Altered Structural Connection Between Hippocampus and Insula in Adolescent Major Depressive Disorder using DTI

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Abstract—The adolescent major depressive disorder is one of the top 10 debilitating psychiatric illnesses and the effectiveness of current treatment methods are constrained by the limited understanding of biological causes. In this paper, we use diffusion tensor imaging to explore changes in anatomical connectivity between the MDD group (n=37) and control group (n=27). Furthermore, along-track analysis is performed to identify locations of alterations along connections with significant connectivity change. For the connection between the hippocampus and the insular cortex in the right hemisphere, decreased connectivity in axial diffusivity (AD), mean diffusivity (MD), and radial diffusivity (RD) was discovered. Additionally, the number of tracks for the same connection is increased for the MDD group. Moreover, for the connection between the parahippocampal gyrus and the insular cortex in the left hemisphere, increased connectivity is observed in fractional anisotropy (FA), AD, MD, and RD. Furthermore, the locations of significant alterations are identified to be between 65% to 100% from the insular cortex to the hippocampus in the right hemisphere and at the 80% location from the insular cortex to the parahippocampal gyrus in the left hemisphere. The significant and consistent white matter changes at the hippocampus end of the insula-hippocampus connection suggest potential correlations to the previously reported grey matter shrinkage and functional abnormalities.

I. INTRODUCTION

Major depressive disorder (MDD) is a highly debilitating disorder with enormous tragic outcomes such as chronic adult disability and suicide. Especially, adolescence is a vulnerable and sensitive period for onset of depression due to brain development and significant changes in physical and social development [1], [2]. According to the World Health Organization (WHO), more than 10% of adolescents are affected by MDD in the US [3]. Adolescents suffering from depression usually also develop other health problems, such as physical health problems and substance use disorder. Moreover, it has been shown that early-onset MDD increases the risk of developing adult depression [4]. No effective psychological interventions, antidepressant medication or a combination of these for treating depressive disorders in adolescents has been fully established [5]. It is critical to uncover the neurobiological roots of adolescent MDD to develop more effective treatments, which might differ from the adult form.

Adolescence is a period of rapid brain maturation including structural changes, such as myelination and changes in grey matter density [6], [7]. Therefore, it is important to investigate how the onset of depression affects the development of axon connections (anatomical connectivity) in the early course of the disorder.

Diffusion magnetic resonance imaging (dMRI) can capture the human brain microstructure through measuring water diffusion non-invasively and subsequently diffusion tensor imaging (DTI) could be utilized to characterize tissue microstructure [8] for white matter related investigations in vivo [9], [10]. Different DTI measures characterize axon fiber bundle from different anatomical perspectives. For example, fiber count could represent the bundle strength and the probability of existence. Axial diffusivity (AD) correlates with WM changes and pathology. FA is sensitive to microstructure changes. Mean diffusivity (MD) inversely varies with the measure of membrane density and is sensitive to cellularity, edema, and necrosis. Radial diffusivity (RD) increases with de- or dys- myelination and is affected by axonal diameters and density [10].

Anatomical connectivity between a pair of brain regions usually is defined by the average DTI measures from voxels along the reconstructed streamlines. In other words, anatomical connectivity quantifies the average anatomical properties of an axon fiber bundle. White matter alterations (at the voxel scale) in the frontolimbic areas using hypothesis-based approaches and changes of anatomical connectivity (at the connection scale) using both hypothesis-based and data-driven approaches have been reported in the previous studies [11], [12], [13], [14], [15], [16], [17], [18]. However, none has addressed the altered voxels and the altered connections, i.e., the gap between connectivity and voxel-wise measurements. Additionally, previous studies mostly focus only on fractional anisotropy (FA), one of the many DTI measures, without a complete picture of all the anatomical perspectives.

In this study, we aim to discover altered connections and identify the exact location of alterations along these connections by first investigating the anatomical connectivity and secondly performing the along-track analysis [19] for all the DTI metrics including: AD, FA, MD, and RD.

This paper is organized as follows. In Section II, we outline the pre-processing of diffusion MRI (dMRI) data and provide an overview of the proposed method. Results are
presented in Section III. Finally, we discuss the relevance of the results to the previous findings and future work on identifying biomarkers more accurately in Section IV.

