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ARTICLE

# Decreased levels of glutathione, the major brain antioxidant, in post-mortem prefrontal cortex from patients with psychiatric disorders

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**Abstract**

Accruing data suggest that oxidative stress may be a factor underlying the pathophysiology of bipolar disorder (BD), major depressive disorder (MDD), and schizophrenia (SCZ). Glutathione (GSH) is the major free radical scavenger in the brain. Diminished GSH levels elevate cellular vulnerability towards oxidative stress; characterized by accumulating reactive oxygen species. The aim of this study was to determine if mood disorders and SCZ are associated with abnormal GSH and its functionally related enzymes. Post-mortem prefrontal cortex from patients with BD, MDD, SCZ, and from non-psychiatric comparison controls were provided by the Stanley Foundation Neuropathology Consortium. Spectrophotometric analysis was utilized for the quantitative determination of GSH, while immunoblotting analyses were used to examine expression of glutamyl-cysteine ligase (GCL), GSH reductase (GR), and GSH peroxidase (GPx). We found that the levels of reduced, oxidized, and total GSH were significantly decreased in all psychiatric conditions compared to the control group. Although GCL and GR levels did not differ between groups, the levels of GPx were reduced in MDD and SCZ compared to control subjects. Since oxidative damage has been demonstrated in MDD, BD, and SCZ, our finding that GSH levels are reduced in post-mortem prefrontal cortex suggests that these patient groups may be more susceptible to oxidative stress.

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**Key words**: Bipolar disorder, depression, glutathione, oxidative stress, schizophrenia.

## Introduction

A growing body of evidence implicates that mitochondrial dysfunction is associated with mood disorders. Mitochondria are the major source for production of reactive oxygen species (ROS) that cause oxidative damage. Many studies have reported increased oxidative damage in peripheral blood samples from subjects with mood disorders. For example, investigators demonstrated increased total oxidant status in serum from patients with major depressive disorder (MDD) (Cumcurcu *et al*. 2009). Malondialdehyde (MDA), a marker for lipid peroxidation, was elevated in plasma and erythrocytes in MDD (Bilici *et al*. 2001; Sarandol *et al*. 2007). A meta-analysis conducted by our group on oxidative markers in bipolar disorder (BD) patients indicated increased lipid peroxidation (Andreazza *et al*. 2008). Most recently, studies have identified oxidative damage to mitochondrial proteins in prefrontal cortex (Andreazza *et al*. 2010), increased lipid peroxidation in cingulate cortex and increased RNA oxidation in hippocampus from patients with BD and schizophrenia (SCZ) (Che *et al*. in press; Wang *et al*. 2009). Similar findings have also been reported in prefrontal cortex from SCZ patients (Prabakaran *et al*. 2004). All of these studies together suggest that oxidative stress may play a significant role in the pathophysiology of psychiatric illness (Ng *et al*. 2008).

Glutathione (GSH) is the brain's major antioxidant system (Dringen, 2000) and plays a key role against oxidative stress. GSH is biologically synthesized by two enzymatic reactions: (i) L-cysteine and glutamate are combined to form $\gamma$-glutamyl-cysteine, via the rate-limiting enzyme glutamyl-cysteine ligase (GCL); (ii) glycine is added via GSH synthetase. GSH exists in

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either a reduced GSH ($GSH_R$) or oxidized GSH (GSSG) state and it is the reduced state that detoxifies ROS through the donation of a reducing equivalent. Hydrogen peroxide is detoxified by GSH through GSH peroxidase (GPx), thus forming GSSG that is recycled back to $GSH_R$ by GSH reductase (GR) (Meister, 1983, 1988). Hence, maintenance of adequate levels of GSH is essential for preventing oxidative damage to the brain.

