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 investigate 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

	Healthy controls			Patients			
	N	mean	SD	N	mean	SD	p ttest
Age (year)	19	22.98	3.14	18	23.31	3.62	0.77
		Male	Female		Male	Female	p chi2
Gender	19	63.16%	36.84%	18	72.22%	27.78%	0.56
		Left	Right		Left	Right	p chi2
Handedness	19	21.05%	78.95%	18	10.53	89.47%	0.17

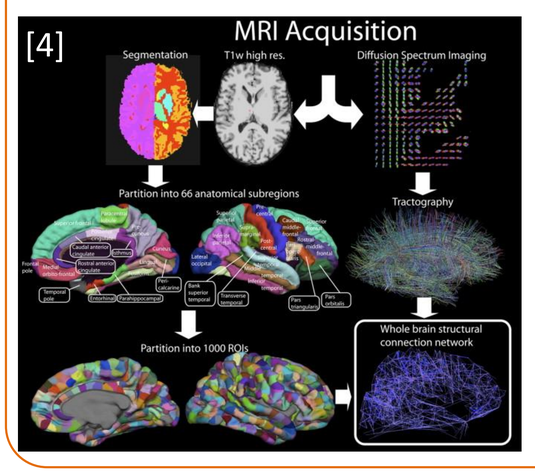
MULTIMODAL MRI

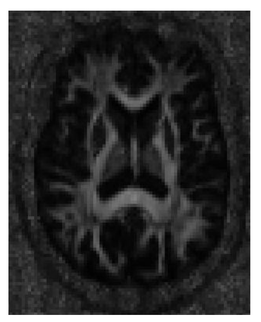
All subjects were scanned at 3T (Siemens Trio), the scan session being composed by:

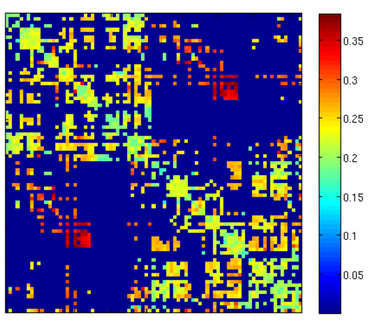
- **magnetic resonance spectroscopy (short TE 1H MRS)**
  TEM volume coil; VOI = 20x20x25 mm3 was positioned in a medial frontal area; TR/TE 4000/6ms, BW = 2 kHz, number of averages (NA) = 148, vector size = 2048. GSH levels were quantified using LCModel.
- **high resolution T1w imaging (MPRAGE)**
  32-channel coil; 240 x 256 x 160 voxels of isotropic 1mm resolution, slice thickness = 1.2mm; TR/TI/TE = 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.

IMAGE PROCESSING and GRAPH ANALYSIS

- DSI and MPRAGE data were processed using the **Connectome Mapper** (www.cmtk.org) in order to obtain *brain tissues masks*, *cortex parcellation into 83 anatomical ROIs*, *whole brain tractography* and *brain connectivity adjacency matrices*.
- A **gFA scalar map** was computed for each subject, and fiber tracts were weighted by the average gFA value along the tract as a measure of WM integrity and connectivity strength.
- **Global network measures** were computed for each subjects from the corresponding structural connectivity matrices weighted by the gFA values.




gFA map

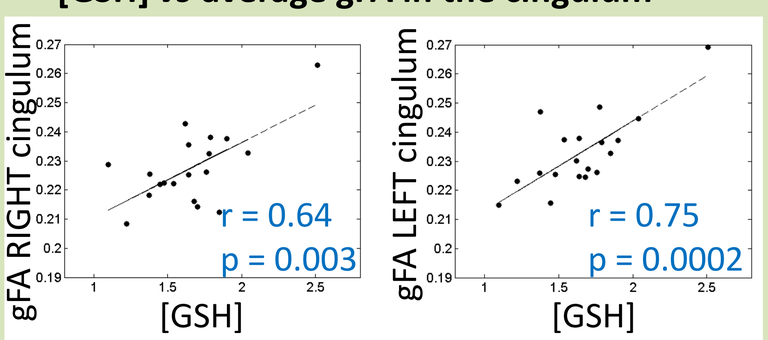


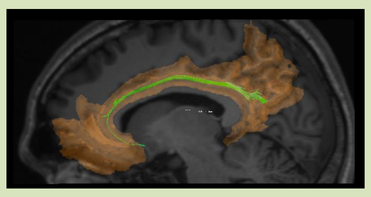
Brain connectivity matrix (color coding: average gFA value along each connecting tract)

