Approximate entropy as a metric for quantifying fMRI changes across time

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Purpose: Functional MRI (fMRI) lacks a stable baseline and therefore is of limited use in longitudinal studies that examine changes over time. To overcome this shortcoming, we applied a time signal processing technique that can facilitate comparisons among two or more fMRI tasks to create a quantitative fMRI (qfMRI) method.

Introduction: Functional MRI is expressed as a correlation between signal fluctuations and the expected model. Unfortunately this quantitative technique is relative, as areas of "activation" are expressed as significant correlations rather than with a "normalized" numerical value that can be used across time. This study hypothesized that a quantitative fMRI basis could be established if the responsivity during an fMRI task of interest (e.g., finger motor movement) could be "normalized" through comparison to a task that would likely be unchanged by commonly studied neurological disease. For the stable task, we chose a very simple vision task because a) it produces robust and reproducible results, b) it has minimal cognitive load, and c) the occipital lobe is generally spared in many neurological conditions. We chose the method of approximate entropy (ApEn) to develop a quantitative measure because it produces an inherently normalized value. ApEn is a calculation that quantifies the regularity or unpredictability of time series data via statistical methods[2]. ApEn can be utilized to determine the complexity or randomness of measurements, including fMRI time series data. ApEn is robust to noise and produces a value that corresponds to the complexity of the signal being studied, with higher values indicating greater unpredictability and complexity[1]. Since patterns do not generally arise from random noise, a signal wherein they are detected must, theoretically, contain some structured information. ApEn is used to quantify the complexity of this information. A fundamental alteration of a signal changes the "information" it contains (which is reflected in ApEn) and indicates a shift in functionality of the system producing the signal. We hypothesized that ApEn could be used to reflect the stability of the signal for a target task (e.g., a motor task) relative to a "control" task (e.g., a visual task) independent of a static baseline.

Methods:

Subject Data and Task Design: All subjects performed motor and vision tasks. Motor tasks consisted of on-off blocks of movement and rest. Visual tasks consisted of on-off blocks of pictures and blank crosshair images. ApEn values for the motor tasks were then compared to ApEn values for the vision tasks (for each subject). Our subjects were members of two different groups: one group designed to theoretically demonstrate stable ApEn ratios ("Caffeine Group"), and one group that we expected to show changes in ApEn ratios over time ("Surgical Group"). The Caffeine Group consisted of 4 healthy normal controls scanned twice, a week apart, with and without having been administered a 100mg caffeine pill. Caffeine was used as an intervention because it increases blood flow uniformly throughout the brain; and therefore would be expected to affect the BOLD signal, but not the ratio between vision and motor task ApEn values, as both ApEn values should be amplified similarly. The Surgical Group consisted of two patients who underwent fMRI assessment prior to surgery for tumor removal and then had repeated fMRI assessments after surgical treatment (and before a second treatment in one case). These two patients were chosen for examination because they were scanned more than once, and demonstrated altered behavioral function. This group was expected to show changes in ApEn ratios based on changes in their behavioral function.

Imaging Parameters: All participants were scanned on the same 3.0 Tesla GE Signa HDX system with an 8-channel head coil. Scan parameters for echo planar imaging (EPI) were: TR = 3000 ms, TE = 25 ms, flip angle = 80°, FOV 24mm, in-plane resolution 64x64, 4 mm slice thickness (covering the entire brain). Each scan varied between 40 and 80 volumes. A high-resolution, 3D T1 SPGR image was obtained for all subjects to facilitate registration. Parameters for those scans were: TR = minimum, TE = 2.5 ms, flip angle = 8°, FOV = 26mm, 1.2 mm slice thickness.

Task Analysis: Data analysis was conducted using SPM5. The collected data were smoothed, coregistered, and resliced to the standard MNI template in order for the dimensions of the data to be consistent between all subjects. The processed data were analyzed using the ApEn technique. A 3-voxel radius sphere centered on the area of greatest activation for each subject was used as the region of interest for study. Time series signals were extracted from this ROI, each corresponding to an individual voxel within the ROI. Errant signals that fell below 70.7% of the maximum signal contained in the ROI were removed, and the average ApEn of the remaining time signals was calculated. The motor ApEn was divided by the vision ApEn to form a ratio that could be used to quantify differences between the longitudinal scans.

Results: All individuals showed significant activation within the motor cortex and occipital lobe via standard SPM analysis. Initial analysis of the time series signals in the activated areas indicated that the signals showed the sinusoidal pattern associated with on-off tasks. Figure 1 shows the ratio between the motor ApEn and the vision ApEn for the 4 control subjects (with and without caffeine), and for the 2 clinical patients (before and after surgery(s)). As shown in the graph, the control subjects demonstrated small changes in the ApEn ratio with and without caffeine, while the surgical patients demonstrated much larger changes in the ApEn ratio. The maximum percent change in the control subjects was 12.4% between caffeinated and non-caffeinated states. In contrast, the changes for the surgical patients ranged from 27.0% to 72.3%.

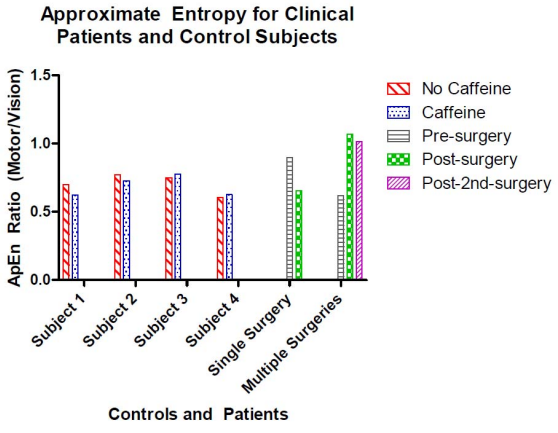

Figure 1. Approximate entropy ratios for the "Caffeine Group" (S1-4) and the "Surgical Group". The former group was characterized by small ApEn ratio changes, while altered function in the latter group resulted in much larger ApEn ratio changes.

Conclusion: Based on our preliminary results, ApEn may be a useful method to provide quantitative information describing fMRI activation. As expected, the ApEn ratios were not altered due to amplification of the BOLD signal caused by caffeine intake. Conversely, they were markedly different between scans for the clinical patients, mirroring the patients' behavioral changes. This strategy of using a "baseline" task, combined with ApEn analysis, showed alterations in a signficant manner when it could be expected to (in this case in surgical patients) but was relatively unaffected merely due to other biological processes or longitudinal drift.

References: 1. Moody et al. 2000 *Circulation*, 101; e215-e220. 2. Pincus 1990 *PNAS*, 88; 2297-2301.

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