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

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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. 73 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 first-episode schizophrenia patients, and these measures are comparable in patients with first-episode bipolar disorder. Antipsychotic medication may be associated with altered measures of error-monitoring in schizophrenia.

Keywords

error-related negativity; error positivity; N450; conflict; performance adjustment; Stroop

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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 on-line 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 frontocentral "conflict N450" (also referred to as conflict N2), which peaks between 400–500 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, 2002b; 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 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,

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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.

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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 ≥ .80 intraclass correlation-coefficient (ICC) for continuous measures and kappa ≥ .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, 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 2 were not taking any psychotropic medication). Table 1 shows the subject characteristics.

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2.2.1 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", "blue") in a specified ink color (red, green, blue). Trials where the word meaning and ink color matched were "congruent" (low conflict), and those where there was a mismatch between the word and color were "incongruent" (high conflict). The experimental phase of the task consisted of 8 blocks, each with 120 trials (70% congruent, 30% incongruent, pseudo-randomized). Subjects were instructed to respond to the ink color, to "answer as quickly and accurately as possible", and were allowed a 1000 ms maximum response window. For responses within 500 ms, the stimulus would terminate upon response, the remainder of 500 ms would elapse, and the jittered inter-trial interval would engage. For responses between 500 and 1000 ms, the stimulus would terminate at 500 ms, the remainder of 1000 ms (from stimulus onset) would elapse, and the jitter period would engage. For responses exceeding 1000 ms, the jittered inter-trial interval would engage (these trials were excluded from analysis). Each response option (red, green, blue) was mapped to one of three buttons on a keypad; this pattern was fixed for a given subject, but randomized across subjects. Congruent and incongruent trials were equally distributed across the three colors. Two practice sessions were first administered: the first consisted of 20 trials (80% congruent, 20% incongruent), where the subject was allowed an unlimited amount of time to respond to each stimulus. The second practice session was structured the same as the first, but with the addition of the 1000 ms response window, as in the subsequent experimental blocks. Practice sessions were repeated until subjects achieved accuracy > 80%. The total task time ranged from 32–40 minutes.

2.3 EEG acquisition, processing and analysis

EEG data were acquired using a Neuroscan 128-electrode Quik-Cap and Neuroscan SynAmps2 hardware, with a sampling frequency of 1000 Hz and a 100 Hz low-pass hardware filter. Data were collected using 32-bit encoding software. Electrode impedances were kept at <5 kOhms. All channels were referenced to the electrode located immediately posterior to electrode 63/Cz. Eyeblinks and eye movements were monitored for gross deflections in the raw EEG, as well as corrected using ICA post-acquisition.

Malfunctioning electrodes were excluded using the impedance map and by visual inspection of recorded waveforms. The remaining data were then imported into EEGLab (Delorme and Makeig, 2004), re-referenced against the average reference, down-sampled to 250 Hz and high-pass filtered at 0.05 Hz. Epochs were extracted from the continuous EEG data as follows: for N450, −200 to +900 ms relative to stimulus onset, and for the ERN and Pe, −400 to +400 ms relative to the response. Each epoch was baseline-corrected, using the pre-stimulus interval for N450, or −400 to −200 ms for ERN/Pe. Independent component analysis (ICA) was performed to remove eye-blink and noise contamination, using the "logistic infomax" algorithm (Bell and Sejnowski, 1995) with the "extended" option (Lee et al., 1999); both available within EEGLab. 75 principal components accounting for the most signal variance were derived, and the top 15 were used to identify and remove eye-blink and

