Degraded Fractal Activity Regulation Predicts Elevated Risk of Alzheimer's Disease in the Elderly*

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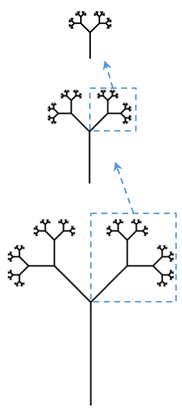
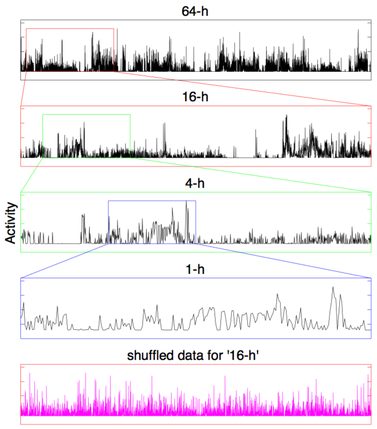
Introduction

- Healthy physiological systems exhibit fractal regulation, generating similar fluctuation patterns in their outputs across different time scales from seconds to hours [1];
- Fractal regulation is mechanistically linked to sleep and circadian control [2,3];
- Sleep and circadian disturbances may be early signs of Alzheimer's disease [4];
- Cross-sectional studies have shown that fractal regulation is degraded in elderly subjects and in people with dementia [5].

Scale-invariant (fractal) structure



Scale invariance in activity (fractal activity regulation)



Hypothesis

- Degradation of fractal regulation predicts elevated risk for Alzheimer's dementia and faster cognitive decline.

Data and Methods

- Continuous actigraphy lasting for up to 10 days were recorded in the Rush Memory and Aging Project (MAP) [6].

Activity counts

- Actical (Phillips Respironic Actical, Bend, OR)
- Accelerometer sensitivity: < 0.01 g
- Sampling frequency: 32 Hz
- Epoch length: 15, 30, 45, 60 sec

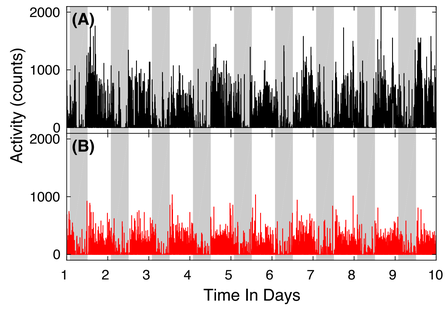
Participants

Characteristics	Mean (SD) or N (%)	
	Non-Alzheimer's	Non-mild cog impairment
N	1,097	855
Female	844 (76.9%)	671 (78.5%)
Age (year)	81.0 (7.4)	80.1 (7.2)
Education (years)	15.0 (3.0)	15.1 (3.0)
Global cognition	0.17 (0.53)	0.33 (0.42)

Data analysis

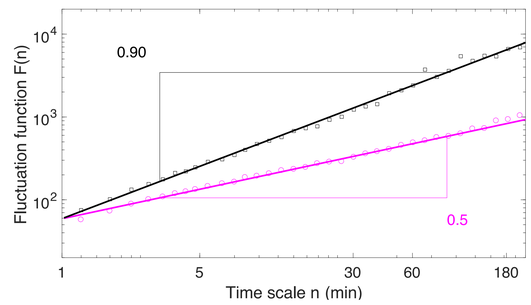
- Fractal regulation was assessed by performing the detrended fluctuation analysis on time scales from 1 minute to 1.5 hours to quantify the temporal correlation α;
- Cognitive function was evaluated by a global cognitive score based on 19 cognitive tests.
- Clinical diagnosis was based on criteria of the joint working group of the NINCDS/ADRDA.

- Motor activity of two representative subjects.



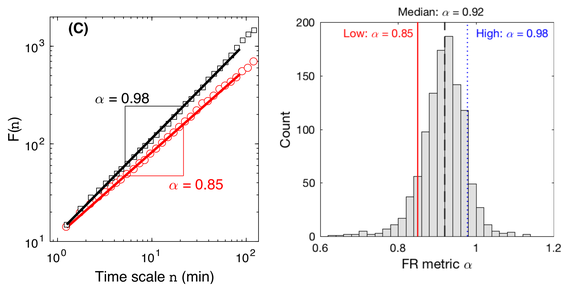
Scaling exponent α for the evaluation of fractal regulation

- The detrended fluctuation analysis is commonly used to quantify the correlations of signals over multiple time scales.
- The analysis calculates the fluctuation amplitude at different time scales [F(n)].
- The power law function $F(n) \sim n^{\alpha}$ indicates fractal patterns.
- The temporal correlations are characterized by the scaling exponent α [1]:
  - ✓ $\alpha > 0.5$: signals with positive correlations;
  - ✓ $\alpha = 0.5$: uncorrelated white noise.

