

Illness insight and neurophysiological error-processing deficits in schizophrenia

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Abstract

Impaired illness insight in schizophrenia is associated with non-adherence and worse outcomes. Schizophrenia patients also exhibit error-monitoring deficits, which have been proposed to cause poor insight. To test this hypothesis, we examined whether schizophrenia patients' deficits in neurophysiological error-monitoring indices, the error-related negativity (ERN) and error positivity (Pe) event-related potential (ERP) amplitudes, are associated with impaired insight. ERPs were recorded in 18 schizophrenia patients and 18 normal comparison participants during a Stroop task. Patients' subnormal ERN and Pe amplitudes did not correlate with insight, suggesting that impaired insight in schizophrenia stems from neurocognitive mechanisms other than deficient error monitoring.

Keywords: Schizophrenia; cognition; illness insight; error processing; event-related potentials; electrophysiology; neurophysiology; error-related negativity; error positivity.

1. Introduction

In schizophrenia, insight into having a mental illness and its symptoms is variable, and at least partially lacking in approximately 50% of patients (Lincoln et al., 2007). Deficient insight in schizophrenia correlates only modestly with symptom severity, which accounts for 3-7% of variance in insight (Mintz and Dobson, 2003). This dissociation suggests that insight is a “core and enduring deficit” of schizophrenia (Buckley et al., 2007) semi-independent from other symptoms. Poor insight is associated with decreased treatment adherence (Beck et al., 2011) and predicts worse outcomes (Drake et al., 2007; Lincoln et al., 2007). Thus, a better understanding of neurophysiological and cognitive mechanisms of poor insight in schizophrenia may help improve patient outcomes.

Researchers have hypothesized that deficits in error monitoring – i.e., monitoring one’s thoughts and actions vis-à-vis external context and feedback – may contribute to poor insight in schizophrenia (Aleman et al., 2006; Drake and Lewis, 2003). Specifically, impaired ability to process information that counters hallucinations or delusions, or to recognize illogicality or inappropriateness in one’s speech or behaviour, might contribute to lack of awareness of these symptoms.

Error monitoring can be probed at the neural level using scalp-recorded cognitive event-related brain potentials (ERPs). The error-related negativity (ERN) is an ERP waveform peaking approximately 50 ms after commission of an error in choice-response tasks (Gehring et al., 1993). Thus, it may index conflict between neural representations of the correct and incorrect responses as stimulus processing continues after an error (Yeung et al., 2004). Errors are also associated with a later, positive waveform, the error positivity (Pe), peaking between 200 and 400 ms after the incorrect response. ERN amplitude is similar regardless of whether the

individual is consciously aware of the error; in contrast, the Pe is significantly larger when there is error awareness (Nieuwenhuis et al., 2001; Hughes and Yeung, 2011). These findings suggest that both preconscious error detection and conscious error awareness require processes reflected in the ERN, whereas conscious awareness also depends on processes indexed by the Pe. ERN amplitude is reduced in schizophrenia (Alain et al., 2002; Foti et al., 2012; Kopp and Rist, 1999; Mathalon et al., 2002; Morris et al., 2006; Morris et al., 2008; Perez et al., 2012), suggesting error-monitoring deficits. Pe amplitude has also been found to be reduced in schizophrenia in some (Foti et al., 2012; Perez et al., 2012) but not all studies (Alain et al., 2002; Horan et al., 2011; Kim et al., 2006; Mathalon et al., 2002; Morris et al., 2006; Simmonite et al., 2012).

As the relationship between neurophysiological error-monitoring deficits and impaired insight in schizophrenia has not previously been examined, we tested for an association between these variables, using the ERN and Pe as neurophysiological probes of deficient error monitoring. We hypothesized that, consistent with previous work, schizophrenia patients would exhibit reduced ERN and Pe amplitudes; and that both these abnormalities would be associated with poorer illness insight, consistent with a role for deficient conscious error recognition in the pathogenesis of impaired insight.

2. Methods

2.1. Participants

Participants included 18 outpatients with schizophrenia and 18 normal comparison participants (NCPs). Patients were recruited in Hamilton, Ontario, Canada from two outpatient clinics specializing in schizophrenia treatment and rehabilitation. NCPs were recruited from the community by advertising online, in local newspapers, and on bulletin boards. All participants

gave informed written consent. The protocol was approved by the St. Joseph's Healthcare Hamilton Research Ethics Board.

