 2012). Thus, our observed changes in the scaling behavior of motor activity fluctuations with aging may thus be a consequence of the aging effects on circadian and cognitive functionalities. In this cohort, the value of α_2 was much smaller than α_1 even at baseline when all participants were still cognitively healthy. This may be explained by the observed faster decline of α_2 as compared to α_1 (Fig. 2) if we assume the same degradation rates of the 2 exponents at younger ages. Further studies with a young population are required to validate this assumption as well as to determine at what age(s) FR starts to degrade and the fractal patterns begin to bifurcate (i.e., different decline rates for the 2 scaling exponents).

Interestingly, the FR degradation at time scales <1.5 hours speeded up at older ages even within the NCI stage (i.e., annual decline of α_1 was faster at older ages). We have confirmed this finding by performing a separate linear mixed-effects model in a subset of the cohort in which all subjects stayed at the NCI stage throughout the study period ($N = 478$; magnitudes of effects are equivalent to these reported in Table 2 at the NCI stage). After this finding, one natural question is whether the observed accelerations of α_1 decline after MCI diagnosis and after Alzheimer's dementia onset were simply due to the nonlinear aging effect because MCI and Alzheimer's dementia occurred at older ages. To address this, we estimated the increases in the decline rate of α_1 at MCI and AD stages using the age effect within the NCI stage as the following. Because the annual decline rate of α_1 increased by 0.0004 per one year old of age during the NCI stage, the average time interval of ~3.4 years between baseline and MCI diagnosis would lead to an increase of ~0.0014 after MCI diagnosis. This estimated increase is only half of the value we observe in the real data (i.e., 0.003 after MCI diagnosis). Similarly, the average time interval of ~6.3 years between baseline and Alzheimer's dementia onset would lead to an increase of ~0.0025 at the onset of Alzheimer's dementia as compared to baseline or an increase of ~0.0011 as compared to MCI stage. The estimated increase is only one-fifteenth of the value we observed in the real data (i.e., 0.017 from MCI to Alzheimer's dementia). Thus, it is unlikely that the nonlinear age effect at the NCI stage can account for the effects of MCI and Alzheimer's dementia.

4.4. Degraded fractal activity regulation independent of nighttime behavior

Our observations persisted after excluding the motor activity segments during the common sleep period, precluding the possibility that the degradations in FR were caused by differences in behavioral patterns during sleep. Actually, the α's obtained using data during the common active time (i.e., 10 AM–9 PM) were highly correlated to those calculated using the complete data ($R^2 = 0.8$ for α_1 and 0.3 for α_2). These results indicate that our observed fractal

degradations in the older individuals do not simply reflect possible disruptions in nighttime sleep; more likely they reflect altered behavioral patterns during daytime (i.e., more random motor activity patterns). Specifically, it is possible that alterations at small time scales (i.e., α_1 at $<$ 1.5 hours) may be linked to less complex voluntary activity as subjects become unable to perform their activities of daily living and that alterations at larger time scales (i.e., α_2 at $>$2 hours) may reflect the disturbances in the circadian and sleep-wake cycles, leading to disrupted rest-active patterns (e.g., more sleepiness and inactive periods during daytime).

We note that it is possible that the scaling patterns of motor activity fluctuations during the night may provide independent information. However, performing the proposed scaling analysis on data only during nighttime requires special caution because of a technical concern related to the nature of the analysis and the sensitivity of accelerometer sensor equipped in the device. Specifically, scaling/fractal analysis examines the temporal fluctuations (i.e., its amplitude and structure) such that reliable results crucially depend on the signal-to-noise ratio. During the nighttime, motor activity levels are normally very low for subjects with normal sleep and circadian rhythms. In addition, with a limited sensitivity of the accelerometer sensors and the current algorithm of filtering random background noise in actigraphy, the signal-to-noise ratio is quite low during the nighttime. As a result, the results of DFA may not be reliable when using only nighttime data. Thus, addressing this technical concern is necessary before the scaling behavior of activity patterns during the nighttime can be applied in research and clinical studies.

4.5. Translational potential in clinical practice in relation to Alzheimer's disease

The related neurodegeneration of AD is believed to start many years before being clinically diagnosed (Dubois et al., 2016; Risacher and Saykin, 2013). One reason for this delayed diagnosis is related to the functional resilience, or compensatory mechanism, of the brain that makes the effect of neurodegeneration on cognition undetectable even for two decades of progression (Bobkova and Vorobyov, 2015). Assessment of FR degradation may thus provide a unique opportunity for earlier, in-time awareness of the neurodegenerative process, which is crucial for a better design of effective treatments of AD (Frisoni et al., 2017; Scheltens et al., 2016). For instance, the accelerated decline in the examined scaling exponents may be indicative of a warning sign that AD has already been progressing silently. The identified patterns of longitudinal FR degradation can help better understand the impacts of the AD progression on behavior and physiology, which may potentially reveal the unknown, mysterious shift from normal aging to pathological aging or neurodegeneration. In a previous study that used the same cohort, we showed that the risk of developing MCI and Alzheimer's dementia increased by 15% and 31%, respectively, for each SD decrease in α_1 at baseline (Li et al., 2018). The time intervals between baseline and incident MCI and incident Alzheimer's dementia were 3.4 and 4.6 years, respectively, in this cohort, suggesting that the fractal degradations already exist $>$3 years before the cognitive symptoms occur. Further studies should be warranted to implement the temporal changes in FR for better prediction of MCI, the conversion from MCI to dementia, and other clinical outcomes (e.g., disability and mortality).