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noise components, identified as non-neurogenic sources of variation in the EEG that are not otherwise explicitly attributable to eye movements, other muscle activity, etc. (McMenamin et al., 2010). Furthermore, N450 epochs were rejected if they did not occur within a −50 to 50 uV threshold, as were ERN epochs not occurring within a −150 to +150 uV threshold, which is consistent with published methods (Alain et al., 2002) and reasonable, given the foregoing use of ICA to identify and exclude artifacts. The N450 epochs were then low-pass filtered at 20 Hz, and ERN epochs were low-pass filtered at 12 Hz, as is typical in ERN and N450 studies in schizophrenia (Alain et al., 2002; McNeely et al., 2003). The ERN was measured between 0–100 ms, relative to response; Pe between 200–350 ms, relative to response; N450 between 450–600 ms, relative to stimulus onset. Trials were sorted by trial type (e.g., error vs. correct trials; congruent vs. incongruent) and then trial-averaged to derive a mean waveform for each subject in each trial type. For the ERN and N450, electrodes 61, 62 and 63 were selected for analysis and inferential testing, as these span the fronto-central scalp locations where these ERPs are typically maximal. For the Pe, electrodes 63, 64 and 65 were used. The N450 was derived from correct trials only. The mean voltages within the pre-specified time windows (see above) were derived for both Correct and Error trials (for ERN and Pe) and Congruent vs. Incongruent trials (for N450) and these values were averaged across the three target electrodes for all inferential tests. We derived and evaluated the ERN and Pe as difference scores between correct and error trials (e.g., for ERN, [mean voltage for Error trials] minus [mean voltage for Correct trials]; for N450, [mean voltage for Incongruent trials] minus [mean voltage for Congruent trials]). See Supplemental Methods for additional detail regarding EEG methods.

3. Results

3.1.1 Electrophysiology—See table 2 for summarized quantitative ERP values, figure 1 for averaged waveforms, and figure 2 for scalp topography, which depict the results within each group.

3.1.2 Within-Group ERP Effects—The HC group showed a significant difference from zero for the ERN ($t=-8.55$, $df = 53$, $p < 0.0005$), the N450 ($t= -2.07$, $df = 53$, $p = 0.043$) and the Pe ($t= 5.62$, $df = 53$, $p < 0.005$). The SZ group showed a significant difference from zero for the ERN ($t= -2.40$, $df = 72$, $p = 0.019$) and Pe ($t= 8.01$, $df = 72$, $p < 0.0005$), but a significant difference from zero for the N450 that was in a paradoxical, positive direction ($t= 2.19$, $df = 72$, $p = 0.032$). The BP group showed a significant difference from zero for the ERN ($t= 5.01$, $df = 25$, $p < 0.0005$), Pe ($t= 3.76$, $df = 25$, $p = 0.001$), and N450 ($t= -2.27$, $df = 25$, $p = 0.034$).

3.1.3 ERP Comparisons Between Groups—Multiple Analysis of Variance (MANOVA) of the three ERP measures revealed a highly-significant effect of Diagnosis ($F= 4.05$, $df = 6,282$; $p=0.001$). We then proceeded to a series of pair-wise comparisons by t test as our main set of inferential tests. The SZ group, compared to the HC group, showed a significantly attenuated ERN and N450, but no difference in Pe (see Table 2 for summary statistics). The BP group, compared to the HC group, showed a significantly attenuated ERN, but no difference in N450 (Cohen's $d = 0.17$) nor Pe. The SZ group, compared to the

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BP group, showed a significantly attenuated N450 but no difference in ERN nor Pe. The pattern of between-group results for males-only subgroups was similar to those for the full sample (see supplementary results). We also repeated the between-groups analyses as ANCOVA, co-varying for mean accuracy and RT (in separate ANCOVA models) to evaluate whether group differences in task performance were related to these group differences in ERN. These analyses showed that all significant effects of diagnostic group on ERPs persisted (results not shown). In addition, while the numbers of trials retained for analysis across the full experiment varied between groups, we conducted an analysis of each ERP derived from the first 200 retained trials in each subject. This analysis showed that the pattern of between-group comparisons was again identical; i.e. both significant and non-significant group differences persisted (results not shown).

3.1.4 ERP Comparisons with Unmedicated Subgroups—We compared the subgroup of SZ patients who were not taking antipsychotics, to those who were (and to the HC group), on each ERP and clinical measure. In the SZ group, the subgroup not taking antipsychotics (n =10) showed a significantly greater ERN than the subgroup taking antipsychotics (n = 63) ($t = 2.44$, $df = 71$, $p = 0.017$). There were no significant differences between the unmedicated SZ subgroup and the HC group in ERN ($t= 0.75$, $df = 62$, $p = 0.45$), Pe ($t= -0.18$, $df = 62$, $p = 0.86$) or N450 ($t=0.53$, $df = 62$, $p = 0.60$).

