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Authors

Lesh, Tyler A
Maddock, Richard J
Howell, Amber
et al.

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Extracellular Free Water and Glutathione in First Episode Psychosis – A Multi-modal Investigation of an Inflammatory Model for Psychosis

Tyler A. Lesh, Ph.D.[1], **Richard J. Maddock, M.D.**[1], **Amber Howell, B.S.**[1], **Huan Wang, B.S.**[1], **Costin Tanase, Ph.D.**[1], **J. Daniel Ragland, Ph.D.**[1], **Tara A. Niendam, Ph.D.**[1], **Cameron S. Carter, M.D.**[1]

[1]Department of Psychiatry, University of California, Davis

Abstract

Evidence has been accumulating for an immune-based component to the etiology of psychotic disorders. Advancements in diffusion magnetic resonance imaging (MRI) have enabled estimation of extracellular free water (FW), a putative biomarker of neuroinflammation. Furthermore, inflammatory processes may be associated with altered brain levels of metabolites, such as glutathione (GSH). Consequently, we sought to test the hypotheses that FW is increased and associated with decreased GSH in patients with first episode schizophrenia (SZ) compared to healthy controls (HC). SZ (n=36) and HC (n=40) subjects underwent a multi-shell diffusion MRI scan on a Siemens 3T scanner. 1H-MR spectroscopy data were acquired using a GSH-optimized MEGA-PRESS editing sequence and GSH/creatine ratios were calculated for DLPFC (SZ: n=33, HC: n=37) and visual cortex (SZ: n=29, HC: n=35) voxels. Symptoms and functioning were measured using the SANS, SAPS, BPRS and GSF/GRF. SZ demonstrated significantly elevated FW in whole-brain gray (p=.001) but not white matter (p=.060). There was no significant difference between groups in GSH in either voxel. However, there was a significant negative correlation between DLPFC GSH and both whole-brain and DLPFC-specific gray matter FW in SZ (r=−.48 and −.47, respectively; both p<.05), while this relationship was nonsignificant in HC and in both groups in visual cortex. These data illustrate an important relationship between a metabolite known to be important for immune function – GSH – and the diffusion extracellular FW measure, which provides additional support for these measures as neuroinflammatory biomarkers that could potentially provide tractable treatment targets to guide pharmacological intervention.

Correspondence: Dr. Tyler A. Lesh, Imaging Research Center, University of California, Davis, 4701 X Street, Ste. E, Sacramento, CA 95817, Phone: 916-734-7174, Fax: 916-734-8750, talesh@ucdavis.edu.

Conflict of Interest

The authors declare no conflicts of interests.

Supplementary information is available at MP's website.

Introduction

Evidence has been accumulating for an immune-based component of schizophrenia (SZ) etiology. Mednick and colleagues [1] provided some of the first evidence many decades ago, identifying increased rates of psychotic disorders in the offspring of women who were exposed to infection while pregnant [2 see for review]. In more recent years genetic links have been identified with the major histocompatibility complex, a section of the genome critical for immune function[3]. Furthermore, alterations in molecular markers mediating immune function, such as the cytokines IL-6, IFN-g, and TNF-a, have been repeatedly observed both in first episode and chronic individuals with schizophrenia, both on and off medication [4].

Recently, several groups have attempted to identify this “neuroinflammatory” signal using various brain imaging techniques. Initial studies using positron emission tomography and translocator protein (TSPO) ligands provided some evidence of increased microglial activity in gray matter and hippocampus [5, 6]. However, more recent studies using second generation TSPO ligands, including some with larger samples, have not replicated this result [7–10].

Other putative markers of neuroinflammation may be measured using magnetic resonance imaging techniques, including diffusion imaging and proton spectroscopy. Pasternak and colleagues have recently demonstrated the utility of measuring extracellular free water, both as a method of adjusting for free water in the calculation of fractional anisotropy [11], but also as a separate biomarker that may be associated with inflammation or other neuropathological processes. This research group has demonstrated a pattern of increased free water and comparable white matter integrity in first episode psychosis samples [12], while a chronic sample showed more prominent reductions in fractional anisotropy [13]. There is also preliminary evidence that chronically ill individuals with present state delusions show elevated free water compared to controls, particularly in the cingulum bundle, although free water did not distinguish those with present delusions from other patient groups with either past delusions or no lifetime history [14].