RESULTS

[GSH] *vs* average gFA in the cingulum

Healthy subjects

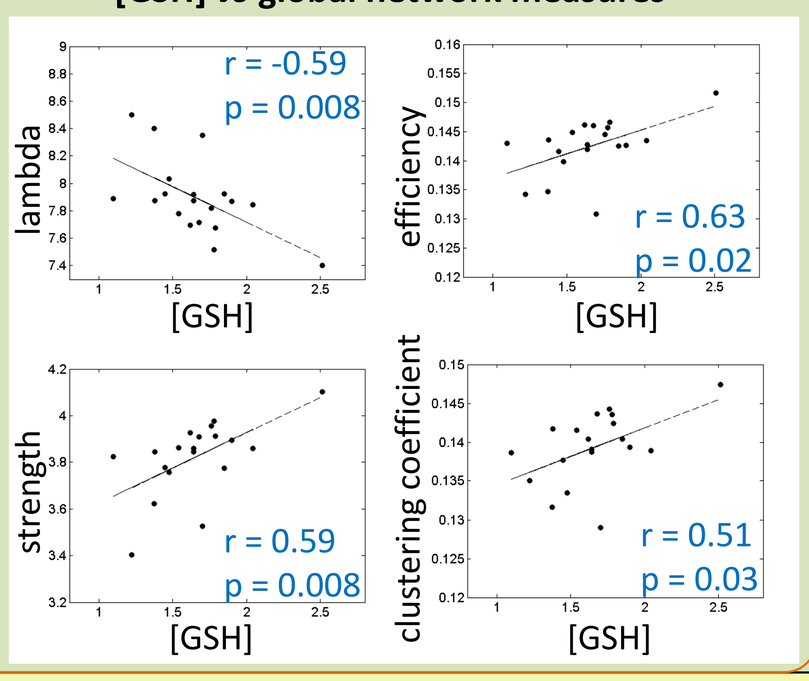




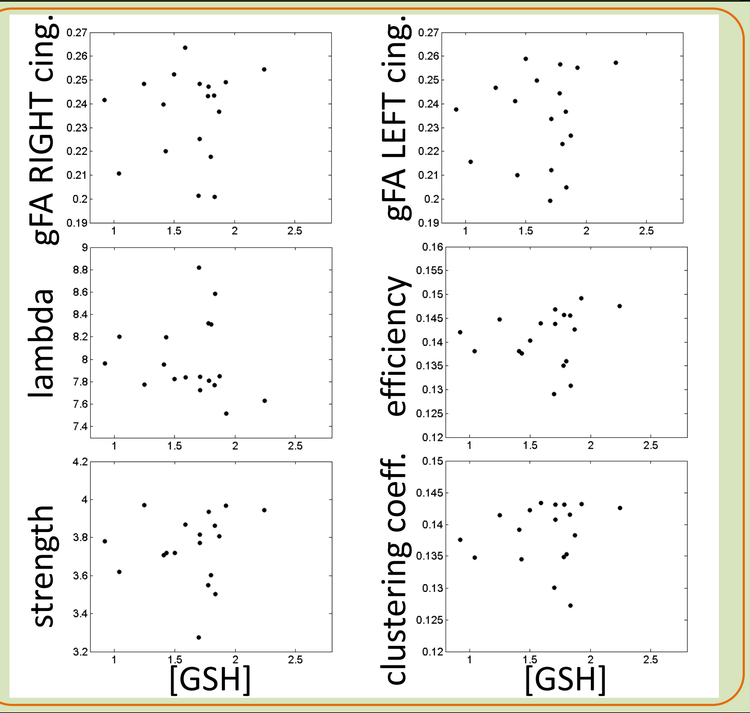
r: Pearson correlation coefficient
p: p-value associated to r

Each point in the graphs corresponds to a subject.

[GSH] *vs* global network measures



Early psychosis subjects



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.

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