Neurophysiological Evidence of Error-monitoring Deficits in Patients with Schizophrenia

The present study was designed to investigate the time-course of neural activity underlying the disruption of response monitoring in patients with schizophrenia. Event-related brain potentials were recorded from 12 patients with schizophrenia and from 12 age-matched controls while they performed a computerized version of the Stroop color-naming task. In control participants, but not in patients with schizophrenia, intrusion errors elicited an error-related negativity (ERN) that peaked at ~40 ms after the response and was maximum over the central region of the scalp. Brain electrical source analysis revealed an anterior cingulate generator for the ERN. Patients also showed reduced error-related slowing of response time following intrusion errors. These findings provide neurophysiological evidence indicating that deficits in error monitoring in schizophrenia arise from a disruption of error-detection processes, possibly attributable to anterior cingulate dysfunction.

Introduction

Recent models of the cognitive deficits associated with schizophrenia emphasize a disruption of conscious awareness in situations requiring goal-directed action and motor control as a hallmark of the disorder (Frith et al., 2000). These deficits may contribute to a dissociation of action and intention that arises from the impairment of a mechanism that serves to compare the consequences of an action with a prospective model of the intended sequence of motor commands (Shallice and Burgess, 1996; Frith et al., 2000). The impairment of this mechanism can produce a variety of behavioral outcomes, including the disruption of error correction in patients with schizophrenia (Malenka et al., 1982; Stirling et al., 1998; Carter et al., 2001); however, other researchers have drawn a different conclusion (Kopp and Rist, 1994).

Error correction depends on an individual’s ability to detect the occurrence of an error and to successfully implement some corrective action in response to the detection of an error. A disruption of error detection would therefore represent one source of failed error correction. It is also possible that failures of error correction could result from the inability to implement a corrective strategy following error detection. The current study was designed to determine whether deficits in response monitoring in schizophrenia result from a failure of error detection or disruptions of error-correction processes. The amplitude of the error-related negativity – ERN (Falkenstein et al., 1991; Gehring et al., 1993), a component of the human event-related brain potentials (ERPs) – was used as an index of error detection and error-related slowing of response time was used as an index of corrective processing (West, 1999; Gehring and Knight, 2000).

Recording of ERPs provides a powerful tool for characterizing the time-course of neural events underlying error-related processing (Gehring et al., 1993). ERPs reflect the synchronized post-synaptic neural activity of several populations of neurons distributed across the cortex and therefore provide an online measure of information processing. Response-locked ERPs allow the examination of neural events associated with the preparation and execution of correct and incorrect responses. By examining the latency, amplitude and distribution of response-locked modulations of the ERPs, inferences can be made about the timing, level of processing and anatomical location of those neural mechanisms supporting error-related processing.

Errors in forced-choice response tasks are often associated with a biphasic negative–positive complex in the ERP (Falkenstein et al., 1991; Gehring et al., 1993). The negative wave typically peaks ~100 ms after the response and is maximal in amplitude over the midline fronto-central region of the scalp. This component of the ERPs has been labeled the ERN (Gehring et al., 1993) or error negativity – Ne (Falkenstein et al., 1991). Dipole source localization of the ERN indicates that the scalp topography of this component is modeled well by an anterior cingulate generator (Dehaene et al., 1994). The ERN or Ne component is followed by a positive wave referred to as the Pe component (Falkenstein et al., 1991). The Pe peaks at ~300 ms after an errant response and is maximal in amplitude over the central-parietal region of the scalp. The ERN increases in amplitude with the probability of error correction and with the degree of confidence that an error has occurred (Scheffers and Coles, 2000). Some evidence indicates that the amplitude of the ERN is greater when individuals are aware that an error has been made (Luu et al., 2000), suggesting that the ERN may provide an index of the internal monitoring of goal-directed behavior or may activate a neural system supporting the realization that an error has occurred. However, other data indicate that the amplitude of the Pe, but not the Ne (ERN), is modulated by the awareness that an error has occurred (Nieuwenhuis et al., 2001). These findings indicate that awareness may not be a necessary condition for generation of the ERN.