There were no other differences between unmedicated and medicated SZ subgroups in Pe, N450, performance adjustments, symptom severity or functional status (all $p > 0.18$). In the BP group, the subgroup not taking antipsychotics (n = 10) was not different on any of these measures compared to those taking antipsychotics (all $p > 0.48$).

3.1.5 Relationships of ERPs to Demographic, Clinical Measures and Dynamic Post-Error Performance Adjustments—There were no correlations of any ERP with age, parental or personal education, nor full-scale IQ, within any of the three groups ($-0.19 < r < 0.26$; all $p > 0.16$). In the SZ group, the Pe was significantly positively correlated with GAS scores ($r= 0.28$, $p < 0.02$). Otherwise, ERPs in SZ were not significantly correlated with BPRS, SAPS, SANS, nor Strauss-Carpenter scores ($-0.10 < r < 0.20$; all $p > 0.11$). In the BP group, the Pe was significantly negatively correlated with the BPRS total ($r = -0.48$, $p = 0.032$); there were no other significant associations of ERPs with clinical measures ($-0.23 < r < 21$; all $p > 0.26$). In addition, none of the four measures of dynamic performance adjustment were significantly associated with the ERN, N450 nor Pe, within any of the three subject groups ($-0.14 < r < 0.18$; all $p > 0.16$).

We also repeated these exploratory correlation analyses with the patient groups combined to test whether there were associations of reduced-amplitude ERPs with clinical measures or performance adjustments across diagnoses. Among the full patient group (SZ + BP), the Pe was not significantly correlated with GAS ($r = 0.15$, $p = 0.15$), nor with the BPRS ($r= 0.06$, $p = 0.61$), as they were in the SZ and BP groups alone, respectively; nor were other ERPs significantly correlated with symptoms or performance in the pooled patient group.

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4. Discussion

In this study, we found both an attenuated ERN and N450 in recent-onset schizophrenia. This is consistent with, and extends, prior studies of each component tested separately in chronic schizophrenia patients (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) and in a single study of recent-onset patients (Perez, et al., 2012). The present evidence suggests that the neurobiological basis of action monitoring is disturbed early in the course of schizophrenia. Convergent evidence from fMRI studies (Carter, et al., 1997; Laurens et al., 2003; Kerns, et al., 2005; Polli et al., 2008; Becerril et al., 2011) indicates that chronic schizophrenia patients exhibit impaired error-related activity in the ACC, which is the likely generator of the ERN (Gehring et al., 1993; Dehaene et al., 1994).

Interestingly, we also found that the ERN was attenuated in the bipolar group. Additionally, BP patients failed to show a significant N450, though they were not significantly different from either HC or SZ. These findings suggest that the ERN in particular may serve as a continuous measure of shared pathophysiology associated with action monitoring in recent-onset psychosis patients with these disorders.

These observations raise the possibility that the underlying neural basis for these two ERP measures (ERN vs. N450) may be dissociable, in relation to either neuroanatomy and/or fundamental cognitive processes in which they arise. One set of theories regarding the ERN proposes that it reflects error detection through either comparator-based or reinforcement learning-based mechanisms (e.g. Holroyd and Coles, 2002). Such a model posits a source in the ACC that detects a mismatch between intended and actual outcomes, a mechanism that is distinct from that occurring during correct responses in which there is conflict. The potential divergence of these components between our two first-episode psychosis groups in the present study could be interpreted as evidence for such a model. An alternative view (Carter et al., 1998; Botvinick et al., 2001) posits that during errors, the ACC detects conflict between the executed incorrect response and activation of the correct response due to ongoing stimulus evaluation. Within this model, dysfunction of multiple elements in the cognitive control network involved in task-relevant responding, in addition to the ACC, may lead to reduced conflict processing and related brain activity in that brain region. For example, previous studies (Gehring and Knight, 2000; Botvinick et al., 2004) have implicated the DLPFC in the generation of the ERN, according to conflict theory, by supporting the ongoing evaluation of the stimulus during the commission of errors. Hence, the findings of similar reductions in the ERN, but less of a reduction in the N450 in BP than in SZ, might be interpreted in terms of different cognitive and neural mechanisms underlying the two components. However, it could also suggest differences within the distributed neural circuitry underlying cognitive and control and performance monitoring that is disrupted in the two disorders. For example, SZ might have substantial disruption in both DLPFC and ACC, while in BP the pathology might involve relatively more the DLPFC and less the ACC. Adjudicating between these two hypotheses will require the use of other methodologies such as fMRI and MEG that offer the ability to better-localize disturbances in functional neural circuitry.