Furthermore, there is evidence that neuroimmune activation may alter brain levels of metabolites that can be measured non-invasively with proton magnetic resonance spectroscopy (1H-MRS). Glutathione (GSH) is a potentially informative inflammatory biomarker, as it is one of the major antioxidants in the human body and plays a role in cell proliferation, apoptosis, and immune function. GSH can be depleted by oxidative stress and is reduced in several neuroinflammatory conditions (e.g., multiple sclerosis, AIDS) [15, 16]. In addition, recent mouse and in vitro studies have shown that GSH (directly and via its precursor, NAC) also has specific, protective interactions with neuroimmune response cascades, including inhibition of microglial activation and reduction of brain inflammatory markers evoked by neuroimmune activating agents [17, 18]. One influential model that is supported by epidemiological studies as well as a large body of work using animal model systems posits that in some individuals, maternal immune activation, which may be related to maternal infections, exposures or other stressors in utero, causes a long-lasting sensitization of neuroimmune response elements in individuals who later develop schizophrenia. These sensitized systems might include the neuroimmune and proinflammatory functions of microglia and astrocytes. While GSH may not prevent this

initial sensitization, it could plausibly protect against some of the consequences of such sensitization. Sensitization renders the neuroimmune response elements vulnerable to activation by normally subthreshold provocations. GSH could inhibit such activation, as has been shown with its precursor, NAC, for microglial activation by LPS [17]. Consequently, GSH is a strong candidate biomarker for psychotic disorders and the majority of studies have found GSH to be reduced in blood [19–35] and to some degree in CSF [29, 36] compared to control subjects. Useful measurement of GSH in brain with 1H-MRS requires either high field MR systems not generally available in clinical centers or advanced acquisition sequences, such as J-difference editing [37–39]. In the earliest study of GSH in prefrontal cortex, Do and colleagues [36] used a double quantum coherence sequence at 1.5 Tesla and reported reduced medial prefrontal cortex (mPFC) GSH in 14 schizophrenia patients compared to 14 comparison subjects. However, more recent studies using a STEAM sequence at 4 Tesla [40] and a MEGA-PRESS editing sequence at 3 Tesla [41] observed no group differences in mPFC GSH. A study by Wood and colleagues [42] reported increased medial temporal cortex GSH in a psychotic disorder sample. However, the use of a conventional PRESS sequence at 3 Tesla makes it challenging to interpret these data [39]. Of the four largest and most recent studies, two showed significantly lower GSH in patients compared to controls using a STEAM sequence at 7 Tesla [43, 44], while the other two studies showed no differences between patients and controls [19, 45] . It is not clear why GSH reductions have not been consistently observed. Small sample sizes, varying clinical features of the patient groups, and different technical methods may account for some of these differences.

The goal of the present study is to leverage the use of these two biomarkers, extracellular free water and cortical GSH, to further investigate the role of immune disruption in the brain in individuals with a first episode psychotic disorder. Given that free water may be influenced by a variety of factors, including inflammation, degeneration, or edema, testing the relationship to an established measure of immune function in brain—GSH—will inform the validity and clinical utility of this measure. Building upon previously published single-shell diffusion studies in first episode psychosis [12] we used a multi-shell diffusion weighted acquisition optimized for the measurement of free water in brain tissue. We hypothesize that free water will be increased in individuals with first episode psychosis. We also predict that dorsolateral prefrontal cortex (DLPFC) GSH level will correlate negatively with free water in patients, reflecting a convergence of factors associated with neuroinflammation that varies in degree among individuals with first episode psychosis. In addition, we will test the hypothesis that GSH is reduced in the patient group as a whole.

Methods and Participants

Thirty-nine first episode schizophrenia patients (See Table 1 for diagnoses and clinical status) and 41 control subjects between the ages of 16 and 30 were recruited for the study. After exclusions for data quality, 36 schizophrenia and 40 control participants remained with good diffusion data. Of this sample, 33 patients and 37 controls had good quality DLPFC GSH data and 29 patients and 35 controls had good visual cortex GSH data (see Supplementary Information for details). Participants with schizophrenia-spectrum diagnoses were outpatients within two years of their first psychotic episode. All participants were

assessed using the Structured Clinical Interview for the DSM-IV-TR SCID-I/P; [46]. Clinical ratings were collected in the patient group using the Scale for the Assessment of Negative Symptoms SANS; [47], Scale for the Assessment of Positive Symptoms SAPS; [48], Brief Psychiatric Rating Scale BPRS; [49], and Global Functioning: Social [50] and Role [51] scales. Exclusion criteria for both groups included: Wechsler Abbreviated Scale of Intelligence (WASI) IQ score below 70, alcohol or drug dependence or abuse within 3 months before testing, positive urine toxicology screen for illicit drugs, prior head trauma worse than a Grade I concussion, or contraindication to MRI scanning. Control subjects were excluded for the following *additional* criteria: any lifetime diagnosis of an Axis I or Axis II disorder or any first-degree relatives with a psychotic disorder. Before testing, a detailed description of the study was provided and written informed consent obtained. The study was approved by the University of California, Davis Institutional Review Board and all subjects consented to and were paid for their participation.

