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Disturbed glutathione antioxidative defense is associated with structural brain changes in neuroleptic-naïve first-episode psychosis patients☆

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ABSTRACT

Background: Oxidative stress and impaired antioxidant defense are reported in schizophrenia and are thought to be associated with disturbed neurodevelopment, brain structural alterations, glutamatergic imbalance, negative symptomatology, and cognitive impairment. To test some of these assumptions we investigated the glutathione (GSH) antioxidant defense system (AODS) and brain structural abnormalities in drug-naïve individuals with first acute episode of psychosis (FEP).

Method: The study involved 27 drug-naïve FEP patients and 31 healthy controls (HC). GSH AODS markers and TBARS (thiobarbituric acid reactive substances) were measured in blood plasma and erythrocytes. High-resolution T_1-weighted 3T MRI were acquired from all subjects. To investigate brain structural abnormalities and effects of illness on interactions between GSH metabolites or enzyme activities and local grey matter density, voxel-based morphometry (VBM) with the computational anatomy toolbox (CAT12) was used. Symptomatology was assessed using the Positive and Negative Syndrome Scale (PANSS) and the Symptom Checklist 1990 revised (SCL-90-R).

Results: (i) In FEP patients, glutathione reductase activity (GSR) was lower than in the HC group. GSR activity in plasma was inversely correlated with SCL-90-R scores of depression and PANSS scores of the negative symptom subscale. (ii) A reduction of GM was observed in left inferior frontal, bilateral temporal, as well as parietal cortices of FEP patients. (iii) Interaction analyses revealed an influence of illness on GSR/GM associations in the left orbitofrontal cortex (BA 47).

Conclusion: Our findings support the notion of altered GSH antioxidative defense in untreated acute psychosis as a potential pathomechanism for localized brain structural abnormalities. This pathology relates to a key brain region of social cognition, affective motivation control and decision making, and is clinically accompanied by depressive and negative symptoms.

1. Introduction

Regional structural brain changes are among the best replicated findings in schizophrenia [1–4]. Grey matter changes that have been identified by voxel-based morphometry (VBM) in medial temporal lobe structures such as hippocampus, entorhinal and parahippocampal cortex, are hypothesized to constitute a neuroanatomical correlate of vulnerability to develop schizophrenia [5–7]. Frontal lobe changes, particularly in orbitofrontal and dorsolateral prefrontal regions, appear to arise subsequently to medial temporal lobe abnormalities [8,9]. Structural abnormalities have been related to a variety of pathomechanisms observed during the first acute manifestation of psychosis, such as neurodevelopmental abnormalities, monoaminergic imbalance, neurotoxicity, occurrence of and/or response to oxidative stress [10–12], dysapoptosis and neuroinflammation [13–18]. According to the membrane lipid hypothesis of psychosis [19], all structural changes in the brain observed in patients involve, to various extend, molecular modification of brain lipids, particularly of the unsaturated fatty acid

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profile [19,20], which is highly vulnerable to oxidative damage. Although research has considerably progressed in characterizing associations between structural changes, stage of disorder, severity of symptoms and treatment response, little is known about the biochemical pathomechanisms underlying structural alterations [21–26].

This study focuses on the oxidative stress reported in psychosis as a possible cause of the observed structural abnormalities. Oxidative stress corresponds to an imbalance between the production of reactive oxygen species (ROS) and protective mechanisms. It occurs when the production of oxidants exceeds local antioxidant capacity. As mentioned above, the brain is considered as being particularly vulnerable to oxidative stress damage due to the high levels of polyunsaturated fatty acids in brain lipids, its high demand for oxygen (20% of the body consumption), and its comparatively poor endowment with antioxidant defense systems (AODS) [27]. ROS are produced during normal biochemical processes (such as cellular respiration), following nicotine use and negligent diet, or they accumulate in the context of somatic (brain trauma and cerebral ischemia), neurodegenerative (Parkinson's or Alzheimer's disease) or neurodevelopmental disorders such as schizophrenia, depression, autism or attention deficit hyperactivity disorder [11,12,28–31]. In first-episode psychosis (FEP) patients, diverse biomarkers indicative of increased oxidative stress have been measured [32–36]. Those markers were found to be associated with neurological soft signs [37], positive symptoms [38], negative symptoms [39] and impaired cognitive functioning [40].

