Schizophrenia Research xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Schizophrenia Research

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

Treatment in early psychosis with *N*-acetyl-cysteine for 6 months improves low-level auditory processing: Pilot study

Chrysa Retsa [a,b], Jean-François Knebel [a,b,c], Eveline Geiser [a,b], Carina Ferrari [d,e], Raoul Jenni [d,e], Margot Fournier [d], Luis Alameda [d,e,f], Philipp S. Baumann [d,e], Stephanie Clarke [a,b], Philippe Conus [e], Kim Q. Do [d], Micah M. Murray [a,b,c,g,h,*]

[a] The LINE (Laboratory for Investigative Neurophysiology), Radiodiagnostic Service, University Hospital Center and University of Lausanne, 1011 Lausanne, Switzerland
[b] Neuropsychology and Neurorehabilitation Service and Radiodiagnostic Service, University Hospital Center and University of Lausanne, 1011 Lausanne, Switzerland
[c] The EEG Brain Mapping Core, Center for Biomedical Imaging (CIBM), University Hospital Center and University of Lausanne, 1011 Lausanne, Switzerland
[d] Center for Psychiatric Neuroscience, Department of Psychiatry, University Hospital Center and University of Lausanne, Prilly-Lausanne, Switzerland
[e] Service of General Psychiatry, Department of Psychiatry, University Hospital Center and University of Lausanne, Prilly-Lausanne, Switzerland
[f] Psychiatric Liaison Service, Lausanne University Hospital (CHUV), Lausanne, Switzerland
[g] Department of Ophthalmology, University of Lausanne, Fondation Asile des Aveugles, Lausanne, Switzerland
[h] Department of Hearing and Speech Sciences, Vanderbilt University, Nashville, TN, USA

ARTICLE INFO

Article history:
Received 20 March 2017
Received in revised form 27 June 2017
Accepted 3 July 2017
Available online xxxx

Keywords:
Auditory
Auditory evoked potential
Mismatch negativity
N-acetyl-cysteine
Glutathione
Redox

ABSTRACT

Sensory impairments constitute core dysfunctions in schizophrenia. In the auditory modality, impaired mismatch negativity (MMN) has been observed in chronic schizophrenia and may reflect *N*-methyl-D-aspartate (NMDA) hypo-function, consistent with models of schizophrenia based on oxidative stress. Moreover, a recent study demonstrated deficits in the N100 component of the auditory evoked potential (AEP) in early psychosis patients. Previous work has shown that add-on administration of the glutathione precursor *N*-acetyl-cysteine (NAC) improves the MMN and clinical symptoms in chronic schizophrenia. To date, it remains unknown whether NAC also improves general low-level auditory processing and if its efficacy would extend to early-phase psychosis. We addressed these issues with a randomized, double-blind study of a small sample ($N = 15$) of early psychosis (EP) patients and 18 healthy controls from whom AEPs were recorded during an active, auditory oddball task. Patients were recorded twice: once prior to NAC/placebo administration and once after six months of treatment. The N100 component was significantly smaller in patients before NAC administration versus controls. Critically, NAC administration improved this AEP deficit. Source estimations revealed increased activity in the left temporo-parietal lobe in patients after NAC administration. Overall, the data from this pilot study, which call for replication in a larger sample, indicate that NAC improves low-level auditory processing in early psychosis.