To our knowledge, only two studies have combined behavioral and ERP measures to investigate response monitoring in patients with schizophrenia (Kopp and Rist, 1999; Mathalon et al., 2002). In both studies, the amplitude of the ERN was reduced in patients with paranoid schizophrenia relative to age-matched controls. In contrast, the amplitude of the Pe and the magnitude of error-related slowing of response time was similar in patients and controls (Mathalon et al., 2002). In addition, patients generated a negative wave on correct trials that was similar in morphology, topography and amplitude to the ERN. This finding is similar to one reported in patients with lesions of the dorsolateral prefrontal cortex (DLPFC), where a pronounced negativity is also elicited by both correct and incorrect trials (Gehring and Knight, 2000). An important difference between the effects of schizophrenia and focal DLPFC lesions is that schizophrenia is associated with both a reduction in the amplitude of the ERN and increased negativity for correct trials, while DLPFC lesions are associated with a robust ERN that is similar in amplitude in patients and controls, and enhanced...
negativity on correct trials. Together, these results indicate that a distributed network, which is differentially affected by schizophrenia and focal lesions of the DLPC, supports response monitoring.

The present study was designed to further investigate possible deficits in response monitoring in patients with schizophrenia using behavioral and electrophysiological methods. The ERPs were recorded from a moderately dense array of electrodes to permit dipole source modeling. Participants performed a computerized version of the Stroop color-naming task, which requires individuals to name the color of printed letters and/or words in a congruent (e.g. the word RED printed in the color red), incongruent (e.g. the word RED printed in the color blue) and neutral (e.g. XXX or DOG printed in the color red) conditions (Stroop, 1935; MacLeod, 1991). Our focus was on intrusion errors, which reflect those instances on incongruent trials when individuals identify the word instead of the color. These errors are thought to reflect a disruption of goal-directed action and are associated with a robust ERN (West and Alain, 2000).

In addition to the ERP data, we also considered the response-time data for correct trials preceding and following an error in both patients and controls. Previous research has shown that large ERNs are usually associated with longer response time on trials following an error (Gehring et al., 1993; Gehring and Knight, 2000). Past research has also demonstrated that both patients with schizophrenia and focal DLPC lesions exhibit normal patterns of error-related slowing of response time in contrast to pathology-related alterations of the ERN (Gehring and Knight, 2000; Mathalon et al., 2002).

Based upon current evidence, we hypothesized that if difficulties in response monitoring in patients with schizophrenia result from a disruption of error detection, ERN amplitude and error-related slowing of response time would be reduced in patients relative to controls. In contrast, if deficits in response monitoring result from a disruption of corrective processing rather than error detection, ERN amplitude would be relatively intact in patients and Pa amplitude and error-related slowing of response time would be reduced in patients relative to controls.

Materials and Methods

Participants

Twelve adults (aged between 19 and 50 years, mean = 31.1 ± 8.77, seven men) diagnosed with schizophrenia (n = 11) or schizoaffective disorder (n = 1) and 12 healthy controls (aged between 21 and 48 years, mean = 31.5 ± 8.74 years, six men) were recruited to participate in the study. The patients were outpatients of the Schizophrenia and Continuing Care Division of the Centre for Addiction and Mental Health (CAMH) in Toronto, Ontario. Controls were recruited from the Toronto community through advertisements. Diagnoses were confirmed with the Structured Clinical Interview for the DSM-IV Axis I disorders (First et al., 1998).

Positive and negative symptoms were rated using the Structured Clinical Interview for the Positive and Negative Syndrome Scale (Kay et al., 1992). All patients were mildly ill at the time of testing (group mean positive symptoms 14.3 ± 6.6 and negative symptoms 15.4 ± 5.0). Controls were free of any history of psychotropic medication use and any personal history or first-degree family history of an Axis I disorder. Exclusion criteria for all participants also included: substance abuse within the previous 6 months; neurological illness or history of head trauma with loss of consciousness; English language not acquired before age 5; and color blindness. All participants were right-handed, had normal or corrected-to-normal vision, provided written informed consent according to CAMH ethical guidelines and received a nominal payment in return for their participation. Patients and controls did not differ on a measure of premorbid verbal intellectual functioning (Wechsler Adult Intelligence Scale – Revised, Information subtest).

Ten patients were medicated and two were medication-free at the time of the ERP recording. One patient was neuroleptic-naïve and one had discontinued neuroleptic (olanzapine, 5 mg/day) use 5 days prior to participating. Patients’ medications included oral antipsychotics such as olanzapine at doses of 10, 15 and 25 mg; clozapine at 250 and 400 mg; loxapine at 10 mg; quetiapine at 400 mg; and risperidone at 1 mg. Five patients were also taking a selective serotonin reuptake inhibitor: paroxetine hydrochloride at 20 and 40 mg and sertraline hydrochloride at 50 and 100 mg. One patient was taking an anticonvulsant, valproic acid at 1000 mg.