The pathomechanisms of oxidative stress in FEP patients have not been resolved yet. Besides increased nicotine use or careless diet (which are common among FEP patients), there are several other potential causes including (i) genetic variability in key enzymes of AODSs (see below), (ii) hyperactivation of the hypothalamic–pituitary–adrenal (HPA) axis as observed in schizophrenia (review and meta-analysis by [41–44]) that could lead to oxidative stress as reflected by increased ROS (meta-analysis by [45]), (iii) genetic alterations of cellular respiration as being reported in schizophrenia (review by [46]), and (iv) glutamatergic regulation deficits [47].

Glutathione (GSH) represents the most important cellular redox regulator and AODS in the brain [30,48,49]. It is a major target in animal and clinical studies in schizophrenia research [12]. GSH was found to be decreased in the dorsolateral prefrontal cortex, cerebrospinal fluid and post mortem brain tissue [48,50,51] of chronic schizophrenia patients, but also in erythrocytes and blood plasma of FEP [38,52–54]. In terms of the GSH metabolites, the ratio between oxidized GSH (GSSG) and reduced GSH (GSHr) represents an important marker of the oxidative balance of the cell, i.e., it is critical that the cell maintains high levels of the GSHr and low GSSG levels. This narrow balance is maintained by glutathione-disulfide reductase (GSR), which catalyzes the reduction of GSSG to GSHr [55]. GSHr reduces the oxidized form of the enzyme glutathione peroxidase (GPx), which in turn reduces hydrogen peroxide (H_2O_2), a highly reactive ROS within the cell. Finally, the conjugation of GSHr to exogenous substrates for the purpose of detoxification is catalyzed by the Glutathione S-transferase (GST) [56].

In FEP patients, total GSH and GSHr were found to be decreased, while GSSG levels and GPx activity were increased [36,53,57] (meta-analysis by Zhang [58]; reviews by Ciobica [59] and Morris [60]). In terms of GSR, while no alterations have been reported so far in FEP (e.g. [61]), a link has been observed between the GPx/GSR quotient and low-level auditory dysfunction in schizophrenia patients [62]. The GSH pathway is influenced by genetic polymorphisms in a number of key enzymes that have been linked to schizophrenia, such as a trinucleotide repeat polymorphism in the gene coding for the catalytic subunit of glutamate-cysteine ligase, the rate-limiting enzyme for GSH synthesis [61,63–67]. In early psychosis patients, this genetic polymorphism was linked to decreased medial prefrontal GSH, which, was negatively correlated with blood GPx indicating high peripheral oxidation status [61].

Following those recent observation, the present report proposes to investigate the potential associations between GSH levels (total GSH, GSHr and GSSG) and the activity of related enzymes (GSR, GPx and GST) with brain structure abnormalities, as assessed by structural imaging techniques.

Our hypotheses are at this state of knowledge explorative, and are the following:

(i) Primary: In FEP patients, oxidative burden as indicated by increased lipid peroxidation (i.e. increased levels of thiobarbituric acid reactive substances, TBARS), decreased GSHr, decreased GSR activity, increased GSSG or increased GPx will be linked to local grey matter loss.
(ii) Secondary: Whole brain analysis of the links hypothesized in (i) will disclose regions in prefrontal, orbitofrontal, medial temporal and thalamic structures that are crucially involved in the symptomatology of schizophrenia.

2. Subjects and methods

2.1. Description of study population

Analyses were performed in 27 neuroleptic-naïve FEP patients fulfilling DSM-IV criteria for schizophrenia or schizophreniform disorder and 31 healthy controls (HC). Both groups mainly overlap with a population that has been previously investigated by combined ^{1}H- and ^{31}P-MR spectroscopy [68]. Clinical diagnoses were determined by two trained and board-certified psychiatrists (St.S., B.M.) and confirmed by standardized structured clinical interviews (SCID-IV) [69]. Psychopathology was assessed using PANSS (Positive and Negative Syndrome Scale) scores [70]. PANSS scores were used from the above mentioned study. PANSS ratings of 3 FEP patients were not available. To identify psychological problems and symptoms of psychopathology in all subjects, the symptom checklist 1990 revised (SCL-90-R) was used [71]. In our analysis we included the following symptom dimensions: somatization, obsessive compulsive, interpersonal sensitivity, depressive symptoms, anxiety, anger-hostility, phobic anxiety, paranoid ideation, and psychoticism. We also calculated a score of the general psychological burden (Global Severity Index; GSI) according to the test manual. Apart from sporadic medication with benzodiazepines (Lorazepam 1 mg) no other medication was prescribed to FEP patients. All HC were free of any medication at the time of study participation.

