Depression in elderly: a DTI study of white matter abnormalities with two control groups

Poster No.: C-1378
Congress: ECR 2013
Type: Scientific Exhibit
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Keywords: Neuroradiology brain, MR-Diffusion/Perfusion, Diagnostic procedure
DOI: 10.1594/ecr2013/C-1378

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Purpose

Depression along with dementia is the most prevalent psychiatric illness in the elderly. Our objective is to demonstrate a relationship between white matter abnormalities seen in DTI and geriatric depression. For that purpose, we investigate changes of white matter tracts in late life depression (LLD) patients compared to similar aged subjects with early life depression (ELD) and healthy status (HS) using DTI with tract-based spatial statistics (TBSS).
Methods and Materials

Patient population
16 subjects with more than 60 years old were prospectively recruited in the context of an ongoing study at the Clinica Universidad de Navarra. Subjects belonged to 3 different categories: Subjects with LLD (n=6; first episode after 50 years old; patient group, LLD), subjects with ELD (n=4; first episode of depression before 50 years old; control-patient group, ELD) and healthy subjects (n=6; Healthy controls, HS). All subjects had a DTI study performed on a 3 T scanner following clinical and cognitive assessment. Approval of the local ethic committee and written consent were obtained in all cases.

MRI acquisition (Fig. 1 on page 5)
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 Generalised 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.

DTI postprocessing (Fig. 2 on page 5)
Diffusion tensor images were processed and analysed using the Functional MRI of the Brain software library (FSL 4.1 (6)). 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 artefacts, 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.

Data analysis

For the data analysis, voxel-by-voxel basis of both whole brain as well as different anatomical parts was performed using Tract-based-spatial-statistics (TBSS). Initially, preprocessing for TBSS was performed to ensure that files were in the right format and
to check the artefact 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 every image to every other ones. 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. 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. Localisation of differences between groups was done with the use of the JHU White-matter Tractography Atlas. The twenty major tracts analysed were: 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.

**Statistical analysis**

To compare the whole-brain results three independent two sample T test were performed for LLD-ELD, LLD-HS and ELD-HS comparatives. Each tract information was compared to the information of other groups, with an independent two-sample t test (LLD-ELD, LLD-HS and ELD-HS) and an Anova F-test was done for the all-to-all comparative (LLD-ELD-HS).
**Figure 1.** DTI axial image obtained with 3T MR before postprocessing

**Fig. 1:** DTI axial image obtained with 3T MR before postprocessing

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**Figure 2.** Postprocessed DTI axial image. Red and yellow regions show decreased FA. Mean FA skeleton (green tracts) and FA results are superimposed.

**Fig. 2:** Postprocessed DTI axial image. Red and yellow regions show decreased FA. Mean FA skeleton (green tracts) and FA results are superimposed.

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Results

1. Whole brain analysis:
The results are showed in table 1 (Fig. 3 on page 9)
Attending to the FWE corrected analysis, subjects with LLD have significant decreased FA values compared to subjects with ELD (P<0.05) and non significant decreased FA values when compared with HS (P <0.09), although it does show trend to signification. When comparing ELD patients with HS, results show on the contrary an increase FA values on ELD patients. Again, this result is not significant but shows trend to signification.
FWE uncorrected results are also shown, as corrected ones can be unnecessarily conservative, most of all in whole brain analysis (9). In the FWE uncorrected analysis, previous findings show statistical significance (P <0.001).
Summary:
- LLD patients have decreased FA values of whole-brain white matter compared to ELD patients and HS.
- ELD patients have increased FA values when compared to HS.
- All these findings are significant or at least show trend to signification.

2. Major white matter tracts analysis
The major tracts in which significant differences were found are:
Right cingulum (Cingulate gyrus), Right cingulum (Hippocampus), Forceps minor, Right uncinate fasciculus and left superior longitudinal fasciculus (Temporal part).
Results are shown in tables 2, 3, 4 and 5 (Figures 2-5)

In the LLD-ELD comparative (Fig. 4 on page 9), significant decreased FA values were found in the right cingulum (cingulate gyrus).
In the LLD-HS comparative (Fig. 5 on page 10), right uncinate fasciculus and left superior longitudinal fasciculus (temporal part) were the areas with significant decreased FA values.
In the ELD-HS comparative (Fig. 6 on page 11), right cingulum (cingulated gyrus and hippocampus) and forceps minor areas are increased creased FA. The left superior longitudinal fasciculus (temporal part) showed increased FA with trend to signification.
In the all-to-all group comparative (Fig. 7 on page 12) there were significative differences in the right cingulum (hippocampus), forceps minor and superior longitudinal fasciculus. The right uncinate fasciculus shows FA differences that trend to signification (P<0.07).

