Wavelet Based Multiscale Entropy Analysis of Resting-State FMRI

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

Introduction: The complex mental wandering of the brain at rest may be an indicator of mental health. Temporal fluctuations in resting state BOLD fMRI arise primarily from spontaneous fluctuations of brain physiology and neuronal activity. Far from being the result of random neural firing, conventional linear statistical methods suggest these spontaneous fluctuations have an underlying fractal nature that gives rise to self-similarity over multiple time scales and a power spectrum that can be well characterized by a 1/f function. Recently, non-linear complexity measures such as approximate entropy (ApEn) (1) and multi-scale entropy (MSE)(2) have been applied to investigate the complexity and regularity of rs-fMRI on short and long time scales (0.07< f <0.3 Hz) with promising results. However, experimental confounds such as random noise, and limitations on the signal length can inject a large amount of uncertainty at these time scales. We present here a wavelet based multiresolution entropy calculation that employs noise estimation measures to better determine the complexity of the underlying neural behavior. We develop a pseudo-complexity measure using the stationary wavelet transform (SWT) of the original rs-fMRI time series to investigate the intrinsic irregularity of the energy density fluctuations at multiple temporal scales.

Theory: In the presence of nonstationary data, wavelet analysis holds a significant advantage over Fourier analysis. Wavelet analysis is built upon a local frequency representation through the use of wavelets, 'little waves'. These wavelets are formed through dilations and translations of 'father' and 'mother' wavelet functions. Each dilation introduces a new function sensitive to a lower frequency scale. The SWT uses an orthogonal set of wavelet functions to investigate minimally-overlapping frequency bands of logarithmically equal (scale-free) widths, i.e. each band is twice/half the width of the next lower/higher band. Translations of the dilated wavelet along the time series create a new time series representing local frequency content from the corresponding band. The SWT is widely used in pattern analysis for its high signal fidelity and thus is capable of scale-invariant feature extraction across multiple temporal scales. The regularity of each wavelet scale is determined using sample entropy (H_S) (3):

$$H_S(m,r,N) = -log\left(\frac{C^{m+1}(r)}{C^m(r)}\right)$$

where,

$$C^m(r) = \frac{1}{(N-m)}\sum_{i,j=0}^{N-m+1}\frac{\Theta(r - \| u_i^m - u_j^m \|)}{N-m+1}$$

where u_i and u_j are two subsequences of length m, r is a threshold and N is the length of the time series. H_S is the negative logarithmic likelihood of two randomly chosen $m+1$-length subsequences 'matching' (reside within r of each other), given that they matched for the first m points. A wavelet based noise level estimator is used to set the threshold voxelwise: $r = \sqrt{(2-r_0^2)\sigma_n^2 + (r_0\sigma_S)^2}$, where σ_n and σ_S are the standard deviations of the estimated voxel noise and signal, respectively, and r_0 is a tunable constant to compensate for changes in signal fluctuation amplitude.

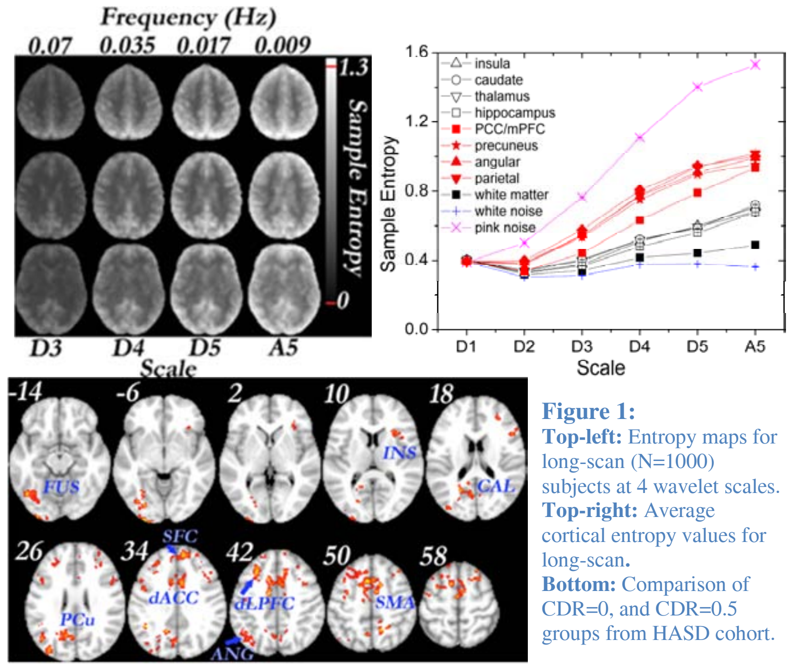

Figure 1:
Top-left: Entropy maps for long-scan (N=1000) subjects at 4 wavelet scales.
Top-right: Average cortical entropy values for long-scan.
Bottom: Comparison of CDR=0, and CDR=0.5 groups from HASD cohort.