ROS are detoxified by specific antioxidant defences. Oxidative stress is an imbalance between the oxidant and antioxidant systems, where the production of free radicals outweighs a system's ability to detoxify reactive intermediates (Halliwell, 2001). Therefore, deficiency of the antioxidant defence system also results in oxidative stress. Reduced total antioxidant capacity in serum has been reported in MDD (Cumcurcu *et al*. 2009; Sarandol *et al*. 2007; Yanik *et al*. 2004). In BD patients, Benes *et al*. (2006) demonstrated lowered gene expression of several antioxidant enzymes in hippocampus, including catalase, GSH, GPx, GSH S-transferase (GST), and superoxide dismutase (SOD). Taken together, psychiatric patients, especially those with SCZ, MDD, and BD have increased levels of oxidative stress; however, to our knowledge no studies have examined GSH and its associated enzyme levels in MDD and BD. Thus, in this study we examined the GSH antioxidant system in post-mortem brain from patients with MDD, BD, and SCZ, and report diminished levels of $GSH_R$ in all patient groups studied.

## Methodology

### *Sample*

Post-mortem brain tissues were donated by the Stanley Medical Research Institute's brain collection courtesy of Drs Michael B. Knable, E. Fuller Torrey, Maree J. Webster, and Robert H. Yolken. Subjects were divided into four groups including BD, MDD, SCZ, and non-psychiatric, non-neurological control groups. Detailed information was available on all subjects through medical records that included demographic data, medical history, substance abuse history, psychotropic drug treatment history, cause of death, and medication at time of death (Dowlatshahi *et al*. 1999; Knable *et al*. 2004; Torrey *et al*. 2000). Diagnoses were established according to DSM-IV criteria by two senior psychiatrists after reviewing the medical records and interviewing family members. Similar review of control subjects confirmed lack of psychiatric illness and substance abuse. All groups were matched for age, sex and post-mortem delay interval. In our studies we used area BA 10 of prefrontal cerebral cortex, a region in which abnormalities have been demonstrated in subjects with mood disorders. For GSH oxidized and reduced measurements, one control subject was not included and for protein level measurements of GCL, GR, and GPx one MDD subject was not included as there was not sufficient tissue for respective analyses.

### *Assay for GSH*

Post-mortem prefrontal cortical tissue was homogenized on ice at 25 mg/ml in a 0.1 M potassium phosphate buffer with 8.8 mM EDTA disodium salt (pH 7.5) containing 0.6% sulfosalicylic acid and 0.1% Triton-X (Sigma-Aldrich, USA). Brain homogenates were centrifuged at 8000 *g* for 10 min at 4 °C before the supernatants were collected and stored at −20 °C. For determination of total glutathione ($GSH_T$), 20 $\mu$l brain homogenate was added to each well of 96-well microplate followed by 120 $\mu$l of 1.68 mM 5,5′-dithiobis (2-nitrobenzoic acid) (DTNB) and 3.3 units/ml GR prepared in 0.1 M potassium phosphate buffer with 8.8 mM EDTA disodium salt (pH 7.5). After 30 s, 60 $\mu$l of 0.8 mM $\beta$-NADPH prepared in potassium phosphate buffer with 8.8 mM EDTA disodium salt (pH 7.5) was added to each well. Absorbance was immediately measured at 405 nm by plate reader (Multiskan Ascent, Thermo Labsystems, USA) every 30 s for 5 min. The rate of 2-nitro-5-thiobenzoic acid formation was calculated from the change in absorbance/min and we determined the $GSH_T$ concentration in our samples by using linear regression to calculate these values from the standard curve. For determination of GSSG, 50 $\mu$l brain homogenate was mixed well with 1 $\mu$l 2-vinylpyridine for 1 h at room temperature. To this mixture, 3 $\mu$l triethanolamine was added to the solution for 10 min. The resulting sample solution was run according to the aforementioned method of $GSH_T$. All solutions were prepared fresh before use and were protected from light exposure. Reduced GSH ($GSH_R$) levels were calculated by subtracting GSSG levels from $GSH_T$ levels. Samples were run in triplicate and were blind to diagnosis.