1. Introduction

Low-level sensory impairments, both in auditory and in visual processing, seem to constitute part of the core dysfunctions in schizophrenia (Ethridge et al., 2015; Javitt and Freedman, 2015; Javitt, 2009). Increasing evidence indicates that oxidative stress related to glutathione (GSH) synthesis deficits in conjunction with *N*-methyl-D-aspartate (NMDA) hypofunction are major contributors to the pathophysiology of schizophrenia (Hardingham and Do, 2016). Previous work has shown that add-on administration of the glutathione precursor NAC in chronic schizophrenia patients improves auditory MMN generation to tone deviants (Lavoie et al., 2008) and clinical symptoms (Berk et al., 2008). However, it remains unknown whether NAC can also improve general low-level auditory processing impairments and whether its efficacy extends to the early stages of the disease. The contribution of an impaired antioxidant system in schizophrenia is supported by a variety of findings. Polymorphisms in key genes for GSH synthesis have been associated with schizophrenia (Rodriguez-Santiago et al., 2010; Do et al., 2009; Gysin et al., 2007; Tosic et al., 2006) and are related with decreased GSH levels in the cerebrospinal fluid, prefrontal cortex and post-mortem caudate of patients (Do et al., 2000; Yao et al., 2006; Flatow et al., 2013; Gawryluk et al., 2011; Xin et al., 2016; for a review see Koga et al., 2016; Yao and Keshavan, 2011). GSH-deficient animal models reproduce schizophrenia phenotypes including hypofunction of NMDA receptors (NMDAR) (Steullet et al., 2006). Several studies

* Corresponding author at: University Hospital Center and University of Lausanne, Department of Radiology, CIBM, BH08.078, Rue du Bugnon 46, Lausanne 1011, Switzerland.
E-mail address: micah.murray@chuv.ch (M.M. Murray).

http://dx.doi.org/10.1016/j.schres.2017.07.008
0920-9964/

have demonstrated that the administration of NMDAR agonists induces in healthy controls clinical symptoms as well as sensory processing impairments similar to those observed in schizophrenia and exacerbates these symptoms in patients. Specifically, impairments in the P50, N100, and P300 components of the AEP as well as in oscillatory activity have been observed after acute administration of NMDAR agonists (Chen et al., 2015; Javitt, 2009; Krystal et al., 1994).

MMN, an AEP component generated by deviant stimuli within an oddball paradigm, has been extensively used to measure NMDAR dysfunction in schizophrenia and it is often found decreased in amplitude in both chronic schizophrenia and earlier stages of the disease (Coyle, 2012; Moghaddam and Javitt, 2012; Turetsky et al., 2007). Previous studies have shown that administering NAC to chronic schizophrenia patients led to improved MMN responses (Lavoie et al., 2008), and increased EEG synchronization (Carmeli et al., 2012), in addition to improvement of negative symptoms (Berk et al., 2008). NAC has been used in various studies as a cysteine donor and given orally is quickly absorbed; peak plasma concentration of cysteine is reached within 120 mins (Borgstrom and Kagedal, 1990). NAC crosses the blood-brain barrier, and cysteine can be used in the brain as a GSH precursor (Farr et al., 2003; Conus et al., in revision). Animal studies have previously shown that administration of NAC protects the brain against GSH depletion (Atkuri et al., 2007; Fu et al., 2006; Kamboj et al., 2006) and its neurochemical and morphological consequences (das Neves Duarte et al., 2012; Cabungcal et al., 2013).

Deficits in the P50 and N100 components of the AEPs are well established in patients with schizophrenia (Bodatsch et al., 2015; Brockhaus-Dumke et al., 2008; Rosburg et al., 2008; Turetsky et al., 2008). Schizophrenia patients show a significant diminution in the amplitude of N100, especially for long ISIs (>1 s) (Rosburg et al., 2008; Shelley et al., 1999). Two recent studies using an auditory oddball paradigm demonstrated that psychotic disorder patients show impairments in response to standard/frequent stimuli in both P50 and N100 (Geiser et al., 2017), as well as the alpha-frequency range, the latter of which is thought to reflect deficient thalamo-cortical connectivity (Lee et al., 2017). The low-level AEP deficit observed by Geiser et al. resulted from weaker responses within the left temporo-parietal lobe and it was correlated with peripheral measures of GSH levels, specifically the ratio of glutathione peroxidase and glutathione reductase activities (GPx/GR) which correlates negatively with brain GSH levels in early psychosis patients (Xin et al., 2016). This AEP deficit in response to standard stimuli within the oddball sequence points to impaired input to auditory cortex (Lee et al., 2017). Previous studies have shown that the responses to standard sounds within oddball ERP tasks are impaired not only in chronic schizophrenia, but also in first–episode schizophrenia patients and clinical high-risk individuals (Salisbury et al., 2010; del Re et al., 2015). In addition, Foxe et al. (2011) demonstrated a significant amplitude reduction of the N100 in clinically unaffected first-degree relatives and highlighted the importance of the use of high numbers of trials for the reliable quantification of the evoked responses of interest.

