Application of Canonical Correlation Analysis to Identify Regions of Significant Correlation between Symptom Scores and DTI Measures in Schizophrenia

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Introduction

Canonical correlation analysis (CCA) [1] is applied to find relationships between two sets of multi-dimensional variables, diffusion tensor imaging (DTI) measures of white matter integrity and concomitantly measured positive and negative symptom scale (PANSS) scores for schizophrenia patients. Disturbances in white matter (WM) connectivity between different brain regions, the 'disconnection hypothesis', has been proposed as a possible pathology in schizophrenia [2]. DTI measures can consist of axial diffusivity (AD), radial diffusivity (RD), mean diffusivity (MD), and fractional anisotropy (FA). PANSS scores measure severity of schizophrenia symptoms. Ratings measure symptom severity positive score e.g. 'delusions'; negative score e.g. 'poverty of speech' and general score e.g. 'anxiety'. CCA seeks to find a pair of linear transformations to maximize correlation between the four DTI measures and the three PANSS summary scores. The group CCA analysis was carried out on skeletonized images of FA, MD, AD and RD obtained from tract-based spatial statistics (TBSS/FSL) [3].

Theory

Let x and y be two vectors with dimensions p and q respectively. In this study x is a sample of DTI measures and y of PANSS scores. We define the squared canonical correlation r^2 as the maximum squared correlation between a linear combination of x and a linear combination of y. In terms of sample correlations, r^2 is the largest eigenvalue of $S_{xx}^{-1}S_{xy}S_{yy}^{-1}S_{yx}$, where S_{xx} and S_{yy} are the sample covariance matrices of x and y, and S_{xy} is the sample covariance between x and y. We calculate canonical correlation r at each voxel on the skeletonized image. The significance of r^2 was tested by the Roy's largest root statistic $\theta = r^2$ [1]. Let $s = \min(p,q)$, $m = (|p-q|-1)/2$ and $N = (n-p-q-2)/2$, where n is the number of samples (subjects). Then Table B5 in [1] gives the test statistic for θ in terms of s, m and N for $p = 0.05$.

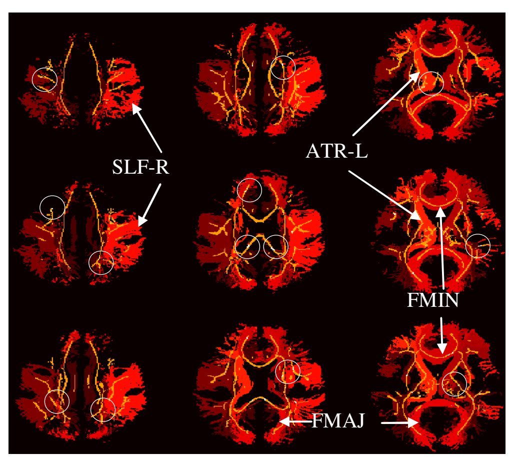
Methods

Data from 41 patients with stable chronic schizophrenia (mean age =39.3 ±12) were collected at the, Institute of Living, Connecticut. All subjects provided written informed consent to participate in the study. Patients were diagnosed using the structured clinical interview for DSM-IV (SCID) and review of the case file. PANSS scores for the subjects were as follows, *+ve* =15.6 ±5.3 (range =7-28), *-ve* =15.7 ±6.0 (range =7-31), *gen* =31.8 ±9.1 (range =18-57). The DTI images were obtained on a 3.0T Siemens Allegra scanner equipped using a single-shot spin-echo EPI. Eddy current distortions were reduced with a twice refocused balanced echo sequence with a 12 direction standard Siemens sequence with b =1000s/mm^2. Field of view (FOV) =200mm, slice thickness =3mm, 45 slices, echo time (TE) =83ms, and repetition time (TR) =5900 ms. DTI images were processed using the FSL toolbox (http://www.fmrib.ox.ac.uk/fsl/) and consisted of eddy current correction, calculating FA, MD, AD, and RD (Dtifit, FSL), where the TBSS/FSL algorithm was used for calculating the FA, AD, RD, and MD skeleton images. The CCA analysis was performed for voxels on the skeleton. In this study there are four DTI measures ($p = 4$), three PANSS scores ($q = 3$) and 41 subjects ($n = 41$). For the significance test, these values imply that s=3, m=0 and N=16. From Table B5 [1], significance of p<0.05 corresponds to $|r|$>0.6.

Results

Voxels on the skeleton with $|r|$>0.6 are identified and the number voxels on the skeleton and within the JHU atlas (part of FSL) regions are reported in the Table. The left anterior thalamic radiation, splenium of the corpus callosum and right superior longitudinal fasciculus were atlas regions with the largest number of significantly correlated voxels. On the figure we have shown the atlas regions with descending brightness of red, shades sorted by the order of number of significant voxels. In the atlas definition SCC and forceps major (FMAJ) are overlapping and we show FMAJ. The locations of the skeleton and the significantly correlated voxels are shown by orange and white (some circled) respectively.

White matter tract	Number of significant voxels
Anterior thalamic radiation L (ATR-L)	187
Superior long. fasciculus R (SLF-R)	158
Splenium of corpus callosum (SCC)	158
Forceps major (FMAJ)	132
Forceps minor (FMIN)	116
Anterior thalamic radiation R	111
Inferior fronto-occipital fasciculus R	107
Superior longitudinal fasciculus L	102



Discussion

Many studies analyze FA values alone to investigate WM disruptions. However, AD, MD and RD can hold valuable information that FA cannot reveal. We investigate how the 4 DTI values can be correlated with the 3 PANSS summary scores using CCA, a multivariate analytic approach. We find correlations at locations on a skeleton found with TBSS which accounts for spatial variability of WM tracts across different subjects. We report regions with significant correlation between DTI measures and PANSS scores. The finding in the superior longitudinal fasciculus related to symptom severity is consistent with two recent studies [4, 5] and the study as a whole supports a "disconnection" hypothesis of schizophrenia. Classification of subjects using information from these regions is a future research interest. If successful imaging techniques of this nature can help to develop diagnostic tools to support existing behavioral based techniques.

References

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