Imaging Parameters and Data Analysis

Imaging data were obtained using a 3T Siemens Tim Trio MRI scanner. T1-weighted MPRAGE structural images were acquired with the following settings: TR=2,530-msec, echo time=3.5-msec, flip-angle=7˚, field of view=256mm, 1mm isotropic voxels. 1H-MRS data were acquired from voxels placed in the DLPFC and in the visual cortex, as a control region (see Supplementary Information). GSH was measured with a MEGA-PRESS, J-difference, editing sequence optimally adapted for GSH [37, 52–54]. Parameters included: TE/TR = 131/2000; bandwidth = 2000 Hz; on and off resonance SLR edit pulse frequencies = 4.56 and 4.90 ppm; edit pulse bandwidth = 30 Hz; edit pulse duration = 39.68 msec. The edited spectra were acquired in two sequential acquisitions of 176 averages each (total 352 averages, 11.7 minutes total duration). A conventional PRESS sequence was acquired from the same voxels with TE/TR = 30/1500 and 160 averages.

The diffusion sequence was acquired with the following settings: TR=11,400-msec, echo time=92.4-msec, field of view=240mm, 1.7mm isotropic voxels. The sequence included 56 directions acquired P-A with the following b-shells: 12 x b=0, 10 x b=500, 30 x b=900, 16 x b=1400. Diffusion images were first visually inspected for image quality and images containing artifacts were discarded. The remaining diffusion weighted images underwent eddy current correction and realignment using FSL's eddy [55], including rotation of b-matrices. The Dipy diffusion imaging library [56] and included free water elimination model [57] were used to calculate all diffusion metrics. This model expands the typical DTI model and assumes that each voxel contains two components: an anisotropic tissue-bound component and an isotropic extracellular free water component. In this study, we evaluated both the free water component and tissue-specific fractional anisotropy (FA-t), which reflects traditional FA with the free water component eliminated.

In order to calculate free water values specific to gray and white matter, brain extraction and segmentation of MPRAGE images was performed using Freesurfer 5.3 [58]. White and gray matter masks from Freesurfer were brought into alignment with each subject's free water image using bbregister [59]. Each MPRAGE underwent a rigorous quality inspection by individuals blind to group—including talairach alignment evaluation, meninges/skull

removal, white matter editing, and surface inspection, according to standard Freesurfer documentation. Mean free water values were calculated across all voxels within gray and white matter masks for each subject.

To further explore the regional specificity of gray and white matter free water, two additional analyses were performed (see Supplement). Briefly, free water maps were projected onto individual subject cortical surfaces using Freesurfer's mri_vol2surf to assess free water in a vertex-wise manner using mri_glmfit. Multiple comparisons correction was employed using cluster analysis with Freesurfer's precomputed Z Monte Carlo simulation (cluster threshold of $p<0.01$ and clusterwise probability of $p<0.05$). White-matter free water and FA-t maps were nonlinearly aligned to the FMRIB58_FA image using FNIRT and projected on the white matter skeleton using FSL's Tract Based Spatial Statistics (TBSS) [60]. Randomise[61] and threshold-free cluster enhancement[62] were used to define clusters and correct for multiple comparisons.

GSH was quantified by peak integration of the MEGA-PRESS difference spectra using LCModel 6.3–1L [63], jMRUI 5.2 [64] and custom software in an operator-independent sequence of processing steps. The on and off resonance spectra from each acquisition were first zero-filled (2x), phase-aligned, and apodized in jMRUI. The on and off resonance spectra were then frequency-aligned using custom software and subtracted to generate difference spectra. The two difference spectra were phase and frequency aligned to each other and summed. The GSH cysteine resonance at 2.95 ppm was then quantified by line-width optimized peak integration in the final difference spectrum. The creatine resonance at 3.02 ppm was similarly quantified by peak integration in the final summed spectrum and used to calculate the GSH/creatine ratio (Supplementary Figure 1). To explore the specificity of the correlation between free water and GSH, five supplementary metabolites (total choline, total NAA, total creatine, glutamate, and inositol) from the PRESS acquisition were tested for relationships with whole-brain gray/white free water values (see Supplement).

Statistical Methods

Differences in demographic characteristics were assessed with Pearson Chi-Square or independent samples t-tests, where appropriate. Between-group free water and GSH/creatine ratios were assessed with independent samples t-tests and relationships between free water and GSH/creatine ratios were tested with Pearson r correlations. Any measures that were not normally distributed underwent follow-up non-parametric tests and are reported if significance changed. Alpha was set at $p<.05$, two-tailed, to determine significance for all tests.

