Psychiatry Research: Neuroimaging 221 (2014) 114–121

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

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

Disrupted action monitoring in recent-onset psychosis patients with schizophrenia and bipolar disorder

Michael J. Minzenberg [a,*], Glenn C. Gomes [b], Jong H. Yoon [b], Tamara Y. Swaab [c], Cameron S. Carter [b]

[a] Department of Psychiatry, University of California, San Francisco School of Medicine, San Francisco, CA, United States
[b] Department of Psychiatry, University of California, Davis School of Medicine, Sacramento, CA, United States
[c] Department of Psychology, University of California, Davis, CA, United States

ARTICLE INFO

Article history:
Received 26 March 2013
Received in revised form
18 October 2013
Accepted 9 November 2013
Available online 20 November 2013

Keywords:
Error-related negativity
Error positivity
N450
Conflict
Performance adjustment
Stroop

ABSTRACT

Schizophrenia patients experience cognitive control disturbances, manifest in altered neural signatures during action monitoring. It remains unclear whether error- and conflict-monitoring disturbances co-occur, and whether they are observed in recent-onset psychosis patients with schizophrenia or bipolar disorder. We tested electrophysiological measures of action monitoring in these patients. Seventy-three schizophrenia patients (SZ), 26 bipolar disorder type I patients (BP), each within one year of psychosis onset, and 54 healthy control subjects (HC) underwent EEG during Stroop task performance. In the trial-averaged EEG at three midline scalp electrodes, the error-related negativity (ERN), error positivity (Pe) and conflict-related N450 were measured. Compared to HC (1) SZ exhibited an attenuated ERN and N450, and Pe unchanged and (2) BP exhibited an attenuated ERN but normal Pe and N450. Between patient groups, SZ showed an attenuated N450; ERN and Pe were not significantly different. A small ($n=10$) SZ subgroup that was not receiving antipsychotic medication showed normal ERPs. Altered error- and conflict-monitoring occur together in the first-episode schizophrenia patients, and these measures are comparable in patients with the first-episode bipolar disorder. Antipsychotic medication may be associated with altered measures of error-monitoring in schizophrenia.

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1. Introduction

Schizophrenia is a serious, chronic mental illness characterized by impairments in several cognitive processes subserved by distributed circuits that are supported by the prefrontal cortex (PFC) (Minzenberg et al., 2009; Lesh et al., 2011). One of the more important impairments is the online monitoring of performance, including altered neural responses to both response conflict and errors (Carter et al., 1997, 2001; MacDonald and Carter, 2003; Kerns et al., 2005). Using electroencephalography (EEG), several well-established event-related potential (ERP) correlates of performance monitoring have been observed, including the error-related negativity (ERN), which is manifest as a negative deflection in the ERP waveform peaking around 50–150 ms following error commission, and maximal at fronto-central electrode sites (Gehring et al., 1995); the error positivity (Pe), a positive deflection peaking around 150–400 ms following an error (van Veen and Carter, 2002b), and the fronto-central "conflict N450" (also referred to as conflict N2), which peaks between 400 and 500 ms following the onset of a conflict stimulus during the Stroop Task (Liotti et al., 2000; McNeely et al., 2003; West, 2003). Source localization analyses of scalp EEG data suggests generators in the anterior cingulate cortex (ACC) for the ERN (Gehring et al., 1993; Dehaene et al., 1994), Pe (van Veen and Carter, 2002a,b; Herrmann et al., 2004) and N450 (van Veen and Carter, 2002b; Nieuwenhuis et al., 2003), though these ERPs may reflect the activity of somewhat different sectors within the ACC (ERN and N450 in dorsal ACC; Pe in both dorsal and rostral ACC; see van Veen and Carter, 2006 for discussion). Convergent evidence for an ACC generator comes from ERN-like electrical potentials detected in the ACC with intracranial recordings (Brazdil et al., 2002), and ACC activation in response to errors and conflict in functional MRI studies (Carter et al., 1998; Kerns et al., 2004). The ERN is typically related to both the motivational significance of error commission and (often, but not always) to post-error adjustments in behavioral performance (e.g., post-error slowing, PES, and post-error increases in accuracy, PEA) (see review in Danielmeier and Ullsperger, 2011). The significance of the Pe is less clear, though it has been related to error-awareness (Mathalon et al., 2003), and also to post-error adjustments in performance (Hajcak et al., 2003; reviewed in Taylor et al., 2007). These performance adjustments are generally

* Corresponding author. Tel.: +1 415 221 4810x6554; fax: +1 415 750 6921.
E-mail addresses: Michael.minzenberg@ucsf.edu, minzenberg@gmail.com (M.J. Minzenberg).