In the present study, we investigated if the effect of NAC on MMN responses also applies to low-level auditory deficits in psychosis, specifically to the reduced N100 response to standard sounds. Additionally, as the group of patients that participated in this study was in the early stages of the disease, we assessed whether the efficacy of NAC can extend to early psychosis (EP). We show for the first time, that NAC administration results in improved low-level auditory processing.

2. Methods and materials

2.1. Clinical trial protocol

NAC (2700 mg/day) and placebo were administered to EP patients for 6 months following a double-blinded, randomized design. Electroencephalographic (EEG) recordings and blood sampling were performed at the onset of the protocol (baseline measurements), and at the end of the study (after the 6 months of the NAC administration) (Swiss Medic (2008DR2308), ClinicalTrial.gov. (NCT01354132)).

2.2. Participants

Fifteen patients (13 men, 13 right-handed; aged 26 ± 1.4 years; mean ± SEM) meeting criteria for psychosis, as defined by the "Psychosis threshold" subscale of the Comprehensive Assessment of at Risk Mental States scale (CAARMS; Yung et al., 2005) at the baseline participated in this study. The patients were recruited from the Treatment and Early Intervention in Psychosis Program, (TIPP, University Hospital, Lausanne; Baumann et al., 2013), which is a 3 year program specialized in the treatment of early phase of psychosis that included patients that had not received >6 months of previous treatment. The diagnosis was confirmed 3 years after the data acquisition (Table 2). The participants we report here are thus part of a larger clinical trial (Conus et al., in revision). Only the data from patients that completed the EEG sessions both before and after treatment are reported here. Data from these patients at the onset of the protocol were compared with those from 18 gender and age-matched healthy controls (15 men, 16 right-handed; aged 27.3 ± 2 years) (Table 1). Healthy controls were assessed by the Diagnostic Interview for Genetic Studies (Preisig et al., 1999). Major mood, psychotic or substance-use disorder and having a first-degree relative with a psychotic disorder were exclusive 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. Some of the data collected in the baseline measurement were reported as part of a study focusing on low-level auditory impairments in EP patients (Geiser et al., 2017).

Among the 15 patients, 8 were among the group that received NAC, and the remaining 7 received placebo. Following their recruitment, patients were given an ID number, and both patients and investigators were blinded until the time of analysis. Patients that received NAC and patients that received placebo did not differ in their clinical and demographic characteristics (Table 1).

2.3. Stimuli and task

Participants performed an active oddball detection paradigm. An active task ensured attention to the auditory modality and to the stimulus features. Such attention has been shown to enhance early ERP components (Woldorff et al., 1993). Their task was to press a button on a

Table 1
Demographic and clinical characteristics of early psychosis (EP) patients that received NAC ($n = 8$) and patients that received placebo treatment ($n = 7$) at baseline. Mean and standard error are indicated.

	NAC treatment	Placebo treatment	
	Patients	Patients	p values
Daily chlorpromazine (CPZ)-equivalent [mg/day]	385.5 ± 100	397.13 ± 111	$p = 0.94$
Education of patients in years	12.42 ± 0.89	11.42 ± 1.04	$p = 0.58$
PANSS: positive symptoms	16.6 ± 1.6	15.3 ± 1.3	$p = 0.56$
PANSS: negative symptoms	15.5 ± 1.8	17.4 ± 2.8	$p = 0.57$
PANSS: total	68.62 ± 5.4	69.14 ± 5.5	$p = 0.95$
Time lapse between psychosis threshold and EEG recordings in days	783 ± 255	771 ± 280	$p = 0.97$

Please cite this article as: Retsa, C., et al., Treatment in early psychosis with *N*-acetyl-cysteine for 6months improves low-level auditory processing: Pilot study, Schizophr. Res. (2017), http://dx.doi.org/10.1016/j.schres.2017.07.008