Finite Number of Brain Network Configurations Revealed from Time-varying Connectivity Assessment of Resting State fMRI

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Introduction: Recent studies revealed that functional connectivity (FC) and effective connectivity (EC) of resting state brain networks is dynamically changing in time [1-3]. Resting fluctuations have been shown to be correlated with smoothed and downsampled versions of EEG microstates which are finite, quasi-stable scalp electrical topographies of approximately 80-100 ms duration [4, 5]. This coupling between fast and slow temporal dynamics of EEG and fMRI, respectively, has been attributed to the fractal properties of EEG microstates, covering scales from 256ms to 16s range [6]. This raises the possibility that connectivity dynamics derived from fMRI may also have finite, quasi-stable configurations. In this study, we tested this hypothesis using a unified framework involving dynamic estimation of whole brain FC and EC, and subsequent evolutionary clustering and segmentation into finite number of patterns.

Methods: EPI data (TR=1 s, total length=1000s) was acquired from a 3T Verio Siemens Scanner from 22 healthy volunteers. After standard resting state fMRI pre-processing, mean fMRI time series were calculated from 164 functionally homogeneous brain regions which were previously reported [7], and band-pass filtered (0.01-0.1Hz) for subsequent analysis. Our framework included 3 steps: dynamic connectivity estimation, 1st level evolutionary clustering and 2nd level static hierarchical clustering. For the first step, we employed sliding Hamming window based Pearson's correlation to obtain time-varying FC, while the dynamic Granger causality method (DGC) [8, 9] was adopted for calculating time-varying EC. For FC, group value was obtained by averaging across subjects while for EC, DGC parameters were updated with every subject's data such that a group DGC value was obtained. Group values of first 100s were removed (in order to allow DGC to converge) and then fed to subsequent analysis. For the second step, customized transformation algorithm was applied to connectivity values such that the outcome meets the requirement of a distance measure, which can be subsequently fed into a clustering algorithm. For FC, we used windowed time series to calculate normalized cross correlation *Xcorr*, such that *Xcorr* ranged from 0 to1, and then used 1- *Xcorr* as a distance measure. For EC, we calculated the histogram of causal connectivity, *conn* obtained from DGC, and fit this histogram using an "S" shaped transform function such that $distance = 1/(1 + a \times b^{conn})$, where a and b are parameters to be determined by fitting. We used surrogate data method [10] to estimate the null distribution of causalities, and found thresholds *th1* and *th2* which correspond to p-values of 0.05 and 0.01, respectively. Then a and b were determined such that when *conn* equals *th1*, *distance* equals 0.5 and when *conn* equals *th2*, *distance* equals 0.1. By doing so, we guaranteed that the *distance* converged to 0 as *conn* approached infinity and to 1 as *conn* approached zero. Next, the distance measures were fed to an adaptive evolutionary clustering algorithm (AFFECT toolbox [11]) which determined clusters of brain regions, based on their distance measure, at each time instant. The maximal number of clusters was set to 10. The outputs from evolutionary clustering were fed into a 2nd level static hierarchical clustering algorithm in order to partition the evolutionary clustering patterns into a finite number of states. The 'silhouette' criterion was adopted for determining the number of clusters at this stage.

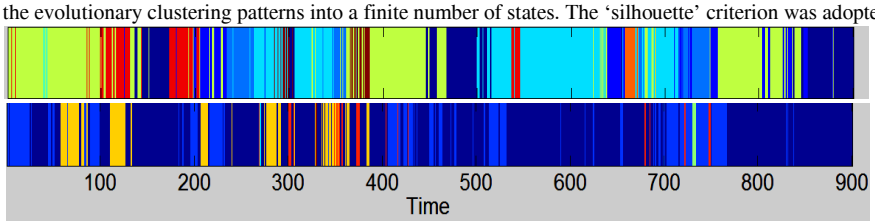
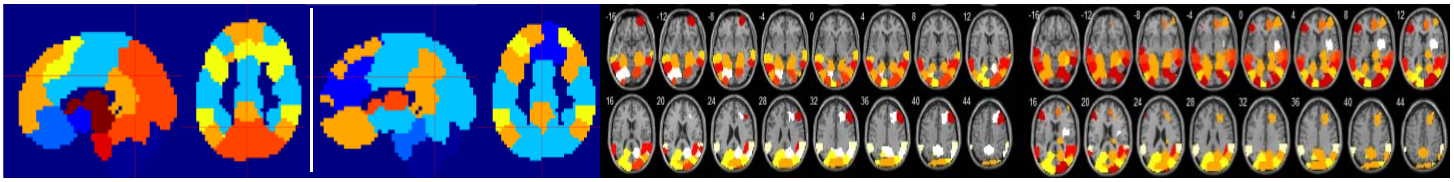


Table 1 *Summary of 2nd level clustering*

Statistics of 2nd level clustering	EC	FC
No. of clusters	7	10
Time spent (s) before any state transition	5.92±5.13	5.17± 4.92
Time spent (s) in each cluster (descending)	591, 193, 85,24, 4, 2, 1	291, 215,139, 76, 75, 65, 22, 13, 3, 1

Fig.1 *2nd level clustering result for FC (top) and EC (bottom). Different colors represent different clusters. X-axis is time in seconds*



FC cluster-1 FC cluster-2 EC cluster-1 EC cluster-2

Fig.2 *Centroids of two most dominating clusters for FC and EC*

Results and Discussion: As listed in Table.1, we found 7 and 10 2nd level clusters for FC and EC, respectively. This is in agreement with previous studies showing 7 [4] and 13 [12] EEG microstates. The mean time spent (plus one standard deviation) before any given transition was around 10 s, which is in agreement with the dominant low frequency nature of resting state fMRI. The segmentation of the total experimental duration into different clusters (Fig.1) showed 2-3 dominant modes for both FC and EC. These modes recurred repeatedly throughout the length of the experiment. Fig.2 shows the centroids of these dominant patterns. For FC, both cluster centroids showed visual, sub-cortical and motor networks. While the first FC cluster centroid showed the traditional default mode network (DMN), second one had a DMN with medial frontal regions being more ventral. Given that the DMN is the most dominant resting network, our results show that it recurred more than 50% of the time. Both dominant patterns for EC involved interactions between frontal and visuo-parietal regions, as well as within visuo-parietal regions. Sensory regions receive external input which moves up the cognitive hierarchy onto the frontal regions. Therefore, there is a strong causal relationship between the two, constituting feedback and feed-forward networks. The dominant EC patterns, which covered ~80% of the experimental duration, may underlie this phenomenon. It is noteworthy that FC and EC have very different dominant patterns, indicating that synchronization and causality serve different functions in the brain, and there is much to be gained by studying both. Our results prove the hypothesis that connectivity dynamics derived from fMRI have finite, quasi-stable configurations. Even though the time scale of these configurations is on the order of seconds, they may underlie fast electrical dynamics since it has been shown that EEG microstates possess fractal properties [6]. The clinical relevance of connectivity dynamics obtained from fMRI remains to be investigated.

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