0925-4927/$ - see front matter Published by Elsevier Ireland Ltd.
http://dx.doi.org/10.1016/j.pscychresns.2013.11.003

considered to emerge from feed-forward signaling of the ACC to the lateral PFC, which augments goal-relevant processing in attention, sensory and motor regions (Botvinick et al., 2001; van Veen and Carter, 2006).

There is consistent evidence for a reduced-amplitude ERN among chronic schizophrenia patients, compared to healthy control subjects, during performance on a range of tasks (Kopp and Rist, 1999; Alain et al., 2002; Bates et al., 2002, 2004; Mathalon et al., 2002, 2009; Kim et al., 2006; Morris et al., 2006, 2008, 2011; Horan et al., 2012). The Pe, however, appears to be normal in many (though not all: Foti et al., 2012) of these studies (Alain, et al., 2002; Bates et al., 2004; Mathalon et al., 2002; Kim et al., 2006; Morris, et al., 2006; Horan et al., 2012; Simmonite et al., 2012), suggesting that they may index divergent cognitive processes. It is also possible that this variation arises from the existence of multiple generators for the Pe. The N450 has been investigated in only a single study in chronic schizophrenia, where it was found to be reduced in amplitude (McNeely et al., 2003). Post-error performance adjustments have been evaluated in some of these studies, which have found attenuations of the PES (Alain et al., 2002) and PEA (Morris et al., 2006) in the patients; other studies have found either normal PES in both schizophrenia and control subjects (Mathalon et al., 2002; Foti et al., 2012; Perez et al., 2012), or alternatively no PES detectable in either group (Bates et al., 2002, 2004; Morris, et al., 2006).

To date, only one study has evaluated the ERN in a recent-onset schizophrenia sample (within two years of overt illness onset). In this study, the schizophrenia group exhibited an attenuated ERN and Pe, similar to a more chronically ill schizophrenia group, though both groups showed intact PES (Perez et al., 2012). This type of clinical sample is important to study, to determine whether neural measures of impaired performance monitoring are present at the onset of overt illness, and not merely a consequence of illness chronicity, long-term medication exposure, or other clinical determinants. In addition, none of these studies have evaluated and reported the ERN and N450 concurrently, leaving it unclear whether ERP measures of error- and conflict-monitoring are reduced in amplitude within the same patients, as suggested with fMRI (Kerns et al., 2005).

There is also growing interest in identifying dimensional measures of brain activity that reflect pathophysiological mechanisms that cross diagnostic boundaries (exemplified in the RDoC initiative) (Insel et al., 2010), and a growing literature suggests potential convergence in pathophysiology between schizophrenia and bipolar disorder (Potash and Bienvenu, 2009). While electrophysiological measures of action monitoring appear consistently reduced in schizophrenia, it is unknown whether this extends to other disorders presenting with psychosis. Only one study has evaluated these ERP measures in both schizophrenia patients and other clinical groups with psychosis (Foti et al., 2012). This study compared a schizophrenia group to a heterogeneous group with other psychotic disorders (unspecified mood and substance-related), finding that the ERN was not different between the two clinical groups (though only the schizophrenia group was significantly reduced in amplitude compared to a healthy control group), with a smaller Pe in the schizophrenia group compared to the other psychosis group, and normal PES in each.

To our knowledge, there are no studies that have utilized ERP or cognitive measures of performance monitoring with patients identified with bipolar disorder type I, which is a prevalent, high-impact psychotic disorder that shares a clinical/diagnostic boundary with schizophrenia. A meta-analysis of 15 whole-brain structural imaging studies found decreased right rostral ACC gray matter concentration (using voxel-based morphometry) (Houenou et al., 2011). fMRI studies of chronic bipolar patients have found evidence for impaired ACC activation (relative to healthy control groups) during conflict monitoring among patients in the manic phase (Altshuler et al., 2005), euthymic phase (Gruber et al., 2004) and a pooled manic/mixed-phase inpatient sample (Strakowski et al., 2011), and reduced conflict-related activity in the adjacent supplementary motor area in a pooled-phase bipolar group (Roth et al., 2006). However, other studies have found normal ACC activity in a pooled-phase bipolar group (Blumberg et al., 2003), and relatively greater dorsal ACC activity in response to emotional distractors in euthymic bipolar patients (Wessa et al., 2007). It remains unknown whether altered ACC activity is observed in first-episode bipolar patients, or if ACC dysfunction is directly related to error-monitoring.

