Evaluation of white matter integrity in drug-naive patients with major depressive disorder by diffusion tensor imaging

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Purpose

In major depressive disorder, development of noninvasive biomarkers for diagnosis, assessment of disease severity and monitoring of treatment response is desired. Diffusion tensor imaging (DTI) is an MRI technique that can assess the microstructural integrity of white matter, non-invasively\(^1\). It reflects the microstructural integrity of white matter through its major indexes, fractional anisotropy (FA) and mean diffusivity (MD)\(^2\). Previous studies on major depressive disorder involving non-geriatric patients in treatment-naïve state have revealed abnormal FA values in cerebral white matter, suggestive of impaired integrity\(^3\)\(^-\)\(^9\). However, location of abnormalities is inconsistent among the studies - which calls for further investigations. This study was aimed to determine if the microstructural white matter integrity is impaired in major depressive disorder in treatment-naïve state, using histogram and voxel-based analyses of DTI.

Methods and Materials

<Participants>

1. Patients

The patients were recruited during a 35-month period (August' 2007 - March' 2010).

Inclusion criteria;

- Age = 20-69 years
- Fulfillment of the criteria for major depressive disorder according to Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV-TR)
- Treatment-naïve # 6 months

Exclusion criteria;

- Comorbid other axis I or II disorders
- Diseases or medications which might affect white matter integrity (e.g., diabetes, hypertension, migraine)
- Significant abnormality on routine MRI sequences of the brain
- Absolute contraindications to MRI
2. Age- and gender-matched normal subjects

Demographic characteristics of the patients and normal subjects are listed in Table 1.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients</th>
<th>Normal subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>Age (years)</td>
<td>38.6 ±13.5 (20-61)</td>
<td>36.5 ±12.5 (22-60)</td>
</tr>
<tr>
<td>Gender distribution</td>
<td>13 men and 6 women</td>
<td>13 men and 6 women</td>
</tr>
<tr>
<td>Total disease duration (months)</td>
<td>18.37 ±28.17(1-96)</td>
<td></td>
</tr>
<tr>
<td>Duration of current episode (months)</td>
<td>5.89 ±5.69 (1-24)</td>
<td></td>
</tr>
<tr>
<td>HDRS</td>
<td>19.00 ±4.00 (11-26)</td>
<td></td>
</tr>
<tr>
<td>MADRS</td>
<td>26.21± 5.57(20-39)</td>
<td></td>
</tr>
<tr>
<td>GAF scale</td>
<td>43.79± 9.90 (28-58)</td>
<td></td>
</tr>
<tr>
<td>SASS*</td>
<td>24.67 ±6.20 (18-40)</td>
<td></td>
</tr>
</tbody>
</table>

Table 1. Demographic characteristics of the patients and normal subjects.

Data are presented in mean ± standard deviation (range). *SASS was evaluated in 15 patients. Abbreviations: HDRS = 17-item Hamilton Depression Rating Scale, MADRS = Montgomery-Åsberg Depression Rating Scale, GAF = Global Assessment of Functioning, SASS = Social Adaptation Self-evaluation Scale.

<MR Imaging>

All MR examinations were performed on a 1.5T scanner.

Imaging sequences and parameters

DTI

Single-shot spin-echo EPI; TR/TE = 5100/139 ms, b = 1000 s mm\(^{-2}\), number of diffusion gradient directions = 12, FOV = 240 x 240 mm, matrix size = 128 x 97, slice thickness = 5 mm, interslice gap = 1.5 mm, NEX = 2, plane = axial, number of slices = 23.
MPRAGE

3D-GRE imaging; TR/TE = 1900/3.9 ms, TI = 1100 ms, flip angle = 15°, FOV = 240 x 240 mm, Slab thickness = 240 mm, matrix size = 256 x 256, partition = 240, NEX = 1, interslice gap = 0 mm, plane = coronal.

T2WI

FSE imaging; TR/TE = 4500/ 96 ms, ETL_{eff} = 7, FOV = 240 x 180 mm, matrix size = 448 x 185, slice thickness = 5 mm, interslice gap = 1.5 mm, NEX = 1, plane = axial, number of slices = 23.

FLAIR

Fast inversion recovery imaging; TR/TE = 9000/ 114 ms, TI = 2500 ms, ETL_{eff} = 17, FOV = 240 x 180 mm, matrix size = 256 x 176, slice thickness = 5 mm, interslice gap = 1.5 mm, NEX = 2, plane = axial, number of slices = 23.

