



Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

The coupling of low-level auditory dysfunction and oxidative stress in psychosis patients

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ARTICLE INFO

Article history:

Received 28 October 2016

Received in revised form 30 January 2017

Accepted 1 February 2017

Available online xxxx

Keywords:

Auditory

Event-related potential (ERP)

Glutathione (GSH)

Oxidative stress

Schizophrenia

Psychosis

ABSTRACT

Patients diagnosed with schizophrenia often present with low-level sensory deficits. It is an open question whether there is a functional link between these deficits and the pathophysiology of the disease, e.g. oxidative stress and glutathione (GSH) metabolism dysregulation. Auditory evoked potentials (AEPs) were recorded from 21 psychosis disorder patients and 30 healthy controls performing an active, auditory oddball task. AEPs to standard sounds were analyzed within an electrical neuroimaging framework. A peripheral measure of participants' redox balance, the ratio of glutathione peroxidase and glutathione reductase activities (GPx/GR), was correlated with the AEP data. Patients displayed significantly decreased AEPs over the time window of the P50/N100 complex resulting from significantly weaker responses in the left temporo-parietal lobe. The GPx/GR ratio significantly correlated with patients' brain activity during the time window of the P50/N100 in the medial frontal lobe. We show for the first time a direct coupling between electrophysiological indices of AEPs and peripheral redox dysregulation in psychosis patients. This coupling is limited to stages of auditory processing that are impaired relative to healthy controls and suggests a link between biochemical and sensory dysfunction. The data highlight the potential of low-level sensory processing as a trait-marker of psychosis.

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1. Introduction

Low-level sensory deficits are increasingly recognized as core dysfunctions in patients with chronic schizophrenia (Ethridge et al., 2015; Javitt, 2009; Turetsky et al., 2008). However, it is largely uninvestigated whether there is a link between disease-related pathology of schizophrenia and low-level sensory deficits. We investigated low-level auditory processing in a group of psychosis disorder patients in the early phases of the disease, and correlated it with blood measures of oxidant state. This should reveal whether low-level auditory processing is linked to a key pathological hub in schizophrenia and could serve as a biomarker for psychosis and schizophrenia.

Sensory processing deficits have been observed in patients with chronic schizophrenia (Doniger et al., 2002; Foxe et al., 2005, 2001; Javitt, 2015; Knebel et al., 2011; Oribe et al., 2013; Rosburg et al., 2008) as well as in patients at early stages of the disease (Foxe et al., 2011; Hall et al., 2011; Hong et al., 2009; Oranje et al., 2013; Salisbury et al., 2010). In the auditory modality, the P50 and the N100 components of the auditory evoked potential (AEP) reflect this sensory impairment. Differences in the P50 between patients and controls have been found in isolated auditory stimulus processing (Clementz and Blumenfeld, 2001; Jin et al., 1997) as well as in gating paradigms identifying a less than typically-reduced P50 amplitude in the second of a pair of tones in patients (Onitsuka et al., 2013; Potter et al., 2006). Compared to controls, patients also show reduced amplitude of the N100 components (Ahveninen et al., 2006; Anokhin et al., 2007; Ethridge et al., 2015; Force et al., 2008; Rihs et al., 2013; Turetsky et al., 2008; Wu et al., 2013), on the basis of which schizophrenic patients and controls can be distinguished on the group level (del Re et al., 2015) and on a single-subject level (Neuhaus et al., 2014). Moreover, there is evidence that

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low-level sensory deficits might be a characteristic trait marker of individuals with a genetic risk for developing schizophrenia (Light and Makeig, 2015; Light and Swerdlow, 2015) as indicated by the P50 in healthy subjects carrying a hereditary risk for the development of schizophrenia (Turetsky et al., 2012) and the N100 in first degree relatives or in subjects carrying a genetic risk (Ahveninen et al., 2006; Anokhin et al., 2007; Foxe et al., 2011; Frangou et al., 1997; Rihs et al., 2013).

