ANALYSIS OF FUNCTIONAL CONNECTIVITY BY LOCAL BOLD SIGNAL VARIANCE

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TARGET AUDIENCE: Researchers who study functional brain connectivity and psychiatry researchers who study connectional models of mental disorders.

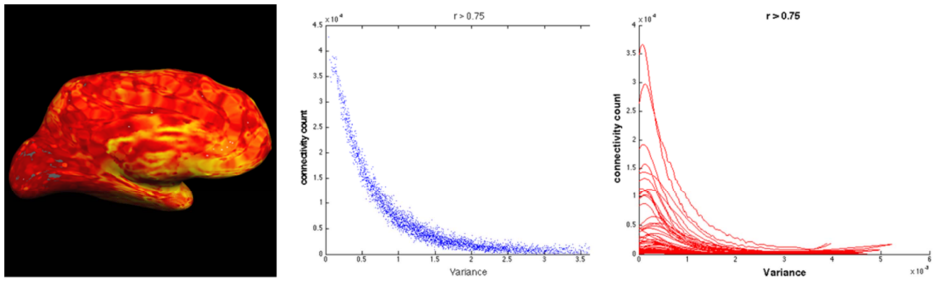
PURPOSE: Recently it has been shown that the local signal variance from resting fMRI experiments may be used to parcellate the cerebral cortex in into functionally homogenous regions [1]. The local signal variation corresponds to the variance of regional signals integrated across time and is a measure of cortical synchrony. Areas with low local signal variance appear to be functionally related. In this study, local signal variance was related to functional connectivity over the entire cortical surface. We hypothesize that points on the cerebral cortex with strong local synchrony (low local signal variance) will exhibit large scale functional connectivity.

METHODS: We analyzed resting fMRI data from 20 neurologically healthy subjects with 6 repeated scans per subject during a single session (ages 35 ± 18 years, 10 females). All subjects provided informed consent according to an IRB approved protocol. Each functional scan was 10 minutes in length and acquired with the same echo planar imaging (EPI) sequence (TR = 2.6 s, TE = 25 ms, flip angle = 60 degrees, FOV = 224 mm x 224 mm, matrix size = 64 x 64, slice thickness = 3.5 mm, number of slices = 40). Whole-brain T1-weighted (T1w) structural images with 1mm isotropic resolution were acquired using an MPRAGE sequence. EPI data were preprocessed by standard methods: motion correction, slice-timing correction, band-pass filtering and z transformed. The cortical surface was reconstructed from the 3D T1w using Freesurfer. The fMRI and T1w data were co-registered using boundary based registration and fMRI data were resampled onto the cortical surface. To calculate the local variance measure at a cortical vertex v, we first construct the set of vertices within 3mm Euclidean distance of v and the orthogonal coordinates of each. We then construct a MxN matrix, where M is the number of timepoints in the EPI time series and N is the cardinality of the set of vertices within 3mm of the vertex in question, including the vertex v. Specifically, D_v is formed for each vertex v $D_v = d_{ij}$ where i is the bold time series index and j is the vertex index.
We calculate S = D – M where $m_{ij} = \left(\sum_{j=1}^{N} d_{ij}\right)/N$; we form S by subtracting the row wise mean of D from every element of the same row of D.

Now we define the total variance of S by $V_v = \frac{\left(\sum_{i=1,j=1}^{i=N,J=m}(s_{ij}-\hat{s})\right)}{N}/(N*M-1)$

where $\hat{s} = \left(\sum_{i=1,j=1}^{i=N,j=M} s_{ij}\right)_{/N*M}$ is the mean of the entire matrix. The subscript v on V_v indicates that this is the local variance at the vertex v. We produce the vector V of local variance measures at each vertex on both hemispheres of the cortical surface in this manner. Given the normalization of the time series data D_v measures the synchrony of the bold time series within the 3mm neighborhood. To show the relationship between local variance and connectivity we calculate the functional connectivity maps using each vertex on both hemispheres of the cortical surface as a seed, i.e., approximately 300,000 connectivity maps for each scan. Global connectivity of a vertex v was defined as the count of other vertices with Pearson correlation coefficient above a specific threshold r = 0.75. The variance vector V was sorted in ascending order and apply the same reordering to the connectivity counts. This gives c(v), the connectivity counts as a function of the local signal variance. The connectivity counts and variance values were partitioned into 100 intervals and averaged. We define the connected component of a vertex v as the number of vertices correlated at or above a reference level r in the connectivity map resulting from using the time series at v as a seed.

RESULTS: A representative pattern of local signal variance is mapped on the medial surface of a subject in the Figure below. The map shows an interesting and anatomically heterogeneous pattern of regions and bands of high and low fMRI synchrony, which was observed in all cases. Areas of high synchrony (low local signal variance) generally appeared as relatively small islands on the cortical surface outside of visual, motor and posterior cingulate areas. The variance values were dramatically different across within-subject repeated fMRI exhibiting a very high rate of dynamic changes as is verified by direct calculation of the corresponding connectivity maps. The shapes of structures visible on the surfaces were invariant across within subject scans, only the brightness of the structures changed. Cortical regions with low synchrony displayed very little connectivity to other cortical regions, while regions with high synchrony exhibited extended functional connectivity across the cortex. Thus the local signal variance of the fMRI time series appears to be related to the degree of global functional connectivity of a point on the cortex. These observations are further summarized in the Figure plots of the connectivity count versus local signal variance. In general vertices with high variance (low synchrony) have very little connectivity while low variance (high synchrony) regions have more large scale functional connectivity, though the degree of connectivity co-varied considerably across subjects and scans with the variance.



a *b*
c

Figure: a. left medial cortical surface with the local signal variance overlaid in color, low variance areas are dark. b. Plot of the size of connected components versus local signal variance. c. Loess line plots describing the connectivity vs. variance relationship for 60 scans, which demonstrate that large scale connectivity occurs only in low variance regions.

DISCUSSION AND CONCLUSION: This study presents evidence of a much more complex spatial and temporal structure of cortical functional connectivity than previously described. Local signal variance appears to be highly but inversely related to the degree of connectivity to other cortical regions. These regions of high local synchrony are quite heterogeneous and relatively sparse across the cortex. This suggests that functional connectivity with fMRI is fairly discrete and localized. The relationship of local synchrony to subcortical brain areas has not yet been investigated. The observation that sparse and focal regions have most of the cortico-cortical functional connectivity likely have significant implications for the analysis and interpretation of resting fMRI studies in general.

References

1. Blumensath T, et al. 2013 Spatially constrained hierarchical parcellation of the brain with resting-state fMRI. Neuroimage 76:313-24.