Early-onset and Late-onset Major Depressive Disorder in the Elderly: A DTI Study with Tract-based Spatial Statistics


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Abstract

Major depressive disorder (MDD) is the most prevalent psychiatric illness in the elderly. DTI (Diffusion tensor imaging) has been applied widely in order to study the aetiology and physiopathology of major depressive disorder. DTI provides in vivo measures of the brain and numerous studies have discovered white matter abnormalities in MDD in the elderly. The objective is to investigate the changes in white matter in late onset depressive patients (P) compared to early onset depressive patients (CP) and healthy control subjects (C) using tract based spatial statistics (TBSS). First conclusions of this work suggest that abnormalities are found in the hippocampus, forceps minor and superior longitudinal fasciculus of late onset depressive patients.

1. Introduction

Depression, along with dementia, is the most prevalent psychiatric illness in old age. Physiopathology is unknown for Late Life Depression (LLD), as with other psychiatric diseases. However, over the past few years, research and clinical evidence have contributed to increasing our knowledge of lifelong depression, and also of LLD [1].

Diffusion-weighted Imaging (DWI) is a Magnetic Resonance technique that describes the molecular motion of water [2] [3]. Diffusion is described using a scalar parameter and it represents diffusion in one direction, appropriate for isotropic environments. However, in neuroanatomy, brain tissues restrict the free diffusion of the water behaving as obstacles and causing anisotropy. Therefore, anisotropic diffusion cannot be characterized with a single scalar but requires a tensor, D, in order to fully characterize diffusion in all directions. The diffusion tensor is a mathematical description of the magnitude and directionality (anisotropy) of the movement of the water molecules in a three dimensional space [4]. Acquiring more than six diffusion-weighted measurements is required to calculate directional variation in the diffusion rate. Hence, the technique of extracting the tensor from diffusion weighted images is called Diffusion Tensor Imaging. This tensor can be decoupled in a linear combination of the eigenvectors (v₁, v₂, v₃) and eigenvalues (λ₁, λ₂, λ₃). The eigenvector associated with the largest eigenvalue (λ₃) is defined as the principal diffusion direction (PDD).

DTI has been widely used in the research of different neurological diseases, including depression. Depression in the elderly is a heterogeneous illness and it is hard to describe its aetiology and psychopathology. However, DTI allows specifying the location, type and extent of abnormalities and to understand more about the disease itself.

For this purpose, tensor derived measure fractional anisotropy (FA) has been used in the majority of the studies (Equation 1). FA quantifies the directionality of the tracts measured in a voxel using the eigenvalues defined before. Fibers that are highly aligned exhibit high FA values; whereas other fibers located in crossing-fiber areas have a lower FA. Besides, it is said that FA is a noise insensitive measure compared to other diffusion measures [5] [6]. For all these reasons, FA has become the most used quantity in order to describe the anisotropy in the diffusion of biological tissues. On the other hand, it is also useful to measure the changes in the myelin integrity of the white matter in vivo.

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FA = \frac{1}{\sqrt{2}} \frac{\sqrt{(λ₁ - λ₂)^2 + (λ₂ - λ₃)^2 + (λ₁ - λ₃)^2}}{(λ₁ + λ₂ + λ₃)}
\]

In this paper, a clinical research in depression in the elderly using DTI is presented. The whole brain is explored in order to describe major depressive disorder in geriatric patients using tract based spatial statistics (TBSS), a novel technique for the analysis of DTI datasets. The aim of this study is to demonstrate a relationship between white matter abnormalities seen in DTI and geriatric depression.

2. Method

2.1. Participants

Sixteen subjects were recruited from The Navarra University Clinic, all older than 60. Subjects were categorized in three groups: a healthy control group (C), early onset major depressive subjects (first episode before 50, control patient group, (CP)) and late onset major depressive subjects (first episode after 50, patient group, (P)). There are six controls, four control patients and six patients (N = 16).
2.2. MRI acquisition
A brain MRI protocol, including structural MRI and DTI, was performed on each subject using a Siemens 3T Tim/Trio scanner (Siemens Medical System, Germany) and a Standard 12-channel head coil. Parallel imaging with Generalized Autocalibrating Partially Parallel Acquisition (GRAPPA) was used in all scans. For structural MRI, axial 3D T1-weighted multiplanar magnetization prepared rapid gradient echo (MPRAGE) imaging with TR=1900 ms, TE=3.42 ms and slice thickness of 1 mm. In addition, fluid-attenuated inversion recovery (FLAIR) sequence with TR=9000 ms, TE=90 ms and 3-mm slice thickness were collected to detect structural pathology. For DTI, images were recorded in the axial direction with 67 slices and 2-mm thickness with no gap. Directional sensitized diffusion-weighted single-shot spin-echo echo-planar imaging sequence with 30 gradient directions was used with the following imaging parameters: TR=9200 ms, TE= 94 ms, b values of 0 or 1,000 s/mm², 2 signal average and matrix size = 122 x 122.

2.3. DTI preprocessing and statistical analysis
Earlier DTI studies on depression have mainly used the ROI method. However, it is well known that locating the regions may be difficult and only abnormalities found in the selected ROIs can be found. Therefore, several studies have used recently tract-based spatial statistics

In this study, we explored the structure in a voxel-by-voxel basis of the whole brain as well as different anatomical parts with TBSS. 3 Tesla brain DTI-MRI was performed on all subjects. Diffusion tensor images were processed and analyzed using the Functional MRI of the Brain software library (FSL 4.1 [7]). Eddy current correction was performed for diffusion weighted images in order to align all volumes within the subject and correct for subject motion and eddy currents. After that, non brain voxels were excluded with brain extraction tool (BET) and visual inspection was performed to check artifacts, intensity range problems and general data quality. Finally, anisotropy measure images such as eigenvalues, MD or FA were calculated by fitting a tensor model at each voxel with DTIFit.

