ELSEVIER

Alzheimer's & Dementia ■ (2018) 1-12

Alzheimer's & Dementia

Featured Article

Fractal regulation and incident Alzheimer's disease in elderly individuals

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Abstract

Introduction: Healthy physiological systems exhibit fractal regulation (FR), generating similar fluctuation patterns in physiological outputs across different time scales. FR in motor activity is degraded in dementia, and the degradation correlates to cognitive decline. We tested whether degraded FR predicts Alzheimer's disease dementia.

Methods: FR in motor activity was assessed in 1097 nondemented older adults at baseline. Cognition was assessed annually for up to 11 years.

Results: Participants with an FR metric at the 10th percentile in this cohort had a 1.8-fold Alzheimer's disease risk (equivalent to the effect of being ~5.2 years older) and 1.3-fold risk for mild cognitive impairment (equivalent to the effect of being ~3.0 years older) than those at the 90th percentile. Consistently, degraded FR predicted faster cognitive decline. These associations were independent of physical activity, sleep fragmentation, and stability of daily activity rhythms.

Discussion: FR may be a useful tool for predicting Alzheimer's disease dementia.

Keywords: Longitudinal cohort study; Prediction of Alzheimer's disease; Mild cognitive impairment; Fractal physiology; Fractal regulation

1. Introduction

Outputs of many physiological systems display intrinsic self-similarity, or fractal patterns, across a wide range of temporal scales from seconds up to 24 hours, suggesting an underlying fractal regulatory mechanism [1,2]. Fractal regulation (FR) challenges the traditional theory of homeostasis as it indicates that the physiological systems do not simply settle down to a stable state [1,3–5]. Numerous studies have provided an overwhelming evidence that FR is a hallmark of healthy physiology, imparting considerable physiological advantage in terms of plasticity and adaptability (i.e., system integrity despite vastly changing conditions) [1,3–5]. For instance, FR in cardiac function is degraded with aging and under varied pathological conditions [6]; and such degradation is associated with decreased survival in patients with stroke or myocardial infarction [7–9].

Our previous cross sectional study revealed that FR in motor activity is degraded with aging and in Alzheimer's disease (AD) [10], and in a short longitudinal study, we found that the degradation of FR in motor activity over time is associated with cognitive decline in very old adults with dementia [11]. The goal of the present study is to determine whether FR perturbation at baseline in older individuals without dementia is associated with increased risk of the development of AD dementia and mild cognitive

Conflicts of interest: F.A.J.L.S. has received speaker fees from Bayer Healthcare, Sentara Healthcare, and Philips.

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https://doi.org/10.1016/j.jalz.2018.03.010

impairment (MCI) and rate of cognitive decline. To achieve this goal, we analyzed the data of 1097 older adults participating in the Memory and Aging Project (MAP) at Rush AD Center [12]. Subjects have been followed up for up to 11 years at the time of analysis. FR at baseline was evaluated using wrist actigraphy continuously monitored for up to 10 days. To evaluate the cognitive function and to identify AD dementia and MCI development, a battery of 21 neuropsychological tests and a detailed clinical evaluation were administered each year during the baseline and follow-up assessments. We hypothesized that subjects with more degraded FR at baseline were at increased risk for incident AD dementia and MCI and had a faster cognitive decline.

2. Methods

2.1. Subjects

The MAP is an on-going longitudinal, community-based cohort study of aging and dementia that began in 1997 [12]. Actigraphy was added in 2005. At the time of analysis (July 07, 2016), 1836 participants were enrolled in the MAP (parent study). Among them, 348 participants died; 79 withdrew before actigraphy was added; and 54 could not be followed (e.g., moving out of the state). Of the remaining 1355 who were eligible for actigraphy assessment, 16 refused to participate, and 30 had yet to have device placement. Thus, there were 1309 subjects who had actigraphy assessment(s). As compared with the parent study, these 1309 participants had similar baseline age (79.7 ± 0.2 years old, parent study: 79.9 ± 0.2, $P > .1$), but had slightly more female subjects (76.8%, parent study: 73.7%, $P = .046$) and higher baseline cognitive score (0.10 ± 0.02, parent study: 0.00 ± 0.02, $P < .01$). Further exclusion criteria in the present study were as follows: (1) baseline dementia (103); (2) bad quality baseline actigraphy (10; see Sub-Section 2.2); and (3) no valid baseline or at least one follow-up cognitive assessment to allow the determination of incident AD dementia and MCI and rate of cognitive decline (99). Thus, 1097 subjects (including 855 without MCI at baseline) were included in the final analysis. Written informed consent was obtained from all participants. 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.

2.2. Data collection and preprocessing

For assessment of daily motor activity (Fig. 1), subjects wore an activity monitor (Actical, Philips Respironics, Bend, OR) on their nondominant wrist for up to 10 days. The device predominantly measures acceleration in a direction parallel to the face of the device with a continuous sampling frequency of 32 Hz and integrates the data into a proprietary count value every 15 seconds. To ensure good signal quality, all actigraphic recordings were checked with the assistance of a self-designed MATLAB GUI program (Ver. R2015a, the MathWorks Inc., Natick, MA, USA). The most common types of quality issues were as follows: (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 (likely occurred when subjects took the device off). The episodes with those issues were marked as gaps [13,14].

2.3. Clinical diagnoses and cognitive assessment

Cognitive function was assessed with a battery of 21 neuropsychological tests administered each year. Nineteen tests across a range of cognitive abilities were used to construct measures of five cognitive domains: (1) episodic memory (based on seven tests including Word List Recall, Word

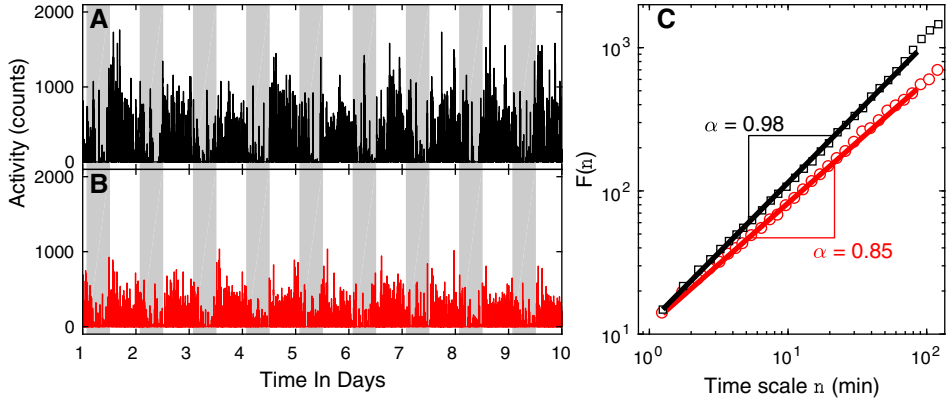

Fig. 1. Fractal correlations in motor activity fluctuations. (A-B) Representative activity recordings of two ~80-year-old female subjects. Subject corresponding to (B) developed AD and the other corresponding to (A) did not. Gray shaded area indicates 9 PM–7 AM. (C) The corresponding detrended fluctuation analysis results of the signals in (A) and (B). The fluctuation function F(n) is shown versus time scale, n, in log-log scale, where F(n) is log-linearly fitted in the region of 1.25–90 min. The slope of the fitting line is defined as FR metric α. The value of α was lower for the signal in (B), indicating more random activity fluctuations. Abbreviations: FR, fractal regulation; AD, Alzheimer's disease.