



State dependent changes in error monitoring in schizophrenia

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Abstract

The aim of this study was to determine if error negativity/error-related negativity (N_e /ERN), error positivity (P_e), correct response negativity (CRN) or correct response positivity (P_c) amplitude are influenced by state changes in schizophrenia. Event-related potentials (ERPs) were recorded from nine schizophrenic patients while they performed a simple go/no-go task during the early stages of an acute episode and again following 6 weeks of treatment with antipsychotics. ERPs were also recorded from nine healthy participants while they performed the same task. Response-locked potentials were computed for errors of commission and for correct responses. Scores for reality distortion syndrome, psychomotor poverty syndrome and disorganization syndrome were determined for the schizophrenic participants before and after treatment using the Signs and Symptoms of Psychotic Illness (SSPI) Scale. N_e /ERN amplitude was significantly reduced, compared with that in healthy participants, in the schizophrenic patients when acutely ill, and increased significantly following treatment. N_e /ERN amplitude remained significantly larger in the healthy group than in the patients with schizophrenia after treatment. This study suggests that N_e /ERN and CRN amplitude are modulated by clinical state in schizophrenia and provides further support to findings that decreased N_e /ERN amplitude is a potentially useful trait marker for schizophrenia, while P_c and P_e amplitude are not abnormal.

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1. Introduction

Beginning with the work of Hohnsbein et al. (1989), Falkenstein et al. (1990) and Gehring et al. (1990,1993), there have been many reports of a distinct negative event-related potential (ERP) that occurs when participants make errors of commission on a wide variety of experimental tasks. There has been an accumulation of evidence that this error negativity (N_e) or error-related negativity (ERN) reflects activity in a general error-checking or behavior-monitoring system in the brain

(see Falkenstein et al., 2000 for an overview). N_e /ERN typically peaks 100–150 ms after the onset of electro-myographic activity associated with an erroneous response or around the time of incorrect response with an amplitude approaching 10 μ V (Gehring et al., 1993; Scheffers et al., 1996). The majority of work on the N_e /ERN suggests that it is associated with an error-detection signal and perhaps preceding response checking that triggers that signal (Falkenstein et al., 2000). However, Vidal et al. (2000) have suggested that N_e /ERN may not be the result of error detection itself, but the result of an accompanying emotional response. Others, such as Carter et al. (1998), have suggested that the N_e /ERN reflects response competition rather than pure error detection.

Although the identity of the exact cognitive function associated with the N_e /ERN remains under debate,

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several lines of evidence including dipole source analysis (Dehaene et al., 1994; Miltner et al., 1997; Coles et al., 1998; Holroyd et al., 1998; Badgaiyan & Posner, 1998; Luu et al., 2000), event-related functional magnetic resonance imaging (fMRI) (Kiehl et al., 2000; Menon et al., 2001; Ullsperger & von Cramon, 2001; Laurens et al., 2003) and intracranial electrode studies in monkeys (Gemba et al., 1986) suggest that the primary source of post-synaptic potentials responsible for the N_e /ERN is the anterior cingulate cortex. Therefore, there is overwhelming evidence that the primary source of the N_e /ERN recorded at the scalp is the anterior cingulate cortex. However, it should be noted that intracerebral ERP recordings reveal many areas that may be associated with the N_e /ERN (Brázdil et al., 2002).

Hohnsbein et al.'s (1989) and Falkenstein et al.'s (1990) early reports of N_e /ERN also included descriptions of a positive potential that followed the N_e /ERN. This error positivity (P_e) generally has a centro-parietal maximum amplitude that occurs 200–500 ms after an incorrect response (Falkenstein et al., 2000). However, many studies describing the N_e /ERN have not included any mention of the P_e . This is likely due to debate over whether the P_e is a response-locked potential associated with erroneous responses or the result of a stimulus-locked P300 potential. Falkenstein et al. (2000) have argued convincingly that the P_e is not a manifestation of the P300 potential. Their alternative hypothesis is that the P_e is related to “additional processing after errors that is functionally different from error detection or response checking” and “reflects a subjective/emotional error assessment process, which is modulated by the individual significance of an error”. Suggestions that the N_e /ERN and/or the P_e are related to emotional processes are supported by fMRI studies by Kiehl et al. (2000), Menon et al. (2001), and Laurens et al. (2003) that demonstrate activation of the rostral anterior cingulate cortex (an area thought to be associated with affective processing (Devinsky et al., 1995)) during error processing. There is also a corresponding, but smaller and generally earlier, positivity for correct responses called the correct response positivity (P_c), but it has generally been used as a baseline comparison for the P_e (e.g. Mathalon et al., 2002) and little has been written about it.

