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Impaired error processing in late-phase psychosis: Four-year stability and relationships with negative symptoms

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ABSTRACT

Error processing is impaired in psychosis, and numerous event-related potential studies have found reductions in the error-related negativity (ERN) and, more recently, the error positivity (Pe). The stability of reduced ERN/Pe in psychosis, however, is unknown. In a previous cross-sectional report, reduced ERN was associated with negative symptom severity and reduced Pe with a diagnosis of schizophrenia versus other psychosis. Here, we test the stability of impaired error processing over a four-year follow-up and relationships with subdimensions of negative symptoms. The ERN and Pe were recorded from individuals with psychotic disorders twice: 79 individuals were assessed 15 years after first hospitalization, and 69 were assessed at 19 years; 59 (26 with schizophrenia, 33 with other psychotic disorders) had data at both assessments. At 19 years the Pe was blunted in schizophrenia. The ERN and Pe exhibited temporal stability over the four years ($r = 0.59$ and 0.60, respectively). Reduced ERN and Pe correlated with the negative symptom subdimensions of inexpressivity and avolition, respectively, and not with psychotic or disorganized symptoms. Moreover, 15-year ERN predicted an increase in inexpressivity by year 19. No evidence was found for the reverse: negative symptoms did not predict change in ERN/Pe. Similar to non-clinical samples, the ERN and Pe show impressive four-year stability in late-phase psychosis. The ERN and Pe are promising neural measures for capturing individual differences in psychotic disorders, particularly with regard to negative symptomatology. They may prove to be useful clinically for forecasting illness course and as treatment targets.

1. Introduction

Executive function is impaired in schizophrenia (Kerns et al., 2008) and is a proposed cognitive mechanism for poor functioning (Bowie et al., 2008). One key aspect of executive function is error processing, which entails the evaluation of errors as salient events followed by the dynamic adjustment of cognitive control to improve performance (Kerns et al., 2008). Event-related potential (ERP) studies of error processing in schizophrenia have focused on the error-related negativity (ERN), which occurs 0–100 ms following errors on speeded tasks (Falkenstein et al., 1991; Gehring et al., 1993) and reflects error-related activation of the anterior cingulate cortex (ACC) (Holroyd and Coles, 2002). Numerous studies have observed a blunted ERN in schizophrenia (Alain et al., 2002; Bates et al., 2002, 2004; Foti et al., 2012, 2013; Horan et al., 2012; Kansal et al., 2014; Kopp and Rist, 1999; Mathalon et al., 2002; Morris et al., 2006), which is related to poor executive function (Kim et al., 2006). A blunted ERN has also been observed in other psychotic disorders (Foti et al., 2012, 2013; Minzenberg et al., 2014), high-risk individuals (Laurens et al., 2010; Perez et al., 2012) and unaffected siblings (Simmonite et al., 2012).

Studies have also examined the error positivity (Pe), which peaks 200–400 ms following errors. The ERN and Pe track distinct stages of error processing: early, automatic error detection and later, conscious error recognition, respectively, (Hughes and Yeung, 2011; Nieuwenhuis et al., 2001). Pe relates to post-error adjustment at the between-subjects level (Hajcak et al., 2003), whereas ERN relates to trial-by-trial adjustment (Cavanagh and Shackman, 2015). Initial studies in schizophrenia failed to find group differences in Pe amplitude versus controls (Alain et al., 2002; Horan et al., 2012; Kim et al., 2006; Mathalon et al., 2002; Morris et al., 2006), perhaps due to limited sample sizes and signal filters that attenuated the Pe (but not the ERN). By contrast, three recent studies have observed a blunted Pe specifically in schizophrenia, both early (Perez et al., 2012) and later in the course of illness (Foti et al., 2012; Kansal et al., 2014).

The ERN and Pe are promising measures of impaired error processing, with the ERN reduced in psychotic illness broadly and the Pe reduced specifically in schizophrenia. Previous studies have primarily been cross-sectional, however, leaving it unclear how impaired error

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processing relates to course of illness. In non-clinical samples, the ERN and Pe are highly stable, (Weinberg and Hajcak, 2011). Similarly high temporal stability among patients would indicate chronic neural deficits rather than indicators of current clinical state. In this case, it is possible that reduced ERN/Pe amplitudes may relate to long-term illness course. On the other hand, if the ERN and Pe fluctuate over time in patients (i.e., show low temporal stability), this would raise the question of what is responsible for fluctuations over time (e.g., whether changes in ERN/Pe amplitudes map onto concurrent changes in symptoms and functioning). In one study, ERN amplitude partially normalized following antipsychotic treatment over a six-week follow-up, suggesting short-term improvement with clinical sate (Bates et al., 2004); longer-term assessment is necessary to more fully capture the stability of these neural indices.

An additional question is which specific illness features relate to impaired error processing. We previously observed that reduced ERN mapped onto concurrent negative but not positive or disorganized symptoms, independent of diagnosis (Foti et al., 2012), which is consistent with neuropsychological research (Ventura et al., 2009) and proposals that negative symptoms and cognitive deficits are related aspects of psychotic illness (Harvey et al., 2006). A longitudinal approach is necessary, however, to clarify the direction of effects (i.e., whether neural deficits predict or are a consequence of negative symptoms). Moreover, recent structural research indicates that negative symptoms are comprised of two distinct dimensions—inexpressivity and avolition (Blanchard and Cohen, 2006; Kring et al., 2013; Strauss et al., 2013)—yet links between error processing and these subdimensions have yet to be examined.

