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

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A B S T R A C T
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 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
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 state (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; Straus 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 usable 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 (hallucinations, 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.
EEG was segmented for each trial, spanning −400 to 800 ms relative to the response, and corrected for blinks and eye movements (Gratton et al., 1983). Channels were rejected trial-wise using a semi-automated procedure, with artifacts defined as a step of 50 μV, a difference of 300 μV within a trial, or a difference of <0.50 μV within 100-ms intervals; additional artifacts were identified visually. ERP averages were created for correct and incorrect responses, with a baseline of −400 to −200 ms. The ERN was scored as the mean from 0 to 100 ms at Cz, and the Pe from 200 to 400 ms at Pz.

2.5. Data analysis

Temporal stability and cross-sectional associations were described using Pearson’s r. Stability was examined among patients with available data at both time points (N = 59); cross-sectional associations were conducted with all available patients at each time point. Cross-sectional associations between ERPs and symptoms were further evaluated using partial correlations to adjust for demographics (age, gender, ethnicity), medication status (past month; coded as yes/no for each of antipsychotic, antidepressant, mood stabilizer, and benzodiazepine), diagnosis (SZ vs. OP), and task accuracy (% correct). These results were used to select candidate pairs of ERP and symptom variables for longitudinal analyses, for which we used structural equation modeling to simultaneously test both directions of effects (i.e., ERP → Clinical and Clinical → ERP). We specified a cross-lagged model in which 19-year variables were jointly predicted by relevant 15-year ERP and symptom variables (i.e., predicting change from 15 to 19 years). The model was estimated in Mplus (Version 7) (Muthén and Muthén, 1998-2012) using WLMSV estimator.

3. Results

3.1. Cross-sectional associations

ERP data are presented in Fig. 1. Modulation of the Pe on error versus correct trials was significant at both assessments (15-year: t(78) = 8.09, p < 0.001; 19-year: t(68) = 8.75, p < 0.001); modulation of the ERN was weaker and non-significant (15-year: t(78) = −1.57, p = 0.12; 19-year: t(68) = −1.94, p = 0.06). Group comparisons (SZ vs. OP) of ERP variables are in Table 2. ΔPe amplitude (error minus correct) was blunted in the SZ group at both assessments. ΔERN amplitude was blunted in the SZ group at year 15, but did not differ by year 19.

Cross-sectional associations between ERPs and symptoms are in Table 3. Trends were observed between reduced ΔERN and inexpressivity at both assessments; associations were significant after adjusting for covariates. Psychotic and Disorganized symptoms were not associated with ERP amplitudes at either assessment. Reduced ΔPe was associated with Avolition, but relationships were non-significant after adjusting for covariates, largely due to effects of diagnosis and antipsychotic medication.

3.2. Four-year stability

Mean-level changes and retest correlations from years 15–19 are presented in Table 4; scatterplots are in Fig. 2. There were no significant mean-level changes across assessments for ERP variables or task accuracy; participants were slower overall at year 19. Symptom severity increased across assessments in each domain. Temporal stability was high for ERP and task performance variables (r’s ≥ 0.50). The ERN and Pe exhibited greater temporal stability than either Psychotic or Inexpressivity symptom scores, but lower than Avolition scores. For the ΔERN, temporal stability estimates were similar for the SZ (r = 0.55, p < 0.01) and OP groups (r = 0.60, p < 0.001; comparison: z = 0.28, p = 0.78). For the ΔPe, temporal stability was higher in the SZ (r = 0.78, p < 0.001) than the OP group (r = 0.39, p = 0.05; comparison: z = 2.30, p < 0.05).

Past-month antipsychotic medication status was highly stable across assessments: 53 patients (89.8%) reported no change, 4 (6.8%) were prescribed at year 19 but not 15, and 1 (1.7%) was prescribed at year 15 but not 19. Changes in ΔERN and ΔPe across assessments were not

Fig. 1. ERP waveforms and headmaps depicting error-related neural activity at the 15-year (left; n = 79) and 19-year (right; n = 69) assessments. Headmaps depict the difference between error and correct trials from 0 to 100 ms (ERN, top) and 200–400 ms (Pe, bottom).
and task accuracy as covariates. Symptom variables are from the Scales for the Assessment of Positive (SAPS) and Negative Symptoms (SANS).