FA images were used for voxelwise statistics using TBSS [8]. Initially, preprocessing for TBSS was performed to ensure that files were in the right format and to check the artefacts’ outliers from the diffusion tensor fitting. Next, non linear registration aligned all the FA data across subjects to a 1x1x1mm standard space using a single subject's FA image as the target. This target was identified as the most representative of the group by aligning each image to every other one. This step resulted in a standard-space version of each subject's image. They were all merged into an all FA 4D image, the mean image of all of them is created in mean FA and its skeletonised version, mean FA skeleton. This last image was thresholded in order to define the set of voxels used in the last step: the voxelwise cross-subject statistics. The randomise tool was used, performing a permutation-based non parametric independent two-sample t test and generating raw, uncorrected and family-wise error (FWE) corrected test statistic images. Localization of differences between groups was done with the use of the JHU White-matter Tractography Atlas [9]. Three independent two sample t test were performed for CP-C, P-C and CP-P comparatives.

Based on JHU White-matter Tractography Atlas, statistics of the twenty major tracts were performed: left anterior thalamic radiation, right anterior thalamic radiation, left corticospinal tract, right corticospinal tract, left cingulate gyrus, right cingulate gyrus, left hippocampus, right hippocampus, forceps major, forceps minor, left inferior fronto-occipital fasciculus, right inferior fronto-occipital fasciculus, left inferior longitudinal fasciculus, right inferior longitudinal fasciculus, left superior longitudinal fasciculus, right superior longitudinal fasciculus, left uncinate fasciculus, right uncinate fasciculus, left temporal part of the Superior longitudinal fasciculus and right temporal part of the superior longitudinal fasciculus.

Each tract information was compared to the information of other groups, with an independent two-sample t test and an Anova F-test done for the all-to-all comparative (CP-P-CS).

3. Results
The obtained results for the whole brain are summarized in Table 1 and can be visualized in Fig. 1.

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<th>FWE corrected</th>
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<td>CP &gt; P</td>
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<tr>
<td>C &gt; P</td>
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<td>CP &gt; C</td>
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Table 1 – Whole Brain results for the three comparatives

Whole brain statistics showed that patients have significant decreased FA values compared to control patients (0.95). However, in the other two comparatives, although decreased FA values are shown, these results are not significant enough (0.89 and 0.91 in FWE corrected analysis) but they suggest a trend of decreased FA [15]. FWE uncorrected results are also shown, as corrected ones can be unnecessarily conservative, most of all in whole brain analysis [10] [11] [14]. In an FWE uncorrected analysis, three comparatives (CP-P, C-P, CP-C) obtained significant decreased FA values (0.99) in patients (CP-P, C-P) and healthy subjects (CP-C).

To sum up, in the whole brain FWE corrected analysis, there is a statistical relevance of 95% to conclude that patients have areas with lower FA than control patients; an 89% statistics relevance to infer that patients have areas with lower FA than healthy controls and a statistical relevance of 91% to confirm that healthy subjects have areas with lower FA than control patients.
Areas with significant results were also obtained in the atlas based statistics (highlighted in grey in the tables). In the CP-P comparative, decreased FA values were found in the right cingulum (cingulate gyrus) (Table 2); in the C-P comparative, right uncinate fasciculus and left superior longitudinal fasciculus (temporal part) were the areas with decreased FA values (Table 3); in the CP-C comparative, right cingulum (cingulated gyrus and hippocampus) and forceps minor areas had decreased FA (Table 4); and in the all-to-all group comparative there are significative differences in the right cingulum (hippocampus), forceps minor and superior longitudinal fasciculus (Table 5).

### 4. Discussion

The majority of studies compare DTI measures such as FA, between depressive and control elderly people. In our case, as stated before, subjects are divided into three groups: healthy controls, control patients and patients. To our knowledge this is the first study that distinguishes early-onset and late-onset major depressive elderly patients and compares both groups, and those groups and control subjects.

Previous studies (a few of them summarized in [12] and later works [13] [14]) have found lower values of FA in frontal and temporal regions, corpus callosum, several
right hemisphere regions, cingulate and frontostriatial paths and fronto-occipital and cingulated bundles.

In the present study, we first focused not only on the whole brain, but we also performed an analysis of the major tracts defined by the JHU White-matter Tractography Atlas. Significant differences were found in fronto-limbic pathways affecting right cingulum and forceps minor, with differences of FA age of onset mediated. These results suggest different physiopathology of LLD by age at onset, with more damage of white matter bundles in late-onset LLD patients.

Our findings are similar to those described in recent published studies by Mettenburg et al [16] who report most prominent regional differences in white matter integrity detected in LLD patients located in uncinate and cingulate. Colloby et al [14] demonstrated low FA in frontal temporal and midbrain regions. A review article from Naismith et al [1] reports changes in white matter studied by DTI in frontal and temporal lobes.

4.1. Limitations

Our results are suggestive and future work is needed in order to obtain more relevant conclusions. The increase of the sample size may increment the statistical power of the research.

5. Conclusions and future work

In this paper we present a DTI based study of geriatric depression using Tract-based Spatial Statistics. Areas with significant reductions have been found in the hippocampus, forceps minor and superior longitudinal fasciculus of late onset depressive patients compared both to early onset depressive ones and control patients. Further work is needed to better describe the disease.

This study is the preliminary phase of a more challenging project and suggestive results were found, but the study should be enhanced with a bigger sample. Therefore, several improvements must be made and future work will include the recruitment of more subjects in the study in order to obtain more significant results and the use of different DTI measures altogether in combination with FA, such as, MD, AD or RD.

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References