### *Immunoblotting analyses*

The levels of GCL (1:1000; Rb-1679-P0; Thermo Scientific), GPx (1:1000; ab16798; Abcam, USA), GR (1:3000; ab55075; Abcam), and $\beta$-actin (1:3000; ab8226; Abcam) were measured by immunoblotting in post-mortem prefrontal cortex as previously described (Tian *et al*. 2007). Briefly, protein extracts were subjected to SDS–PAGE electrophoresis with a 12% acrylamide gel at 100 V for 90 min at 4 °C. Proteins were

**Table 1.** Demographic data for post-mortem brain tissue

| | Con | SCZ | MDD | BD | *F* | *p* |
|---|---|---|---|---|---|---|
| Age, yr (mean ± SD) | 49.3 ± 11.0 | 44.6 ± 13.6 | 46.7 ± 9.6 | 41.5 ± 11.7 | 1.051 | 0.378 |
| Range (yr) | 29–68 | 25–62 | 30–65 | 25–61 | | |
| *n* | 12 | 14 | 14 | 14 | | |
| Gender | 7M, 5F | 8M, 6F | 9M, 5F | 8M, 6F | | |
| PMI (h) (mean ± SD) | 23.2 ± 11.1 | 32.5 ± 14.4 | 27.1 ± 11.1 | 32.1 ± 16.6 | 1.37 | 0.263 |
| Range (h) | 8–42 | 12–61 | 7–47 | 13–62 | | |
| pH | 6.2 ± 0.2 | 6.2 ± 0.2 | 6.2 ± 0.2 | 6.2 ± 0.2 | 0.41 | 0.75 |
| Range | 5.8–6.5 | 5.8–6.6 | 5.8–6.5 | 5.8–6.5 | | |
| Cause of death | | | | | | |
| Suicide | 0 | 4 | 6 | 8 | | |
| Cardiopulmonary | 10 | 7 | 7 | 5 | | |
| Accident | 2 | 2 | 0 | 0 | | |
| Other | 0 | 1 | 1 | 1 | | |
| Current alcohol/drug abuse | 0 | 3 | 3 | 4 | | |
| Past alcohol/drug abuse | 2 | 3 | 1 | 3 | | |
| Medication at time of death | | | | | | |
| Antipsychotic | 0 | 11 | 0 | 7 | | |
| Antidepressant | 0 | 5 | 10 | 8 | | |
| Mood stabilizer | 0 | 2 | 2 | 9 | | |

Con, Controls; SCZ, schizophrenia; MDD, major depressive disorder; BD, bipolar disorder.
*n*, Number of individuals; M, male; F, female; PMI, post-mortem interval.

transferred to polyvinylidene difluoride membranes for 1 h at 100 V and 4 °C. Membranes were dried at room temperature overnight prior to blocking in 5% milk-Tris-buffered saline with 0.01% Tween-20 for 1 h at room temperature. Blots were washed and incubated with secondary antibody goat anti-rabbit, rabbit anti-goat, or goat anti-mouse immunoglobulin G (IgG; Abcam) conjugated to horseradish peroxidase diluted to 1:2000 in blocking buffer for 1 h at room temperature and immunoreactive bands detected with the enhanced chemiluminescence system. Each gel contained a pre-stained broad range protein ladder (Fermentas International, Canada) to measure molecular weights of individual bands. Samples were run in duplicate and blind to diagnosis.

### *Data analyses*

Statistical analyses were computed with SPSS version 17.0 for Windows (SPSS Inc., USA). Normal distribution of data was determined by the Kolmogorov–Smirnov test. Parametric tests were used as data presented a normal distribution. One-way analyses of variance (ANOVA) were employed to analyse data between groups followed by least squares derivation *post-hoc* comparisons. The influence of age, post-mortem interval, and pH were determined by analysis of covariance (ANCOVA). We also examined if our measures were affected by the presence or absence of substance abuse and suicide by independent-samples *t* tests. Correlations were analysed by Pearson correlation test. Data are presented as means and standard deviations (S.D.). Significance was set at $p \leq 0.05$. Outliers were defined as data-points that fall more than 2 S.D. from the mean and were subsequently removed from a particular analysis. For the BD group, we found a single outlier in each of the GSSG, GCL, and GPx measurements.