Another ERP relevant to error processing is the correct response negativity (CRN). Ford (1999), Falkenstein et al. (2000), Vidal et al. (2000) and others have reported the presence of this N_e /ERN-like potential on correct hit trials. The CRN has a similar peak latency and topography to the N_e /ERN, but it is much smaller in amplitude. Falkenstein et al. (2000) have suggested that the CRN may be the result of the response checking process that allows for the error-detection system associated with the N_e /ERN. This hypothesis suggests that the N_e /ERN is in fact the CRN with an added

error-detection component that greatly increases the amplitude of the observed ERP.

1.1. Error monitoring in schizophrenia and the anterior cingulate cortex

A number of researchers have proposed that a failure of internal monitoring of errors contributes to the generation of schizophrenic symptoms. For example, Frith and Done (1988, 1989) proposed that failure to monitor self-generated activity contributes to delusions of alien control. Others, such as McGrath (1991), have suggested that failure of the internal monitoring of speech output might contribute to formal thought disorder. Some evidence suggests that the temporal variation of monitoring failures is related to the temporal variation of thought disorder (Kuperberg et al., 2000), while other studies have not found a relationship between monitoring failures and current symptom profile (Leudar et al., 1994). If the anterior cingulate cortex is indeed a key element in a system that detects behavioral errors, as suggested by the ERP and fMRI work described above, there is reason to believe that abnormalities of the anterior cingulate cortex in schizophrenia may contribute to disturbances in error monitoring. Anatomical and functional abnormalities of the anterior cingulate in schizophrenia are well documented (e.g. Benes et al., 2000; Carter et al., 1997; Honer et al., 1997; Liddle et al., 1992; Sahara et al., 2002). The majority of evidence suggests a pathological increase in activity due to increased microstructural elements supporting excitatory neurotransmission that may lead to a frequent inability of the area to be recruited for normal function (see Bates et al., 2002 for a more detailed discussion). This may explain findings suggesting overactivity in the anterior cingulate at rest (Holcomb et al., 1996), and underactivation during the performance of specific tasks (Holcomb et al., 2000; Mulert et al., 2001).

1.2. N_e /ERN, P_e and CRN in schizophrenia

Using a variation of the Eriksen Flanker Task (Eriksen & Eriksen, 1974), Kopp and Rist (1999) found that the amplitude of the N_e /ERN was reduced, relative to that in healthy controls, in paranoid [as defined in DSM-III-R (American Psychiatric Association, 1987)] schizophrenic patients but not in non-paranoid schizophrenic patients. Mathalon et al. (2002) reported that, in a picture–word matching task, schizophrenic patients exhibited a smaller N_e /ERN than healthy controls, but they also reported that schizophrenic patients showed an anomalously large CRN, such that the amplitude of the CRN was equal to that of the N_e /ERN. Mathalon et al. (2002) also analyzed the P_e and the P_c , but found no difference in P_e or P_c amplitude between groups. Alain et al. (2002) examined N_e /ERN and P_e to errors in a

Stroop task and found an N_e /ERN in healthy participants but not in schizophrenic participants. They found no difference in P_e amplitude between groups. Most recently, using the go/no-go task employed in the present study, we found a reduction in both N_e /ERN and CRN amplitude in schizophrenic patients compared with healthy controls (Bates et al., 2002). In addition, in an fMRI study using an almost identical task, we found that errors produced decreased rostral anterior cingulate cortex activation in schizophrenic patients compared to healthy controls (Laurens et al., 2003).

In summary, all four independent groups who have published studies of the N_e /ERN in schizophrenia have reported decreased amplitude, and both that have published details of the P_e have reported that it is not abnormal. The lack of P_e abnormality provides further evidence that the P_e is not the result of stimulus-locked P300 potentials because the P300 is one of the most reliably attenuated ERPs in schizophrenia research (Ford, 1999; Bharath et al., 2000). Finally, CRN abnormalities are inconsistent with Mathalon et al. (2002) reporting an increased amplitude and Bates et al. (2002) reporting a decreased amplitude.

There are also inconsistencies in the reported relationships between N_e /ERN and CRN amplitudes and symptom profile. Kopp and Rist (1999) reported that N_e /ERN amplitude was decreased in paranoid patients (whose illness is characterized by delusions and hallucinations) but not in non-paranoid patients. Inconsistent with their finding of increased CRN amplitude overall in schizophrenia, Mathalon et al. (2002) reported that reduced CRN amplitude was associated with greater severity of hallucinations. They also found trends associating decreased N_e /ERN amplitude with greater severity of hallucinations and greater conceptual disorganization. No significant correlations between N_e /ERN amplitude and positive or negative symptoms were found by Alain et al. (2002). Consistent with our finding that activation is decreased in the rostral (affective) division of the anterior cingulate cortex in schizophrenia (Laurens et al., 2003), our results (Bates et al., 2002) indicated that decreased N_e /ERN amplitude was related to increased severity of psychomotor poverty symptoms (which includes blunted affect). We also found that decreased CRN amplitude was related to increased disorganization.