A potential pathophysiological mechanism of schizophrenia is an impaired antioxidant defense system involving glutathione (GSH) in conjunction with N-methyl-D-aspartate receptor (NMDAR) hypofunction. This combination has been suggested to lead to effects across both acute and long-term timescales. The former entails impaired sensory processing of the variety discussed above, and the latter is supported by altered excitation-inhibition induced by aberrant function of fast-spiking parvalbumin-positive interneurons (PVI) (Do et al., 2009; Hardingham and Do, 2016). Altered levels of GSH and other antioxidants are found in CSF and post-mortem tissue (Do et al., 2000; Flatow et al., 2013; Gawryluk et al., 2011; see also Kim et al., 2016 for NAD⁺/NADH alterations) and are consistent with polymorphisms in key genes for GSH synthesis reported for schizophrenia (Gysin et al., 2007; Rodriguez-Santiago et al., 2010; Tosic et al., 2006). The impaired antioxidant defense mechanism is further confirmed by increased lipid and protein oxidation in the blood, the cerebrospinal fluid and post-mortem tissue (for reviews see Do et al., 2009; Yao and Keshavan, 2011) and has been validated in GSH-deficient animal models reproducing schizophrenia phenotypes including NMDAR hypofunction (Steullet et al., 2006) and impaired PVI activity (Cabungcal et al., 2013; Steullet et al., 2010). Causal links between NMDAR hypofunction and sensory processing impairments have been provided by neuropharmacological interventions and more recently by studies of genetic models (e.g. Chen et al., 2015; Javitt, 2009). More specifically, auditory processing impairments have been observed in auditory evoked potentials, including P50, N100, and P300 components, as well as in oscillatory activity across frequency bands following acute administration of NMDAR agonists in patients as well as in some cases in healthy participants. Additionally, administering N-Acetyl-Cysteine (NAC) which is a GSH precursor to chronic schizophrenia patients led to improved MMN generation (Lavoie et al., 2008).

Given this collective evidence, we hypothesized that early sensory processing deficits will be linked to GSH dysregulation measures in psychosis. A peripheral measure of brain GSH levels is a high oxidative status of blood redox indices, namely the ratio of GPx/GR which correlates negatively with brain GSH levels in early-psychosis patients (Xin et al., 2016). The present study investigated for the first time the link between the sensory deficits and potential pathophysiological characteristics of psychosis. AEPs and peripheral GPx/GR was measured and correlated in psychosis disorder patients and healthy controls and reveal a potential association between sensory deficits and oxidative stress in patients.

2. Methods and materials

2.1. Participants

A total of 51 individuals participated in this study. There were 21 psychosis disorder patients (19 men, 17 right-handed) aged 18–35 years (mean \pm SD = 24 ± 4 years) at the time of EEG recording. The patients were recruited from the TIPP program (Treatment and Early Intervention in Psychosis Program, University Hospital, Lausanne) (Baumann et al., 2013), which is a 3 year program specialized in the treatment of the early phase of psychosis that included only patients that had not received >6 months of previous treatment (Table 1). The diagnosis was confirmed 3 years after the data acquisition (Table 2). The control population included 30 individuals (19 men, 26 right-handed) aged 18–37 years (mean \pm SD = 25 ± 5 years). There was no reliable age difference between the two groups [$t(49) = 0.73$; $p = 0.46$].

Table 1

Demographic and clinical characteristics of early-phase psychosis patients ($n = 21$). Mean and standard error are indicated.

Daily Chlorpromazine (CPZ)-equivalent [mg/day] ($n = 18$)	451.78 \pm 57.41
Education of patients in years	12.09 \pm 0.56
PANSS: Positive Symptoms	15.52 \pm 1.06
PANSS: Negative Symptoms	16.72 \pm 1.25
PANSS: General	35.91 \pm 2.33
Time lapse between psychosis diagnosis and EEG recordings in days	613 \pm 104 (range: 116–1439)

All patients met threshold criteria for psychosis, as defined by the “Psychosis threshold” subscale of the CAARMS at the point of measurement (Comprehensive Assessment of at Risk Mental States scale (Yung et al., 2005)). This threshold is based on a combination of intensity frequency and duration of psychotic symptoms. Details regarding clinical evaluation and medication are provided in Table 1. In a follow-up diagnostic 3 years later, all patients met criteria either for affective psychosis ($n = 3$) or non-affective psychosis ($n = 18$) according to DSM-IV criteria (Table 2). Healthy controls, recruited from similar geographic and socio-demographic areas, were assessed by the Diagnostic Interview for Genetic Studies (Preisig et al., 1999) and matched on gender, age and handedness. Major mood, psychotic, or substance-use disorder and having a first-degree relative with a psychotic disorder were exclusion criteria for controls. All participants reported normal hearing. All participants provided their written, informed consent and the procedures were approved by the local Ethics Committee.

2.2. Stimuli and task

The task entailed an active oddball detection paradigm. Participants were instructed to press a button on a response pad as fast as possible when they heard infrequent stimuli. The frequent stimulus (70% of trials) was a 1000 Hz centrally-presented tone of 100 ms duration. The infrequent stimuli (30% of trials each) varied in pitch (1200 Hz), perceived lateralization (700 μ s inter-aural timing difference), or duration (150 ms) (1:1:1). The remaining parameters matched the frequent stimulus. A central visual fixation cross was present throughout the experiment. All tones were presented with an average inter-stimulus-onset-interval of 916 ms jittered with a maximum of ± 67 ms. Stimulus delivery and response recordings were controlled by E-Prime (Psychology Software Tools Inc., Pittsburgh, USA; www.pstnet.com/eprime).