## Results

Demographic data is presented in Table 1. Factors such as age, post-mortem interval, and pH can affect protein levels and enzymatic reactions (Halliwell & Gutteridge, 2000). We therefore assessed the potential influence of these factors by analysing their correlation and covariance (ANCOVA) with our data. We found no influence of any of these factors on the GSH measures in all subjects (Fig. 1*a–c*) nor in any individual diagnostic group. However, we found a negative correlation between age and GR in all subjects

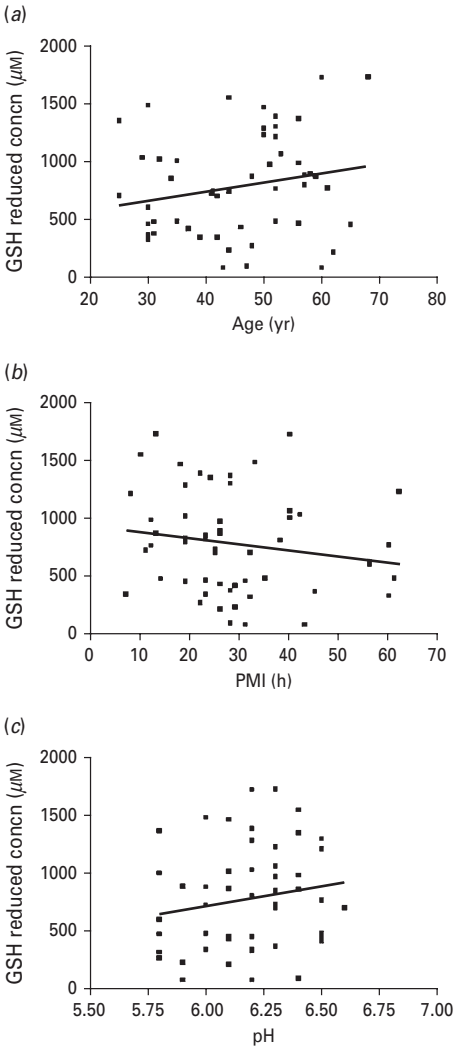


**Fig. 1.** Relationship between reduced glutathione (GSH) with (*a*) age, (*b*) post-mortem interval (PMI) and (*c*) pH.

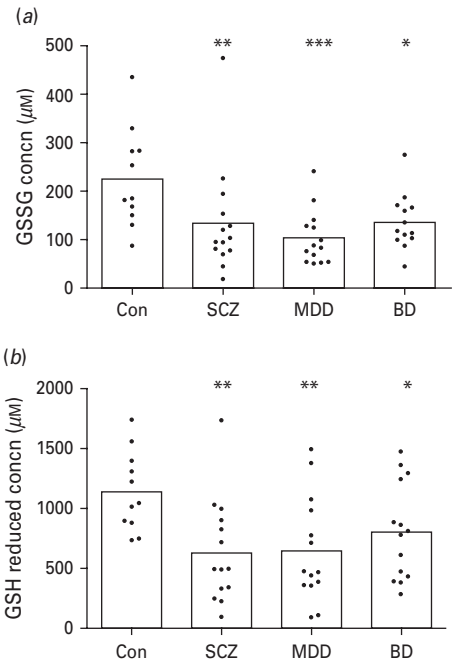


**Fig. 2.** Glutathione (GSH) levels were measured by a chromophoric enzymatic recycling method in controls (Con), schizophrenia (SCZ), major depressive disorder (MDD), and bipolar disorder (BD) patients. (*a*) Concentration levels for oxidized GSH (GSSG) are significantly reduced in SCZ, MDD, and BD compared to Con. (*b*) Concentration levels for reduced GSH are significantly diminished in SCZ, MDD, and BD compared to Con. Bar results are the means of individual data-points. Significance was measured by a one-way ANOVA: * $p \leq 0.05$, ** $p < 0.01$, *** $p < 0.001$ when specific psychiatric groups were compared to the least significant difference *post-hoc* test against control.