Exclusion criteria were (1) a history of previous psychotic disorder or manic episode, (2) substance induced psychotic disorder, (3) acute suicidal or aggressive behaviour, (4) a current DSM-IV diagnosis of substance dependence, (5) neurological disorders (e.g., epilepsy), (6) IQ < 70, (7) structural brain changes apparent on MRI scan, (8) previous treatment with an antipsychotic or mood stabilizing agent, and (9) any implanted metal or device that would be affected by the magnetic field of the scanner. Only right-handed individuals were included.

All subjects gave written informed consent to participate in this study which was approved by the Research Ethics Committee of the University Hospital Jena.

2.2. Acquisition/storage of plasma and erythrocyte lysates

Blood from an antecubital vein of fasting individuals was taken in a lithium heparin tube (S-Monovette Plasma Lithium-Heparin, Sarstedt) and centrifuged (3000 rpm, 20 min), followed by separation of plasma which was stored at −80 °C until analysis. After plasma separation, erythrocytes were washed 3 times (each time 10 min, 3000 rpm) and lysis was carried out by adding 4 times its volume of ice-cold HPLC-grade water before centrifuging at 10,000 × *g* (4 °C) for 15 min. The collected supernatant was stored at −80 °C whereby analysis was performed within 1 month.

2.3. Analysis of total glutathione (GSHt) and glutathione disulfide (oxidized glutathione (GSSG)) in blood plasma

GSHt and GSSG concentrations were determined in blood plasma by means of a commercially available test kit (Cayman Chemical catalog No. 703002) according to the manufacturer's instructions. This GSH assay is based on the reaction of the sulfhydryl group of GSH with DTNB (5,5′-dithio-bis-(2-nitrobenzoic acid), Ellman's reagent) which results in a yellow-colored 5-thio-2-nitrobenzoic acid (TNB). The concomitantly produced mixed disulfide GSTNB (GSH and TNB) is reduced by glutathione reductase (GSR) to TNB and recycled GSH. The formed TNB rate is directly proportional to this recycling reaction which in turn is directly proportional to GSH levels in the sample (for more details see Smesny et al. [72]). The assay measures the total GSH concentration (GSH; i.e., both oxidized and reduced) of the sample. In order to additionally measure oxidized GSH (GSSG) and thus calculating the concentration of reduced GSH (GSHr), an independent test with additional 2-vinylpyridine derivatization was conducted. The calculation for GSHr was done using the following formula: ((2xGSHt) – GSSG)/2. Total glutathione (GSHt) and oxidized glutathione (GSSG) concentrations were assessed in μmol/L blood plasma.

2.4. Analysis of glutathione S-transferase (GST) and glutathione peroxidase (GPx) activity in blood plasma, and of glutathione reductase (GSR) activity in plasma and erythrocyte lysate

All enzyme activity assays were performed by means of a commercially available test kits (Cayman Chemical catalog No. 703302 (GST), 703202 (GSR), 703102 (GPx)) according to the manufacturer's instructions. While the GST activity is proportional to the conjugation of 1-chloro-2,4-dinitrobenzene (CDNB) with GSHr, the GSR activity is proportional to the oxidation rate of NHDP during the reduction of GSSG to GSH. The GPx assay measures the reduction of hydroperoxide by oxidizing GSH. The produced GSSG is subsequently recycled to GSH by GSR in a NHDP-dependent reduction. GPx activity is proportional to the oxidation rate of NHDP. Enzyme activities were assessed in (nmol/min/mL). For further interpretation (see introduction) the ratio of glutathione peroxidase and glutathione reductase activities in plasma (GPx/GSR) was calculated.

2.5. Lipid peroxidation level measurement

To evaluate the lipid peroxidation level in plasma, the Thiobarbituric Acid (TBA) Reactive Substances (TBARS)-Assay was performed by means of a commercially available test kit (Cayman Chemical catalog No. 10009055) according to the manufacturer's instructions.

Oxidative stress induces the peroxidation of polyunsaturated fatty acids (PUFA) that are very unstable and easily decompose in reactive compounds including malondialdehyde (MDA). The TBARS-Assay is based on the formation and quantification of MDA-TBA adducts which are proportional to the MDA (μM).

2.6. Magnetic resonance imaging (MRI)

High-resolution T_1-weighted MRI data were acquired on a 3T whole-body MR scanner (Magnetom TIM Trio, Siemens Medical Solutions, Erlangen, Germany) using a double-resonance ($^1H/^{31}P$) transmit/receive volume head (Biomedical Rapid, Germany) on the day or the day after blood collection. T_1-weighted 3D MRI data sets with 192 contiguous sagittal slices were acquired with TR of 2300 ms, TE of 3.03 ms, TI of 900 ms and a field-of-view 256×256 mm^2, resolution $1 \times 1 \times 1$ mm^3. Images were visually inspected to exclude image artefacts.

