Quantitative FA analysis based on VBM and probabilistic tractography connectivity between treatment-resistant patients and treatment-responsive patients with major depressive disorder

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Introduction

Major depressive disorder is one of the most common, costly, and severely debilitating of all psychiatric disorders [1]. While depression can be effectively treated in the majority of patients by either medication or psychotherapy, up to 20% of patients fail to respond to standard interventions [1][2]. To study possible microstructural alterations of cerebral white matter between patients with treatment-resistant and treatment-responsive major depressive disorder, we propose an approach that quantifies fractional anisotropy (FA) differences derived from diffusion tensor MRI data [3] between these two depressed patient groups based on voxel-based morphometry (VBM) and structural connectivity using probabilistic tractography.

Material and Method

Data Collection:

5 treatment-resistant and 4 treatment-responsive patients all with unipolar depression were imaged with a 3.0T Siemens MRI scanner for T1 weighted 3D structural MR images and diffusion tensor imaging. Diffusion tensor imaging was performed using a SE-EPI pulse sequence with voxel resolution 2mm*2mm*2mm (64 axial slices, b value of 1000s/mm^2, 64 gradient directions).

Data Processing and Analysis:

Using FSL version 4.0 (FMRIB, Oxford, UK), we first preprocessed the data by applying eddy current correction to the diffusion tensor images and calculating diffusion tensor and FA maps. Subsequently, all subjects' FA maps were registered to structural T1 data and normalized to standard MNI space using SPM5. A whole brain voxel-wise analysis [4][5] was performed on FA maps using *t*-tests to compare the treatment-resistant and treatment-responsive groups. Significant differences in FA values were found between treatment-resistant and treatment-responsive groups (with $p<0.01$ and cluster size > 20 voxels) for three regions of interest (ROI): the subgenual anterior cingulate (sgACC), the thalamus, and the cerebellum. Since both non-cerebellar ROIs are part of Papez's circuit [6], we used the fornix (another component of Papez's circuit) as a seed (3x3x3mm with FA>0.2) for probabilistic tractography with a multi-fiber diffusion model [7] to produce a structural connectivity map that included thalamus and sgACC. The tractography map was thresholded with fiber sample number >50 to exclude erroneous connectivity caused by noise and partial voluming. We calculated the mean FA value on the probabilistic connectivity map for every subject and every group to estimate whole-fiber diffusion characteristics.

Results

Whole brain FA statistical analysis showed that treatment-resistant patients have decreased FA value in sgACC, thalamus and cerebellum, as shown in Figures 1 and 2. The mean FA values for sgACC are 0.24 and 0.31 for treatment-resistant and treatment-responsive groups, respectively. This finding is very robust ($p<0.01$, $t>3.5$) and present in both hemispheres. The related fiber probabilistic connectivity map, which pass through thalamus and sgACC regions, also shows lower fiber integrity in treatment-resistant group (mean FA = 0.29) compared to the treatment-responsive group (mean FA = 0.31).

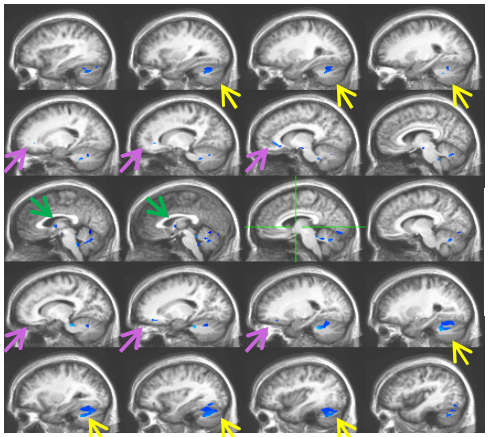

Fig 1. Illustration of significant ROI regions with changes in FA value. Blue means treatment-resistant group has reduced FA value compared to treatment-responsive.

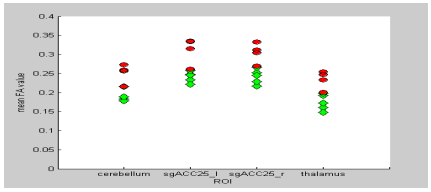

Fig 2. Mean FA values for treatment-resistant subject (green) and treatment-responsive (red) subjects in ROIs: cerebellum, sgACC left, sgACC right, and thalamus (from left to right).

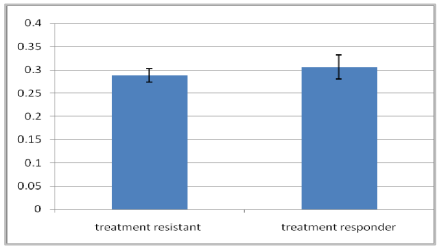

Fig 4. Left chart shows mean FA values for treatment-resistant and treatment-responsive groups in the fiber probabilistic connectivity map shown in Fig 3. Error bars show standard deviation. The group difference approached significance ($p<0.15$).

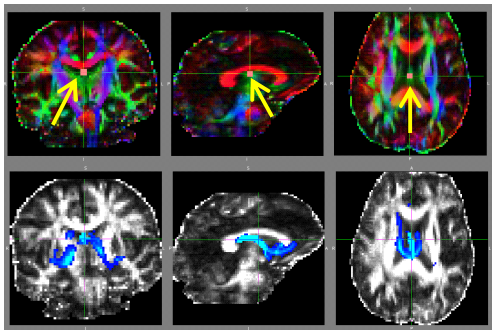

Fig 3. Probabilistic tractography. Top images show seed selection of fornix (pink color); bottom images show probabilistic connectivity distributions map (with threshold (sample number>50) for illustrating a component of circuit connecting sgACC and thalamus.

Discussion and Conclusion

This is the first study of FA changes for treatment-resistant and treatment-responsive patients with major depressive disorder. Whole brain FA statistical analysis showed that treatment-resistant patients have decreased FA value in subgenual cingulate, thalamus and cerebellum ($p<0.01$). One conclusion is that these regions are more seriously affected by chronic depression. Furthermore, probabilistic tractography identified a component of Papez's circuit that connected thalamus and subgenual cingulate. Quantitative FA analysis on this structural connectivity shows a trend of lower FA values for treatment-resistant compared to treatment-responsive patients, which is consistent with the VBM results. These results suggest reduced diffusivity and fiber integrity for this pathway for treatment-resistant patients compared to treatment-responsive patients. In summary, quantitative analysis of FA demonstrates changes between treatment-resistant and treatment-responsive patients based on VBM method and probabilistic tractography. Our findings are robust and will be helpful for further studies of microstructural changes associated with increasing depression severity. These strategies may prove additionally useful in further characterizing optimal targets for deep brain stimulation in treatment-resistant patients.

Reference

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