Accordingly, we evaluated these ERP measures of performance monitoring (ERN, Pe, N450) and dynamic task-performance adjustments (including PES and PEA), concurrently in patients with schizophrenia and the other with bipolar disorder type I who were early in the course of their illness. We predicted that the schizophrenia group would exhibit altered neural measures of both error and conflict monitoring; and we considered whether these two clinical groups would exhibit similar patterns of altered performance monitoring, including relationships with performance and with symptoms.

2. Methods

2.1. Subjects

73 schizophrenia outpatients (SZ group), 26 bipolar disorder type I outpatients (BP group), both with onset of psychosis within the previous 12 months, and 54 healthy controls (HC group) participated. Patients were recruited through the Early Diagnosis and Preventive Treatment of Psychosis (EDAPT) clinic of the Department of Psychiatry at UC Davis School of Medicine (www.earlypsychosis.ucdavis.edu). Diagnoses were established using the Structured Clinical Interview for DSM-IV-TR, and for patients under 18 years of age, the Kiddie-SADS-Present and Lifetime Version (K-SADS-PL; http://www.wpic.pitt.edu/ksads/ksads-pl.pdf). Master's degree and doctoral-level clinicians conducted the diagnostic evaluations, and all diagnoses were confirmed via consensus conference. All diagnosticians have demonstrated reliability on the clinical measures, as defined by ≥ 0.80 intraclass correlation–coefficient (ICC) for continuous measures and kappa ≥ 0.70 for categorical measures, and participated in monthly reliability interviews to prevent drift. Based upon 10 sessions during the course of this study, diagnostic reliability for the SCID for all diagnoses is kappa ≥ 0.7, and for BPRS SANS and SAPS total scores ICC's are ≥ 0.76. Among the bipolar patients, none were experiencing a major mood episode at study: one exhibited mild residual hypomania, seven were exhibiting mild residual depression, and the remainder ($n=18$) were euthymic. Clinical symptom scores for the patients were assessed with the Brief Psychiatric Rating Scale (BPRS) and the Scales for the Assessment of Positive and Negative Symptoms, (SAPS and SANS). We also scored all patients with the Global Assessment Scale (GAS) and the Strauss-Carpenter Outcome Scale (SCOS).

Subjects were enrolled with the following exclusion criteria: (1) IQ less than 70 (by Wechsler Abbreviated Scale of Intelligence), (2) history of neurological illness, including head injury, (3) substance-related disorder (by DSM-IV-TR) within six months of study, (4) uncontrolled medical illness, and (5) history of electroconvulsive therapy. Healthy controls were recruited from the community through advertisements. In addition to the criteria above, control subjects were evaluated with the SCID-Non-patient version to exclude those with a history of an Axis I disorder or first-degree relatives with psychotic disorder. All subjects provided informed consent, using a protocol approved by the Institutional Review Board at the University of California, Davis, and were compensated for participation. All were negative on a comprehensive urine drug screen on the test day. Of the 73 schizophrenia patients, 63 were taking antipsychotic medication and 10 were not. Of the 26 bipolar patients, 24 were taking psychotropic medications; 10 were not taking antipsychotics (of whom two were not taking any psychotropic medication). Table 1 shows the subject characteristics.

2.1.1. Cognitive paradigm

EEG data were acquired during performance of a manual-response Stroop task where color-word incongruence was the condition of interest (Kerns et al., 2005), and was presented using E-Prime (Psychology Software Tools, Pittsburgh, PA). Trial structure was as follows: each visual stimulus was presented for 1000 ms, with jittered 1000–2000 ms intervals between trials. The stimulus was a word ("red", "green", and "blue") in a specified ink color (red, green, and blue). Trials where the word meaning and ink color matched were "congruent" (low conflict), and those