2.7. Voxel-based morphometry (VBM)

Anatomical scans were analysed with CAT12 (Computational Anatomy Toolbox; C. Gaser, Structural Brain Mapping Group, Jena University Hospital, Jena, Germany; http://dbm.neuro.uni-jena.de/cat/), which is an extension to SPM12 (Statistical Parametric Mapping; Institute of Neurology, London, UK). Pre-processing included correction for bias-field inhomogeneities, normalization using the DARTEL-algorithm [73] and segmentation into grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF) [74]. The segmentation was followed by accounting for partial volume effects [75]. Data were smoothed with a 12 mm full-width at half-maximum (FWHM) Gaussian kernel.

2.8. Statistical analysis

Statistical analyses were performed using IBM® SPSS® Statistics 21.0. To investigate the assumptions for parametric testing of GSH AODS markers (GSHt, GSHr, GSSG, GST, GSR, GPx, GPx/GSR ratio) and TBARS, Kolmogorov-Smirnov tests for each parameter were applied. To test for group differences (FEP patients vs. HC) in GSH AODS markers, TBARS and demographic covariates, two-sample *t*-tests were performed. If criteria for parametric testing were not fulfilled, Mann-Whitney-*U* tests were used. Differences in gender distribution and in substance use between groups were tested using the categorical χ^2-test.

For comparisons of grey matter density (in the following abbreviated as GM) and interactions between GM and the GSH AODS markers general linear model analyses implemented in SPM12 were performed. For comparisons of differences in GM between HC and FEP patients we used two-sample *t*-tests. To investigate interactions between GM and the GSH AODS markers that showed group differences in the initial group comparisons, we used the full factorial model (interaction) as implemented in SPM12. In this model, group was defined as factor with 2 levels (level 1: HC, level 2: FEP patients). The GSH marker was modelled as covariate of interest to investigate interaction effects. In each GLM we included total intracranial volume (TIV) as a nuisance variable (covariate of no interest) in order to correct for different brain sizes between subjects. Several studies suggest alterations in regional brain structures influenced by age and gender [76–79]. Therefore we included age and gender as nuisance variables (covariate of no interest) in our VBM analyses to account for potential effects of these variables. An absolute threshold masking of 0.25 was applied to reduce artefacts on the border between grey and white matter. Analyses for comparisons of grey matter differences and interaction effects were thresholded at $p < 0.001$ (uncorrected). To identify the association between GM and GSR activity in FEP patients and HC the eigenvariate for each subject was extracted from the cluster showing a significant interaction effect.

Correlation analysis between SCL-90-R scores/subscores and GSH markers was performed in all participants. Correlation analysis between GSH markers and PANSS scores was performed only in FEP patients. In all analyses the significance level was set at $p \leq 0.05$.

3. Results

3.1. Group characteristics

Detailed demographic information and psychopathological measures are presented in Table 1.

The FEP patients and HC groups did not differ in terms of age ($T = -0.901$, $p = 0.371$), gender ($\chi^2 = 0.570$, $p = 0.450$), use of nicotine ($\chi^2 = 0.515$, $p = 0.473$) and use of cannabis ($\chi^2 = 2.580$, $p = 0.108$). According to PANSS and SCL-90-R scores FEP patients were moderately ill.

Table 1
Demographic details and psychopathological measures of healthy controls (HC) and first-episode psychosis (FEP) patients.

	HC	FEP patients
n	31	27
gender (f/m)	13/18	14/13
age (mean ± SD)	25.12 ± 4.68	25.30 ± 3.52
age (range)	19–32	19–45
nicotine (yes/no/no info)	12/18/1	11/11/5
cannabis (yes/no/no info)	2/28/1	5/18/4
alcohol		
no	5	9
one or two times/year	6	3
monthly	3	2
weekly	14	6
daily	1	2
no information	2	5
Psychopathology (mean ± SD)		
SCL-90-R GSI	0.13 ± 0.11	0.89 ± 0.55
PANSS total score	–	60.4 ± 8.2
PANSS positive subscale	–	29.7 ± 4.1
PANSS negative subscale	–	28.8 ± 9.7
PANSS global subscale	–	40.2 ± 6.6

Abbreviations: PANSS = Positive and Negative Syndrome Scale, SCL-90-R = symptom checklist 1990 revised, GSI = Global Severity Index.