<Image processing and analysis>

Voxel-based analysis

1. Construction of FA and MD maps from DTI.
2. Normalization of echo planar images with no diffusion weighting of each normal subject to the standard EPI template of SPM.
3. Application of transformation information to the FA and MD maps of each subject.
4. Averaging of the normalized FA and MD maps and smoothing with a 6 mm full-width half maximum (FWHM) Gaussian kernel to form customized templates.
5. Normalization of native FA and MD maps of all participants to the respective customized templates.
6. Smoothing with a 6-mm FWHM Gaussian kernel.
7. Voxel-by-voxel comparison of normalized and smoothed MD and FA maps of the patients and normal subjects, using two-sample t-test {significance level set as false discovery rate (FDR)-corrected P<0.05}. 
8. Creation of mask from the FA template by exclusion of voxels with FA <0.2.
9. Application of white matter mask onto the output maps.
10. Test of correlation between abnormal DTI index and clinical variables (Spearman’s rank-correlation or Pearson’s product-moment correlation analysis; significance level set as Bonferroni-corrected P<0.05).
Histogram analysis

1. Construction of FA and MD maps from DTI.
2. Co-registration of MD and FA maps of each participant to the respective MPRAGE images.
3. Generation of white matter masks through segmentation of white matter from MPRAGE images.
4. Application of white matter masks on MD and FA maps.
5. Generation of MD and FA histograms of white matter (Histogram bins were normalized by the total number of voxels contributing to the histogram in order to compensate for the variability of brain size) and calculation of peak height and position of each histogram.
6. Statistical comparison of histogram parameters between patients and normal subjects using two sample t-test (significance level set as P<0.05).
7. Test of correlation between abnormal DTI index and clinical variables (Spearman's rank-correlation or Pearson's product-moment correlation analysis; significance level set as Bonferroni-corrected P<0.05).

Results

<Voxel-based analysis>

No significant difference in FA or MD values of white matter was observed between the two groups (Fig. 1).

<Histogram analysis>

The average FA and MD histograms of the patients and normal subjects are shown in Fig. 2. Histogram-derived measures are shown in Tables 2 and 3.

A significant shift towards the left (or smaller peak position) of FA histogram of the patients was observed (P=0.00097).

Peak height of FA, peak height and position of MD did not vary significantly between the two groups.

When the cut-off value for peak position of FA histogram was set as 0.2, the sensitivity and specificity in distinguishing major depressive disorder from normal were 0.89 and 0.74, respectively.

<table>
<thead>
<tr>
<th>Patients</th>
<th>Normal subjects</th>
<th>P</th>
</tr>
</thead>
</table>
Peak height 0.028 ± 0.003 0.028 ± 0.002 0.79527
Peak position 0.161 ± 0.056 0.255 ± 0.053 0.00097*

Table 2. FA histogram-derived measures of the patients and normal subjects.

Data are presented in mean ± standard deviation. * indicates statistical significance.

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Normal subjects</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak height</td>
<td>0.182 ± 0.021</td>
<td>0.168 ± 0.031</td>
<td>0.11615</td>
</tr>
<tr>
<td>Peak position</td>
<td>0.00079 ± 0.00002</td>
<td>0.00079 ± 0.00003</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 3. MD histogram-derived measures of the patients and normal subjects.

Data are presented in mean ± standard deviation.

*Correlation between peak position of FA histograms of the patients and clinical variables*

The results of correlation are summarized in Table 4.

No significant correlation between peak position of FA histograms of the patients and clinical variables was observed.

<table>
<thead>
<tr>
<th>Variable</th>
<th>#or r</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total disease duration</td>
<td>0.576</td>
<td>0.01</td>
</tr>
<tr>
<td>Duration of current episode</td>
<td>0.55</td>
<td>0.015</td>
</tr>
<tr>
<td>HDRS</td>
<td>-0.063</td>
<td>0.798</td>
</tr>
<tr>
<td>MADRS</td>
<td>0.25</td>
<td>0.303</td>
</tr>
<tr>
<td>GAF scale</td>
<td>-0.153</td>
<td>0.531</td>
</tr>
<tr>
<td>SASS</td>
<td>-0.021</td>
<td>0.941</td>
</tr>
</tbody>
</table>

Table 4. Test of correlation between peak position of FA histograms of the patients and clinical variables.