While it is possible that the inconsistencies in the evidence regarding the relationship between the amplitudes of the N_e /ERN and CRN and symptom profile reflect chance findings in some studies, it is also plausible that these inconsistencies arise from differences between the patient samples. A potential confounding issue in attempts to delineate relationships between ERP abnormalities and symptom profile from cross-sectional studies is the possibility that other variables, such as phase of illness, might influence the observed relation-

ships. Full delineation of the relationship between clinical status and an ERP abnormality requires both cross sectional studies that examine variance between cases, and longitudinal studies that examine the variance over time within patients.

Because the relative consistency of the N_e /ERN abnormality suggests that it may be a good trait marker for schizophrenia, it is important to determine if state effects are also present. We report a longitudinal study whose primary objective was to test the hypothesis that the magnitudes of the N_e /ERN and CRN increase as symptoms resolve during treatment of an acute psychotic episode while P_e and P_c amplitude remain unchanged. We employed the same go/no-go task that we used in our previous study of N_e /ERN and CRN in schizophrenia (Bates et al., 2002) which was almost identical to the tasks used by Kiehl et al. (2000) and Laurens et al. (2003) in related fMRI studies. We also performed an exploratory analysis of the relationship between change in symptom scores and change in amplitude of the N_e /ERN, P_e , CRN and P_c .

2. Methods

2.1. Participants

The use of human participants in this experiment was approved by the University of British Columbia Ethics Committee and in accordance with the Declaration of Helsinki. Written informed consent was received from all participants. Fourteen right-handed (as per Annett, 1970) male schizophrenic participants were recruited from Vancouver General Hospital or the University of British Columbia Hospital after admission for treatment of an acute episode. Two of the initial 14 patients were unable to complete the first ERP session and interview and three who completed the first ERP session and interview declined to participate in the second ERP session and interview. Only the nine schizophrenic patients who completed the entire study are considered in this paper. Nine right-handed (as per Annett, 1970) male healthy control participants were recruited through public poster advertising. All participants were between 18 and 45 years of age, had normal or corrected-to-normal vision and received pecuniary remuneration for participating. The mean age of the schizophrenic group was 35.78 (S.D. 7.21) and the mean age of the healthy group was 32.78 (S.D. 6.55).

Schizophrenia was diagnosed by a psychiatrist on the basis of clinical interview and reference to case files according to the criteria in the Diagnostic and Statistical Manual of Mental Disorders [DSM IV (American Psychiatric Association, 1994)]. Eight of the patients met criteria for the paranoid subtype of schizophrenia and one was classified as undifferentiated. Immediately

before or after each ERP session, signs and symptoms were also evaluated and categorized for each patient with schizophrenia with the Signs and Symptoms of Psychotic Illness (SSPI) interview (Liddle et al., 2002). The SSPI is comprised of 20 sign or symptom items that are each given a score of 0–4 according to severity. From the SSPI, syndrome scores were calculated for each of the three distinct syndromes of schizophrenia identified by Liddle (1987). The scores for two items (delusions and hallucinations) were summed to produce the score for the reality distortion syndrome, the scores for three items (thought disorder, inappropriate affect and peculiar behavior) were summed to produce the score for the disorganization syndrome and the scores for another three items (blunted affect, poverty of speech and underactivity) were summed to produce the score for the psychomotor poverty syndrome. The psychiatrist who performed the SSPI interviews did not observe the ERP data collection and had no knowledge of any of the ERP results from either session when scoring the SSPI.

Eight of the schizophrenic participants were treated with atypical antipsychotics (risperidone, olanzapine or quetiapine) and one was treated with flupenthixol. Dose was adjusted according to clinical judgment between ERP sessions. It was not possible to determine duration of medication prior to the first ERP session reliably because it was not possible to assess compliance with prescribed medication schedules reliably prior to hospital admission.

2.2. Procedure

ERP recordings were conducted in a small room in a secluded, quiet location in the University of British Columbia Psychiatry Department. After placement of the electrodes, participants were seated in a comfortable chair approximately 60 cm from the 15 inch CRT SVGA computer monitor on which the stimuli were presented. Participants were instructed not to blink or move during data acquisition periods, except for the finger movement required for the behavioral response marked on a computer keyboard. A series of white 'X's and 'K's were presented on the computer monitor. Participants were instructed to respond as quickly and accurately as possible with their right index finger if the white X was presented (0.80 probability) and not to respond if the white K was presented (0.20 probability) for each of the 300 trials. The presentation order of Xs and Ks was random with the exception that two Ks were never presented sequentially. Reaction time and accuracy were equally stressed. The stimuli were approximately 3×5 visual degrees and were presented for 240 ms on a black background. The inter-stimulus interval varied randomly between 650, 1650, and 2650 ms. Prior to recording, each participant performed a

block of 10 practice trials twice to ensure that instructions were understood. Each schizophrenic participant participated in an ERP session and a sign and symptom assessment immediately following admission to hospital for an acute episode and again after 6 weeks of treatment. Healthy participants only participated in a single ERP session.