3.2. GSH AODS markers and TBARS

In Table 2, the results of all group comparisons are summarized. The only group difference that was observed was with regard to the GSR activity assessed in plasma with significantly lower levels in FEP patients compared to HC ($U = 183.000$, $p < 0.001$) (see Fig. 1).

3.3. Grey matter (GM) abnormalities in FEP

Comparing the FEP patients group to the HC group, we found a significant reduction in GM in FEP patients ($p < 0.001$ uncorrected) in left inferior frontal, bilateral temporal, as well as parietal cortices (see Fig. 2). Coordinates, anatomical regions, number of voxels per cluster (k) and T-values are presented in Table 3.

3.4. Associations between GM and GSH markers

VBM analysis of interactions in FEP patients and HC between GM and GSH markers and their differences between FEP patients and HC was performed with GSR activity in plasma as a covariate of interest,

Table 2
GSH markers levels in healthy controls (HC) and first-episode psychosis (FEP) patients. Data are presented in mean ± standard deviation.

	HC (mean ± SD)	FEP patients (mean ± SD)	p
TBARS	2.328 ± 0.771	2.526 ± 0903	0.366
GSHt	283.411 ± 82.705	292.159 ± 114.022	0.735
GSHr	255.675 ± 79.284	264.032 ± 105.247	0.730
GSSG	55.471 ± 21.058	56.253 ± 22.444	0.891
GPx	1021.632 ± 188.992	1012.851 ± 198.257	0.862
GSR Ery	80.942 ± 42.795	98.973 ± 50.047	0.264
GSR Plasma	7.414 ± 4.118	3.555 ± 2.377	**< 0.001**
GST	7.495 ± 4.094	1.219 ± 1.778	0.097
GPx/GSR	15.357	18.640	0.216

Abbreviations: TBARS = Thiobarbituric acid reactive substances (measured in plasma), GSHt = Total glutathione (measured in erythrocytes), GSHr = Reduced glutathione (in erythrocytes; calculated), GSSG = Oxidized glutathione (measured in erythrocytes), GPx = glutathione peroxidase activity (measured in erythrocytes), GSR Ery = glutathione reductase activity measured in erythrocytes, GSR Plasma = glutathione reductase activity measured in plasma, GST = Glutathione S-transferase (measured in plasma), GPx/GSR = ratio of glutathione peroxidase and glutathione reductase activities (in erythrocytes; calculated).

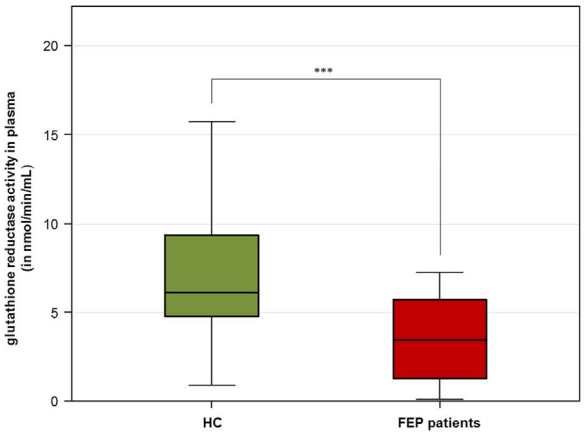

Fig. 1. Glutathione reductase (GSR) activity in healthy controls (HC) and first-episode psychosis (FEP) patients. *** indicates a significant difference ($p \leq 0.001$).

because this marker showed group differences between FEP patients and HC. There was a significant difference of the interaction between GM and GSR activity in the left orbitofrontal cortex, with a regression slope HC > FEP patients (see Fig. 3). Coordinates, anatomical regions, number of voxels per cluster (k) and T-values are given in Table 4. This cluster also showed a significant finding ($p = 0.032$) for FWE correction (peak-level).

Correlation analysis (within each group) between the extracted eigenvariates from the significant cluster identified in the full factorial analysis and GSR activity revealed a negative correlation in FEP patients ($r = -0.686$, $p = 0.005$).

3.5. Associations between GSH and psychopathology

Correlation analysis in the FEP patients and controls revealed a weak negative correlation between GSR activity in plasma and the SCL-90-R scores for the item depression ($r = -0.264$, $p = 0.049$). In the FEP patients group, GST activity in plasma was negatively correlated with the SCL-90-R scores for obsessive-compulsive ($r = -0.399$, $p = 0.039$) and depressive ($r = -0.489$, $p = 0.010$) symptoms. A negative correlation between GSR activity and PANSS negative subscale was shown ($r = -0.438$, $p = 0.027$).