($r = -0.322$, $p = 0.019$) and in BD ($r = -0.593$, $p = 0.026$). A positive correlation was found between post-mortem interval and GR ($r = 0.599$, $p = 0.039$) in all subjects. To examine the influence of alcohol/drug abuse, we divided subjects with psychiatric illness based on this factor. $GSH_R$ was not different between individuals who abused alcohol/drugs and those who did not [$t(40) = 0.159$, $p = 0.874$]. Moreover, the levels of $GSH_R$ were not different in subjects who died by suicide compared to those who did not [$t(40) = 0.217$, $p = 0.829$]. All of the GSH system measurements evaluated in our study did not significantly differ between individuals who abused alcohol/drugs and those who did not. Further, these measurements did not differ between individuals who committed suicide and those who did not. Tobacco-use information was not available for these patients and therefore we could not analyse the influence of smoking on our data.

Significantly reduced levels of GSSG were found in all three patient groups compared to non-psychiatric controls [Fig. 2*a*; $F(3,48) = 4.601$, $p = 0.007$], $GSH_R$ [Fig. 2*b*; $F(3,49) = 3.888$, $p = 0.014$]. The ratio of $GSH_R$/GSSG was not different between subject groups [Con: $5.8 \pm 2.7$; SCZ: $7.7 \pm 11.6$; MDD: $6.3 \pm 3.2$; BD: $5.9 \pm 3.0$; $F(3,48) = 0.7113$, $p = 0.550$]. To determine whether $GSH_R$ levels were due to altered GSH synthesis, we measured the levels of the rate-limiting enzyme, GCL's catalytic subunit, and found no difference between groups [Fig. 3*a*; $F(3,48) = 0.705$, $p = 0.554$]. Next, we examined enzymes involved in GSH metabolism, the recycling enzymes, GR and GPx. Although GR levels did not differ between subject groups [Fig. 3*b*; $F(3,49) = 0.125$, $p = 0.945$], there was a trend towards significantly decreased GPx levels [Fig. 3*c*;