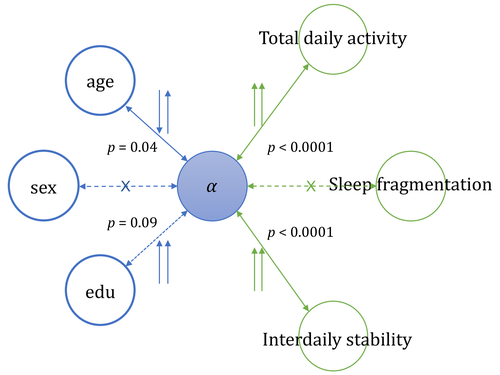


Results

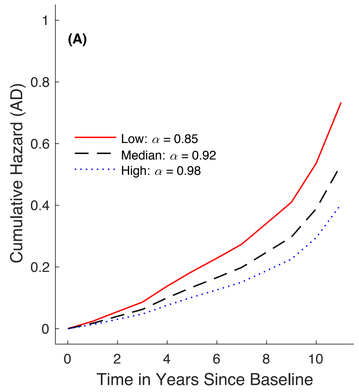
Fractal regulation of motor activity



- Positive temporal correlations in motor activity
- Consistent over a range of time scales (~1 - 90 min)
- Gaussian-like distribution of all α
- α ranges from ~0.6 to ~1.2
- The two representative subjects have α's at the 10th and 90th percentiles, respectively



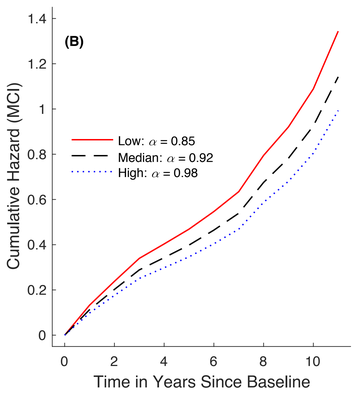
Degraded fractal regulation predicts elevated risk of Alzheimer's dementia



- Red and blue lines show the cumulative hazard of the two representative subjects.
- The subject shown in red line has a 1.8-fold high risk of developing Alzheimer's dementia compared to the subject shown in blue line.

- Hazard ratio = 1.31, per 1-SD (0.06) decrease in α
- Equivalent to the effect of being 5.2 years old
- Does not differ between sexes
- **Independent** from total daily activity, sleep fragmentation, and inter-daily stability (all actigraphy-based)

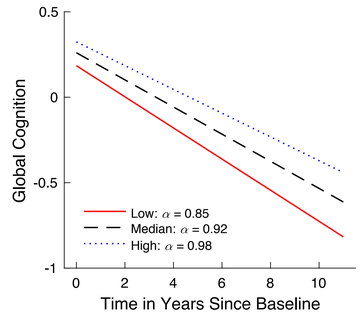
Degraded fractal regulation predicts elevated risk of MCI



- Red and blue lines show the cumulative hazard of the two representative subjects.
- The subject shown in red line has a 1.3-fold high risk of developing Alzheimer's dementia compared to the subject shown in blue line.

- Hazard ratio = 1.15, per 1-SD (0.06) decrease in α
- Equivalent to the effect of being 3 years old
- Does not differ between sexes
- **Independent** from total daily activity, sleep fragmentation, and inter-daily stability (all actigraphy-based)

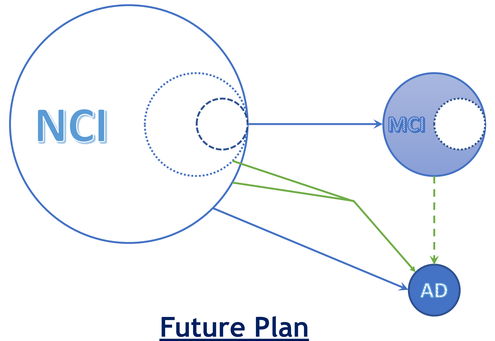
Degraded fractal regulation predicts faster cognitive decline



- Global cognition is a composite measure z-scored from the average z-scores for 5 cognition domains.
- Red and blue lines show the cumulative hazard of the two representative subjects.

- per 1-SD (0.06) decrease in α, decline is speeded by 12.5%
- Equivalent to the effect of being 2 years old
- Does not differ between sexes
- **Independent** from total daily activity, sleep fragmentation, and inter-daily stability (all actigraphy-based)
- Consistently observed in episodic memory, working memory, and perceptual speed

Conclusion



Future Plan

- How does degradation of fractal regulation link to brain pathology?
- Can fractal degradation predict the risk in middle to old aged population?

References

1. Pittman-Polletta B, *et al*. (2013) Biol Rev **8**, 873-894.
2. Hu K, *et al*. (2007) Neuroscience **149**, 508-517.
3. Li P, *et al*. (2017) JSM Biomar **3**: 1008.
4. Ju Y-ES, *et al*. (2013) JAMA Neurol **70**, 587-93.
5. Hu K, *et al*. (2009) PNAS **106**: 2490-2494.
6. Bennett DA, *et al*. (2012) Curr Alzheimer Res **9**, 646-663.

***Results have been published in *Alzheimer's & Dementia: The Journal of the Alzheimer's Association* (DOI: 10.1016/j.jalz.2018.03.010) on May 4**

Funding

National Institutes of Health grants to KH: R00-HL102241, R01AG048108

China Postdoctoral Council, The international postdoctoral exchange fellowship 20150042 (partially supported PL)

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