Summary:
- There are significant differences of FA values of major tracts between all groups.
- Considering both pairing and all-to-all group comparatives, the white matter tracts that show significantly lower FA values in patients with LLD when compared with ELD patients and HS are the right cingulum (cingulate gyrus) and the superior longitudinal fasciculus. The right uncinate fasciculus also seem to show lower values, but only with trend to signification.

- The main difference of the integrity of white matter tracts between LLD and ELD patients is located in the right cingulum (cingulate gyrus).

- ELD patients show higher values of FA than HS in right cingulum (cingulated gyrus and hippocampus) and forceps minor areas.

3. WHAT DOES OUR RESULTS MEAN?

1. Significant differences are found in the amount of white matter integrity loss in elderly patients with depression depending on the age of onset. Those differences are present both in the whole-brain assessment and when it specially focused in the fronto-limbic pathways (right cingulum and forceps minor areas). These results suggest a different physiopathology of elderly depression by age at onset, with more damage of white matter bundles in late-onset patients.

2. Right cingulum (cingulate gyrus) and the superior longitudinal fasciculus show significant decreased FA values on LLD patients when compared with both ELD patients and HS. Therefore, alterations of these tracts might constitute more specific findings of LLD on DTI. The right uncinate fasciculus should also be further investigated.

4. LIMITATIONS

The main limitation of this work is the small sample data, but as the study is still ongoing and results are hoped to be updated with increased statistical power. Nevertheless, they are a good starting point that must be confirmed by further investigation.
Table 1 – Whole Brain results for the three comparatives

<table>
<thead>
<tr>
<th>FA</th>
<th>CORRECTED FWE</th>
<th>UNCORRECTED FWE</th>
</tr>
</thead>
<tbody>
<tr>
<td>LLD &lt; ELD</td>
<td>P&lt;0.05</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td>LLD &lt; HS</td>
<td>P&lt;0.11</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td>ELD &gt; HS</td>
<td>P&lt;0.09</td>
<td>P&lt;0.01</td>
</tr>
</tbody>
</table>

**Fig. 3:** Table 1: Whole brain comparative

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Table 2: Results for different anatomical tracts in LLD-ELD

<table>
<thead>
<tr>
<th></th>
<th>LLD</th>
<th>ELD</th>
<th>T test</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right Cingulum (cingulate gyrus)</td>
<td>0.5567 (0.04119)</td>
<td>0.6203 (0.02939)</td>
<td>-2.85</td>
<td>0.025</td>
</tr>
<tr>
<td>Right Cingulum (hippocampus)</td>
<td>0.5642 (0.06246)</td>
<td>0.5968 (0.08234)</td>
<td>-0.12</td>
<td>0.912</td>
</tr>
<tr>
<td>Forceps minor</td>
<td>0.6482 (0.08927)</td>
<td>0.6944 (0.01451)</td>
<td>-1.24</td>
<td>0.269</td>
</tr>
<tr>
<td>Right uncinate fasciculus</td>
<td>0.5158 (0.1980)</td>
<td>0.5643 (0.04590)</td>
<td>-1.99</td>
<td>0.14</td>
</tr>
<tr>
<td>Left superior longitudinal fasciculus (temporal part)</td>
<td>0.4756 (0.02535)</td>
<td>0.5131 (0.04327)</td>
<td>-1.56</td>
<td>0.193</td>
</tr>
</tbody>
</table>

Fig. 4: Table 2: LLD-ELD comparative

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Table 3 - Results for different anatomical tracts in LLD-HS