Table 2

Specific diagnosis of patients after 3 years and antipsychotic medication at the time of the experiment.

Diagnoses	Number of patients
Schizophrenia undifferentiated	3
Schizophrenia, paranoid type	9
Bipolar disorder	1
Unspecific psychosis disorder	1
Schizophrenia, disorganized type	2
Brief psychotic episode	1
Schizotypal personality disorder	1
Recurrent depressive disorder with psychotic features	1
Major depressive disorder with psychotic features (comorbidity with borderline personality disorder)	1
Schizo-affective disorder, depressive type	1
Antipsychotic medication	Number of patients
Amisulpride	3
Aripiprazole	3
Olanzapine	4
Quetiapine	6
Risperidone	2
None	3

2.3. EEG acquisition and pre-processing

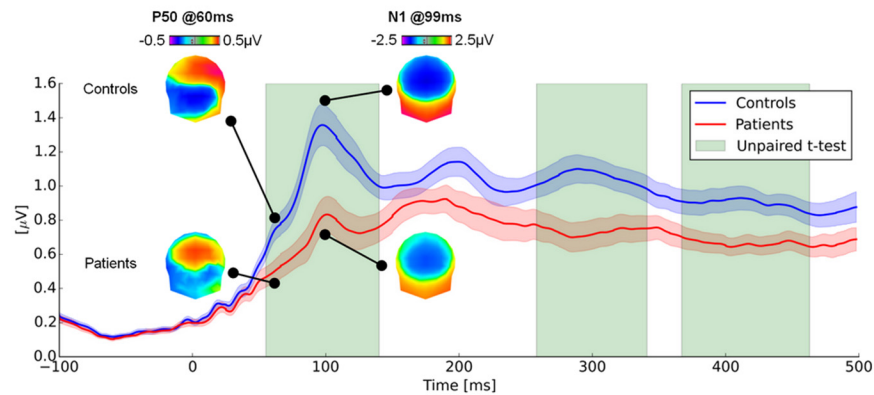
Continuous EEG was acquired at 1024 Hz through a 64-channel Biosemi ActiveTwo system (<http://www.biosemi.com>). EEG data pre-processing and analyses were performed with the Cartool software (Brunet et al., 2011). Data were filtered (second order Butterworth with -12db/octave roll-off; 0.1 Hz high-pass; 60 Hz low-pass; 50 Hz notch). In light of the literature summarized in the Introduction demonstrating both sensory processing impairments as well as impairments in processes subserving MMN and P300 generation, we considered it prudent to focus first on AEPs to frequent stimuli so as to establish to what extent sensory processing is intact in EPP and linked to redox dysregulation. Analyses of MMN and P300 will appear in a separate forthcoming article. AEPs were calculated in response to the frequent stimulus

spanning 100 ms pre-stimulus to 500 ms post-stimulus and pre-stimulus baseline corrected. Epochs with amplitude deviations $\pm 80 \mu\text{V}$ at any channel, and trials with blinks or other transients were excluded. Channels with poor electrode-skin contact were interpolated using 3D splines. Data were then recalculated against the average reference. The average number of accepted epochs was 1520 for controls (min./max. = 656/2020) and 1543 for patients (min./max. = 954/2002). These values did not significantly differ [$t(49) = 0.23$; $p = 0.81$].

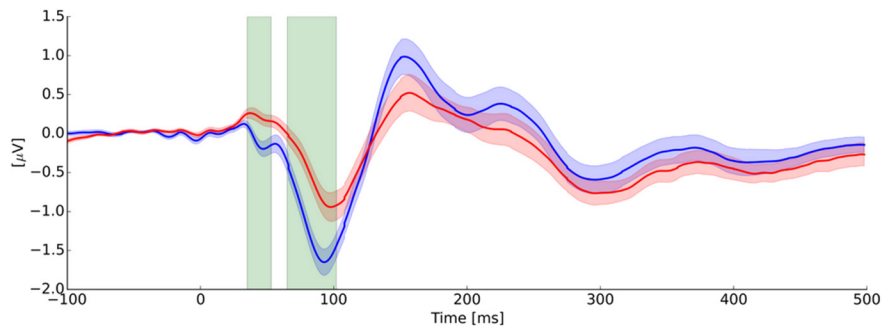
2.4. AEP analyses

The AEP data were analyzed within an electrical neuroimaging framework (Michel and Murray, 2012; Murray et al., 2008). Modulations in AEP strength (quantified by Global Field Power, GFP) and