Results

Participant demographic and clinical information is presented in Table 1. The groups did not differ significantly on age ($t(74)=.70$, $p=.48$), gender ($\chi^{2=}.033$, $p=.86$), or parental education ($t(71)=.42$, $p=.67$). Controls were more highly educated than patients ($t(74)=3.37$, $p=.001$) and showed significantly higher estimated IQ ($t(71)=3.05$, $p=.003$).

Between-group Comparisons

As seen in Figure 1, individuals with first episode schizophrenia demonstrated significantly elevated free water in whole-brain gray ($t(74)=3.79$, $p<.001$) with a trend elevation in white matter ($t(74)=1.91$, $p=.060$). There were no significant group differences in GSH within the DLPFC ($t(68)= 1.07$, $p=.29$) or visual cortex voxels ($t(62)=.19$, $p=.85$). There was a significant negative correlation (Figure 2) between DLPFC GSH and gray matter free water in the patient group ($r=-.48$, $p=.004$), although the relationship with white matter free water did not reach significance ($r=-.26$, $p=.14$). Free water was not correlated to GSH in controls or any visual cortex data. Finally, the relationship between DLPFC GSH and gray matter free water was significantly stronger in first episode participants compared to controls (Fisher's r-to-z, $p=.005$). The strength of the free water-GSH relationship did not differ between groups in the other three comparisons (all $p>.32$).

A follow-up analysis was also performed on free water in tissue specifically restricted to the MRS voxel location and detailed in the Supplement. In brief, these results are very similar to the whole-brain findings, with a significant relationship in patients between DLPFC voxel-specific gray matter free water and DLPFC GSH ($r=-.472$, $p=.006$), with a significantly stronger relationship in patients compared to controls (Fisher's r-to-z, $p=.02$).

Voxel-wise TBSS analyses revealed significantly increased free water in patients with schizophrenia compared to controls (Figure 3) across both hemispheres in a relatively widespread pattern. No group differences were identified in the voxel-wise FA-t TBSS analysis.

Vertex-wise analyses of gray matter free water projected to the cortical surface revealed significantly increased free water in patients with schizophrenia in lateral frontal cortex, right rostral anterior cingulate, bilateral temporal cortex extending into the insula, left hemisphere inferior parietal cortex, left hemisphere posterior cingulate, and occipital cortex (Figure 4 and Supplementary Table 1).

Specificity of GSH-Free Water Relationship

Potential concerns in testing only the relationship between GSH and free water are that the association could potentially be driven by creatine-associated variance in the GSH/Cr ratio or that the GSH-free water association is not specific to GSH. For example, inositol has also been linked to neuroimmune alterations [65–67]. To explore these issues, we evaluated the relationship between free water and the other reliably estimated creatine normalized metabolites (total choline, NAA, glutamate, inositol, and the absolute value of creatine; all CRLB < 10%) from the DLPFC PRESS acquisition. None of these metabolites significantly correlated with gray or white matter free water in either group (all $p > .13$), suggesting a specific relationship with GSH.

Relationships to Symptoms and Functioning

Clinical scores were included in vertex- and voxel-wise whole-brain regressions with free water using Freesurfer and TBSS. Significant positive associations were identified between prefrontal gray matter free water (rostral middle frontal gyrus and anterior cingulate) and

both SAPS and BPRS total scores (Supplementary Figure 3 and Supplementary Table 2). No voxels survived correction for multiple comparisons in white matter free water-symptom analyses.

Discussion

These data represent the first evaluation of both GSH and multi-shell diffusion extracellular free water in a first episode schizophrenia sample. In agreement with results reported by Pasternak et al. [12], free water was elevated in individuals with first episode psychosis in both white and gray matter. Furthermore, while the groups did not differ on GSH, the significant inverse relationship observed between GSH and gray matter free water could reflect a common linkage to neuroinflammatory processes. Consistent with most prior studies, prefrontal GSH levels were not different between psychosis and control groups. While free water could represent an amalgam of biological processes, including inflammation, degeneration, or edema, the significant relationship to a known inflammation-related metabolite, GSH, provides additional support for the link between free water and neuroimmune processes and the use of the combination of measures as complementary biomarkers to guide pharmacological intervention.

Several studies using single-shell diffusion data have shown that extracellular brain free water is increased in patients with first episode schizophrenia [12, 68] and, to a lesser degree, chronic schizophrenia [13, 69]. We show similar increases in free water throughout the white matter skeleton using an optimized multi-shell sequence, which should represent an improvement in estimating free water. Furthermore, we used the novel approach of evaluating gray matter free water projected on the cortical surface, which identified lateral and medial prefrontal, temporal/insula, inferior parietal, and occipital clusters of increased free water in the schizophrenia sample. These specific regions of elevated free water notably overlap with regional disruptions of gray matter density [70, 71], cortical thickness [72, 73], and fMRI BOLD [74] activity that are repeatedly identified in individuals with schizophrenia. Notably, we also found that higher free water in prefrontal gray matter was also associated with worse symptomatology, suggesting that this measure may index clinical severity.

