The influence of frontal glutathione levels on white matter connectivity in healthy and early psychosis subjects: a preliminary study

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INTRODUCTION

Schizophrenia is a diffused developmental disorder involving white matter tracts and grey matter volume alterations, myelination impairment, neurotransmission dysfunction, and faulty connectivity [1]. Recent studies identify redox dysregulation, oxidative stress and glutathione (GSH) deficit as a possible hub of the pathology [2]. Both damages of myelin sheaths and decrease of GSH levels in prefrontal cortex have been reported. The early phase of psychosis is of central interest as critical brain structural and functional modifications occur early in the disease process.

Diffusion imaging, tractography and graph analysis [3] are emerging as powerful instruments for the characterization of the human connectome, in health and disease. Network metrics like global efficiency, characteristic path length and clustering coefficient, are well suited to globally quantify the level of connectivity integration and segregation of anatomical brain connectivity. The generalized Fractional Anisotropy (gFA) is a scalar measure derived from diffusion imaging associated to white matter tissue integrity.

GSH deficit could be indirectly related to connectivity and myelination impairment. In this study we investigated the relationship between the levels of GSH measured in the prefrontal cortex through MRS, and diffusion imaging derived measures of brain connectivity and white matter integrity, healthy and early psychosis (EP) subjects.

SUBJECTS and METHODS

SUBJECTS

<table>
<thead>
<tr>
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<th>Healthy controls</th>
<th>Patients</th>
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<tbody>
<tr>
<td>Age (year)</td>
<td>N</td>
<td>mean</td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>22.98</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>19</td>
<td>63.16%</td>
</tr>
<tr>
<td>Female</td>
<td>19</td>
<td>21.05%</td>
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MULTIMODAL MRI

All subjects were scanned at 3T (Siemens Trio), the scan session being composed by:
- magnetic resonance spectroscopy (short TE 1H MRS)
  TEM volume coil; VOI = 20x20x25 mm3 was positioned in a medial frontal area; TR/TE 4000/6ms, BW = 2 kHz, number of averages (NA) = 148, vector size = 2048. GSH levels were quantified using LCModel.
- high resolution T1w imaging (MPRAGE)
  32-channel coil; 240 x 256 x 160 voxels of isotropic 1mm resolution, slice thickness = 1.2mm; TR/TE/TI = 2300/900/2.89ms.
- diffusion spectrum imaging (DSI q4 half)
  96x96x34 voxels 2.2x2.2x3 mm; 257 directions + 1 b0 image, maximum b-value = 8000 mm2/s; TR/TE 6100/144ms.

RESULTS

r: Pearson correlation coefficient
p: p-value associated to r

Each point in the graphs corresponds to a subject.

<table>
<thead>
<tr>
<th>[GSH] vs average gFA in the cingulum</th>
<th>[GSH] vs average gFA in the cingulum</th>
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<tbody>
<tr>
<td>r = 0.64</td>
<td>r = 0.75</td>
</tr>
<tr>
<td>p = 0.003</td>
<td>p = 0.002</td>
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DISCUSSION

- A multimodal approach allowed to compare and associate frontal GSH levels, with measures characterizing WM integrity and brain connectivity.
- The frontal GSH levels correlate with gFA values in the cingulum area, and more generally with global brain structural connectivity measures. Specifically, higher levels of GSH are associated with higher connection efficiency as measured through gFA ponderation on one hand, and with better supported functional segregation on the other hand. We hypothesize that the GSH may indirectly play an important role in normal development of WM tracts in the human brain.
- The absence of these correlations in EP patients suggests a disrupted interaction between the GSH levels and neuroprotection mechanism, but deserves further investigations.
- These findings are preliminary and future work will be needed, particularly to confirm them in a larger sample. Moreover, the investigation of functional connectivity from resting-state fMRI data will be of interest.

ACKNOWLEDGMENT

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