Participants were screened diagnostically with the Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998). DSM-IV diagnoses were established using a best-estimate approach based on the MINI and information from medical records and clinician reports. Exclusion criteria included: current manic or depressive episode, lifetime substance dependence, substance abuse in the past six months, and lifetime self-reported neurological disorder. NCPs were also excluded if they met criteria for any other Axis I diagnoses, or were taking psychotropic medication. Group demographic characteristics are shown in Table 1. Patient and control groups did not differ significantly on age, sex, or parental socioeconomic status.

2.2. Clinical ratings

Patients were rated on schizophrenia symptoms using the Scale for Assessment of Positive Symptoms (SAPS; Andreasen, 1984b), and Scale for Assessment of Negative Symptoms (SANS; Andreasen, 1984a). Symptoms were rated for the present, and for a past period of acute illness (e.g., period preceding the most recent hospitalization). From these ratings, we derived scores for Psychotic, Disorganized, and Negative symptom factors (Miller et al., 1993).

To assess insight, patients were administered the Scale to assess Unawareness of a Mental Disorder (SUMD; Amador et al., 1993). For the present and past periods identified while administering the SAPS and SANS, for any symptoms identified with these scales, patients were rated on awareness of the symptom, and degree to which they attributed it to a mental disorder. For each period, the average of awareness and attribution ratings for these symptoms was

computed, yielding overall scores for present and past awareness and attribution. Higher scores indicate lower levels of insight.

Patients' clinical ratings are summarized in Table 2.

2.3. ERP assessment

ERPs were recorded while participants performed a Stroop task, with stimuli similar to those of Hajcak and Simons (2002). On each trial, participants were presented one of three colour words ('RED', 'GREEN', 'BLUE') in red or green font on a black background. A fixation mark was presented before each word. Words were presented for 200 ms at random stimulus-onset asynchronies between 2000 and 2400 ms. Participants pressed one of two keys on a response pad with either their right or left thumb, corresponding to the font color (red or green) of the presented word. Thus, there were congruent ('RED' in red, 'GREEN' in green), incongruent ('RED' in green, 'GREEN' in red), and neutral conditions ('BLUE' in red, 'BLUE' in green). Participants were asked to place equal emphasis on speed and accuracy. After completing a practice block of 48 trials, participants completed 4 blocks, each consisting of 32 trials of each type (congruent/red, congruent/green, incongruent/red, incongruent/green, neutral/red, neutral/green), for a total of 768 trials. Trials were presented in a fixed pseudorandomized order, which differed for each block.

ERPs were recorded in a sound-attenuated, electrically-shielded chamber. Participants were seated in a chair, 100 cm in front of a video monitor on which stimuli were presented, with each letter subtending on average 0.36° of visual angle horizontally, and up to 0.55° vertically. Continuous EEG was recorded from 32 approximately equally spaced scalp sites, bandpassed at 0.01-100 Hz, continuously digitized at 512 Hz, and re-referenced off-line to the mean of the mastoids.

Averages of artifact-free ERP trials were calculated for each type of trial (correct and error) after subtraction of the 100 ms pre-stimulus baseline. Consistent with previous work (Foti et al., 2012; Horan et al., 2011), ERN amplitude was measured as mean voltage at Cz from 0-100 ms post-response of the difference waveform obtained by subtracting the ERP average for error trials from the average for correct trials; and Pe amplitude was measured as mean voltage at Pz of the difference waveform from 200-400 ms post-response.

2.4. Statistical analyses

Correct response rates on the experimental task were analyzed in an ANOVA with Group (schizophrenia vs. NCP) as between-subjects factor, and stimulus type (congruent vs. incongruent vs. neutral) as within-subjects factor with Greenhouse-Geisser Epsilon correction. Reaction times were analyzed in an ANOVA with Group (schizophrenia vs. NCP) as between-subjects factor and response type (correct vs. error) as within-subjects factor.

ERN and Pe amplitudes of patients versus NCPs were compared via independent-samples *t*-tests.