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We also found the Pe unchanged in schizophrenia relative to controls, which is largely consistent with studies of chronic schizophrenia patients, with the exception of one study that reported an Pe that was reduced in amplitude relative to healthy comparison subjects (Foti et al., 2012). The only other study of the Pe in a recent-onset schizophrenia sample found it attenuated rather than increased (Perez et al., 2012); the source of this discrepancy remains unclear. The Pe was also intact in the BP group. In addition, dynamic adjustments in task performance were not different between groups, consistent with the modal finding in the ERN literature in chronic schizophrenia (Bates, et al., 2002, 2004; Mathalon et al., 2002; Foti et al., 2012; Perez et al., 2012) and recent-onset schizophrenia (Perez et al., 2012).

Importantly, in exploratory analyses of a small subsample of unmedicated schizophrenia patients, we found that the ERN was intact. Circumstantial evidence suggests that the altered cortical dopamine (DA) signaling proposed in schizophrenia (reviewed in Remington et al., 2011) may impact action monitoring, and a reinforcement learning-based model of error monitoring would predict that a deficit in phasic DA responsiveness during action monitoring would lead to an ERN reduced in amplitude, by attenuating DA signal transmission in the mesocortical DA pathway (Holroyd and Coles, 2002). There is some limited evidence to support a modulatory role for the DA system in the ERN, from pharmacology studies (reviewed in Jocham and Ullsperger, 2009) and genetic studies (reviewed in Ullsperger, 2010). It is unclear whether altered error-monitoring in schizophrenia can be related to a specific deficit in DA signaling, on the basis of the present evidence or the wider existing literature. However, there are at least two potential physiological mechanisms by which chronic antipsychotic treatment could induce or exacerbate this cognitive deficit. First, chronic treatment with either typical or atypical antipsychotics leads to a state of depolarization inhibition in mesocortical DA neurons, attenuating their capacity to respond with phasic bursts of action potentials or DA release at terminals (reviewed in Grace et al., 1997). Secondly, this treatment is also associated with down-regulation of post-synaptic D1 receptors, which largely mediate the effects of DA on neocortical neurons (reviewed in Goldman-Rakic et al., 2004). These effects may form the basis for reported effects of DA antagonists such as the antipsychotic haloperidol in attenuating the ERN in healthy subjects (reviewed in Jocham and Ullsperger, 2009) and the differences between the medicated and unmedicated patients in the present study. It remains unclear how to resolve the present finding with that of Bates et al., 2004, who found antipsychotic treatment to partly remediate the ERN deficit in a sample of schizophrenia patients. However, the sample in that study was quite likely experiencing more active psychotic symptoms at enrollment, with the antipsychotic treatment providing measurable relief from psychotic symptoms that may have interfered with cortical function and/or task performance. In contrast, our sample more likely reflects trait-like neural/cognitive impairments, as our patients were all on stable medication regimens at study.

4.1 Study Limitations

In the present study, the bipolar patients, while all clinically-stable in an outpatient setting, were varied in their phase of illness at study, including euthymia, mild residual depression and hypomania. This may introduce variability in the disturbances in neural and cognitive function as they are measured here, which could lead to type II error in statistical

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comparisons. It remains unknown if action monitoring changes over the phases of illness in bipolar disorder, and this would be an important question to address in future work.

