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

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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.

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 ± 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 ± 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 ± 57.41
Education of patients in years	12.09 ± 0.56
PANSS: Positive Symptoms	15.52 ± 1.06
PANSS: Negative Symptoms	16.72 ± 1.25
PANSS: General	35.91 ± 2.33
Time lapse between psychosis diagnosis and EEG recordings in days	613 ± 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 μs 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
Schizotypical 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

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