Inexpressivity did not predict future symptom severity. Reduced Pe, meanwhile, correlated with avolition, although this was not significant after taking diagnosis and medication into account. Blunted ERN amplitude predicted an increase in expressivity symptoms four years later, but not vice versa. Together, these results provide evidence supporting the temporal stability and potential predictive validity of ERP indices of impaired error processing in late-phase psychosis.

Long-term longitudinal studies of psychiatric biomarkers are necessary to establish the relative stability of neural abnormalities and track changes in relation to symptoms. Here, we demonstrate that the ERN and Pe both have high temporal stability in late-phase psychosis. Rank-order stability was on par with that of symptoms and task performance. Mean-level stability was higher, as sample means remained unchanged even as symptom severity increased. These data complement studies showing a diminished ERN in high-risk individuals (Laurens et al., 2010; Perez et al., 2012) and unaffected siblings (Simmonite et al., 2012), suggesting that reduced ERN may reflect liability for psychosis; ERN impairment is heritable, precedes symptom onset, and persists throughout course of illness. The ERN may also provide prognostic information about illness course. Diminished ERN predicted more severe negative symptoms of expressivity four years later, over and above baseline severity. No evidence was found for the reverse effect—symptom severity did not predict future ERN/Pe amplitude—and medication status did not predict change in ERPs. This suggests that impaired error processing is not a consequence of illness course or treatment; rather, these ERPs may potentially be leveraged to help forecast illness trajectory. Insofar as effective treatments for negative symptoms are lacking (Fusar-Poli et al., 2015), impaired ERN/Pe may also represent a novel treatment target (Carter et al., 2012).

The link between ERN and inexpressivity warrants further evaluation. The ERN is thought to reflect preconscious, automatic error detection (Hajcak et al., 2003; Nieuwenhuis et al., 2001). One possibility is that inexpressivity may reflect a similar dysfunction in the automatic self-monitoring of expressive behavior, perhaps through common neural circuitry. In healthy populations, expressive behavior activates the

correlated with 15-year medication status, nor with change in medication status across assessments (p’s > 0.20).

3.3. Longitudinal associations

We followed-up cross-sectional findings by examining directional effects in longitudinal analyses (ERN with Inexpressivity, Pe with Avolition). The cross-lagged model testing longitudinal associations between ∆ERN and Inexpressivity is shown in Fig. 3. Blunted 15-year ∆ERN predicted higher Inexpressivity scores four years later, over and above 15-year Inexpressivity (β = 0.20, p < 0.05, 95% CI = 0.02–0.38), but Inexpressivity did not predict future ∆ERN amplitude (β = −0.05, p > 0.05, 95% CI = −0.25–0.14). Longitudinal relationships between Pe and Avolition scores were not significant (Pe ➔ Avolition: β = −0.11, Avolition➔Pe: β = −0.09, p’s > 0.05).

4. Discussion

The current results are notable for three reasons: (1) Extending findings from a non-clinical sample (Weinberg and Hajcak, 2011), the long-term temporal stabilities of the ERN and Pe are high in late-phase psychosis. (2) We extend findings linking reduced ERN amplitude to negative symptoms (Foti et al., 2012), showing specificity with the sub-dimension of inexpressivity. Reduced Pe, meanwhile, correlated with avolition, although this was not significant after taking diagnosis and medication into account. (3) Blunted ERN amplitude predicted an increase in inexpressivity symptoms four years later, but not vice versa. Together, these results provide evidence supporting the temporal stability and potential predictive validity of ERP indices of impaired error processing in late-phase psychosis.
ACC (Lindenberg et al., 2012)—the generator of the ERN. Moreover, ACC dysfunction has been proposed as a pathophysiological factor for negative symptoms (Bersani et al., 2014). ERN amplitude is also known to be sensitive to motivation and negative effect, with proposals that it reflects threat sensitivity (Proudfoot et al., 2013). The impact of psychotic disorders on emotion, meanwhile, is complex (Kring and Ellis, 2013; Strauss and Gold, 2012). Given the interplay between cognitive impairment, negative symptomatology, and functional outcome in psychosis (Ventura et al., 2009), future research should consider impaired error processing in the context of other social and affective deficits.