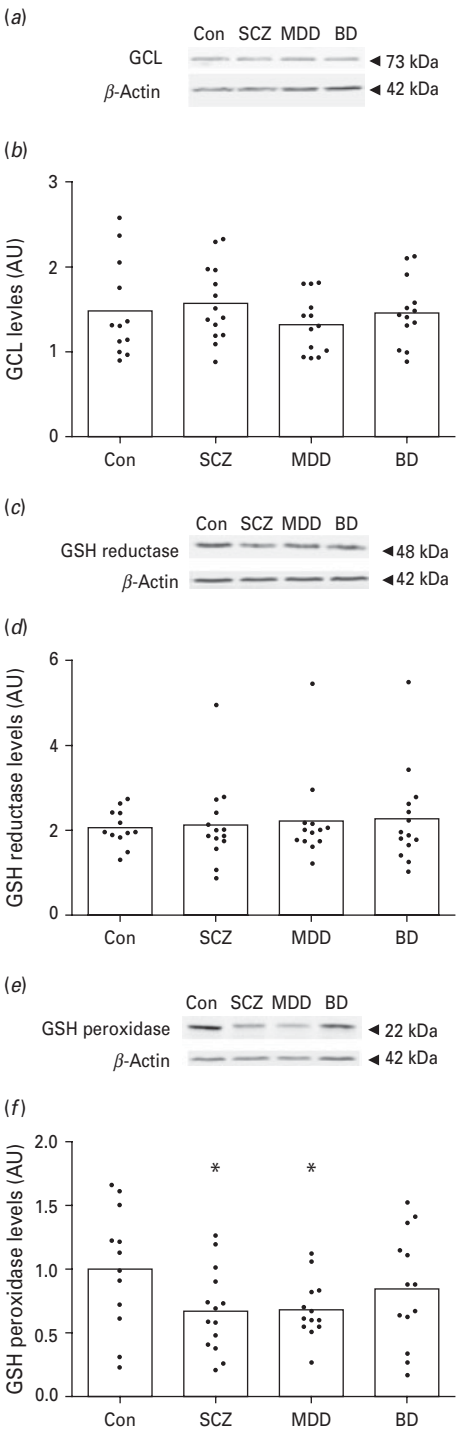


**Fig. 3.** Glutamyl-cysteine ligase (GCL) and glutathione (GSH) recycling enzymes, GSH reductase (GR), and GSH peroxidase (GPx), levels were measured via immunoblotting analyses in controls (Con), schizophrenia (SCZ), major depressive disorder (MDD), and bipolar disorder (BD) patients. (*a*) Representative blot for GCL. (*b*) Levels of GCL were not significantly different between SCZ, MDD, and BD compared to Con. GSH recycling enzymes, GR and GPx, were measured via immunoblotting analyses in Con, SCZ, MDD, and BD patients. (*c*) Representative blot for GR. (*d*) Levels of GR were not significantly different between SCZ, MDD, and BD compared to Con. (*e*) Representative blot for GPx. (*f*) Levels of GPx were significantly reduced in SCZ and MDD compared to Con whereas levels in BD were not significantly different from Con. Bar results are the means of individual data-points normalized to β-actin levels that were standardized to human prefrontal cortical control tissue that is expressed as arbitrary units (AU). Significance was measured by a one-way ANOVA: * $p \leq 0.05$ when specific psychiatric groups were compared to the least significant difference *post-hoc* test against control.

$F(3, 48) = 2.221$, $p = 0.098$]. In *post-hoc* analysis, SCZ ($p = 0.028$) and MDD ($p = 0.037$) patients were significantly decreased compared to controls.

## Discussion

We report here decreased, reduced and GSSG levels in post-mortem prefrontal cortex from individuals with SCZ, MDD, and BD compared to age- and sex-matched healthy non-psychiatric controls. We found no changes in the levels of the rate-limiting enzyme for GSH synthesis, GCL, however, we did find that patients with MDD and SCZ had significant reductions in the level of an enzyme that utilizes GSH, GPx. These results suggest that GSH levels are lower in post-mortem prefrontal cortex from patients with SCZ, MDD, or BD, which can compromise the antioxidant capacity and make brain from these patients more vulnerable to oxidative damage.

GSH's antioxidant system is the primary endogenous means by which the brain defends against oxidative stress and includes GSH, GPx, and GR. We found significantly lower levels of GSH in psychiatric illness and supporting our findings, GSH levels are significantly reduced in MDD patient blood samples (Kodydkova *et al*. 2009) and reduced in erythrocytes (Altuntas *et al*. 2000), cerebrospinal fluid, and post-mortem brain from SCZ patients (Yao *et al*. 2006). GSH is a tri-peptide that contains the amino acids glutamate, cysteine, and glycine. In fact, both GSH (Agarwal & Shukla, 1999) and glutamate levels (Grant *et al*. 2009) can be elevated with pharmacological treatment by *N*-acetylcysteine (NAC). Translating these studies from the bench to the clinic; double-blinded, randomized, placebo-controlled trials have demonstrated that NAC improves the positive and negative symptoms of SCZ (Berk *et al*. 2008*b*) and the depressive symptoms of BD patients (Berk *et al*. 2008*a*), which

emphasizes the importance of maintaining cerebral GSH levels. To date, no trial has examined if GSH-promoting compounds have a beneficial effect for MDD symptoms.