Methods: Resting state MRI was performed with a 3T Siemens TIM Trio system, using 12ch head coil. A long rs-fMRI scan was performed on 5 healthy young volunteers (age 21 ± 2 years), using standard gradient-echo EPI (FOV=256mm, matrix=[64x64], 27 slices, TR/TE=1370/30 ms, 1000 acquisitions. Analysis of 52 data sets, 26 cognitively normal (clinical dementia rating scale (CDR) = 0, 70 ± 4 years) and 26 mild cognitively impaired (CDR = 0.5, 74 ± 5 years) individuals, from Healthy Aging and Senile Dementia (HASD) program project have also been carried out. For the HASD data, resting state fMRI data were collected on a 3T Siemens TIM Trio. Each subject had 2 rs-fMRI scans using standard gradient echo EPI (FOV=256mm, matrix=64x64, 36x4mm slices, TR/TE=2200/ 27ms, FA=80°, 164 acquisitions for 6min each scan), along with a high-resolution (1x1x1mm^3) 3D T1-weighted MPRAGE scan. Each subject also underwent comprehensive neurocognitive assessments including mini mental state exam (MMSE) and CDR sum of boxes (CDR-SOB). The rs-fMRI data is pre-processed including compensation for rigid body correction for head movement, intensity scaling, spatial smoothing using a 6mm FWHM kernel, linear detrend and reduction of spurious variance by regression of nuisance waveforms derived from head motion correction (including derivatives of motion) and extracted time series in white matter and CSF. Each data set was registered to MNI space for group analysis. The Daubechies wavelet was used for its good temporal/frequency specificity. For this study m(+1) = 1(2), the median absolute deviation of the highest temporal frequency scale is used to determine σ_n, and r_0 = 0.1. Group statistics are performed with a multivariate t-test using Hotelling's T^2 statistic. Group statistics are based on comparing the distance between mean 'entropy vectors' normalized by a pooled covariance matrix, and adjusted for multiple comparisons within the gray matter volume.

Results: The entropy maps in Fig.1(top-left) show an increasing gray/white matter contrast with increasing wavelet scale. Figure 1(top-right) show the average regional entropy across the five long-scan (N=1000) subjects. For comparison, entropy for Gaussian distributed uncorrelated (white) noise and correlated (pink - 1/f) noise at multiple time scales are shown. White matter exhibits nearly constant entropy across all scales, very similar to white noise. Contrastingly, the average entropy increases with increasing wavelet scale (decreasing frequency) for most gray matter regions. Further, substantial intercortical variation is seen with several areas exhibiting increased entropy corresponding to regions of the default mode network (DMN) (posterior cingulate, medial prefontal cortex, precuneus, angular gyri). Gray matter regions exhibiting the lowest entropy values include the caudate, thalamus, hippocampus, and insula. Figure 1(bottom) shows the regional entropy differences ($p<0.001$, cluster corrected for $p<0.05$) between cognitively normal (CDR=0) and mild cognitively impaired (CDR=0.5) individuals).

Discussion: The flat behavior of the white matter entropy is consistent with no neural activity being present. Thus the white matter entropy may prove useful as a measure of non-neural signal contamination (i.e. motion, physiological). The substantial cortical differences in Fig.1(top-right), with regions pertaining to the DMN exhibiting some of the largest entropy values supports previous reports that the DMN is more active at rest. The reduced entropy seen in default mode regions for CDR=0.5 individuals in Fig.1(bottom) is consistent with the results of Fig.1(top-right).

Conclusion: We present a novel wavelet based MSE analysis of rs-fMRI that is able to show enhanced contrast in entropy between gray and white matter, as well as between aged subjects of CDR 0 and 0.5.

References (1) C. Liu et al, JMRI 2012; (2) R.X. Smith et al., BIOR, 2013; (3) J. S. Richman et al., Am. J. Physio Heart Circ Physio. 278, 2000