4. Discussion

Oxidative stress, alterations of AODS and abnormalities of frontal and temporal brain regions have been consistently reported in first-episode psychosis. The current study aimed to identify potential associations between these biological features, investigating markers of the GSH AODS and local GM abnormalities in neuroleptic-naïve FEP patients. Our main results are the following: (i) In FEP patients, the GSR activity in plasma was significantly decreased compared to healthy controls. (ii) In FEP patients, GM was reduced in left inferior frontal, bilateral temporal and parietal cortices. (iii) Interactions between GSR activity in plasma and GM differed between FEP patients and HC in a cluster located in the left orbitofrontal cortex. (iv) GSR and GST activity in plasma were inversely correlated with SCL-90-R scores for the item depression. GSR activity was also negatively correlated with scores of the PANSS negative symptom subscale.

As a basis for the investigation of the core question of this study, the previously reported brain structural abnormalities in left inferior frontal, bilateral temporal and parietal cortices in FEP patients have been replicated (compare with Gong et al. [4]). The previously reported disturbance of the GSH redox system in FEP patients has also been observed in the present study. However, this disturbance did not present as a decrease in GSHr levels or increased GSSG or GPx activity as expected. In this study, decreased GSR activity in plasma of FEP

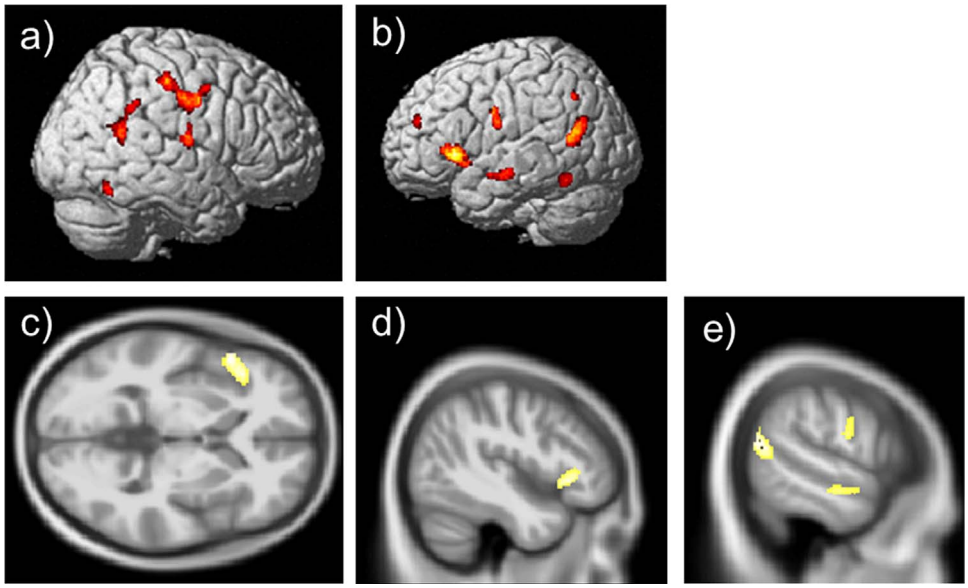

Fig. 2. Results of VBM analysis: significantly reduced GM in first-episode psychosis (FEP) patients ($p < 0.001$ uncorr.) as a) and b) render overlay, c) transversal and d) sagittal overlay (left frontal operculum/ left inferior frontal gyrus) and e) sagittal overlay (left middle temporal gyrus, left angular gyrus, left postcentral gyrus).