Statistical significance is determined as Bonferroni-adjusted P<0.05, adjusted for multiple comparison (i.e., P<0.0083).
Fig. 2: (A) Average FA histograms of white matter of the patients (black line) and normal subjects (broken line). A shift to the left in peak position of FA is observed in the patients. Peak height of FA did not vary significantly. (B) Average MD histograms of white matter of the patients (black line) and normal subjects (broken line). No significant difference in peak position or height is observed.
**Fig. 1:** Maximum intensity projections ("glass brain") of voxel t values, to show areas in which FA in the patients, is smaller than that in normal subjects. There are no areas in which FA of the patients is smaller than that of normal subjects.
Conclusion

Discrepancy between voxel-based and histogram analyses

Discrepancy of results between the two techniques is observed in this study (i.e., voxel-based analysis did not show any abnormality whereas histogram analysis revealed significant decrease in peak position of FA histograms of the patients).

It is speculated that heterogeneity in the distribution of voxels with FA decrease be responsible for the discrepancy. Heterogeneity in the distribution of abnormalities in a study population can give rise to false negative findings in a voxel-by-voxel statistical comparison technique. Histogram analysis, however, is unaffected.

Inconsistency of results among the previous studies (Table 5 and Fig. 3) is supportive of the assumption that heterogeneity in the distribution of abnormalities exist in major depressive disorder\textsuperscript{3-9}. As microstructural abnormalities at different points in a distributed circuit could all lead to similar abnormalities in behavior/mood, heterogeneity in spatial distribution can present with similar clinical features.

Certain technical factors such as imperfections in image registration and inappropriate smoothing kernels may also account for false negative results in voxel-based analysis. Although these factors cannot be completely excluded, their contribution is thought to be small as the image processing algorithms closely follow the previous studies\textsuperscript{3-5, 7-9}.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Condition</th>
<th>Abnormality</th>
<th>Location of abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood et al\textsuperscript{3}</td>
<td>treatment-naïve, non-geriatric depressive disorder</td>
<td>FA#</td>
<td>right ventral tegmentum</td>
</tr>
<tr>
<td>Blood et al\textsuperscript{3}</td>
<td>treatment-naïve, non-geriatric depressive disorder</td>
<td>FA#</td>
<td>dorsolateral prefrontal white matter</td>
</tr>
<tr>
<td>Zhu et al\textsuperscript{4}</td>
<td>first episode, treatment-naïve young adults</td>
<td>FA#</td>
<td>left anterior limb of internal capsule, right parahippocampal gyrus, left posterior cingulate</td>
</tr>
</tbody>
</table>
Table 5. Summary of DTI findings in previous reports.

Decrease in peak position of FA histograms

Decrease in peak position of FA histograms is indicative of inclusion of many voxels with smaller FA values in the population.

Decrease in FA values of cerebral white matter in major depressive disorder has been revealed by the previous studies. The underlying pathological process is not exactly known, but decrease in FA values of white matter is suggestive of impaired integrity in terms of directional coherence of highly-ordered axons

Lack of alteration of MD may imply that the aforementioned impairment in white matter integrity occurs without significant changes in cell size or density.
Lack of correlation with clinical variables

Lack of significant correlation between peak position of FA histograms and disease duration (total disease duration or duration of current episode) may suggest that FA decrease is present since the early course of disease. This is in consistence with the finding of a previous report in which FA decrease is observed in single-episode, medication naïve patients with disease duration of less than 3 months\(^8\). Presence of FA decrease in pre-treatment state or early course of the disease implies that impaired white matter integrity is an etiological factor for major depressive disorder.

Lack of correlation with clinical severity scales suggests that the clinical severity scales do not reflect the entire pathological processes in major depressive disorder.

In conclusion, white matter integrity is impaired in major depressive disorder in treatment-naïve state, and distribution of the white matter abnormalities may be different among patients. Peak position of FA histograms may become a non-invasive index for evaluation of white matter integrity in major depressive disorder.

Images for this section:
**Fig. 3:** Axial and coronal illustrations of the brain showing areas of FA decrease in previous reports. Heterogeneity in the distribution of FA decrease is seen. (Note that the illustration is for easy understanding about the distribution of abnormalities and may differ from the actual extent reported.)
References


Personal Information