2.3. Physiological recording

Scalp potentials were recorded from 29 tin electrodes (ElectroCap International) distributed over the scalp according to the 10-10 International System of electrode placement. These channels were referenced to an electrode located on the tip of the nose. Eye movements were recorded from a bipolar derivative consisting of one electrode placed to the right side of the right eye and another placed below the right eye. Two additional channels, one located at the left mastoid process and the other located at the right mastoid process, were also recorded. Electrical impedance for each site was below 8 kOhms throughout the experiment.

The electroencephalography channels (SA Instrumentation) were amplified with a bandpass of 0.1–100 Hz, digitized on-line at a rate of 256 Hz, and recorded on computer hard disk. All ERP trials were time-locked to participant response. Artifact rejection was performed before averaging to reject trials contaminated by blinks, excessive muscular activity, or amplifier blocking. Specifically, trials with a difference of 100 μ V or greater between the largest negativity and largest positivity and trials with 60 or more data points in a row with the same value were rejected automatically. Remaining trials were then screened manually for smaller artifacts. There were no significant differences in the number of trials averaged between the healthy group, the patient group at time 1 and the patient group at time 2 for correct hits (means of 204.62, 189.49, and 177.60, respectively) or false alarms (means of 18.61, 18.30, and 21.27, respectively). Averaged data was digitally filtered with a zero-phase shift 10 Hz low pass filter and a zero-phase shift 2 Hz high pass filter. All averages were baseline corrected to a 50 ms period beginning 200 ms before participant response.

2.4. Data analysis

We performed between-subjects comparisons between the schizophrenic patients at time 1 and the healthy control participants and between the schizophrenic patients at time 2 and the healthy control participants and within-subjects comparisons between the schizophrenic patients at time 1 and the schizophrenic patients at time 2. SSPI and syndrome scores were computed and compared between the schizophrenic patients at time 1 and the schizophrenic patients at time 2 using

paired samples *t*-tests. Reaction times for correct hits, reaction times for false alarms, number of correct hits, and number of false alarms were computed. Differences in behavioral measures were assessed with paired samples *t*-tests for comparisons between patients at time 1 and patients at time 2 and with independent samples *t*-tests for comparisons between the patients and the healthy group. Reaction times for correct hits that directly followed false alarms were also computed to allow assessment of response slowing after errors in each group using paired samples *t*-tests. The N_e /ERN, P_e , CRN and P_c were the ERP components of interest measured. Based on visual inspection of individual participant average ERP plots from this experiment and grand-average ERP plots from other studies of N_e /ERN, P_e , CRN and P_c (e.g. Falkenstein et al., 2000; Mathalon et al., 2002), a 150 ms pre-response to 150 ms post-response latency window was chosen for the N_e /ERN and CRN and a 100 ms post-response to 380 ms post-response latency window was chosen for the P_e and P_c . Component amplitudes were defined as the difference between the largest peak within the latency window and baseline. Because almost all previous research of the N_e /ERN, P_e , CRN and P_c has focused on fronto-central and central midline channels and preliminary analyses revealed nothing novel to report from lateral channels in the present study, statistical analyses of ERP amplitudes were performed at the Fz, Fcz, Cz and Cpz channels. Statistical analysis of ERP amplitudes was performed using three-way Group (Healthy, Schizophrenia) or Session (time 1, time 2) × Response [correct hit (CRN or P_c), false alarm (N_e /ERN or P_e)] × Channel (Fz, Fcz, Cz, Cpz) multivariate analyses of variance (MANOVAs) with F tests based on Wilk's lambda for within-subject effects and interactions. This procedure is more robust against violations of the assumptions of compound symmetry and sphericity than repeated measures analysis of variance (ANOVA) with repeated measures factors with more than two levels (Statsoft, 2002). Significant interactions were followed-up with lower-order ANOVAs.

Two-tailed Spearman correlations were used to assess relationships between changes in ERP amplitudes and changes in SSPI score and syndrome scores between time 1 and time 2 for the schizophrenic group.

3. Results

3.1. SSPI scores and syndrome scores at time 1 and time 2

The mean SSPI score for the schizophrenic patients was decreased at time 2 (10.78, S.D. 3.15) compared with time 1 (17.89, S.D. 4.01) [$t(8) = 5.58$, $P = 0.001$]. The mean reality distortion score for the schizophrenic patients was decreased at time 2 (4.22, S.D. 1.72) compared with time 1 (6.44, S.D. 1.81) [$t(8) = 5.12$, $P = 0.001$]. The mean disorganization score for the schizophrenic patients was decreased at time 2 (0.33, S.D. 0.71) compared with time 1 (1.33, S.D. 1.41) [$t(8) = 2.45$, $P = 0.04$]. Finally, the mean psychomotor poverty score for the schizophrenic patients at time 2 (2.11, S.D. 2.62) was also decreased compared to time 1 (3.44, S.D. 3.28) [$t(8) = 2.82$, $P = 0.022$].