The levels and activities of GCL, GR, GPx and GSTs affect GSH levels. The enzymes GCL and GSH synthetase, with GCL being rate limiting to the reaction, catalyse GSH synthesis. To probe if altered GSH levels were due to alterations to GSH synthesis, we measured the levels of the catalytic subunit for GCL in prefrontal cortex and did not find any differences between groups. Others have found that GCL alterations modulate GSH levels (Lavoie *et al*. 2009), this enzyme's gene is a potential susceptibility gene in SCZ (Tosic *et al*. 2006), and its expression is affected by mood-stabilizer treatment (Cui *et al*. 2007). Since GSH synthesis was not altered, we examined the enzymes that use GSH, GR and GPx, which function to remove hydrogen peroxide. Peripheral studies on psychiatric illnesses have reported increased activity of GR in MDD (Bilici *et al*. 2001; Kodydkova *et al*. 2009) but to our knowledge no changes have been observed in SCZ or BD. Studies on GPx in patients with psychiatric illness have been inconsistent. In SCZ, GPx has been reported elevated (Herken *et al*. 2001), decreased (Altuntas *et al*. 2000), and unchanged (Abdalla *et al*. 1986) in erythrocytes. Whereas in BD patients the activity of GPx is increased in serum (Andreazza *et al*. 2007), unchanged (Abdalla *et al*. 1986), and decreased (Ozcan *et al*. 2004) in erythrocytes. Last, in MDD, GPx activity is diminished in blood (Kodydkova *et al*. 2009) and elevated in erythrocytes (Bilici *et al*. 2001). Although the GSH antioxidant system has not been previously studied in post-mortem brain from individuals with MDD or BD, evidence demonstrates reductions to cerebral levels of GSH and GPx activities in patients with SCZ (Yao *et al*. 2006). Abnormal expression of antioxidant genes, largely associated with the GSH metabolic pathway, has been reported in BD (Benes *et al*. 2006; Sun *et al*. 2006). Our results in combination with data published by others suggests that the GSH antioxidant system is altered in brain from patients with psychiatric illness; however, conclusive evidence that $GSH_R$ levels are due to specific modifications to GSH synthesis and detoxification enzyme levels, activities, or expression has not been demonstrated. Our data suggest that in the central nervous system of subjects with psychiatric illness, changes to GSH levels are not due to alterations to GSH synthesis, but in MDD and SCZ may be associated with decreased GPx enzyme levels. Interestingly it appears that the mechanism(s) responsible for reduced prefrontal cortex GSH levels in patients with BD is different than the mechanism(s) for individuals with MDD and SCZ.

The GSH antioxidant system has been studied in animal models of depression, such as chronic mild stress. Chronic mild stress reduces GSH levels (Eren *et al*. 2007*a*), and GPx activity in rat cerebral cortex (Eren *et al*. 2007*a*, *b*). These studies support our results of significantly decreased GPx levels in MDD compared to controls. In addition, chronic mild stress induces oxidative stress and lipid peroxidation (Eren *et al*. 2007*a*, *b*; Lucca *et al*. 2009*a*, *b*), protein carbonylation (Lucca *et al*. 2009*a*), superoxide (Lucca *et al*. 2009*b*), and nitric oxide (Eren *et al*. 2007*b*) levels in rat brain. Our observations that $GSH_R$ and GPx levels are reduced in prefrontal cortex from MDD patients support these findings and emphasize the importance of maintaining GSH levels. Furthermore, our findings suggest that GSH-elevating compounds may protect against oxidative damage in these psychiatric illnesses.

While our results are of potential interest, there are a number of limitations. There exists variability between individuals for measurements of biological factors and lengthy post-mortem intervals for their collection and storage. These factors are matched between groups in the Stanley Consortium in order to minimize confounding variables but it may be that the measurement of a factor's levels may be vastly different from each person's true levels. Addition of GSH synthesis and recycling enzyme activity would provide a more detailed cerebral analysis of this antioxidant system in these patient groups; however, tissue amounts required for these assays constrained us from gathering these measurements. Unfortunately perfect animal models of psychiatric illness do not exist.

Our study demonstrates decreased $GSH_R$, GSSG, and $GSH_T$ levels in post-mortem prefrontal brain from patients with MDD, BD, or SCZ. We observed significantly diminished levels of GPx in MDD and SCZ patient samples but not in BD patient samples.

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**Statement of Interest**

Dr Young is an occasional speaker for Eli Lilly and AstraZeneca.

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