

Increased glutathione levels in chronic and recent onset schizophrenic patients

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TARGET AUDIENCE: Neuroscientists, psychiatrists and imaging researchers interested in schizophrenia (Sz).

PURPOSE: It has been suggested that oxidative stress plays a role in the pathogenesis of Sz. The purpose of this study, therefore, was to investigate levels of the major antioxidant in the brain, glutathione (GSH), in both recent onset and chronic Sz patients, and to compare to control subjects.

METHODS: 14 patients with Sz (four with recent onset, 10 with chronic disease; median age 41.8 years, 5 female) were compared to seven healthy controls (median age 23.5 years, 1 female). All subjects gave written IRB-approved informed consent. GSH-edited MEGA-PRESS spectra of the anterior cingulate cortex (ACC) and dorsolateral prefrontal cortex (DLPFC) were acquired on a Philips Achieva 3T scanner using an 8-channel head coil with the following parameters: TR/TE 2000/130ms; 32 dynamic repeats (alternating editing frequency) of a 16-scan phase cycle with on/off editing pulses at 4.56 and 5.50 ppm respectively; voxel size 4x3x3.5 cm³; VAPOR water suppression; scan time 17 minutes.

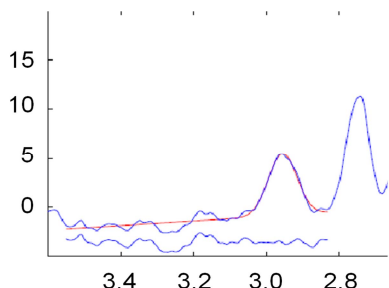


Figure 1: Fitted GSH peak of GSH-edited spectrum from a control subject

Spectral analysis was performed using an in-house software (GSHanet). Statistical analyses included repeat measures ANOVA and Wilcoxon rank sum test for pairwise comparisons, and Spearman correlation to assess the relationship between GSH levels, positive or negative symptoms¹ (available in 7 patients), and cognitive tests² (available in 12 subjects [9 patients, 3 controls]).

RESULTS: GSH/creatine (Cr) ratios in the ACC were higher in patients compared to controls (median GSH/Cr 0.063 vs. 0.049, $p=0.0014$) but did not differ significantly between recent onset vs. chronic disease (median GSH/Cr 0.063 vs. 0.062, $p=0.94$). In the DLPFC, GSH/Cr was also higher in patients (median GSH/Cr 0.044 vs. 0.035, $p=0.02$) and did not differ between chronic and recent onset cases (median GSH/Cr 0.047 vs. 0.049, $p=0.20$). For all subjects, GSH/Cr was higher in the ACC than DLPFC (median 0.058 vs. 0.040, $p<0.001$). No significant associations were

seen between positive or negative clinical symptoms and GSH/Cr (ACC, $p=0.35$; DLPFC, $p=0.57$), however this may be in part due to the fact that clinical data was available for only 7 subjects. Among the 12 subjects with available cognitive test data, ACC GSH/Cr correlated negatively with processing speed ($\rho=-0.67$, $p=0.03$) and verbal ability ($\rho=-0.70$, $p=0.02$). There was no significant correlation between and either processing speed or verbal ability ($\rho=-0.10$, $p=0.75$ and $\rho=0.03$, $p=0.91$, respectively). No significant differences in [Cr] concentration (as measured by LCModel analysis of conventional MRS from the same voxels) were found between groups.

DISCUSSION: MRS studies of GSH, the brain's dominant antioxidant, in psychiatric disease are sparse. It has been suggested that an impaired capacity to synthesize GSH under oxidative stress is a vulnerability factor for Sz. This study provides further evidence of significant changes in brain GSH in patients with Sz, which (in the ACC) correlate with measures of processing speed & verbal ability. Results of prior *in vivo* MRS studies are variable, perhaps due to both methodological differences, as well as differences in study populations. However, consistent with the current results in both chronic and recent onset cases, elevated GSH was found in a prior study of subjects experiencing a first psychotic episode³. It's possible that an increase in GSH in patients with Sz may be a compensatory response, and studies of the stage-dependent gene expression for enzymes in the GSH pathway may shed light on the pathophysiological mechanisms.

CONCLUSION: This study provides support for altered GSH levels in Sz, but further studies are still needed to determine underlying mechanisms, including the effects of treatment, and to investigate the relationship between GSH levels, other markers of oxidative stress, and severity of both positive and negative symptoms in a larger number of subjects.

Acknowledgements: This research was funded by NIH grant R01MH92443.

References 1. Andreasen NC: Scale for the Assessment of Negative Symptoms (SANS). Scale for the Assessment of Positive Symptoms (SAPS). Iowa City, IA, University of Iowa, 1984 2. Schretlen et al. Calibrated Neuropsychological Normative System professional manual. Odessa, FL: Psychological Assessment Resources, Inc. (2010) 3. Wood, S. J. et al. Medial temporal lobe glutathione concentration in first episode psychosis: a 1H-MRS investigation. *Neurobiol. Dis.* 33, 354-357 (2009)

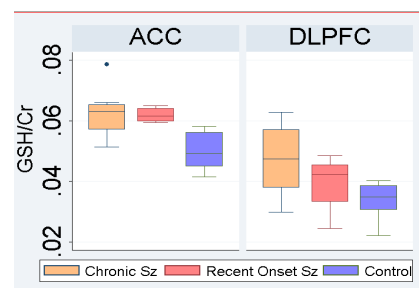


Figure 2: Boxplots of GSH/Cr ratios in patients and controls