Although free water was the primary diffusion metric for the present study, we also investigated FA-t in order to evaluate microstructural white matter integrity between groups. Our analyses revealed no significant differences in FA-t throughout the white matter skeleton. While the majority of published studies suggest decreases in fractional anisotropy [75–77] only more recent studies have applied the free water elimination model to evaluate FA-t. This is critically important, given that free water contamination of voxels may artificially lower traditional FA values in individuals who have more free water. Specifically, the studies that evaluated FA-t in first episode samples identified relatively isolated FA-t decreases [12, 68] in contrast to the more widespread traditional FA decreases in chronic schizophrenia. The young, first episode sample in the present study, with a short duration of illness, treated with relatively low doses of antipsychotics, and an absence of substance abuse may also partially explain the lack of FA-t differences.

Our finding of similar levels of GSH in patient and control groups is relatively consistent with the GSH literature, given that the majority of published studies have also shown no significant differences [19, 40, 41, 45]. Since the pioneering work of Do and colleagues [36], there have been only two additional published reports of lowered brain GSH in schizophrenia [43, 44], although a negative relationship between GSH levels and negative symptoms has been reported [41].

Interestingly, the relationship between GSH and free water was only identified in individuals with first episode psychosis and only in the DLPFC voxel. In addition, the specific relationship between DLPFC GSH and gray matter free water was significantly stronger in the patient group compared to controls. One interpretation of these findings is that this relationship may emerge only in the presence of an inflammatory process. Additionally, the lack of any relationships between free water and the visual cortex control region suggests that there may be some regional specificity to these findings, and add to the large body of existing literature demonstrating DLPFC dysfunction across many imaging modalities in first episode schizophrenia. Several interacting homeostatic mechanisms regulate brain tissue GSH levels, tending to keep them within a range of normal values [78, 79]. Some inflammatory processes can alter this process sufficiently to cause low GSH levels, such as in multiple sclerosis [80, 81]. Some inflammatory processes do not have this effect, and GSH levels remain normal, as in ALS, for example [82, 83]. It is possible that an inflammation-related process in schizophrenia could cause elevated free water without causing reduced GSH at the mean group level, as is suggested by our data. In this case, GSH could be serving a protective function. Those patients who maintain a relatively high GSH level may benefit from greater protection against inflammation compared to those patients who maintain a relatively low GSH level. In the absence of an underlying inflammatory process in the control group, GSH levels are not expected to correlate inversely with free water values in this group. This is because GSH is not serving a protective role against a pathogenic process causing elevated free water in this group.

Limitations

GSH is a difficult metabolite to measure, particularly at lower field strengths. Our approach was to use an optimized MEGA-PRESS sequence at 3 Tesla and to quantify GSH relative to creatine. It is possible that more sensitive measures of GSH or larger sample sizes might have revealed further associations with GSH levels. There have been reports in the literature that creatine levels may be reduced in schizophrenia [84], although a recent meta-analysis found no evidence for decreased creatine in schizophrenia or bipolar disorder [85]. Lower creatine levels in the patient group would tend to skew results in the opposite direction of our hypotheses, with the patient group potentially showing a bias towards a higher GSH/creatine ratio. Given that our findings reveal no significant differences between groups, it remains possible, although unlikely, that differences in creatine may have contributed to the null result. However, an exploratory evaluation of other metabolites normalized to creatine revealed a specific relationship with the GSH/creatine ratio and free water, which suggests creatine is not the main driver of these findings. An additional concern is that neuroinflammation is only one possible mechanism that could account for the pattern of findings we report here. For instance, increases in free water could reflect other

neuropathological processes unrelated to immune processes, although the lack of group differences in FA-t suggests that free water increases are not likely due to white matter degradation. An additional concern is that the majority of subjects in the sample were taking antipsychotic medication and a growing body of literature suggests that antipsychotics may have anti-inflammatory properties. Recent meta-analyses of the cytokine literature [4, 86] highlight antipsychotic-related decreases of pro-inflammatory cytokines in the peripheral circulation, particularly IL-1B, IL-6, and IFN-g. Additionally, antipsychotics have been associated with inhibition of these same pro-inflammatory cytokines in stimulated microglia cultures [87]. Additional work, particularly in animal models and antipsychotic-naïve individuals, is needed to investigate these relationships.