Behavioral Design and Procedure

Participants were tested individually in two separate test sessions, performed on different days. In the first session, clinical and neuro-psychological measures were administered. In the second session, the ERPs were recorded while participants performed the Stroop task. Stroop stimuli were presented on an IBM-compatible computer using MEL 2 software. Participants were seated in a dimly lit room in front of a computer monitor. They were instructed that they would see stimuli on the screen in one of four colors (red, blue, green, or yellow). Participants were asked to identify the color in which the stimuli were printed by pressing one of four color-coded response keys (v, b, n, m) using the middle and index fingers of their right and left hands. In addition to these color words, participants were presented with color-words printed in gray (e.g. BLUE printed in the color gray) and were asked to press one of four color-coded response keys (v, b, n, m) that corresponded to the name of the color. Word naming trials were included to increase the inhibitory demands of the task (West and Alain, 1999).

The importance of speed and accuracy was equally emphasized. The experiment was divided into a color-key acquisition phase, a practice phase and a test phase. The color-key acquisition phase consisted of a single block of 100 trials with each of the four colors randomly presented 25 times as series of Xs. A 25-trial practice block composed of a neutral series of Xs and congruent and incongruent stimuli was then completed. This was done to allow participants to become familiar with the task and ensure that they understood the instructions. The test phase was divided into 10 blocks of trials in which neutral, congruent, incongruent and word identification (i.e. word printed in gray) stimuli were presented in a random fashion. The proportion of word identification trials alternated between 25 and 50% between blocks of trials. Blocks also alternated between 96 and 144 trials (i.e. 25 or 50% word identification trials). Participants initiated stimulus presentation by pressing the space bar. The stimuli appeared on the screen for 400 ms, followed by a blank screen until 1000 ms after a response had been made, at which time the next stimulus appeared. Participants were provided with short rest breaks between test blocks as needed. The entire Stroop task required ~60 min to complete.

ERP Procedure

The electroencephalograph (EEG) was digitized continuously (250 Hz per channel, bandwidth 0.05–50 Hz) from an array of 33 electrodes based upon an extended 10-20 system. Vertical and horizontal ocular movements were also recorded from electrodes placed lateral to and below both eyes. Activity was referenced to the midline central electrode (i.e. Cz) during recording and re-referenced to an average reference off-line prior to analysis. The analysis epoch included 400 ms of pre-response activity and 400 ms of post-response activity. Trials contaminated by eye blink or excessive peak-to-peak deflection (≤ 150 µV) at the electrodes not adjacent to the eyes were automatically rejected before averaging. The ERPs were then averaged separately for each site, stimulus type (i.e. congruent, incongruent and neutral) and response type (correct, incorrect). ERPs were digitally low-pass filtered to attenuate frequencies >12 Hz. For each individual average, the ocular contaminations (e.g. blinks and lateral movements) were corrected by means of ocular source components using Brain Electrical Source Analysis (BESA) software (Picon et al., 2000).

ERN amplitude was quantified as the mean voltage between 20 and 60 ms following a button press relative to a baseline measured from –400 to –200 ms pre-response. Pa amplitude was quantified as the mean voltage between 300 and 400 ms post-response relative to the pre-response baseline. Behavioral data were analyzed using a mixed design repeated
measures analysis of variance (ANOVA) with clinical group as a between-subjects factor and response type (correct or incorrect response) as a within-subjects factor. Analyses of the ERP data included electrode as an additional within-subjects factor. Because the ERN is typically largest at frontal and central sites, the analyses included the left, midline and right frontal and central electrodes (i.e. F3, Fz, F4, C3, Cz and C4). The Pe component has a more central-parietal distribution than the ERN and was therefore quantified using three midline electrodes (i.e. Fz, Cz and Pz).

**Results**

**Behavioral Data**
Participants made more errors for incongruent (10.7%) than for congruent (2.4%), neutral (4.0%), or word identification (3.9%) trials \( F(3,66) = 72.13, P < 0.001 \), pairwise comparisons, \( P < 0.001 \). For incongruent trials, patients committed between 7 and 46 intrusion errors across the task (mean 21.4, SD = 12.2), while controls made between 8 and 28 intrusion errors (mean = 16.2, SD = 7.0). Both the absolute number and the proportion of intrusion errors (number of intrusion errors divided by the total number of errors on incongruent trials) did not differ between the two groups \( t(22) = 1.29 \) and 1.02, respectively). In both patients and controls, there were no significant differences in response times for correct and incorrect incongruent trials (for patients correct RT = 1235 ± 259 ms and incorrect RT = 1225 ± 274 ms; for controls correct RT = 913 ± 79 ms and incorrect RT = 844 ± 150 ms).

