A Clustering Strategy for Quantitative Assessment of Functional Connectivity in Resting-state fMRI Data

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Introduction

Fluctuations in resting-state BOLD contrast images have been used to identify functional connectivity[1] in the human brain. While many previous studies relied on the specification of "seed" location, the detection of functionally connected regions may be performed automatically through a clustering process[2]. This approach may greatly reduce the subjective character of seed-based methods, and also allow a broader class of analyses that consider multiple regions across the brain.

Two issues need to be addressed in characterizing functional connectivity: 1) Which brain regions are correlated with a given region of interest (ROI)? 2) How strongly is the ROI correlated with other areas? When a "seed" location must be specified for the analysis, the result is not only dependent on the location but also the size of the seed, because the average time course over a seed area is used as the reference for cross correlation computation. With the clustering approach this arbitrariness may be reduced by considering each voxel time course in turn as the reference and identifying voxel groups with strong inter-correlations. In this study, we further extend the clustering approach into the context of a comparative study between two groups of subjects. Two characteristics of interest are the spatial extent and the "strength" of the clusters. Spatial extent may be measured by voxel count and the number of spatially isolated components comprising each cluster, while cluster strength may be measured by the average correlation coefficient over all pairs comprising a cluster.

Methods

A clustering algorithm which keys on the correlation coefficient (CC) was developed for this study. The algorithm automatically identifies clusters such that the members of a given cluster are "connected" (CC>0.7) to a single representative member (the cluster "center"). The implementation of the algorithm ensures that voxels within a given cluster exhibit some degree of mutual correlation, and that the solution is objective and unique (i.e. does not depend on order of traversal). A typical color-encoded clustering map is shown in Fig. 1a.

We explored this clustering approach in characterizing functional connectivity differences between age and IQ matched adolescents with and without disruptive behavior disorders (DBD). The patients were identified and characterized using a battery of cognitive tests (DSM-IV) by experienced pediatric psychiatrists. Resting state BOLD images were collected for each subject using a single-shot gradient echo EPI technique in a 1.5T GE Signa MRI scanner. The acquisition parameters were as follows: TE/TR=50/250ms, matrix=64×64, slice thickness=7.6mm, flip angle=30°, N=1100, and 2 slices. The slice locations were chosen to intersect the prefrontal dorsolateral and anterior cingulate cortices (DLPFC and ACC).

To reduce motion artifacts each subject used an individually fitted bite bar. Motion correction was performed by using the "imreg" program from AFNI, and data with detected motion >1mm were excluded. Prior to the clustering analysis, a low pass filtering with 0.1Hz cutoff and a baseline drift correction by subtracting the best-fit quadratic were performed for each data set. The clustering results were further subjected to motion artifacts screening by excluding data sets with large and ring-like clusters. The remaining functional connectivity maps from 24 subjects (DBD/control =12/12) were statistically analyzed for group comparison using the following procedures: 1) High resolution anatomical images co-registered with Talairach template were used to define ROI in the DLPFC and the ACC for each subject; 2) Clusters that intersected the ROIs were retained for further statistics (see Fig. 1b); 3) The cluster size, the number of spatially connected components distal to the ROI, the average cross correlation coefficient, and other parameters were analyzed; 4) For all these parameters, group differences between DBD and control subjects were assessed using student t-test.

Results and Discussion

Functional connectivity in motor and visual cortices identified using the clustering procedure agrees with previously published literature results. The more important finding from this study is that the average cross correlation for the local cluster components in the ACC are significantly different (P<0.03) between the DBD and control groups. The patient group exhibited a significantly greater average local correlation (0.77±0.04) in the ACC over the control group (0.74±0.03), which may indicate more coherent cortical activities in the ACC for the kids with DBD symptoms. A plausible mechanism behind this is that DBD patients may have some minor developmental deficiencies (i.e. less diversity) in their ACC functions. The development of anterior cingulate cortex is known to be essential for normal conflict control and detection capability. This notion is also supported by recent fMRI studies[3] which reported reduced functional activation in the ACC for DBD patients during performance of inhibition tasks.

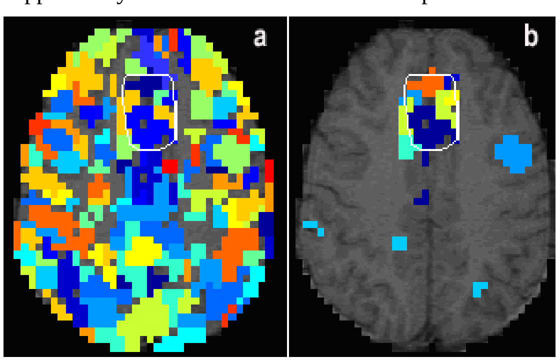

Fig. 1 Initial cluster map encoded with randomized color labels (a). Clusters with components intersecting the selected ROI in ACC (b).

To summarize, we have developed a procedure based on clustering of cross correlations of resting state BOLD signals between voxels to statistically characterize inter-correlated brain regions and applied this technique to study brain developmental deficiencies in subjects with conduct disorders. In comparison to the "seed" dependent method, the clustering approach has the following advantages: 1) reduction of arbitrariness associated with "seed" specification; 2) broadening of connectivity detection to the entire brain by considering each voxel as a seed; 3) capability for characterizing connectivity differences between subjects; 4) enhancement of motion artifacts detection. Similar to the seed-based method, the clustering is also very sensitive to subject motion, because the time course itself is used as the reference function for cross correlation computation. But our procedures provide an additional step after the initial computation of the cluster maps to exclude data with unusually large or ring-like clusters along the perimeter of the brain which are likely to be signs of severe motion artifacts.

References

[1] Biswal, B. et al., *NMR in Biomed* **10**, p. 165-170, 1997.
[2] Cordes D. et al., *Mag Res Imag* **20**, p. 305-317, 2002.
[3] Wang Y. et al., *ISMRM*, p. 727, 2002.