Conclusions and Future Directions

These data provide compelling evidence that the simultaneous acquisition of different imaging measures including extracellular free water and GSH can inform our understanding of altered neuroinflammatory processes that may underlie the developmental biology of psychotic disorders. However, the overlap between control and patient groups in both free water and GSH values is considerable and consequently only a subset of patients may evidence a strong immune component to the etiology of their illness. Indeed, post mortem analyses in schizophrenia have suggested that there is increased expression of inflammation-related genes in perhaps thirty [88] to forty [89] percent of patients. This heterogeneity may partly explain why several clinical trials evaluating add-on treatment using anti-inflammatory agents have shown relatively modest benefits in relieving symptomatology [90–95], with one additional study showing no benefit [96]. Consequently, the use of MRI-based markers such as those used in the present study may offer the potential of a more personalized approach to clinical trials of inflammation-related therapies, in which patients are stratified based upon diffusion MRI data and offered targeted intervention based upon these measures.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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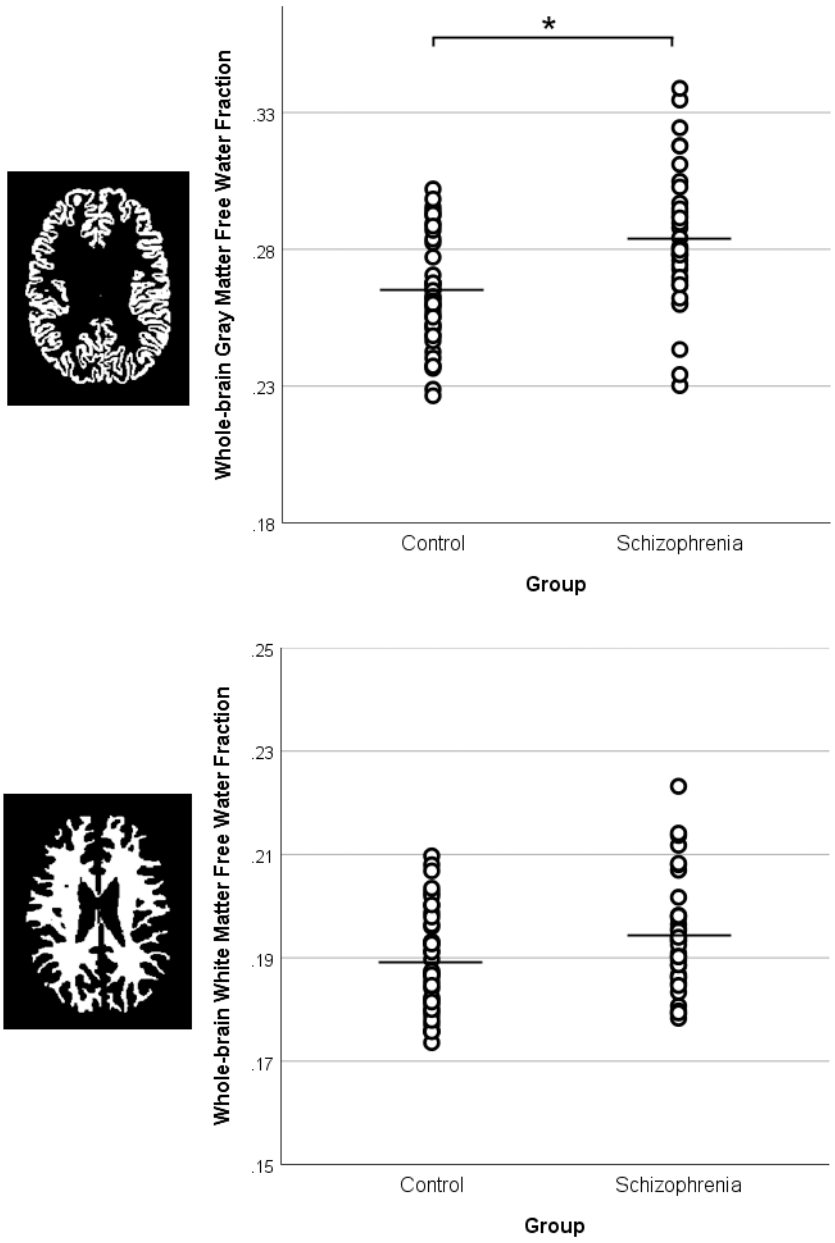

Figure 1:

Whole-brain gray and white matter free water values. Independent samples t-test revealed increased free water in first episode schizophrenia patients (SZ) compared to controls (HC) in gray matter ($p<.001$), with a trend elevation in white matter ($p=.060$). Black lines represent the mean. Means and standard deviations are presented in Supplementary Table 3.