A. Average Global Field Power and AEP Topographies



B. Group-averaged AEPs at Electrode Cz



C. Percentage of the Electrode Montage Exhibiting a between-Group Difference

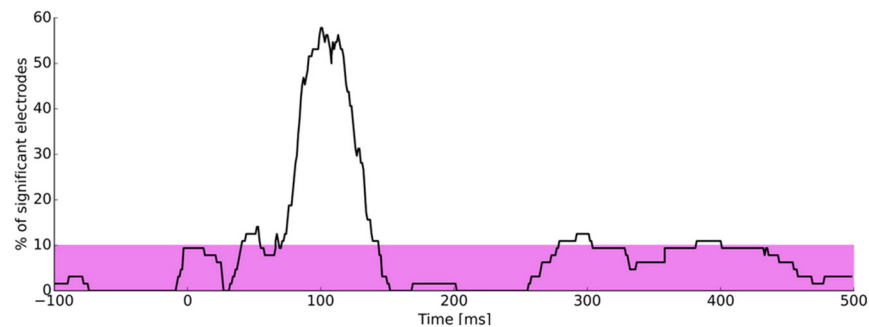


Fig. 1. A) Group-averaged global field power waveforms show that responses from early-phase psychosis patients (red) were significantly weaker than those from healthy controls (blue). Shadows depict standard errors of the mean. Periods shaded in green indicate significant differences ($p < 0.05$; > 15 consecutive time frames). Insets display topographic voltage maps at 60 ms and 99 ms post-stimulus onset to illustrate the P50 and N100 components, respectively (top-view shown). B) Group-averaged AEPs are shown at an exemplar midline scalp site (Cz) indicating a differential response between early-phase psychosis patients compared to controls in the P50/N100 time window. Conventions are otherwise as in panel A. C) The percentage of electrodes exhibiting a significant difference as a function of time is displayed. The magenta bar indicates a threshold of 10% of the electrode montage. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

topography (quantified by global dissimilarity) were analyzed separately as a function of time (Lehmann and Skrandies, 1980). We likewise include an analysis of electrode Cz as a function of time. Except where otherwise noted, comparisons of AEPs between groups were performed using independent samples *t*-tests. To correct for temporal autocorrelation, only effects meeting the criterion for at least 15 consecutive significant time points are reported (Guthrie and Buchwald, 1991). In the distribution of 10^6 randomizations of all time-points, 99.89% of consecutive significant time points fall below this length.

2.5. Source estimations and analyses

Source estimations were performed using a distributed linear inverse solution, applying the local autoregressive average (LAURA) regularization approach (Grave de Peralta Menendez et al., 2004, 2001; Michel et al., 2004). The solution space implemented here included 5013 nodes, selected from a $6 \times 6 \times 6$ mm grid equally distributed within the gray matter of the Montreal Neurological Institute's average brain (courtesy of Grave de Peralta Menendez and Gonzalez Andino). The head model and lead field matrix were generated with the Spherical Model with Anatomical Constraints (Spinelli et al., 2000). As an output, LAURA provides current density measures; the scalar values of which were evaluated at each node. The time periods used for source estimations were determined from AEP analyses. Data from each subject and condition were first averaged as a function of time to generate a single data point. The inverse solution was then calculated for each of the nodes in the solution space for each participant. These data matrices were then submitted to statistical analyses comparing source estimations from each group. A cluster size of 10 contiguous nodes was determined using the AlphaSim program (available at <http://afni.nimh.nih.gov>) and assuming a spatial smoothing of 2 mm FWHM and cluster

connection radius of 8.5 mm. As measure of effect size, the coefficient of determination is indicated.

2.6. Peripheral ratio of GPx/GR enzymatic activity

The ratio of enzymatic activities of glutathione peroxidase relative to glutathione reductase (GPx/GR) was measured in the blood of patients. Blood was collected by venipuncture in Vacutainer-tubes coated with Li-heparinate (Becton Dickinson), between 7 and 8:30 AM under restricted activity conditions and fasting from the previous midnight. GPx and GR enzymatic activities were assessed in blood cells (Xin et al., 2016). The GPx/GR ratio per subject was used as a measure for GSH redox homeostasis, compared between patients and controls with an independent samples *t*-test and used as a covariate in an ANCOVA on the GFP with one between subject factor 'group'. The analysis was performed using STEN (<http://www.unil.ch/line/home/menuinst/about-the-line/software-analysis-tools.html>).

3. Results

3.1. Impaired early-latency responses

Patients compared to controls showed a weaker auditory response to frequent stimuli at P50/N100 and at a later time windows as measured by GFP (mean r^2 for = 0.08, min/max = 0.14/0.22) (Fig. 1A) as exemplarily also shown by Cz (mean r^2 = 0.15, min/max = 0.08/0.22) in Fig. 1B. There was no evidence for significant topographic differences between groups as quantified by global dissimilarity (maximum number of consecutive and significant time points: 12; max/min = 1.48/0.22). No violation of normality over this period of significant GFP modulations (i.e. 56–137 ms) was found with the Shapiro-Wilk test.

