Complexity and synchronicity of resting state fMRI in normal aging and familial Alzheimer's disease

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Introduction

Over the past decade, BOLD fMRI has gained increasing popularity for characterizing intrinsic brain activity and resting state functional connectivity (1). Existing approaches for resting state fMRI include analyses of temporal correlation and amplitude of low frequency fluctuation. Approximate entropy (ApEn) is a family of non-linear statistics that quantifies regularity (or orderliness) in serial data (2). This has been successfully applied to biological signals (e.g. EEG, heart rate data, hormonal release) (3,4). Higher ApEn values generally implicate that the process is less predictable (or more complex). In addition, the asynchrony between two time-series can be characterized by cross-approximate entropy (C-ApEn). The present study applies both ApEn and C-ApEn to resting state BOLD fMRI to quantify the complexity of the time series in each brain voxel, as well as the asynchrony of each voxel relative to a reference or seed voxel, in normal aging and familial Alzheimer's disease (fAD).

Methods

As described in the 1991 paper by Pincus SM (1), the calculation of ApEn depends on 2 parameters: *m* and *r*. Briefly, ApEn (*m*, *r*) measures the logarithmic likelihood that runs of patterns that are close (within the same tolerance width *r*) for *m* contiguous observations remain close on subsequent incremental comparisons (*m+1*).

$$ApEn(m, r) = \ln (Cm(r) / Cm+1(r)) \text{ and } Cm(r) = n(m, r) / (N-m+1)$$

The calculation of C-ApEn was identical to that of ApEn except 2 time series were compared. Based on literature, *m* was chosen as 2 and 1 for ApEn and C-ApEn calculation, respectively, while r was 0.25 x standard deviation (SD) of time series. Raw time series and low-pass filtered (<0.1Hz) time-series were compared in the above analyses. As a comparison with C-ApEn, we performed seed-based cross-correlation analysis between a reference voxel in the precuneus/PCC region, the major hub of the default mode network, and all other brain voxels, with low-pass filtering (<0.1Hz). Resting state BOLD fMRI were acquired from 16 healthy volunteers (n=8 in the 'young' group, age 20-26 years; 8, in the 'old' group, age 59-69 years). For the fAD group, resting state BOLD fMRI were acquired from 15 subjects from families carrying genetic mutations related to fAD (10 presenilin-1 mutation carriers and 5 non-carrier siblings, age 19-64yr, 9 males). These images were obtained on a Siemens 3T TIM Trio scanner, using a gradient-echo echo-planar sequence. Imaging parameters were: TR/TE=2000/35ms, FOV=22cm, matrix=64x64, 240 acquisitions.

Results

As shown in **Fig 1&2**, the mean ApEn of white matter (1.17+/-0.005) was significantly higher than that of gray matter (1.10+/-0.01, p<0.001, Wilcoxon signed-rank test), calculated using raw time series. After low-pass filtering, both gray and white matter ApEn values decreased by 20-30%, while their differences remained significant (p<0.001). Significant differences were also observed between the old and young groups in both gray and white matters (p<0.001; **Fig 3**). The mean ApEn of gray and white matters decrease significantly with aging (p<0.001, **Fig 3**). As expected, ApEn of CSF did not show significant difference between the age groups (p=0.21).

Figure 1. ApEn Differences in the Brain

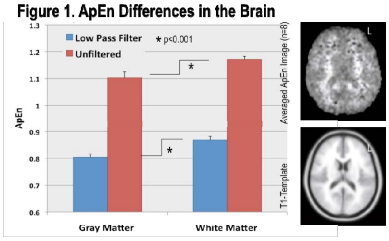


Figure 2. Comparison of Low-Pass Filtered and Unfiltered ApEn

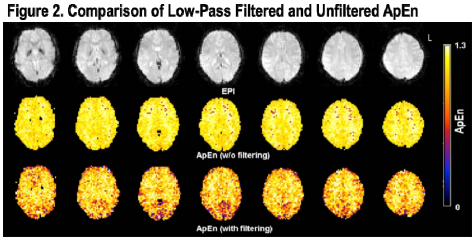
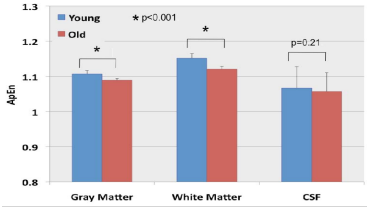


Figure 3. ApEn Differences in Aging



Voxel-wise C-ApEn using a single seed-voxel in the PCC/precuneus demonstrated relatively higher synchrony (lower C-ApEn) in ACC, superior temporal gyri, prefrontal, and parietal regions. Comparison of C-ApEn and cross-correlation analyses showed that there was a strong negative association between cross-correlation and C-ApEn across brain voxels (p<0.001, **Fig 4**). In 15 fAD subjects, mean ApEn in gray matter was strongly correlated with mini-mental state examination (MMSE)(r=0.69, p=0.004, **Fig. 5**) and reversely correlated with clinical dementia rating (CDR) scores (r=-0.65, p=0.009). The global mean ApEn of the whole brain was reduced in mutation carriers compared to non-carriers (p=0.08).

Figure 4. C-ApEn and Cross-Correlation Maps Show Inverse Correlation

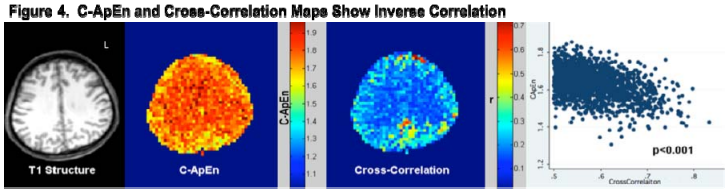
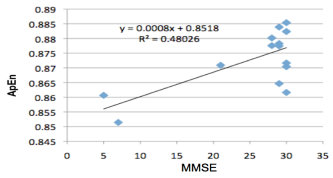


Figure 5. Gray matter ApEn decreases with lower MMSE scores



Summary

In this pilot study, we find neuro-anatomical differences in ApEn calculated using resting state BOLD time-series. Also, the complexity of resting state BOLD fMRI decreases with normal aging and cognitive deficits (low MMSE and high CDR scores) in fAD. C-ApEn, as a measure of synchronicity, can detect functional connectivity of BOLD activity in major regions of the default-mode network. As such, ApEn and C-ApEn provide novel interpretations of resting state BOLD fMRI that may advance our understanding of aging and neurodegenerative diseases, such as Alzheimer's disease.

References

1) Fox MD, Raichle ME. Nat Rev Neurosci 2007 8:700-11. 2) Pincus SM, PNAS,1991;88:2297-2301. 3) Pincus SM, Ann NY Acad Sci. 2001 954:245-67. 4) Srinivasan V, IEEE TITB 2007 11:288-95.