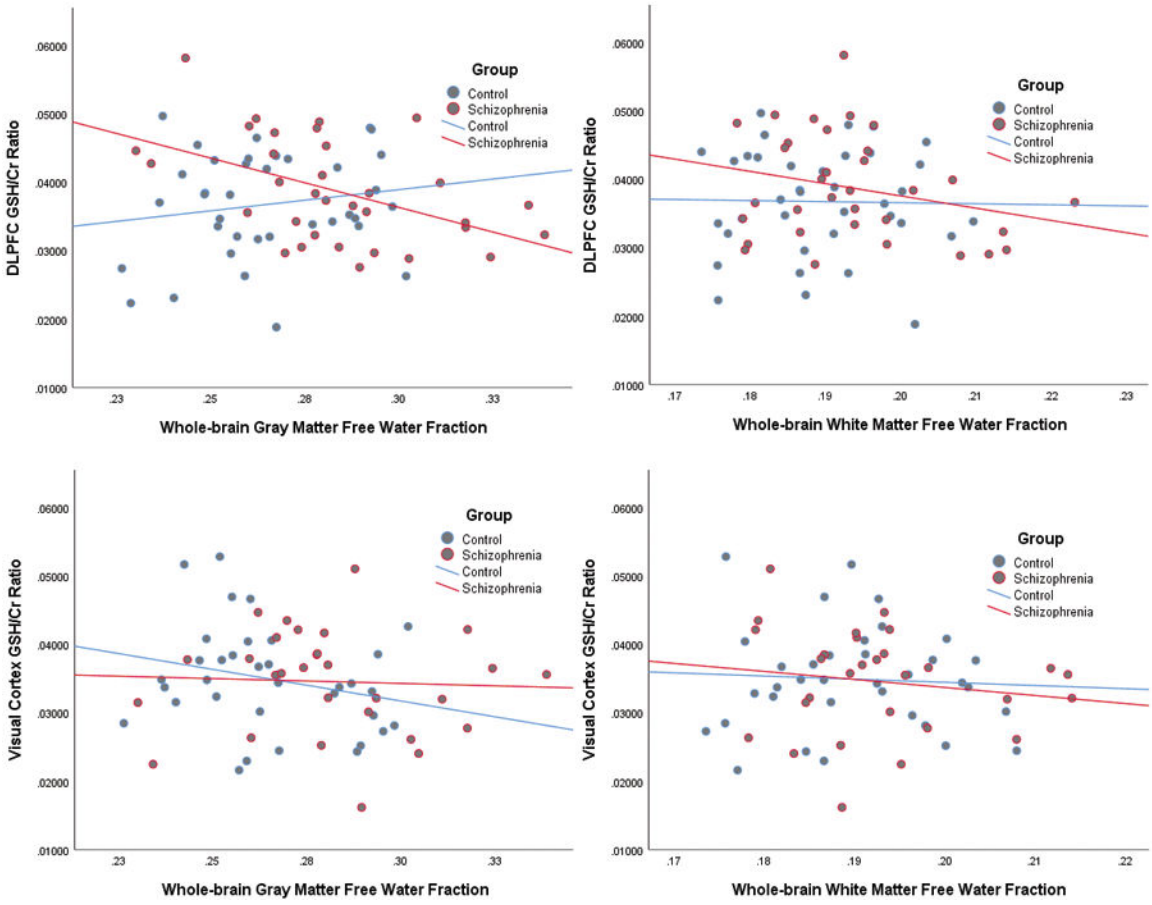

Figure 2:

Relationships between glutathione (GSH) and free water measures were tested with Pearson r correlations. The top two panels present the relationship between gray (top left) and white (top right) free water and DLPFC GSH values. The bottom two panels present the relationship between gray (bottom left) and white (bottom right) free water and visual cortex GSH values. A significant inverse relationship was identified between GSH in the hypothesized DLPFC region and gray matter free water in schizophrenia patients (p=0.004). Additionally, the relationship between GSH and gray matter free water was stronger in the schizophrenia group compared to the control group (Fisher's r-to-z, p=.005).

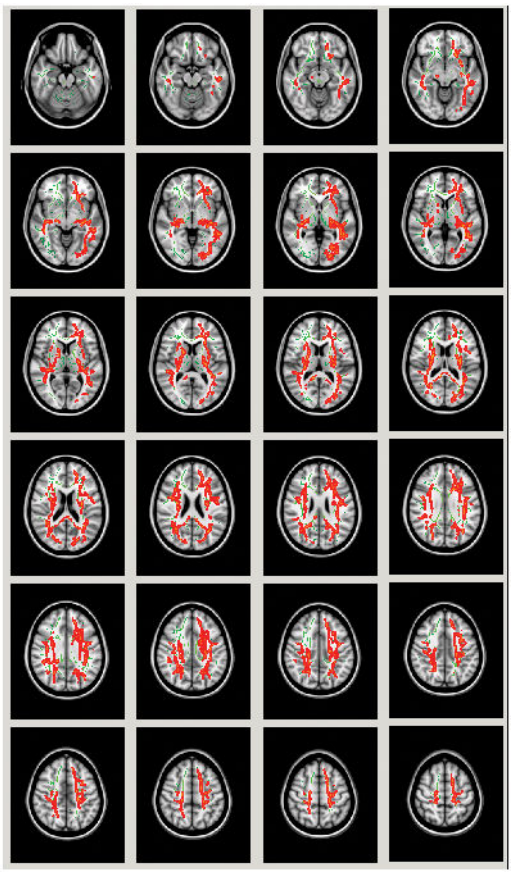

Figure 3:

Tract-based spatial statistics voxel-wise analysis of free water group differences presented in axial slices. Regions in red depict areas in which first episode schizophrenia patients showed significantly higher free water compared to controls. Clusters presented survive correction for multiple comparisons ($p<.05$).