II. MATERIALS AND METHODS

In Fig. 1, the analysis framework is presented. Anatomical connectivity is first calculated as the average DTI measure along fibers connecting the same pair of brain regions. Group differences in connectivity were tested using permutation test for statistical significance (p-value). Connections with the most significant connectivity change were selected and the associated fiber tracks were extracted for performing the along-track analysis.

A. Subjects, Imaging Parameters and Pre-processing

<table>
<thead>
<tr>
<th>TABLE I DEMOGRAPHIC INFORMATION</th>
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<tbody>
<tr>
<td>Gender (male/female)</td>
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<tr>
<td>Age (mean years ± SD*)</td>
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<tr>
<td>IQ (mean ± SD*)</td>
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<tr>
<td>eTIV** (mean ± SD*) (10^6)</td>
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SD: standard deviation.
**eTIV: estimated-total-intracranial-volume.

Sixty-four adolescents including 37 MDD subjects and 27 healthy controls from 15 to 19-year-old were recruited to participate in this study. For the control group, participants who met the criteria for any major current or past DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th Edition) [20] diagnosis were excluded. For the MDD group, patients who are diagnosed with any of the following psychiatric disorders were excluded: bipolar disorder, schizophrenia, pervasive developmental disorder, eating disorder with active symptoms in the past 12 months, and substance-related disorder with a history of use in the past 60 days. The demographic information is summarized in Table I. The experimental procedures involving human subjects described in this paper were approved by the University of Minnesota Institutional Review Board.

T1-weighted and diffusion weighted imaging (DWI) data were acquired using Siemens 3 Tesla TIM Trio scanner at the Center for Magnetic Resonance Research, University of Minnesota. DWI images were collected along 30 noncolinear directions. A dual-spin each, single shot, echo planar imaging sequence was used with TR = 8,000 ms, TE = 85 ms, FOV = 256 mm, voxel size 2 × 2 × 2 mm³, 64 slices, b-value = 1,000 and GRAPPA = 2. In addition, a gradient echo fieldmap sequence was collected to correct the DWI for geometric distortions caused by magnetic field inhomogeneity with parameters identical to the DWI scans [11].

Freesurfer is utilized to perform brain parcellation following the Desikan-Killiany atlas and 87 cortical/subcortical regions (41 for each hemisphere and 5 for corpus callosum) [21]. DWI data were first preprocessed following the Human Connectome Project (HCP) diffusion processing pipeline [22] and then further corrected for the eddy-current-induced distortions and gradient nonlinearity distortion using eddy and topup in FSL [1]. In addition, the diffusion tensor estimation and tractography construction were conducted using the diffusion toolkit (DTK) in TrackVis (trackvis.org) [23].

B. Anatomical Connectivity Estimation

Anatomical connectivity of a connection between a pair of brain regions is defined by the average of the DTI measurements from voxels along the reconstructed fiber tracks connecting the region pair. Since the parcellation contains 87 regions, there exist 3,741 anatomical connections for each tensor metric including: AD, FA, MD, and RD. Additionally, linear correlations to the gender, age, IQ, and eTIV are removed from all the connectivity.

C. Permutation T-test

The average group connectivity difference, D, is calculated to test the null hypothesis that the observed group difference (Group1 > Group2 or Group1 < Group2) could occur by chance. To test the hypothesis, 100,000 random permutations were performed to estimate the p-value of D. In each permutation, subjects were randomly reassigned to any of the two groups without replacement, and form pseudo-groups. The group average difference between pseudo-groups, D′, was compared to the original difference, D, to test the null hypothesis. In the 100,000 permutations, the probability of the event that D′ is greater or less than D depending on the sign of D, is the empirical tail probability, i.e., p-value, of D. Note that the resolution of p-value equals 1/(number of permutations), which is 0.00001 for 100,000 permutations. In addition to the p-value, the effect size of D and the statistical power of the test were also calculated. The effect size calculation follows Cohen’s d with pooled standard deviation [24]. The statistical power with significance level 0.05 is calculated based on the group means, standard deviations and sample sizes [25].