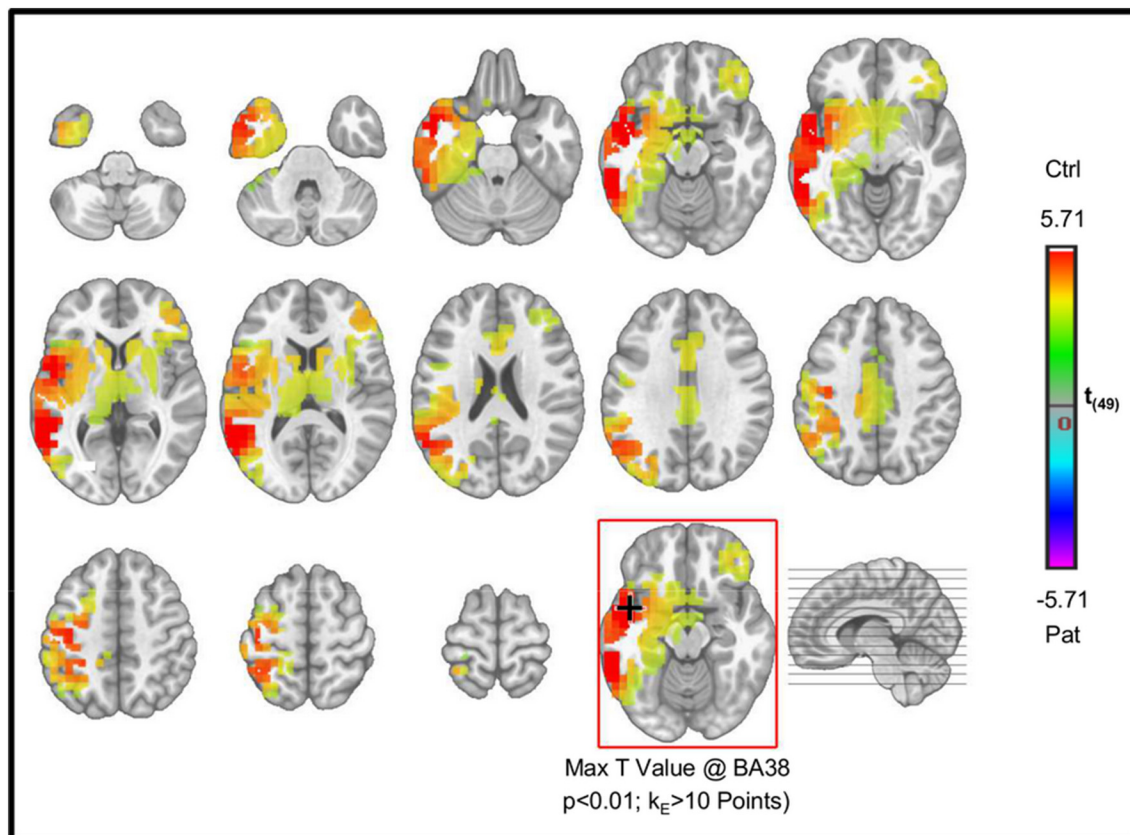


Fig. 2. Statistical comparison between early-phase psychosis patients and controls on distributed source estimations (56–137 ms post-stimulus onset). Controls exhibited significantly stronger activity within the left temporo-parietal cortices. The color bar depicts *t*-values. Statistical results were thresholded at $p < 0.01$ at the single-node level in conjunction with a 10-node spatial extent criterion to correct for multiple comparisons (i.e. $k_E > 10$ points).

Correlations between GFP and the dose of medication (CPZ, chlorpromazine daily equivalent) were below the significance threshold of $r = \pm 0.44$ ($p > 0.05$ for all time points (max/min = 0.41/–0.29). Statistical analysis of source estimations indicated that the difference between controls and patients in the time-window of 56–137 ms was a result of differential cortical activity in the left temporo-parietal lobe. The maximum t -value ($t(49)_{\max} = 5.71$; average $r^2 = 0.22$) was located in Brodmann's Area 38 (i.e. Superior Temporal Gyrus; Fig. 2).

3.2. AEP covariance with peripheral redox homeostasis

Patients and healthy controls did not significantly differ in their ratio of peripheral GPx/GR (patients: 6.02 ± 0.68 , controls: 7.48 ± 0.7 , $t(47) = 1.46$; $p = 0.14$); average $r^2 = 0.17$ (Fig. 3A). However, the GPx/GR ratio significantly covaried with GFP in a time-frame by time-frame regression over the P50/N100 period in EPP (i.e. 66–97 ms post-stimulus onset (Fig. 3B–C) as revealed by an interaction in the ANCOVA and post-hoc testing (p (max/min) = 0.049/0.02, F (min/max) = 4.43/6.42). No significant correlations were observed at other post-stimulus latencies, and no such relationship was observed in healthy controls.