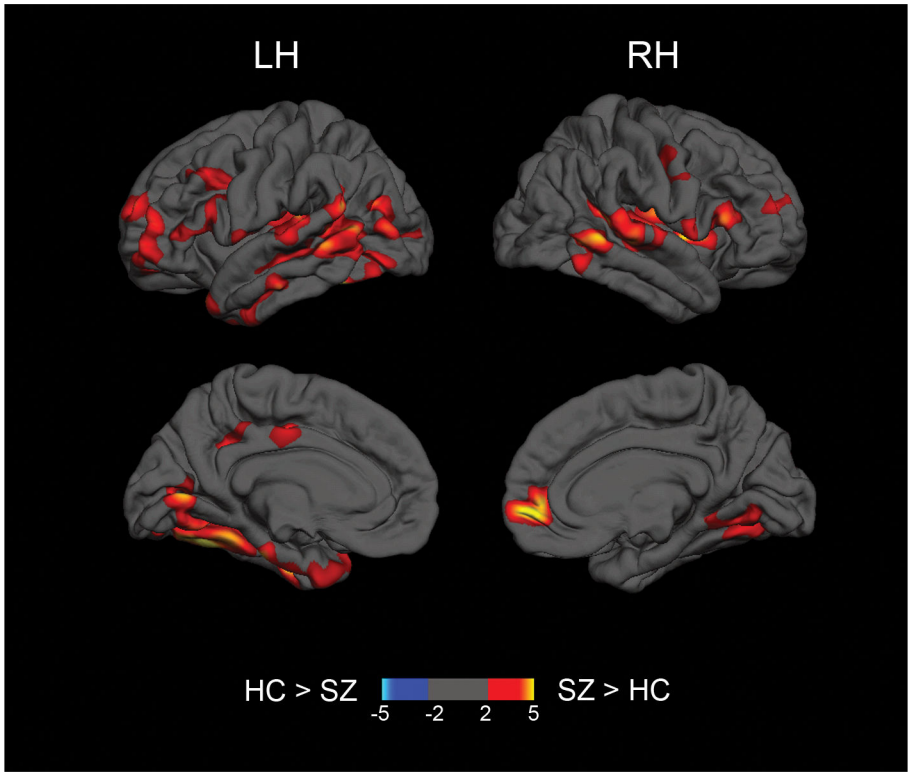

Figure 4:

Representation of regional group differences in free water in the cortical gray matter. Free water was projected on the cortical surface and tested for group differences using Freesurfer tools. Hot colors represent clusters in which first episode schizophrenia patients (SZ) show significantly higher free water compared to controls (HC) in the left (LH) and right (RH) hemispheres. Clusters presented survive correction for multiple comparisons ($p<.05$). The color scale ranges from 2 to 5, representing $-\log10$(p-value) of p=.01 to .00001.

Table 1:

Sample demographic and clinical characteristics.

	Control (n=40)	Schizophrenia (n=36)
Age: mean (SD)	21.9 (2.8)	21.4 (3.4)
Gender: number Male/Female	27 / 13	25 / 11
Education: mean (SD)	14.3 (2.6)	12.5 (1.9) *
Parental Education: mean (SD)	14.7 (3.5)	14.4 (2.9)
WASI: mean (SD)	115.8 (12.3)	104.6 (18.6) *
Diagnosis: (n)		
Schizophreniform	-	3
Schizophrenia	-	18
Schizoaffective	-	15
Antipsychotic Dose: mean CPZ equivalent (SD)	-	226.64 (168.7)
SANS	-	11.2 (3.6)
SAPS	-	4.4 (3.4)
BPRS	-	46.8 (12.0)
Global Functioning: Social	-	6.1 (1.5)
Global Functioning: Role	-	3.5 (2.5)

SD: Standard Deviation; WASI: Wechsler Abbreviated Scale of Intelligence; CPZ: chlorpromazine; SANS: Scale for the Assessment of Negative Symptoms; SAPS: Scale for the Assessment of Positive Symptoms; BPRS: Brief Psychiatric Rating Scale.

* $p<.05$.