A novel approach for group fMRI studies using BrainSync transform and pairwise statistics

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Introduction

Due to the spontaneous nature of resting fMRI (rfMRI) signals, cross subject comparison and group studies of rfMRI is challenging. Existing group comparison methods reduce the fMRI time series either to lower dimensional connectivity features or use ICA to reduce dimensionality. Our laboratory previously described BrainSync, an orthogonal transform that allows direct comparison of rfMRI time-series across subjects[1]. This orthogonal transform performs a temporal alignment of time-series at homologous locations across subjects allowing a direct comparison of scans. In contrast with existing fMRI analysis methods, this transform does not involve dimensionality reduction and preserves the rich functional connectivity information in rfMRI scans (Fig 1). We then described BrainSync Alignment (BSA), a group-based extension of the pairwise BrainSync transform, that jointly synchronizes fMRI data across time-series data of multiple subjects[2]. BSA can be used to create a reference fMRI atlas, useful in group studies where individual subjects can be synchronized to the reference to perform direct comparisons[3]. Pointwise distance measures, or Pearson correlations, can be computed between the reference and synchronized data to compute a measure of similarity. In some studies, however, choosing the appropriate reference subjects for atlas creation may be ambiguous. Therefore, we developed an alternative statistical method for performing rfMRI group studies based on BrainSync transform. We describe a pairwise comparison method for these aligned time series and demonstrate its application to an ADHD study that reveals a correlation of activity in the executive control network with ADHD index.

Methods

rfMRI data was collected as a part of the ADHD-200 Global Competition at Peking University[4] and preprocessed using the BrainSuite Functional Pipeline (BFP)[5]. 200 subjects with ADHD measured using the ADHD Rating Scale IV (ADHD-RS) was retained. We used 150 test subjects comprised of 85 ADHD subjects (age=12.0±2.0; 75M:10F; ADHD Index=50.6±8.5) and 65 control subjects (age=11.1±1.8; 39M:26F; ADHD Index=29.2±6.3) to test the relationship of ADHD Index with rsfMRI using two methods, atlas-based and pairwise test using BrainSync. First, we explored the atlas-based method as previously proposed. We used BSA to create an average atlas from 50 control subjects (age=11.3±1.8; 29M:21F; ADHD Index=30.1±6.5) then synchronized 150 test subjects to the atlas. At each point, we used the distance between synchronized time-series of subject and the atlas as a univariate statistical feature. We correlated this measure to the ADHD index and p-values were obtained using permutation testing procedures (nperm=2000, $\alpha \leq 0.05$). Next, we performed a pairwise statistics in order to perform regression analysis. We synchronized and computed distance measures between 2000 random pairs from the 150 test subjects. The distance between the synchronized pairs is used as a statistic (fmri-diff). We also compute the difference between the ADHD indices of the two subjects (var-diff) in each pair. Then we correlated fmri-diff to var-diff using the Pearson correlation and converted to p-value using permutation test (nperm=2000). Benjamini-Hochberg FDR correction was done for both methods. For further validation, to test the repeatability of the tests, we repeated the whole experiment for the pairwise statistic. Additionally, randomly permuted ADHD indices were assigned to the subjects and the test was repeated.

Results

Results of the correlation tests between ADHD Index and fMRI measures greatly differed between the atlas-based and pairwise test. (Fig 2a) Significant points were found sparsely throughout the brain with few highly significant clusters in the frontal pole, temporal lobe and insular cortices. However, after FDR correction, only 3 small clusters remained. The pairwise test on the other hand showed large, highly significant clusters across the frontal and temporal lobes and insular cortices. Highly significant, yet sparser clusters of regions were found posteriorly. After FDR correction, these regions were largely retained. Similar results were found between the repeated pairwise tests (Fig 2b) while randomly permutating ADHD indices (Fig 2c) showed inconsistent and sparse results.

Conclusion

We present a novel method for group studies of fMRI data using BrainSync transform. In comparison to the atlas-based method, the pairwise test was found to be more sensitive to localizing regions predicting ADHD Indices. For the atlas-based method, much of the demographic information would be matched between the subjects used to create the reference atlas and the testing subjects, except for the testing variable. However, it is difficult to completely control for confounding variables in human population studies. The results indicate that the described method is powerful and reliable for group studies.