Results of a 2 (controls vs. patients) \times GPx/GR ANCOVA on each node within the solution space showed a significant interaction within the frontal lobe ($F(1,45)_{\max} = 13.5$). The maximum F value was located in Brodmann's Area 9 (medial prefrontal cortex) (Fig. 4A). Post-hoc regression performed in each group separately showed a significant correlation between the source estimation in the time-window 56–137 ms

post stimulus onset for the EPP only. The maximum correlation value was located in Brodmann Area 10 (Anterior prefrontal cortex) (Fig. 4B).

4. Discussion

This study showed that early auditory ERPs are severely impaired in psychosis disorder patients in the early stages of the disease and moreover are coupled with peripheral measures of redox balance. This coupling was delimited in time to specifically those post-stimulus latencies when responses from patients were significantly weaker than those from controls and was limited in space to the anterior prefrontal cortex; a brain area previously identified as vulnerable to oxidative stress (Hardingham and Do, 2016; Steullet et al., 2014). Thus, by linking the spatio-temporal dynamics of specific brain processes with the dysfunction of antioxidant pathway we identified low-level sensory processing as a potential trait marker of the disease.

AEP analysis showed that responses from patients were significantly weaker than those from healthy controls 56–137 ms post-stimulus onset encompassing the P50/N100 complex; a set of stimulus-evoked components previously shown to be impaired in both chronic schizophrenia as well as early psychosis. It is well established that the N100 is generated by neural populations in the primary and association auditory cortices in the temporal lobe (Godey et al., 2001; Zouridakis et al., 1998). Consistently, the source-localization revealed that differences in the P50/N100 complex were the result of differential activity in the temporo-parietal lobe between patients and controls. An important advance of the present study is that sensory impairments are due to the