Replicating our cross-sectional findings at year 15 (Foti et al., 2012) within new follow-up data at year 19, Pe amplitude was reduced in schizophrenia, whereas the ERN did not reliably distinguish diagnostic groups. The ERN appears to be impaired in psychotic illness broadly, while reduced Pe is relatively specific to schizophrenia. In fact, stability of the Pe was higher in the schizophrenia group, whereas stability of the ERN was comparable across groups. Diagnoses were based on two decades of observation, enabling precise estimates of diagnostic effects on error-related ERPs. Indeed, we found that initial SCID-based consensus diagnoses misclassified many cases compared to 10-year gold-standard diagnoses (κ = 0.47 for schizophrenia; Bromet et al., 2011), partially masking differences in other neural measures (Perlman et al., 2015).

Whereas a reduced ERN related to inexpressivity, reduced Pe related to avolition, suggesting a dissociation between error-related ERPs and negative symptom sub-dimensions. This is tempered by the finding that Pe-avolition associations were not significant after taking into account covariates, including diagnosis and medication status. It is possible that the link with avolition, therefore, may be explained by the diagnostic differences in Pe amplitude. A theme across these findings is that the ERN and Pe map onto distinct phenotypes within psychotic disorders, consistent with the notion that they capture functionally distinct stages of error processing (Hajcak et al., 2003; Nieuwenhuis et al., 2001).

The current findings are qualified by several limitations. Longitudinal data from a control sample was not available. It would be valuable for research studies to compare ERN/Pe trajectories across patients and controls. Our patient sample, while larger than most studies of its kind, was modest in size and may have precluded the detection of other associations. We were primarily interested in negative symptoms

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**Table 4**

<table>
<thead>
<tr>
<th>Variable</th>
<th>15-year assessment</th>
<th>19-year assessment</th>
<th>Change from years 15–19</th>
<th>Test-retest correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
<td>M</td>
<td>SD</td>
</tr>
<tr>
<td>ERP amplitudes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ERN</td>
<td>1.66</td>
<td>4.14</td>
<td>1.86</td>
<td>4.17</td>
</tr>
<tr>
<td>ΔERN</td>
<td>−0.73</td>
<td>3.70</td>
<td>−0.98</td>
<td>4.57</td>
</tr>
<tr>
<td>Pe</td>
<td>5.63</td>
<td>6.71</td>
<td>5.45</td>
<td>5.39</td>
</tr>
<tr>
<td>ΔPe</td>
<td>−0.13</td>
<td>2.64</td>
<td>−0.41</td>
<td>2.85</td>
</tr>
</tbody>
</table>

Flankers task performance

| Accuracy (% correct) | 93.15 | 4.98 | 92.70 | 5.35 | 0.56 | −0.10 | 0.62***|
| Correct RT (ms)      | 536.12 | 111.54 | 562.60 | 114.48 | 4.82* | 0.30 | 0.70***|
| Error RT (ms)        | 396.93 | 99.87 | 452.27 | 136.01 | 11.38** | 0.47 | 0.51***|

Symptoms

| SAPS Psychotic       | 2.28   | 5.50  | 5.33   | 11.00 | 11.38** | 0.37  | 0.51***|
| SAPS Disorganized    | 2.12   | 3.86  | 5.28   | 6.75  | 24.68*** | 0.67  | 0.61***|
| SANS Inexpressivity  | 2.40   | 4.34  | 5.14   | 7.30  | 16.78*** | 0.48  | 0.51***|
| SANS Avolition       | 8.79   | 8.39  | 12.69  | 8.56  | 24.46*** | 0.69  | 0.78***|

Note: N = 59 participants completed both assessments. Symptom variables come from the Scales for the Assessment of Positive (SAPS) and Negative Symptoms (SANS).

* p < 0.05.

** p < 0.01.

*** p < 0.001.

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Fig. 2. Scatterplots depicting the association between 15- and 19-year ERPs.

Fig. 3. Cross-lagged model testing the longitudinal association between ΔERN amplitude and SANS inexpressivity scores. "p < 0.05."


D.F. wrote the letter in a nonsearch task. Percept. Psychophys. 16 (1), 143–149.