3.2. Behavioral measures

Table 1 contains means and standard deviations for reaction time on correct hit trials, reaction time on false alarm trials, reaction time on hit trials that directly followed false alarm trials, percentage of Xs responded to correctly and percentage of Ks responded to incorrectly for all three groups. There was no significant speeding or slowing of reaction times for correct hit trials that immediately followed a false alarm trial for the healthy group [$t(8) = 1.99$, $P = 0.082$], the schizophrenic group at time 1 [$t(8) = 0.335$, $P = 0.75$] or the schizophrenic group at time 2 [$t(8) = 1.12$, $P = 0.30$]. There were no significant differences in any of the behavioral measures between the schizophrenic group at time 1, the schizophrenic group at time 2 and the healthy group.

3.3. Grand-average event-related potentials

Group mean event-related potentials for the Fz, Fcz, Cz, Cpz and EOG channels are presented for correct hits and false alarms in Fig. 1. Only minimal deflections from baseline appear for the EOG channel for both kinds of trials indicating that the plots of the other channels are unaffected by contaminating artifacts due to blinking or eye movement.

Table 1
Behavioral measures (reaction times in milliseconds) and means with Standard Deviations in parentheses

	Mean RT (Hits)	Mean RT (FA)	Mean RT (Hits after FA)	% Xs (Responded to)	% Ks (Responded to)
Patients time 1	400 (89.4)	344 (60.1)	395 (119)	96.9 (3.86)	39.7 (15.4)
Patients time 2	375 (40.7)	338 (30.0)	356 (70.0)	95.4 (10.3)	42.6 (18.2)
Healthy controls	364 (37.4)	320 (38.1)	338 (44.9)	99.6 (0.527)	46.0 (15.6)

3.4. N_e/ERN , P_e , CRN and P_c

The group mean amplitudes for the N_e/ERN , P_e , CRN and P_c for the Fz, Fcz, Cz and Cpz channels are presented in Table 2. For the comparison of response-related negativity amplitude between the schizophrenic group at time 1 and the healthy group, there was a significant main effect of Group [$F(1, 16)=13.8$, $P=0.0019$] indicating larger negativities in the healthy

group, and a significant main effect of Response [$F(1, 16)=85.3$, $P<0.001$] indicating larger negativities for false alarms than for correct hits. There was also a significant Group \times Response interaction [$F(1, 16)=31.6$, $P<0.001$]. Follow-up ANOVAs examining the Group \times Response interaction indicated that negativities were significantly larger in the healthy group than in the patients with schizophrenia at time 1 for false alarms [$F(1, 16)=22.44$, $P<0.001$] but not for correct hits.