D. Along-Track Analysis

For those connections with a significantly altered anatomical connectivity (average tensor measure), we further perform along-track analysis to identify locations of changes [19]. Unlike performing averaging for anatomical connectivity, in
the along-track analysis, the DTI measures from the voxels of each individual fiber track are interpolated into a 100-point tuple (or extrapolated if the track is shorter than 100 data points) to maintain the location information. For each of the 100 locations of a connection, the mean and variations are computed and examined for samples from all tracks associated with the connection. Additionally, the average tuple for the connection for each subject is formed from the means and utilized to conduct group comparisons. In the statistical test, the correction of p-value is carried out by the comparison to the maximal statistics obtained from random label permutations.

III. RESULTS & DISCUSSION

A. Changes in Anatomical Connectivity

From the permutation test, we found that the anatomical connectivity of two connections, hippocampus-insular cortex in the right hemisphere and parahippocampal gyrus-insular cortex in the left hemisphere, is significantly changed. For the connection between the hippocampus and insular cortex in the right hemisphere, the connectivity defined by the number of tracks (TR) is increased for MDD group with uncorrected empirical p-value of 0.0007, effect size (Cohen’s d) of 0.72, and statistical power of 0.85. Fig. 2 shows box plots for connectivity defined by various DTI measures for the connection between the hippocampus and the insular cortex in the right hemisphere. Except the connectivity defined by the number of tracks (TR), most of the connectivity is slightly decreased for the MDD group.

Fig. 3 shows that, for the connection between parahippocampal gyrus and insular cortex in the left hemisphere, the connectivity defined by FA is increased for the MDD group with p-value of 0.0017, effect sizes (Cohen’s d) of 0.9, and statistical power of 0.8. The connectivity defined by AD is increased for the MDD group with p-value of 0.0004, effect sizes (Cohen’s d) of 0.7, and statistical power of 0.6. Based on the significance, these two connections are selected for further along-track analysis.

B. Along-Track Result

Fig. 4 shows the number of streamlines reconstructed and utilized for the two connections during the along-track analysis, which again confirms the significant elevation of TR connectivity for the MDD group for the hippocampus-insula connection shown in Fig. 2.

Fig. 5 shows the tensor measurements along the connection between insular cortex at the left most of the panels (0% location) and hippocampus at the right most position of the panels (100%) in the right hemisphere. The tensor measures corresponding to the AD, MD and RD are shown in the top, middle and bottom panels, respectively. Curves for each
subject are shown in light color and curves for group average are presented in bold color. Group is color coded (red for the MDD group and blue for the control group) and the thickness indicates the number of streamlines. The result shows that on the segment from insular cortex to the 65% of the track, the MDD group and the control group have about the same tensor measures. However, on the segment from about 65% of the connection to the hippocampus (100%), the control group has a higher AD, MD, and RD than those of the MDD group, which confirms the increased average measures shown in Fig. 2. Moreover, Fig. 6 shows the false-discovery-rate (FDR) corrected p-value less than 0.05 (colored in green) on the same segment (65% to 100%) for all three tensor measures. In terms of the consistency and intensity, MD (middle panel) and RD (bottom panel) have much smaller and more consistent low p-value than that of the AD.

Fig. 7 demonstrates the FDR corrected p-value for both connections in a brain image. The result shows that, for the connection between insular cortex and parahippocampal gyrus in the left hemisphere, only for the FA connectivity and only at 80% of the connection, the p-value is less than 0.05. The MD measure significantly changes from 65% of the position between insula cortex and hippocampus to 100% position. The changes for the connections between insular cortex and hippocampus/parahippocampal gyrus validate the previous work by [26], [27], [28], [29], [30] with respect to the involvement of the regions in MDD. Additionally, the alterations of the white matter at the hippocampus end are possibly correlated with the changes of the grey matter in the hippocampus region.

IV. CONCLUSIONS

In this study, we examine brain anatomical changes along two connections, hippocampus-insular cortex in the right hemisphere and parahippocampal gyrus-insular cortex in the left hemisphere, in MDD and matched healthy control using DTI measures and show the significant changes at the location close to the hippocampus for the hippocampus-insula connection.

Our analysis also shows that the data-driven approach can successfully identify hypothesized changes. They provide new and important insights into the neural correlates of MDD. Future work will be directed towards investigating changes of the other connections and the correlation to changes in other modalities such as grey matter thickness.

REFERENCES