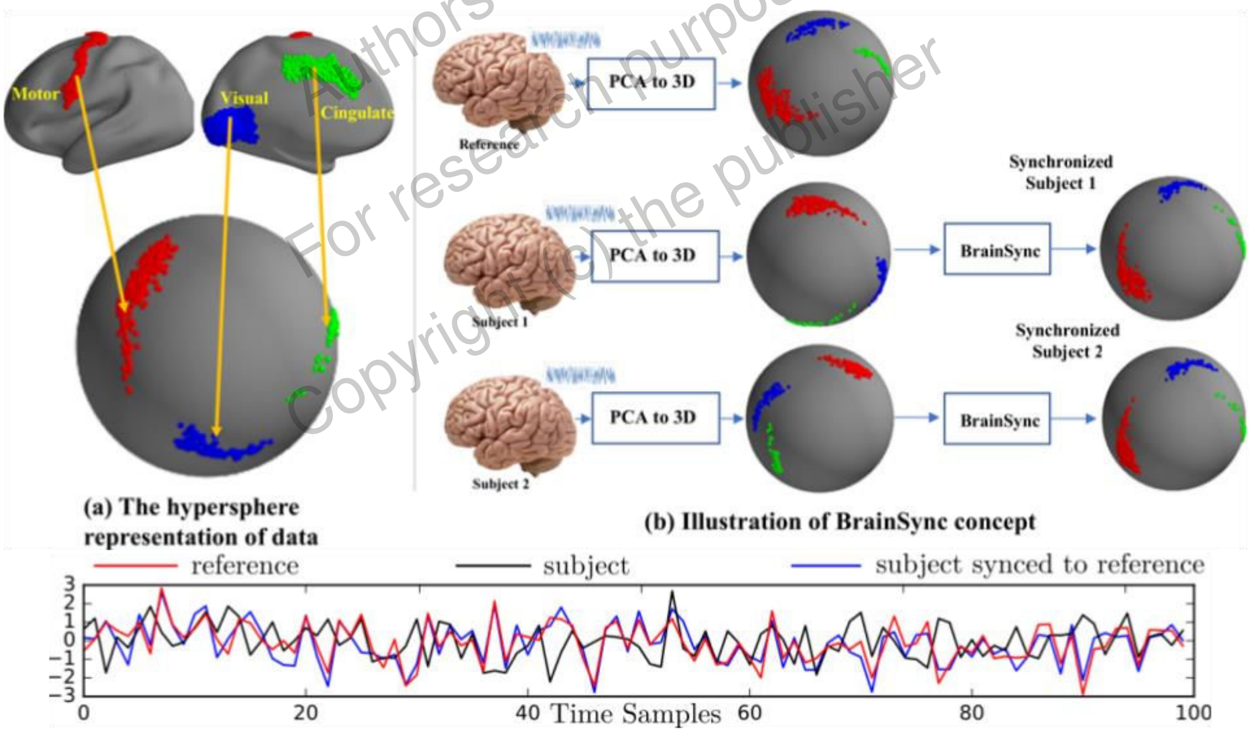

Figure 1: Illustration of the BrainSync concept: (a) Data from motor (red), cingulate (green) and visual (blue) areas was considered. Representation of this data on a hypersphere is depicted. Dimensionality reduction was performed using PCA. (b) Two datasets (subject and reference) from these areas were used as input to PCA. Dimensionality of the data was reduced to 3D and renormalized to generate the mapping to sphere. Application of BrainSync to the subject results in a configuration of data on the sphere very similar to that for the reference dataset. The lower figure shows representative resting fMRI time-series for

two subjects for a single cortical location before and after synchronization. Note the strong correlation of the blue and red time-series curves from the two different subjects after synchronization.

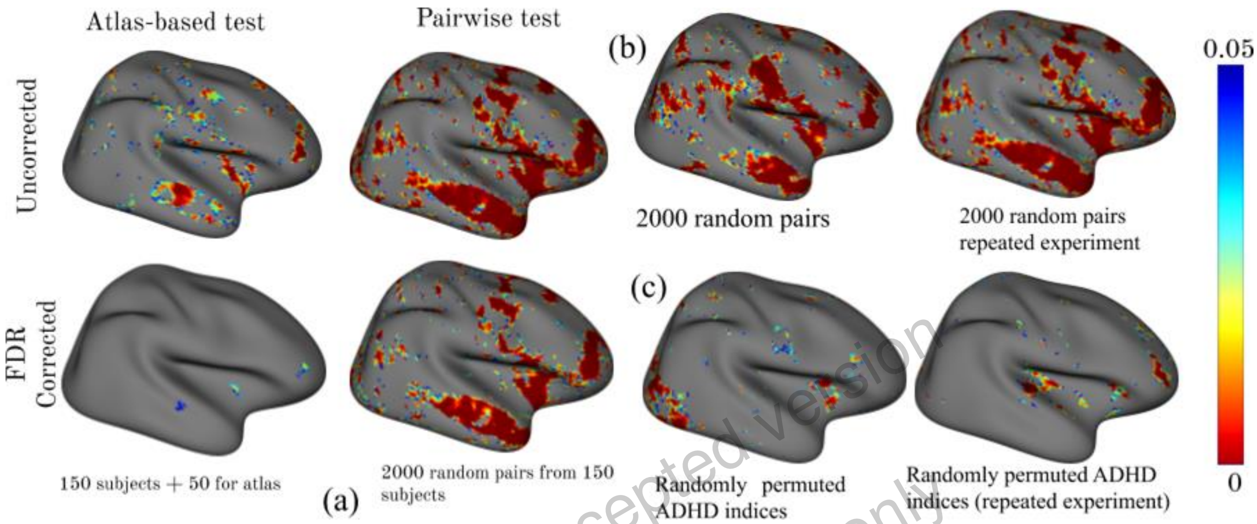

Figure 2: (a) Results of regression using BSA (left) and pairwise test (right); (b) repeating the experiment show consistency for the pairwise analysis; (c) when ADHD indices were permuted, the significant regions are inconsistent and relatively minor, showing reliability of the pairwise analysis.

References

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