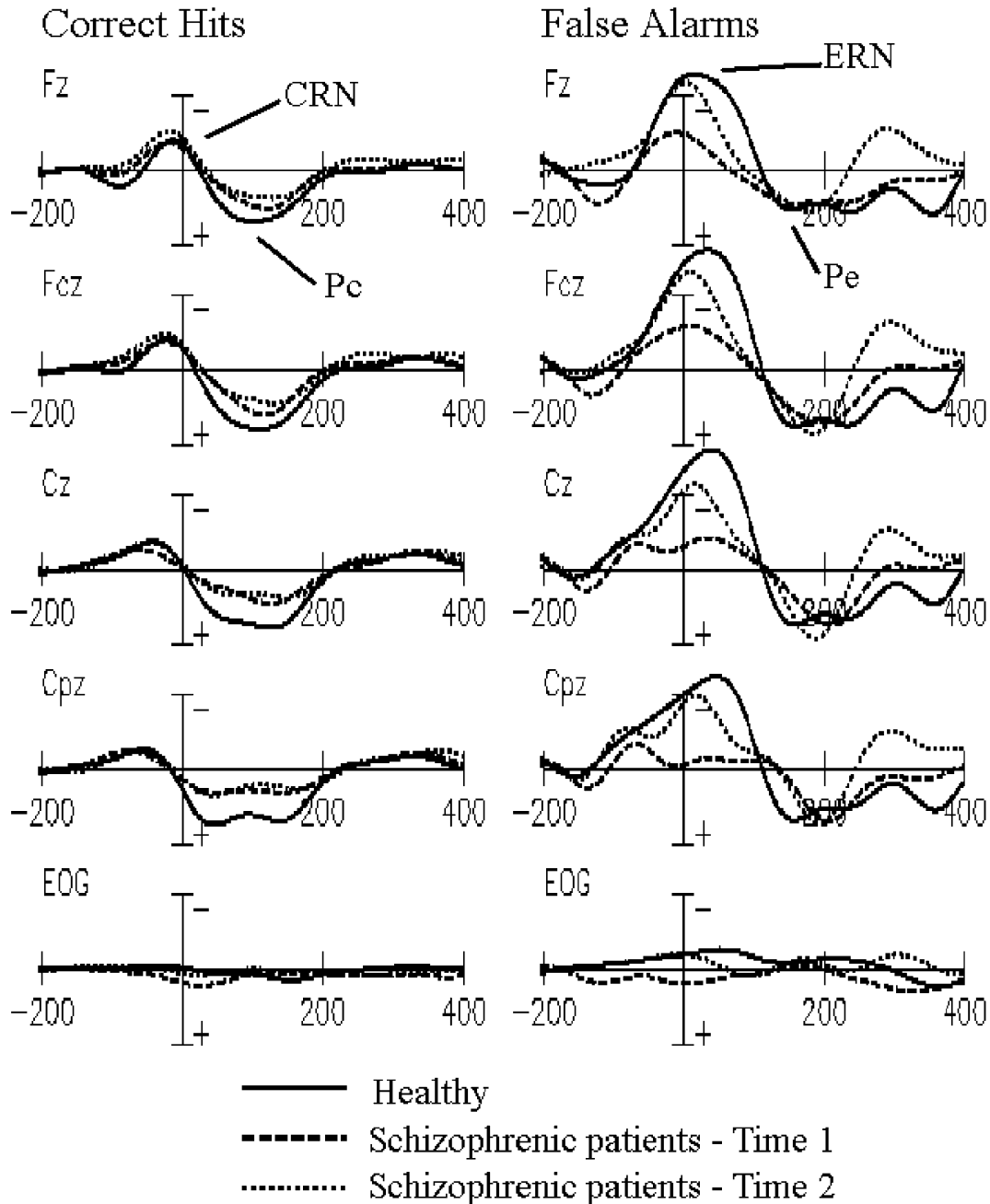


Fig. 1. Response-locked grand-average plots of the Fz, Fcz, Cz, Cpz and EOG channels for both correct hits (left) and false alarms (right). The solid trace represents the healthy group, the dashed trace represents the schizophrenic group at time 1 and the dotted trace represents the schizophrenic group at time 2. The timescale is in milliseconds and the calibration bars indicate positive and negative 5 microvolts. Negative voltage is plotted up.

Table 2

Event-related potential amplitudes in microvolts and means with standard deviations in parentheses

	Healthy controls	Patients time 1	Patients time 2
N _e /ERN, Fz	-9.86 (2.69)	-4.34 (3.54)	-7.77 (3.72)
N _e /ERN, Fcz	-12.4 (3.51)	-5.05 (4.06)	-9.02 (3.98)
N _e /ERN, Cz	-12.5 (3.35)	-4.27 (3.60)	-8.46 (3.90)
N _e /ERN, Cpz	-10.8 (3.10)	-3.69 (2.77)	-6.37 (2.49)
CRN, Fz	-2.47 (1.67)	-2.33 (1.72)	-2.80 (1.95)
CRN, Fcz	-3.03 (2.21)	-2.64 (1.77)	-2.93 (2.39)
CRN, Cz	-3.22 (2.32)	-2.18 (1.69)	-2.62 (1.87)
CRN, Cpz	-2.84 (1.79)	-1.94 (1.84)	-2.13 (1.17)
P _e , Fz	5.84 (1.64)	5.04 (3.18)	4.52 (3.00)
P _e , Fcz	6.88 (2.36)	5.74 (3.98)	5.59 (3.94)
P _e , Cz	6.41 (2.09)	5.06 (3.62)	5.97 (4.03)
P _e , Cpz	5.64 (2.04)	4.64 (3.63)	5.17 (4.54)
P _c , Fz	3.76 (1.83)	3.19 (1.58)	2.17 (1.22)
P _c , Fcz	4.60 (2.06)	3.40 (2.19)	2.60 (1.41)
P _c , Cz	4.52 (1.93)	2.96 (1.93)	2.44 (1.20)
P _c , Cpz	3.89 (1.62)	2.13 (1.73)	1.98 (1.03)

There was also a significant main effect of Channel and a significant Response×Channel interaction reflecting the fronto-central topography of the N_e/ERN.

For the comparison of response-related positivity amplitude between the schizophrenic group at time 1 and the healthy group, there was a significant main effect of Response [$F(1, 16) = 7.92, P = 0.012$] indicating larger positivities for false alarms than for correct hits. There was also a significant main effect of Channel reflecting the topographies of the P_e and P_c.

For the comparison of response-related negativity amplitude between the schizophrenic group at time 2 and the healthy group, there was a significant main effect of Response [$F(1, 16) = 120.64, P < 0.001$] indicating larger negativities for false alarms than for correct hits. There was also a significant Group×Response interaction [$F(1, 16) = 6.53, P = 0.021$]. Follow-up ANOVAs examining the Group×Response interaction revealed that negativities were larger for the healthy participants than for the patients with schizophrenia at time 2 for false alarms [$F(1, 16) = 6.23, P = 0.024$], but not for correct hits. There was also a significant main effect of Channel and a significant Response×Channel interaction reflecting the fronto-central topography of the N_e/ERN.