To examine whether ERN or Pe amplitude deficits were associated with poorer insight, across patients pairwise Pearson's correlations *r* were computed for ERN and Pe amplitudes versus SUMD current unawareness, past unawareness, current misattribution, and past misattribution scores.

All *p*-values are two-tailed.

3. Results

3.1. Behavioral data

Mean task accuracy and response times (RTs) for both groups are shown in Table 3. Accuracy did not differ significantly by Group ($F_{1,34}=2.96, p=0.09$) or Stimulus Type ($F_{2,68}=2.51, p=0.12$), and there was no Group x Stimulus Type interaction ($F_{2,68}=1.18, p=0.28$). RTs were faster for NCPs than for patients ($F_{1,34}=5.25, p=0.03$), but there was no significant effect of Response Type ($F_{1,34}=3.35, p=0.08$) or Group x Response Type interaction ($F_{1,34}=0.03, p=0.86$).

3.2. Grand average ERPs

Grand average ERPs for schizophrenia and NCP groups are shown at all electrodes in Figures 1a and 1b, respectively.

Mean ERN and Pe amplitudes for each group are shown in Figure 2. ERN amplitudes were smaller (less negative) in schizophrenia patients versus NCPs [$-2.09 \mu\text{V}$ vs. $-6.45 \mu\text{V}$; $t(34)=2.72; p=0.03$]. Pe amplitudes were smaller (less positive) in schizophrenia patients versus NCPs [$3.22 \mu\text{V}$ vs. $9.16 \mu\text{V}$; $t(34)=-3.21; p=0.003$].

3.3. Correlations of ERN and Pe amplitudes with insight

Table 4 shows correlations of patients' ERN and Pe amplitudes with insight scores and SAPS/SANS factor scores. For the ERN and SUMD, positive correlations indicate an association between lower insight (higher SUMD scores) and error processing deficits (less negative ERN amplitude). For the Pe and SUMD, negative correlations indicate an association between lower insight (higher SUMD scores) and error processing deficits (less positive ERN amplitudes). None of the correlations were significant (all $p>0.24$).

4. Discussion

We investigated whether impaired illness insight in schizophrenia is associated with error-processing deficits at the neurophysiological level. Specifically, we examined whether schizophrenia patients' deficits in two ERP indices of error monitoring, the ERN and Pe amplitudes, were associated with poor insight as assessed using the SUMD. Such an association would be consistent with the hypothesis that abnormal error monitoring contributes to illness insight in schizophrenia.

Consistent with previous findings, schizophrenia patients exhibited smaller than normal ERNs. We also found reduced Pe amplitudes in schizophrenia patients, adding to previous evidence for this abnormality (Foti et al., 2012; Perez et al., 2012). Although some other studies have not corroborated these findings (Alain et al., 2002; Horan et al., 2011; Kim et al., 2006; Mathalon et al., 2002; Morris et al., 2006; Simmonite et al., 2012), these contrasting results may be due to smaller sample sizes (Alain et al., 2002); higher-frequency cutoffs (1-2 Hz) in high-pass filtering of ERP data (Kim et al., 2006; Morris et al., 2006); or task differences.

Contrary to our hypothesis, we found that neither ERN nor Pe reductions in our patient sample were associated with impaired insight into illness. These results suggest that unawareness of illness in schizophrenia is not related to deficits in error-monitoring processes reflected in the ERN and Pe, but arises instead from other cognitive mechanisms. Deficits in a number of other cognitive domains have been found to correlate independently with impaired insight in schizophrenia. These domains include working and long-term memory, and set-shifting (Nair et al., 2014), which may all be necessary for reflectively analyzing beliefs in light of evidence; and theory of mind (Konstantakopoulos et al., 2014), which includes the ability to apprehend how one is perceived by others. Further research is needed to improve our understanding of whether and how these and other factors contribute to the pathogenesis of poor insight.

Figure 1. Grand average ERPs time-locked to correct responses (black line) and error responses (red line), at all electrode sites, for: (a) schizophrenia patients, and (b) NCPs. Voltage is plotted in μV on the y -axis with negative plotted upward, and time is plotted in ms on the x -axis. Electrode sites Cz and Pz, which were used for mean amplitude analyses for the ERN and Pe, respectively, are highlighted by boxes.

