Multiple Time Scale Complexity Analysis of Resting State Fluctuations

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Target Audience: Neuroimaging scientists in the field of resting state fMRI

Introduction: Various neurological diseases and disorders are known to affect the ability of the brain to function, in multiple capacities, over multiple time scales. The ability to discern between the severities of these conditions is crucial to understanding their evolution. A variety of complexity measures have been developed to describe the dynamics of chaotic systems exhibiting self-similar ('fractal') behavior. Resting state fMRI (rs-fMRI) displays many features indicative of fractal behavior such as a 1/*f* power spectrum. Attempts have been made recently to investigate the complexity and regularity of rs-fMRI on short time scales (f ~ 0.5 Hz) using approximate entropy (ApEn) with promising results (1). However, experimental confounds such as random noise, and limitations on the signal length can inject a large amount of uncertainty at these time scales. Multiscale Entropy (MSE) analysis (2) was developed to exploit the fractal scaling behavior in many complex systems by calculating the entropy of a signal at multiple time scales. It was shown that systems with a 1/*f* power spectrum exhibit constant entropy over many time scales, whereas random noise shows a marked decrease in entropy. This study employs MSE analysis to investigate the complexity of rs-fMRI signals at multiple time scales (0.05 Hz < f < 0.5 Hz).

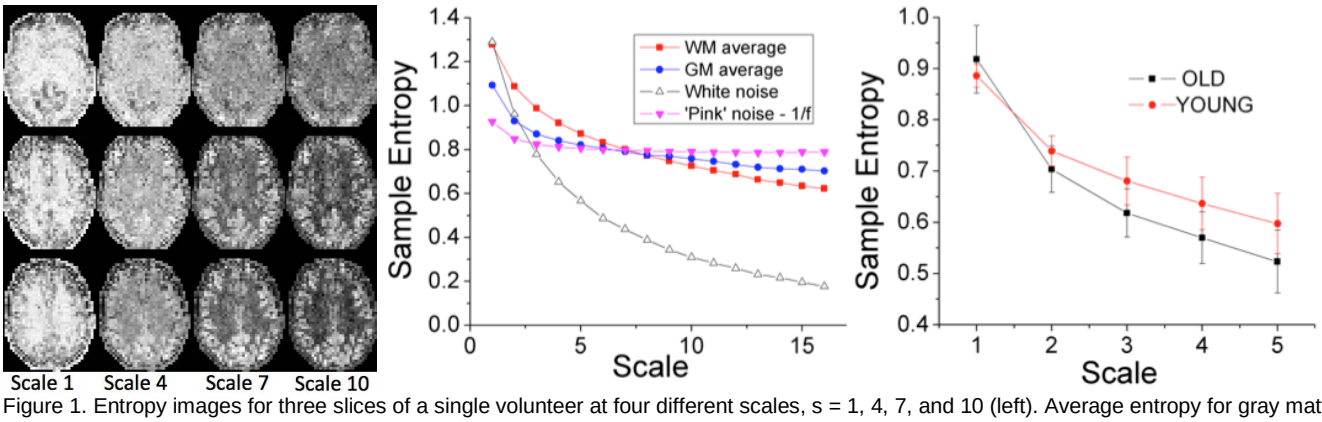

Figure 1. Entropy images for three slices of a single volunteer at four different scales, s = 1, 4, 7, and 10 (left). Average entropy for gray matter and white matter for a single volunteer over multiple time scales (middle). Entropy of Gaussian-distributed uncorrelated (white) and correlated (pink – 1/f) noise are plotted for comparison. Average gray matter entropy for 8 young volunteers (age 23 ± 2 years) and 8 aged volunteers (age 66 ± 3 years). Plotted error bars are the standard deviation (right).

Methods: MRI was performed on a 3T Siemens TIM Trio system, using 12ch head coil. A long rs-fMRI scan was performed on 7 healthy young volunteers (age 21 ± 2 years), using standard gradient-echo EPI. Imaging parameters were: FOV=256mm, TR=1370 ms, 1000 time points, TE = 30 ms. A shorter rs-fMRI scan was performed on 8 healthy young (age 23 ± 2 years) and 8 aged volunteers (age 66 ± 3 years). Imaging parameters were: FOV=256mm, TR=2000ms, TE = 35 ms. Each data set was preprocessed in the following ways: motion correction using FSL's MCFLIRT, co-registration with structural MRI and spatial smoothing (Gaussian FWHM = 5 mm).

Theory: MSE analysis is based on sample entropy (SampEn) (3);

$$\mathrm{SampEn} = -ln\frac{C^{m+1}(r)}{C^{m}(r)}$$

where,

$$C^{m}(r) = (N-m+1)^{-1}\sum_{i=0}^{N-m+1} max(x_i^{(m)} - x_j^{(m)}) < r$$

where x_i and xj are two patterns of length m, r is a threshold and N is the length of the time series. Sample entropy calculates $C^m(r)$, the probability that any two m-length patterns (m-consecutive time points) will match for a given threshold, r. Two patterns match if the distance (maximum norm is used in this study) is less than a selected threshold value, r. The process is repeated for m+1-length patterns. The ratio between these two values is the conditional probability that if two m-length patterns match for a given threshold r, then they will continue to match for an additional time point. MSE analysis investigates the entropy of longer time scale fluctuations through a coarse graining procedure of the original signal where s-consecutive points are averaged to create a new time series of length N/s. Thus MSE investigates the entropy at longer time scales by filtering out high frequency fluctuations.

Results and Discussion: Figure 1 shows the entropy images of three slices acquired at four different scales (s = 1, 4, 7, and 10). For this study m = 3, and the threshold r = 0.5*SD, where SD is the standard deviation of the original time series were chosen for maximum gray/white matter contrast. The lowest scale, s = 1, corresponds to the original signal. At the lowest scale the entropy is dominated by the high frequency fluctuations from random noise. By filtering these fluctuations out the contrast in entropy becomes much sharper between gray and white matter. Figure 2a shows average gray and white matter entropy values for a single subject (N=1000). For comparison, entropy for Gaussian distributed uncorrelated (white) noise and correlated (pink - 1/f) noise at multiple time scales are shown. At lower scales gray matter exhibits entropy values falling in between 1/f and white noise, whereas white matter shows very similar values to white noise. At higher scales (lower frequencies) gray matter exhibits higher entropy values compared to white matter. By filtering out random fluctuations in rs-fMRI, the entropy difference between the young and elderly subjects became more apparent at larger time scales (Fig. 2b).

Conclusion: To the best our knowledge, this is the first study to investigate the entropy of rs-fMRI signals at multiple time scales. The results demonstrated enhanced contrast in entropy between gray and white matter, as well as between age groups using MSE analysis.

References (1) C. Liu et al, JMRI 2012; (2) M. Costa et al., PRL 89, 2002; (3) J. S. Richman et al., Am. J. Physio Heart Circ Physio. 278, 2000