For the comparison of response-related positivity amplitude between the schizophrenic group at time 2 and the healthy group, there was a significant main effect of Response indicating that positivity amplitudes were larger for false alarms than for correct hits [$F(1, 16) = 11.04, P = 0.0043$]. There was also a significant main effect of Channel reflecting the topographies of the P_e and P_c.

For the comparison of response-related negativity amplitude between the schizophrenic group at time 1 and the schizophrenic group at time 2, there was a significant main effect of Session [$F(1, 8) = 7.57, P = 0.025$]

indicating larger negativities in the schizophrenic group at time 2. There was also a significant main effect of Response [$F(1, 8) = 36.8, P < 0.001$] indicating larger negativities for false alarms than for correct hits.

For the comparison of response-related positivity amplitude between the schizophrenic group at time 1 and the schizophrenic group at time 2, there was a significant main effect of Response [$F(1,8) = 9.15, P = 0.016$] indicating larger positivities for false alarms than for correct hits. There was also a significant main effect of Channel reflecting the topographies of the P_e and P_c.

In summary, N_e/ERN amplitude was significantly greater in the healthy group than in the patients with schizophrenia at time 1 and time 2, and N_e/ERN and CRN amplitudes were greater in the patients at time 2 than at time 1.

3.5. Correlation of changes in ERP amplitudes with changes in SSPI score and syndrome scores

There was a significant correlation between increases in N_e/ERN amplitude at Cz between time 1 and time 2 and decreases in disorganization score between time 1 and time 2 in the patients with schizophrenia [$r_s = 0.77, P = 0.016$]. There was also a similar trend at Cpz [$r_s = 0.60, P = 0.090$]. No other significant correlations were found.

4. Discussion

This study provides further support to the four previous reports (Kopp & Rist, 1999; Mathalon et al., 2002; Alain et al., 2002; Bates et al., 2002) that the amplitude of the N_e/ERN is reduced in schizophrenia and extends that finding to the acute phase of the illness. Furthermore, it is the first longitudinal study of the N_e/ERN, P_e, CRN and P_c in schizophrenia and examines variation in N_e/ERN, P_e, CRN and P_c within subjects over the resolving phase of an acute psychotic episode. The findings demonstrate that the amplitude of the N_e/ERN is abnormally decreased during and shortly after acute episode, but increases with 6 weeks of treatment. These findings suggest that the N_e/ERN abnormality in schizophrenia is related to clinical state and can change in a patient group over time. There was moderate correlational evidence suggesting that changes in severity of disorganization may be particularly relevant to such changes. Unlike our previous finding (Bates et al., 2002), the present study did not show any difference in CRN amplitude between healthy participants and patients with schizophrenia. The significant main effect of Session in the MANOVA comparing negativity amplitudes between the patients at time 1 and the patients at time 2 indicated an increase following treatment in response-locked negativities when errors of

commission and correct responses were not distinguished. The lack of a significant Session \times Response interaction suggested that both erroneous responses and correct responses contributed to this effect. However, inspection of Table 2 demonstrates that there was no substantial increase in the CRN, whereas there was an increase in N_e /ERN. Consistent with the findings of Mathalon et al. (2002) and Alain et al. (2002), we did not find any abnormalities in P_e or P_c amplitude in the schizophrenic participants.

There are two main limitations of this study. The first is that because acutely ill patients are difficult to recruit for ERP studies and more likely to decide not to finish a longitudinal study, there was a relatively small sample size. Although the correlational findings discussed below are of interest because of their relevance to previous research, the small sample size as well as the exploratory nature of the correlation analysis must be kept in mind. The second limitation is that the healthy volunteers only participated in a single ERP session. Therefore, some caution should particularly be taken in interpreting the comparisons of the healthy group with the patients at time 2. Although we have no reason to believe that there may be an instability in N_e /ERN, P_e , CRN or P_c amplitudes in healthy people over time, it remains a possibility.

Holroyd and Coles (2002) have suggested that the N_e /ERN is generated when anterior cingulate cortex neurons are disinhibited by a temporary reduction in inhibitory signaling from the mesencephalic dopamine system. This led them to predict that N_e /ERN amplitude would be abnormal in Parkinson's disease, in which the mesencephalic dopamine system is underactive. However, they found that the N_e /ERN was not abnormal in patients with Parkinson's disease following overnight withdrawal of dopamine enhancing medication (Holroyd et al., 2002). In contrast, Falkenstein et al. (2001) observed a reduction in N_e /ERN amplitude in patients with Parkinson's disease receiving dopamine enhancing treatment. Together, these findings support the hypothesis that the N_e /ERN is related to dopaminergic function, but suggests that a reduction in N_e /ERN amplitude occurs when there is an increase in dopamine transmission relative to an underlying deficit in baseline dopaminergic transmission.