To begin to address these gaps, we present data from a four-year follow-up in which the ERN and Pe were reassessed in the previously-reported patient sample (Foti et al., 2012). The current study had two aims: (a) We assessed the long-term temporal stability of the ERN and Pe within the full patient sample. (b) We evaluated the longitudinal associations between these ERPs and symptom dimensions, testing whether ERPs predict subsequent symptoms or vice versa. We expected that the ERN would relate to trajectories of negative symptoms, and we further tested for specificity with regard to the subdimensions of inexpressivity and avolition.

2. Methods and materials

2.1. Participants

The sample was drawn from the Suffolk County Mental Health Project (Bromet et al., 1992, 2011), an epidemiologic study of first-admission psychosis. Participants were recruited from inpatient psychiatric facilities from 1989 to 1995; eligibility criteria were the presence of psychosis, age 15–60, and ability to provide informed consent. Face-to-face assessments were conducted by master's-level interviewers using the Structured Clinical Interview for DSM-IV (SCID) (First et al., 2001). Consensus DSM-IV diagnosis was formulated based on 19 years of observation. This sample included 104 patients, 52 with a schizophrenia spectrum disorder (SZ; schizophrenia, schizoaffective disorder) and 52 with other psychotic disorders (OP; 29 bipolar, 8 depression, 9 substance-induced, 6 not otherwise specified).

The present study includes data from the 15- and 19-year assessments. Cross-sectional analysis of 15-year ERP data has been published previously (Foti et al., 2012, 2013; Jackson et al., 2014; Perlman et al., 2015). Of the 104 patients who completed the 15-year EEG, 87 (83.7%) completed the 19-year EEG. Patients were retained for analyses if they had usable ERP data (>50% artifact-free trials) and adequate task performance (>75% correct). Seventy-nine had usable data at year 15 (37 SZ, 42 OP) (Foti et al., 2012). At year 19, 18 of 87 were excluded from analysis (10 for poor performance, 5 for poor quality data, 3 for committing zero errors), yielding 69 with useable data (32 SZ, 37 OP). Fifty-nine had available ERP data at both assessments (26 SZ, 33 OP). The delay between assessments varied ($M = 41.0$ months, $SD = 6.9$). Sample characteristics at year 19 are presented in Table 1.

2.2. Task and materials

2.2.1. Symptoms

Past-month symptoms were rated using the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1983b) and the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983a). Each was scored as two-factor analytically derived subscales: the SAPS as psychotic (hallucination, delusions) and disorganized (bizarre behavior, thought disorder) (Kotov et al., 2010), and the SANS as inexpressivity (affective flattening, alogia) and avolition (apathy, anhedonia, asociality) (Blanchard and Cohen, 2006; Kring et al., 2013; Strauss et al., 2013).

2.2.2. Task

An arrow flanker task was used to assess error processing (Eriksen and Eriksen, 1974). Five arrowheads were presented on each trial, with half of trials compatible (<<<<< or >>>>>) and half incompatible (<<><< or >><>>). Arrows were presented for 200 ms and followed by an inter-trial interval of 2300–2800 ms. Participants were instructed to press the left or right mouse button corresponding to the center arrow, and to maximize both speed and accuracy. Participants completed 11 blocks of 30 trials. Blockwise feedback was used to keep performance between 75 and 90%.

2.3. Procedure

The procedure was identical across assessments. Written informed consent was obtained at each. Patients completed interviews and then the EEG assessment. They performed multiple tasks, and task order was counterbalanced. Patients received financial compensation for their participation. This research was approved annually by Institutional Review Board at Stony Brook University.

2.4. EEG recording, processing, and data reduction

The EEG was recorded using the ActiveTwo BioSemi System (BioSemi), sampled at 1024 Hz. Recordings were taken from 34 scalp electrodes and two mastoid electrodes. The electro-oculogram was recorded from four facial electrodes. Offline analysis was performed using Brain Vision Analyzer software (Brain Products). Data were re-referenced to the mastoid average and filtered from 0.1–0.30 Hz. The

Table 1
Sample characteristics at the 19-year assessment.

Variable	Schizophrenia ($n = 32$)		Other psychosis ($n = 37$)		Comparison	
	M	*SD*	*M*	*SD*	*d*	95% CI
Age	46.56	10.36	48.03	9.20	−0.15	−2.42–2.12
	N	%	*N*	%	Odds ratio	95% CI
Gender						
Male	21	65.6	21	56.8	1.46	0.55–3.97
Female	11	34.4	16	43.2		
Ethnicity						
White	23	71.9	32	86.5	0.40	0.12–1.35
Other	9	28.1	5	13.5		
Medication						
Antipsychotic	28	87.5	12	32.4	14.58***	4.16–51.08
Antidepressant	14	43.8	13	35.1	1.44	0.54–3.79
Mood stabilizer	12	37.5	10	27.0	1.62	0.59–4.49
Benzodiazepine	5	15.6	5	13.5	1.19	0.31–4.53

Note: Medication variables are past-month prescription status (yes/no). ***$p < 0.001$.

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