patients was observed and, to our knowledge, this observation has not been reported so far. GSR is necessary to catalyze the reduction of GSSG to GSHr. It needs riboflavin (Vitamin B_2) for its activation. GSR reduces GSSG to GSHr with the concomitant oxidation of reduced nicotinamide adenine dinucleotide phosphate (NADP) to $NADP^+$. The activity of GSR is considered an indirect marker of oxidative stress. A disturbance of GSR activity could be explained in various ways, (i) polymorphisms of the GSR gene or disturbed synthesis of the GSR enzyme protein, (ii) a deficiency of riboflavin or (iii) a disturbance of NADP synthesis or function in mitochondria. Genetic variations of the GSR or NADP genes or a deficiency of riboflavin have according to our search not been reported so far in the context of schizophrenia. There is at least a discussion about genetic alterations that cause deficits of Vitamin B resorption in first-episode schizophrenia [80]. In terms of mitochondria several lines of evidence suggest a functional disturbance. Cavalier et al., for instance, reported a 43% reduction of activity of one enzyme complex of the mitochondrial respiratory chain in schizophrenic patients [81]. Further supporting evidence comes from ^{31}Phosphor-MR-spectroscopy studies that found decreased/disturbed energy supply in prefrontal brain regions of different populations of schizophrenia patients (e.g. [82,83]). Finally, mitochondria were found reduced in post mortem anterior cingulate cortices tissue of schizophrenia patients [84]. Thus, a decreased number or disturbed function of mitochondria could lead to a deficiency or functional deficit of NADP, which in turn affects GSR activity. On the other hand, decreased GSR activity could also be caused by GSH depletion, as it could be observed in animal models [85]. Similar to the animal study by Barker et al. [85], also in our study of the three enzymes investigated (GSR, GPx and GST) only GSR was altered. In this study, however, decreased GSR in FEP patients was not accompanied by decreased GSHt or GSHr levels. Therefore, it is unlikely that decreased GSR activity is secondary to a GSH decrease. One could speculate that in this particular FEP patients population the oxidative burden did not reach the critical intensity to cause both a decrease of GSH and of GSR activity.

Although indicators of oxidative stress might be weak in this group of FEP patients, whole brain analysis revealed in the left orbitofrontal gyrus (Brodmann area 47) a significant interaction, i.e, a difference of the association between plasma GSR activity and local GM, between FEP patients and HC. This is in accordance with our hypotheses, as the left orbitofrontal gyrus (Brodmann area 47) is a brain region that is of particular interest in schizophrenia. In fact, the orbitofrontal cortex is crucially involved in reward networks, regulation of motivation and affective decision making [86,87], functions that have been consistently found to be disturbed in schizophrenia [88], and that could be clinically expressed for instance as motivational deficits [89]. In terms of symptomatology, the studied population showed, among others, moderate PANSS negative symptom scores and highly increased SCL-90-R scores of obsessive-compulsive and depressive symptoms, both of which could reflect the disturbance of the networks associated with the orbitofrontal cortex. Furthermore, inverse correlations were observed between GSR activity and PANSS negative symptom scores as well as GSR (and GST) activity and SCL-90-R depressive symptom scores, also

Table 3
Brain regions showing reduced grey matter (GM) in first-episode psychosis (FEP) patients as compared to healthy controls (HC); only clusters with k > 50 are reported.

Coordinates (x; y; z)	Anatomical region	k	T	p at peak-level (uncorr.)
−48; 17; −3	Left frontal operculum, left inferior frontal gyrus	640	4.11	< 0.001
−57; −63; 18	Left angular gyrus, left middle temporal gyrus	411	4.10	< 0.001
48; −14; 36	Right postcentral and precentral gyrus	494	3.98	< 0.001
63; −11; 11	Right central operculum, right postcentral gyrus, right superior temporal gyrus	134	3.95	< 0.001
57; −24; 50	Right supramarginal gyrus, right postcentral gyrus	98	3.80	< 0.001
−51; −56; −17	Left inferior temporal gyrus	97	3.68	< 0.001
50; −60; −20	Right inferior temporal gyrus	69	3.63	< 0.001
−59; −15; −12	Left middle and superior temporal gyrus	184	3.61	< 0.001
−36; 48; 27	Left middle frontal gyrus	58	3.57	< 0.001
−57; −8; 23	Left postcentral and precentral gyrus	200	3.55	< 0.001
60; −51; 20	Right angular gyrus, right middle temporal gyrus	255	3.54	< 0.001
−51; −60; 42	Left angular gyrus	51	3.46	=0.001

k = number of voxel per cluster.