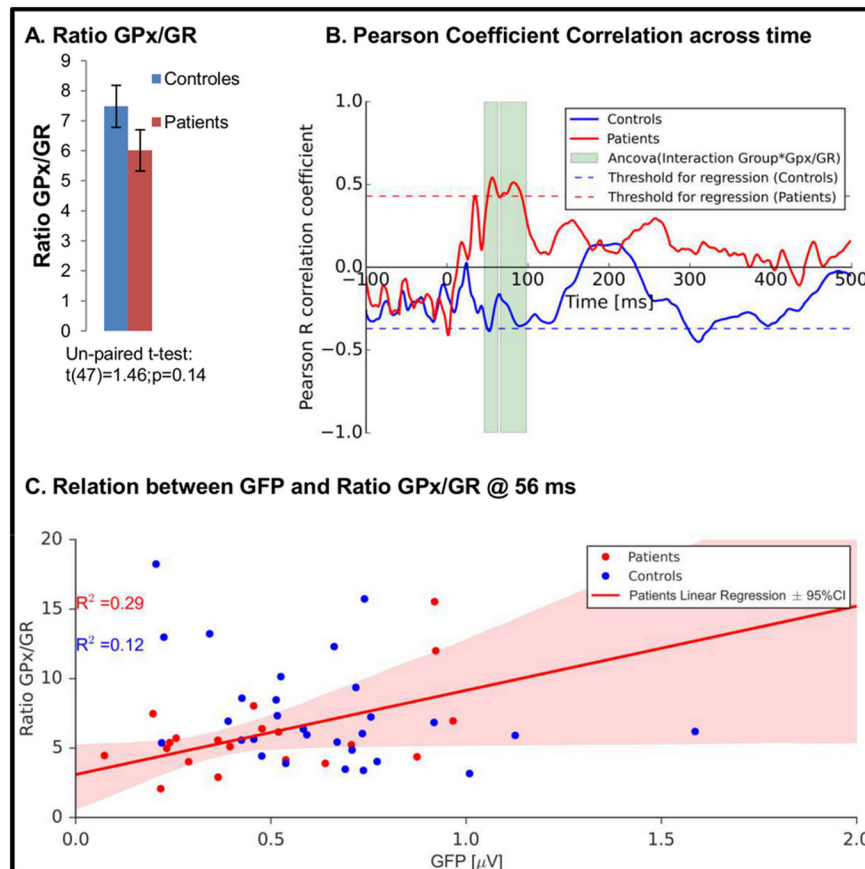


Fig. 3. A) The histogram depicts the average GPx/GR ratio for patients (red) and controls (blue). No significant differences between groups were observed. B) Correlation between GPx/GR and GFP as calculated by the Pearson correlation coefficient, R , as a function of time. Early-phase psychosis patients (red) and healthy control subjects (blue) show pronounced differences between these two curves. Indicated in green are time-frames displaying a significant interaction between the factor group and the correlation coefficient R . Dotted lines indicated the significance threshold for the regression between GPx/GR ratio and GFP, separately for each group. Early-phase psychosis patients display significantly stronger correlations between the GPx/GR ratio and GFP ($p < 0.05$) in the time-window of the N1. Only differences including at least 15 consecutive time frames are reported. C) Illustrates the relation between the GPx/GR and GFP for both groups of participants at the time-point of maximal correlation in the patient group (i.e. 57 ms) and the linear correlation for the early-phase psychosis patients (95% confidence interval shown in the shaded area). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

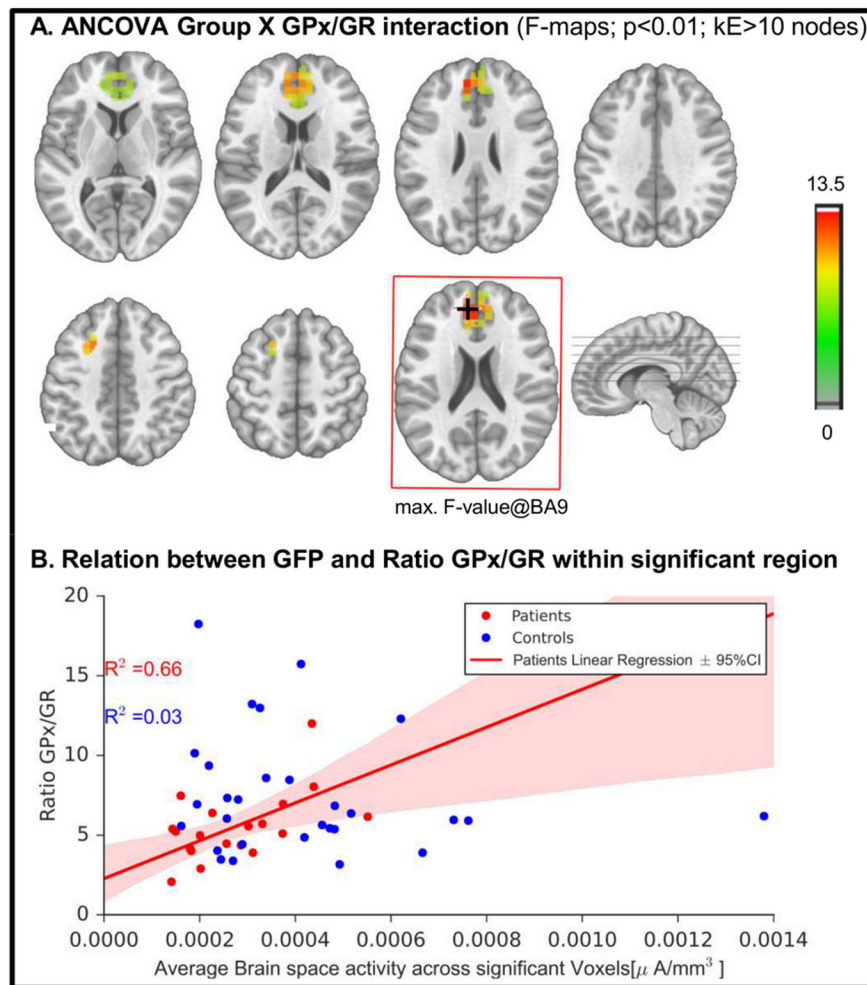


Fig. 4. Statistical correlation between GPx/GR ratio and distributed source estimation in the time-window of 56–137 ms post stimulus-onset. There was a significant interaction between group and GPx/GR in the anterior medial prefrontal cortex (A) which was driven by a significant correlation between the GPx/GR ratio and the distributed source estimation in the early-phase psychosis patients only (B). Color bars in (A) depict F-values, and statistical results were thresholded at $p < 0.01$ at the single-node level in conjunction with a 10-node spatial extent criterion to correct for multiple comparisons.

strength of active brain networks as reflected in GFP, but not due to changes in the network configuration as would be reflected in dissimilarity measures. That indicates that auditory impairment in psychosis is the consequence of generally diminished amplitude of brain activity rather than the activity of a divergent or compensatory network.