Figure 2: Bar plot of mean ERN and Pe amplitudes for schizophrenia patients and NCPs (error bars show standard deviations).

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Table 1. Demographic characteristics of the study sample

	Patients with schizophrenia (<i>n</i> =18)		NCPs (<i>n</i> =18)	
Sex				
Female	7		10	
Male	11		8	
Handedness (Oldfield, 1971)				
Right	15		17	
Left	1		1	
Ambidextrous	2		0	
	<i>Mean</i>	<i>SD</i>	<i>Mean</i>	<i>SD</i>
Age (years)	43.2	7.8	41.1	9.8
Parental socioeconomic status (SES; Blishen et al., 1987)	42.6	8.2	42.8	13.0
Age at onset of illness (years)	25.7	6.8	-	-
Time elapsed since most recent hospitalization (years)	9.1	8.0	-	-
Number of previous hospitalizations	5.6	3.6	-	-

Table 2. Clinical characteristics of patients with schizophrenia ($n=18$)

	Mean	SD
SAPS total score	4.2	4.3
SANS total score	8.9	4.0
SANS/SAPS-derived factor scores		
Psychotic	3.0	3.3
Disorganized	1.2	1.5
Negative	5.8	2.3
SUMD		
Current unawareness	2.32	1.30
Past unawareness	1.99	1.14
Current misattribution	2.56	1.33
Past misattribution	2.40	1.29

Table 3. Accuracy and reaction time in the experimental task

	Patients with schizophrenia (<i>n</i>=18)		NCPs (<i>n</i>=18)		Group comparison
	<i>Mean</i>	<i>SD</i>	<i>Mean</i>	<i>SD</i>	
Overall accuracy (%)	92.2	11.9	97.1	2.4	$t(34)=1.72$
Reaction time (ms)					
Overall	561	99	491	177	$t(34)=1.46$
Correct	564	102	492	179	$t(34)=1.48$
Error	518	129	437	90	$t(34)=4.87^a$

^a $p=0.03$

Figure 1a.