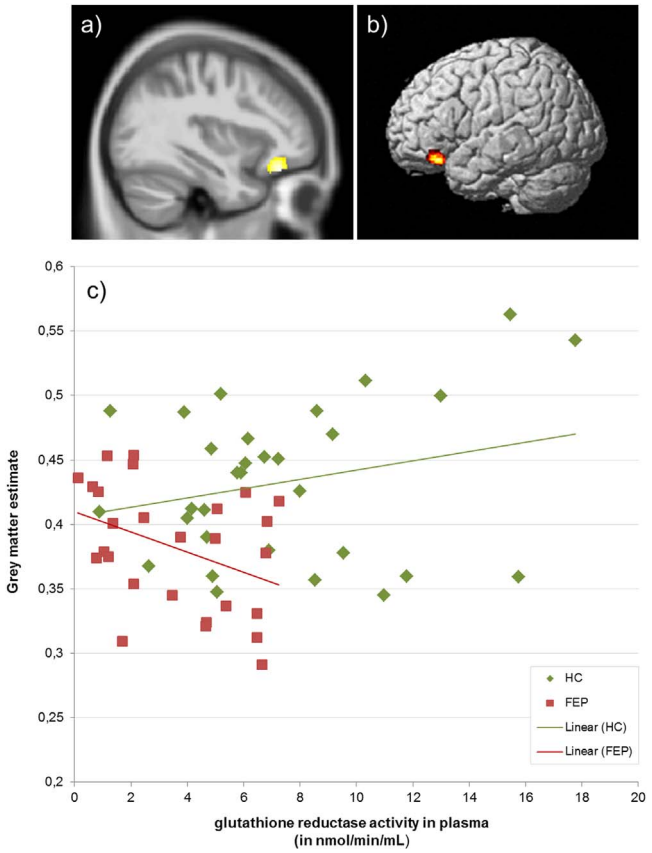

Fig. 3. VBM analysis of interaction between GM and glutathione reductase activity (GSR; $p < 0.001$ uncorr.) in first-episode psychosis (FEP) patients and healthy controls (HC) in the left orbitofrontal cortex as a) sagittal plane and b) render view. To identify the interaction between GM and GSR activity in FEP patients and HC the extracted eigenvariate for each subject were plotted against GSR activity (c)).

Table 4
Results of interaction analysis between local grey matter (GM) and GSR activity.

Coordinates (x; y; z)	Anatomical region	k	T	p at peak-level	
−35; 35; −20	Left posterior and lateral orbital gyrus	492	5.41	p_{uncorr} $p_{FWE-corr}$	$p < 0.001$ $p = 0.032$

k = number of voxel per cluster.

supporting this interpretation. The assumed association between disturbed GSH antioxidative defense (as indicated by decreased GSR activity) and depressive or negative symptoms is also well in line with our previous results in a non-overlapping FEP patients population. In that study an association between intracellular phospholipase A_2 activity (inPLA_2, an enzymatic marker of membrane phospholipid repair that increases in case of oxidative burden) and negative symptom scores had been observed [90]. In both studies, the measured symptom scores also support the occurrence of negative symptoms in the early acute phase of schizophrenia which has also been reported by other groups [91].

We have to notice that the cluster of interactions between GSR activity and GM (left orbitofrontal cortex) is situated close to but not within the brain regions that have been identified in FEP patients with brain structural abnormalities (e.g. left inferior frontal cortex) by VBM analysis. This finding contradicts to our expectations and suggests that markers of GSH antioxidative defense not necessarily indicate manifest structural damage as assessable by VBM. We notice that in healthy controls GSR was positively correlated with the GM of the left orbitofrontal cortex (trend), which obviously reflects the physiological condition that an intact GSH AODS protects grey matter. If a decrease of GSR activity would indicate manifest oxidative stress, and if oxidative stress causes structural damage [39,92], then a positive correlation between GSR activity and local GM would be also expected in brain areas of manifest structural damage. This was not the case in our FEP patient sample. GSR activity was inversely correlated with local GM, and this was observed in a brain region that is close and functionally related to a structurally altered brain region (left inferior frontal cortex). We take into account that the investigated FEP patients suffered their first acute manifestation of illness, i.e., a phase in which structural breakdown and synthesis processes are supposed to be still in balance. Furthermore, in case of increased oxidative burden, compensatory repair and remodeling processes would be expected to be increased. This could explain that we observed in FEP patients an inverse correlation between GSR and GM, while a positive correlation (trend) was observed in HC. We have to acknowledge, that this assumption needs to be substantiated by further studies.

We also acknowledge the fact that this complex multi-method approach was performed in a population of limited sample size and certainly warrants replication in all main aspects. We are aware that the reported VBM results are not corrected for multiple comparisons and are very preliminary. We also consider the fact that the GSH redox state assessed in the peripheral blood may not necessarily reflect the redox state in the brain, introducing one more reason to consider the present results cautiously. As in the above-mentioned genetic investigations, future studies should therefore also include in vivo MR spectroscopy of GSH in target brain regions [93,94].

5. Conclusion

Our findings support the notion of latent oxidative stress in the early untreated phase of psychosis as a potential pathomechanism of localized brain structural abnormalities. This pathology relates to key regions of social cognition, affective motivation control and decision making, and is clinically expressed by higher severity of depressive and negative symptoms.

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The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Conflict of interest statement

We declare that we have no conflict of interest.

Author contributions

Drs Langbein, Smesny and Gussew had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis; all authors contributed to the writing of the paper and have approved the final version.

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