The smaller the ratio of GPx/GR in patients, the weaker was their GFP over the specific time window of the sensory deficit. It is important to note that the correlation was driven by the participants that had reduced ratios of GPx/GR (Fig. 3C). One interpretation of the findings is that the redox state influences the responsiveness of NMDAR and any dysregulation on that redox state reflected in the GPx/GR ratio can lead to generally reduced electrophysiological responses to tones. It is well established that oxidative stress depresses NMDAR function and, inversely, that prolonged NMDAR hypofunction induces an oxidative state, particularly in cortical parvalbumin interneurons (PVI) in patients (Hardingham and Do, 2016). Moreover, in a rodent knockout model affecting NMDAR selective to PVI, the AEP is decreased at N40 (Barnes et al., 2015), which is thought to be homologous to the human N100 response (Amann et al., 2010). It should be noted that a straightforward connection between N100 deficits and PVI dysfunction cannot be demonstrated in the current study, given evidence that acute administration of NMDAR agonists are themselves sufficient to affect such responses. In this vein, Lakatos et al. (2013) have shown that N100 activity occurs primarily in the theta frequency band rather than in the gamma band whose dysfunctions are more closely related to PVI dysregulation (Jadi

et al., 2016). Future studies focusing on oscillatory patterns and redox measures in psychosis could help elucidate potential contributions of NMDAR and PVI dysfunction to specific brain responses.

Our results clearly establish a link between oxidative state and sensory processing in patients. Interestingly and in keeping with Xin et al. (2016), we did not observe any difference in peripheral oxidation status between patients and controls, as measured by GPx/GR. Furthermore, a recent meta-analysis indicated no changes in GPx activity in first episode psychosis or stable medicated outpatients (Flatow et al., 2013). One speculative possibility is that patients with particularly low ratios, which appear to be driven by GPx, may be those who are particularly susceptible to functional impairments; a speculation borne out in results (cf. Fig. 3). Thus, we show for the first time a potential link between the pathophysiology in schizophrenic patients and low-level sensory deficits.

The GPx/GR ratio measured in patients correlated significantly with activity in the anterior and medial prefrontal cortex, indicating that functional activity is affected by oxidative stress in this brain area. Already in the early stages of psychosis the medial prefrontal cortex shows impaired white matter integrity (Stark et al., 2004), correlating significantly with prefrontal GSH levels in these patients (Monin et al., 2015). Moreover, medial prefrontal white matter impairments were observed in animal models with GSH deficiency (Monin et al., 2015). Our findings complement these results by showing that oxidative stress not only influences frontal cortex integrity but, potentially, also the

functional activity in this brain area. Importantly, our results support parallel functional impairments both of which manifest during early post-stimulus processing stages. On the one hand, sensory processing is impaired within low-level auditory cortices extending throughout the left temporo-parietal lobe. On the other hand and contemporaneously, the positive coupling between oxidative stress (viz. GPx/GR) and activity within the anterior medial prefrontal cortex may result from increased top-down control over sensory processing in patients that is not required by controls. This further supports the notion that the low-level sensory deficit is not simply an epiphenomenon of the disease, but could be directly linked to a potential pathophysiology.

We report a reduced auditory P50/N100 in this sample of psychosis disorder patients indicating a low-level sensory processing deficit in early stage psychosis and provide evidence of a direct link between these deficits and peripheral measures of oxidative stress in patients. This supports the notion that auditory deficits are a trait marker of the disease and provide insights on the functional consequences of oxidative stress on brain function.

Role of the funding sources

Financial support was provided by the Swiss National Science Foundation (grants: PY00P1_148184/1 to E.G., 320030_149982 and 320030_169206 to M.M.M.; 320030_122419 to P.C. and K.Q.D, and the National Centre of Competence in Research project “SYNAPSY, The Synaptic Bases of Mental Disease” [project 51AU40-125759]), the Damm-Etienne and Alamaya foundations and the Swiss Brain League (2014 Research Prize to M.M.M.). P.S.B. is supported by the Leenaards foundation. These sources had no further role in this study design, in the data collection and analysis, in the writing of the report, and in the decision to submit the paper for publication.

Author contributions

Conceived and designed the study: MMM, SC, PC, KQD
 Acquired the data: JFK, CR, CF, RJ, MF, LA, PSB
 Analyzed and interpreted the data: EG, JFK, CR, MMM
 Drafted the manuscript: EG, JFK, MMM
 Critically revised the manuscript: all authors
 Supervised the study: MMM, PC, KQD
 All authors contributed to and have approved the final manuscript.

Conflict of interest

Authors report no conflict of interest.

Acknowledgements

Cartool was programmed by Denis Brunet (<https://sites.google.com/site/fbmlab/cartool/cartooldownload>), and the STEN toolbox by Jean-François Knebel (<http://www.unil.ch/line/home/menuinst/about-the-line/software-analysis-tools.html>). Both are freely available and are supported by the EEG Brain Mapping Core of the Center for Biomedical Imaging (CIBM; www.cibm.ch). Lucas Spierer, Fosco Bernasconi, and Aurelie Manuel assisted with the EEG acquisition.

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