4.2 Conclusion

Patients with schizophrenia exhibit multiple disturbances in the neural basis of action monitoring early in the course of illness. These include alterations in cortical activity supporting the detection of both errors and conflict. In addition, recent-onset psychosis patients with bipolar disorder also show ERP evidence of disrupted action monitoring. These results suggest that ERPs related to action monitoring may serve as useful dimensional neural measures related to pathophysiological mechanisms that cut across diagnostic boundaries in individuals with recent-onset psychosis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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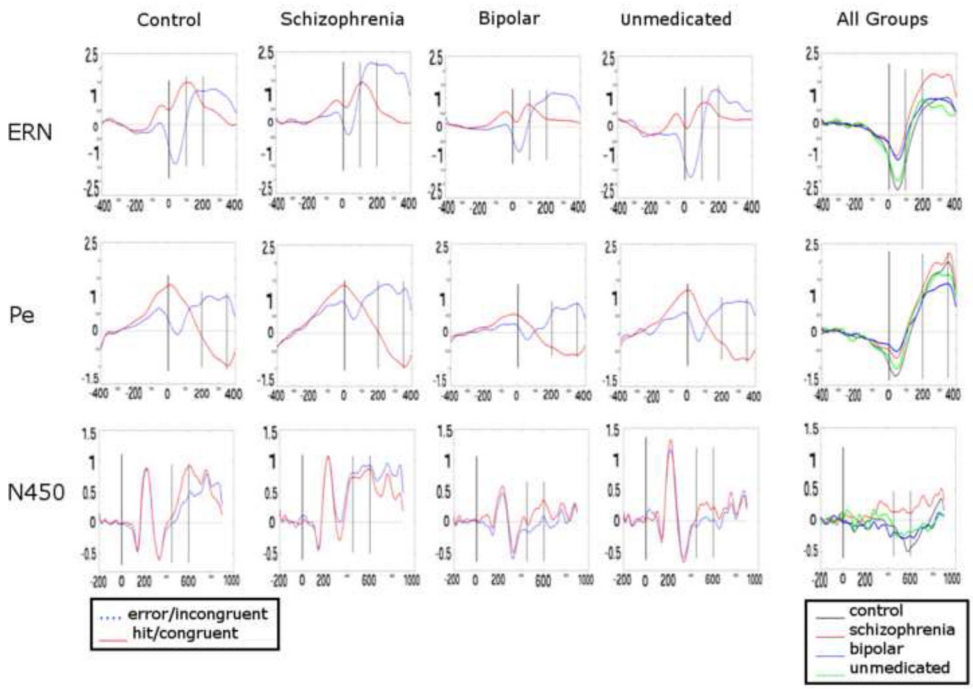

Figure 1. Average waveforms for ERN, Pe and N450 in each subject group, and differences between task conditions

Each group includes both medicated and unmedicated subjects. Trial-averaged values in microvolts. Difference waveforms are in far right column (for ERN and Pe, between error and correct trials; for N450, between congruent and incongruent trials). For ERN and Pe, response is at t=0; for N450, probe onset is at t = 0. ERN is measured between 0–100 ms; Pe between 200 and 350 ms; N450 between 450 and 600 ms (each interval indicated by solid vertical drop lines). Note that the scale for difference waveforms is smaller than that for each component.

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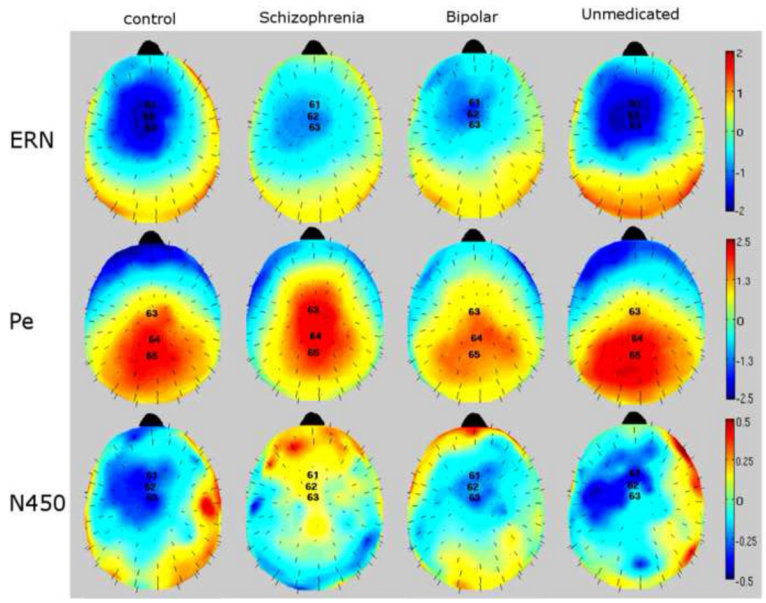

Figure 2. Scalp topography of event-related potentials in each group

Each group includes both medicated and unmedicated subjects. Trial-averaged values in microvolts. The scale for each individual ERP is consistent across subject groups.