<table>
<thead>
<tr>
<th>Anatomical Tract</th>
<th>LLD</th>
<th>HS</th>
<th>T test</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right Cingulum (cingulate gyrus)</td>
<td>0.5291 (0.03073)</td>
<td>0.5551 (0.02534)</td>
<td>1.6</td>
<td>0.145</td>
</tr>
<tr>
<td>Right Cingulum (hippocampus)</td>
<td>0.4205 (0.06829)</td>
<td>0.4127 (0.01419)</td>
<td>0.27</td>
<td>0.797</td>
</tr>
<tr>
<td>Forceps minor</td>
<td>0.5579 (0.02903)</td>
<td>0.5590 (0.04049)</td>
<td>0.05</td>
<td>0.958</td>
</tr>
<tr>
<td>Right uncinate fasciculus</td>
<td>0.4989 (0.01369)</td>
<td>0.5520 (0.01917)</td>
<td>5.52</td>
<td>0.000</td>
</tr>
<tr>
<td>Left superior longitudinal fasciculus (temporal part)</td>
<td>0.5214 (0.02357)</td>
<td>0.5718 (0.01496)</td>
<td>4.42</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Fig. 5: Table 3: LLD-HS comparative

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Table 4 - Results for different anatomical tracts in ELD-HS

<table>
<thead>
<tr>
<th></th>
<th>ELD</th>
<th>HS</th>
<th>T test</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right Cingulum</td>
<td>0.6203 (0.02939)</td>
<td>0.5551 (0.02534)</td>
<td>3.63</td>
<td>0.015</td>
</tr>
<tr>
<td>(cingulate gyrus)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right Cingulum</td>
<td>0.5968 (0.08234)</td>
<td>0.4127 (0.01419)</td>
<td>3.78</td>
<td>0.032</td>
</tr>
<tr>
<td>(hippocampus)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forceps minor</td>
<td>0.6944 (0.01451)</td>
<td>0.5590 (0.04049)</td>
<td>7.5</td>
<td>0.000</td>
</tr>
<tr>
<td>Right uncinate</td>
<td>0.5643 (0.04590)</td>
<td>0.5520 (0.01917)</td>
<td>0.51</td>
<td>0.645</td>
</tr>
<tr>
<td>fasciculus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left superior</td>
<td>0.5131 (0.04327)</td>
<td>0.5718 (0.01498)</td>
<td>-2.61</td>
<td>0.080</td>
</tr>
<tr>
<td>longitudinal fasciculus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(temporal part)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Fig. 6:** Table 4: ELD-HS comparative

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Table 5 – Results for different tracts in LLD-ELD-HS

<table>
<thead>
<tr>
<th>Tract</th>
<th>LLD</th>
<th>ELD</th>
<th>HS</th>
<th>T test</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right Cingulum (cingulate gyrus)</td>
<td>0.5429 (0.03176)</td>
<td>0.6203 (0.02939)</td>
<td>0.5551 (0.02534)</td>
<td>9.41</td>
<td>0.003</td>
</tr>
<tr>
<td>Right Cingulum (hippocampus)</td>
<td>0.4923 (0.04452)</td>
<td>0.5968 (0.08234)</td>
<td>0.4127 (0.01419)</td>
<td>12.54</td>
<td>0.001</td>
</tr>
<tr>
<td>Forceps minor</td>
<td>0.6031 (0.04062)</td>
<td>0.6944 (0.01451)</td>
<td>0.5590 (0.04049)</td>
<td>16.9</td>
<td>0.000</td>
</tr>
<tr>
<td>Right uncinate fasciculus</td>
<td>0.5074 (0.00639)</td>
<td>0.5643 (0.04590)</td>
<td>0.5520 (0.01917)</td>
<td>7.44</td>
<td>0.007</td>
</tr>
<tr>
<td>Left superior longitudinal fasciculus (temporal part)</td>
<td>0.4985 (0.01777)</td>
<td>0.5131 (0.04327)</td>
<td>0.5718 (0.01498)</td>
<td>13.73</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Fig. 7: Table 5: All-to-all group comparative

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Conclusion

1. The integrity loss of white matter on DTI is significantly higher both globally and in some specific tracts in elderly patients with LLD when compared with ELD patients. This fact suggests differences in the pathophysiology and may imply differences in prevention, prognosis or treatment.

2. The alteration of the Right cingulum (cingulate gyrus) and the superior longitudinal fasciculus seems to be more specific findings of LLD, as they will be significantly altered compared to both ELD patients and HS of the same age. The right uncinate fasciculus should also be further investigated.

3. Further investigation must be performed to confirm these findings and assess their impact on prognosis, treatment or prevention.
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Fig. 8
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