Besides a simple consequence of AD-related neurodegeneration, the accelerated degradation of FR might also be a risk factor for Alzheimer's dementia and/or reflect the speedup of the disease progression. For instance, based on the concept that FR indicates system adaptability, the system with degraded FR may become less adaptable to external environmental changes and, thus, more vulnerable to external challenges. Besides, it is well documented that AD-related neurodegeneration can lead to dysfunctions of the circadian control nodes and/or their interactions (Liu et al., 2000; Musiek et al., 2015; Wu et al., 2007), which may contribute to FR degradation in patients with AD (Hu et al., 2013, 2009). On the other hand, perturbed circadian control can disrupt many physiological functions such as glucose metabolism, cerebrovascular function, and sleep (Baron and Reid, 2014; Qian and Scheer, 2016), which may impact neurodegenerative processes and increase risk for neurodegenerative diseases including AD (Bedrosian and Nelson, 2012; Daulatzai, 2017). Indeed recent studies showed that disrupting sleep and circadian rhythms in mice caused increased accumulation of amyloid beta—a hallmark of AD pathology (Kang et al., 2009; Xie et al., 2013)—and that circadian/sleep disturbances in humans are associated with amyloid burden in preclinical AD (Ju et al., 2013; Musiek et al., 2018). Thus, it is highly possible that the interaction between FR degradation and the progression of AD are bidirectional. It also seems plausible that the effect of aging or Alzheimer's progression on α_2 starts earlier and is more pronounced than that on α_1, indicating that their influence on the circadian system might occur earlier or is stronger than that on other control system(s) that contribute to α_1. To formally confirm/refute these possibilities, further studies are required to examine whether improving or maintaining FR can prevent the development of AD or slow down the progression of the disease.

4.6. Study limitations

One limitation of this study is that the progression of AD was estimated based on its clinical symptoms (i.e., MCI and Alzheimer's dementia). To ensure that the FR degradations observed in the cohort represented those in subjects with Alzheimer's pathology, we analyzed a small subset of subjects who died and had pathologically confirmed AD at autopsy. We found similar degradation pattern of FR in these patients with slightly larger effect sizes of aging as compared to the other subjects (e.g., both α_1 and α_2 declined faster after dementia onset in autopsy-confirmed patients with AD). These results support that the neuropathological process of AD may underlie FR degradation and its accelerations over time. Because antemortem Alzheimer's pathology biomarkers were not available, many participants might have already Alzheimer's pathology even during the NCI stage (but not confirmed with postmortem examinations yet) such that the observed fractal degradation should be the combined effect of normal aging and Alzheimer's pathology. Thus, it is highly possible that the aging effect was overestimated while the effect of Alzheimer's dementia progression was underestimated. This may contribute to nonsignificant differences in the decline rate of α_2 (at NCI and MCI stages) between those confirmed with Alzheimer's pathology and the other subjects in the cohort. Recently, National Institute on Aging and Alzheimer's Association recommends a biological definition of AD based on in vivo assessment of amyloid-β and tangles (Frisoni et al., 2017; Jack et al., 2018). It is better to use this biological definition to determine the interaction between FR degradation and the progression of AD. In addition, identifying the pathological changes in specific brain regions that underlie these degradations is important. Besides, it is also interesting to examine whether degraded fractal regulation in motor activity can also be used to identify patients with fractures or Parkinson's disease and/or whether the specific fractal regulation features involved in fractures/Parkinson's disease are different from those involved in AD (e.g., scaling exponents in different time scale regions). If yes, these diseases may potentially confound the observed AD effects on fractal degradation. Moreover, we used the detrended fluctuation analysis to examine the temporal structure in motor activity fluctuations and quantify the changes in

fractal regulation. Although the method has better performances than some methods such as Hurst analysis for signals with certain nonstationarities (e.g., slowly varying trend), it has certain limitations. For instance, the method can be affected by large spikes or jumps that often exist in physiological recordings because of either artifacts or real biological processes (Chen et al., 2002; Hu et al., 2001). Relatedly, there are many other fractal/scaling analysis methods such as multiscale entropy and multifractal analysis that can be also used to assess temporal organization in motor activity. It is worth checking which method(s) can better quantify the effects of age and diseases on motor activity control. Follow-up studies are warranted to address these questions.

Disclosure

The authors declare that there is no competing interest. The study was approved by the institutional review boards of Rush University Medical Center and Partners Healthcare and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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The authors warrant that the data contained in the manuscript have not been published or are being submitted elsewhere. All authors have reviewed the contents of the manuscript being submitted, have approved its contents, and validated the accuracy of the data.

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