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Table 1

Demographic and Clinical Characteristics of Subjects.

Measure	SZ Group (n=73)		BP Group (n=26)		HC Group (n=54)	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
Age	20.6 (†)	3.0	21.6 *	3.8	20.1	2.4
Parental Education	15.0	3.4	15.0	4.0	15.3	1.9
Subject Education	12.2 ***	2.0	12.9	2.1	13.6	2.0
Full-Scale IQ (WAIS)	101 ***	14	102 ***	15	115	9
BPRS	41.7 ††	9.0	36.2	8.6	N/A	
SANS	13.6 †	11.7	7.7	6.3	N/A	
SAPS	9.2	9.3	7.9	13.7	N/A	
SCOS	8.1 †††	2.7	11.5	2.5	N/A	
GAS	40 †††	7.8	50	15.8	N/A	
	N	**%**	**N**	**%**	**N**	**%**
Male	59	81	16	62	28	52
Unmedicated	10	14	2	8	N/A	
Antipsychotics	63	86	15	58	N/A	
Anticonvulsants	10	14	10	38	N/A	
Antidepressants	9	13	7	27	N/A	
Lithium	2	3	5	19	N/A	
Benzodiazepines	5	7	2	8	N/A	
Anticholinergics	3	4	1	4	N/A	
Hypnotics	5	7	3	12	N/A	
Antiadrenergics	3	4	0	0	N/A	

Tabled values are group means ± SD.

* $p < 0.05$,

** $p < 0.01$,

*** $p < 0.005$, by t test between either patient group and HC group.

† $p < 0.05$,

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$\dagger\dagger$ $p < 0.01$,

$\dagger\dagger\dagger$ $p < 0.005$,

$(\dagger)$ $p < 0.10$, by t test between SZ group and BP group.

WAIS, Wechsler Adult Intelligence Scale; BPRS, Brief Psychiatric Rating Scale; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; SCOS, Strauss-Carpenter Outcome Scale; GAS, Global Assessment Scale.

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Table 2

Event-Related Potentials and Task Performance.

Measure	SZ Group (n=73)		BP Group (n=26)		HC Group (n=54)	
	Mean	SD		SD	Mean	SD
ERN	−0.57***	2.02	− 1.01*	0.90	−1.97	1.61
Pe	1.79	1.91	1.63	1.94	1.46	1.84
N450	0.54***†	2.12	−0.66	1.36	−0.86	3.07
Congr acc	88.4%***††	8.6%	93.7%	6.0%	94.4%	5.5%
Incong acc	81.1%*†	12.5%	87.5%	7.9%	86.2%	9.7%
Congr RT	660**	100	666**	63	617	77
Incongr RT	733	113	749*	73	704	88
Interfere RT	73	44	83	45	87	59
PES (ms)	50	58	67 (*)	58	45	43
PEA (%)	−8.0**	9.5	−5.0	5.7	−3.8	5.5
PCS (ms)	7.0	48	7.0	40	19	27
PCA (%)	−7.2	8.5	−7.6	7.2	−6.6	7.8

Values are group means ± SD (ERPs in microvolts; RTs in milliseconds). ERP magnitudes are derived from the mean of electrodes 61, 62 and 63.

*** $p < 0.005$,

** $p < 0.01$,

* $p < 0.05$,

(*) $p < 0.10$, by t test between either patient group and HC group.

†† $p < 0.01$,

† $p < 0.05$,

(†) $p < 0.10$ between SZ and BP groups.

ERN: Error-Related Negativity; Pe, Error-Related Positivity; N450: Conflict-Related Negativity; PES: Post-Error Slowing; PEA: Post-Error Increase in Accuracy; PCS: Post-Conflict Speeding; PCA: Post-Conflict Increase in Accuracy.