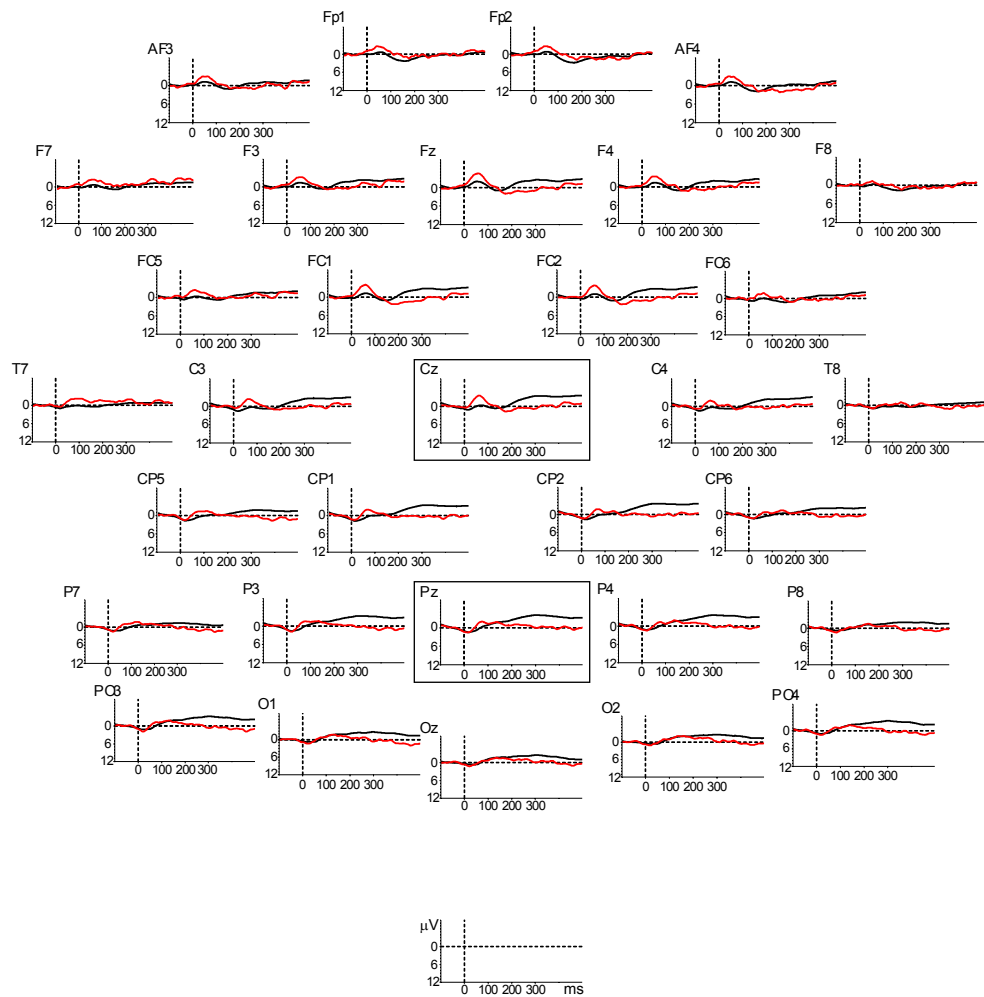


Figure 1b.

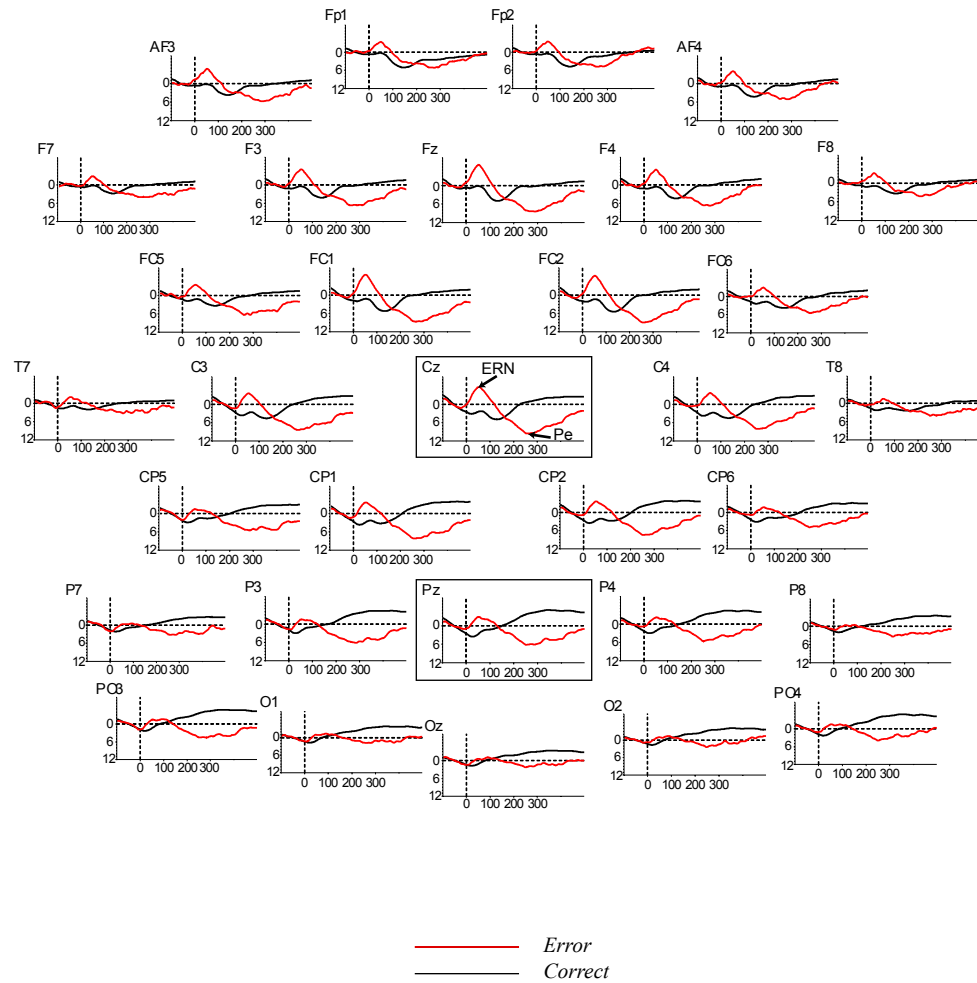


Figure 2.