Although there is little support for the hypothesis that dopaminergic hyperactivity is the central abnormality in schizophrenia, there is nonetheless substantial evidence that dopamine neurotransmission is abnormal (e.g. Laruelle et al., 1996), particularly in the anterior cingulate (Benes et al., 2000; Suhara et al., 2002). The precise nature of this abnormality remains uncertain. One plausible hypothesis is that acute schizophrenia is associated with phasic dopaminergic overactivity occurring against a background of reduced tonic dopaminergic activity (Grace, 1991, 1993; Abi-Dargham et al., 2000).

In this study, we observed that N_e /ERN amplitude is diminished in acute schizophrenia, and tends to recover towards normal levels as the acute episode resolves in response to treatment with dopamine-blocking antipsychotic medication. Thus, our observations are also consistent with the hypothesis that the amplitude of the N_e /ERN is diminished when there is a transient increase in dopaminergic neurotransmission superimposed on a defect in baseline level of dopaminergic transmission. However, because typical and atypical antipsychotics appear to have different effects on anterior cingulate function (Lahti et al., 2003), it is possible that treatment with typical antipsychotics would not produce the same increase in N_e /ERN amplitude seen in this patient group which was mainly treated with atypical antipsychotics.

There is growing evidence that the N_e /ERN may be part of an emotional response that accompanies error commission. For example, Luu et al. (2000) reported that students with high negative affect and negative emotionality show abnormally large N_e /ERNs. More recently, we (Bates et al., 2002) have found that decreased N_e /ERN amplitude in schizophrenic patients is correlated with increased psychomotor poverty which includes blunted affect. These findings are supported by fMRI work demonstrating that the rostral affective division of the anterior cingulate (Devinsky et al., 1995) is active around the time of error commission (Kiehl et al., 2000; Menon et al., 2001; Laurens et al., 2003). Additionally, Gehring et al. (2002) have reported that in a two-choice-guess gambling task, the N_e /ERN to feedback about previous trials is associated with losses of money and not with commission of errors suggesting that the N_e /ERN is not purely an error-detection signal and may have been associated with an emotional response to losing in their task. Due to the well-documented importance of mesencephalic dopamine projections in emotion, rewards, punishments, goal directed behavior and related cognitive deficits in schizophrenia (for a review, see Moore et al., 1999), Holroyd and Coles' (2002) dopamine model of N_e /ERN generation and the theory that the N_e /ERN is primarily the result of an emotional response fit well with each other and with our current findings.

Although there is growing evidence that the N_e /ERN is related to emotional processing and our own previous work (Bates et al., 2002) suggests that there is a relationship between decreased N_e /ERN amplitude in schizophrenia and increased psychomotor poverty which includes blunted affect, this study does not provide conclusive evidence of an association between increases in N_e /ERN or CRN amplitude and resolution of symptoms in any particular syndrome. This may reflect that the small sample size provided limited power to detect associations. Nonetheless, in accordance with the findings of Mathalon et al. (2002) that decreased N_e /ERN

amplitude is related to increased conceptual disorganization, there was evidence of an association between increase in N_e /ERN amplitude at Cz and Cpz and reduction in severity of disorganization symptoms. In light of the evidence that the main generator of the N_e /ERN is located in the anterior cingulate cortex, an association between N_e /ERN amplitude and disorganization would be consistent with previous findings indicating that disorganization symptoms are associated with abnormalities in that area (Liddle et al., 1992; Ebmeier et al., 1993; Yuasa et al., 1995). The hypothesis that deficits in error monitoring in schizophrenia are related to disorganization is also consistent with the work of Kuperberg et al. (2000) who measured reaction times of thought-disordered patients and control participants to target words presented in the context of pragmatically-, semantically- or syntactically-erroneous sentences. They observed an inverse relationship between severity of thought disorder and sensitivity to linguistic violations within individual patients over time, indicating that sensitivity to linguistic errors was related to the state, rather than the trait, of thought disorder.

Trait and state influences have been reported for abnormalities in other ERP measures in schizophrenia. For example, the results of Ford et al. (1999) and Mathalon et al. (2000) suggest that trait diminution of P300 amplitude might be associated with tendency towards negative symptoms, while state diminution is associated with severity of disorganization. Similarly, our results suggest that trait diminution of N_e /ERN amplitude might be associated with psychomotor poverty, while state diminution is associated with severity of disorganization. Perhaps the trait diminution of N_e /ERN amplitude is associated with psychomotor poverty and tonic decreased dopaminergic signaling, while the state diminution of N_e /ERN amplitude is associated with disorganization and phasic increases in dopaminergic transmission.

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