Overall, patients were slower than controls [Fig. 1; \( F(1,22) = 20.73, P < 0.001 \)]. In both groups, correct responses on trials following intrusion errors were slower than for those following correct trials \( F(1,22) = 35.46, P < 0.001 \). To control for the overall group difference in response time, the proportion of error-related slowing of response time (i.e. difference in response time between hits following hits versus hits following intrusion errors, divided by the response time for a hit following a hit) was obtained for each participant. There was a main group effect \( t(22) = 1.91, P < 0.05 \), one-tailed), with controls demonstrating greater error-related slowing of response time following intrusion errors (20%) than patients (11%).

**Electrophysiological Data**
Figure 2 shows the ERPs elicited by correct and incorrect trials from the frontal, central and parietal regions of the scalp in controls and patients with schizophrenia. An ANOVA with group, response type, region (frontal and central) and electrodes (left, midline and right frontocentral sites) as factors yielded a main effect of response type \( F(1,22) = 26.74, P < 0.001 \), with error trials generating greater negativity than correct trials. The group \( \times \) response type interaction was also significant \( F(1,22) = 14.46, P = 0.001 \), reflecting group differences in the ERPs elicited by correct and incorrect trials, as well as greater differences in ERP amplitude elicited by correct and incorrect trials in controls than in patients. A separate \( t \)-test on the patients’ data indicated that correct and incorrect trials generated similar ERP amplitude. Lastly, the group \( \times \) response type \( \times \) electrode interaction was significant \( F(2,44) = 6.08, P = 0.005 \), for unnormalized voltages, reflecting greater group differences in ERN amplitude over the left than the right frontocentral region of the scalp. The main effect of group was not significant \( F < 1.0 \).

Finally, for the patients, there were no significant correlations between ERN amplitude and the severity of positive or negative symptoms.

Incorrect trials also elicited a positive displacement (Pe) between 300 and 400 ms following the response that was similar in amplitude for patients and controls. This difference in positivity is best illustrated in the difference waves between ERPs elicited by correct and incorrect responses (Fig. 3). An ANOVA with group, response type and electrode as factors revealed a main effect of response type \( F(1,22) = 5.76, P < 0.05 \). However, the main effect of group and the interactions involving this variable were not significant \( F < 1.0 \), indicating that the amplitude of the Pe did not differ in patients and controls.

The relationship between ERN amplitude and response time for intrusion errors was examined using linear regression with ERN amplitude as the criterion variable, response time as a predictor variable and group as an indicator variable. There was a significant interaction between group and response time \( [\beta = 0.03; t(22) = 2.40, P < 0.05] \), indicating that the relationship between ERN amplitude and response time was different in patients and controls (Fig. 4). Specifically, in patients the slope was 0.0003 whereas in controls the slope was 0.02. Consistent with the results of the regression analysis, the correlation between ERN amplitude and response time was not significant for patients \( (r = 0.02) \) and was significant in controls \( (r = 0.70; P < 0.02) \). The correlations between the ERN amplitude and response time following intrusion errors and the proportion of error-related slowing of response time were not significant in patients or controls.

The location of the neural generator of the ERN was examined using dipole source modeling. The analysis was limited to the data for the controls because the signal/noise ratio in patients was not sufficient to allow reliable source estimation. The analysis was carried out using a four-shell ellipsoidal head model with relative conductivities of 0.53, 1.0, 0.0042 and 0.33 for the brain, cerebrospinal fluid, skull and scalp, respectively. The thicknesses for head, scalp, bone and cerebrospinal fluid were 85, 6, 7 and 1 mm, respectively. The source analysis was performed on the difference wave of the ERPs elicited for correct trials and those elicited by error trials. The first principal component of the scalp recorded difference wave between 20 and 100 ms accounted for 99.1% of the variance, suggesting that a single source of variability contributed to the ERPs over this time interval. The dipole source was located in or near the anterior cingulate gyrus (Fig. 5). The residual variance for this solution was 5.29%, suggesting that it provides a good fit to the
scalp recorded data. Although the dipole was located in the right hemisphere, the scalp distribution could also be successfully modeled by a dipole having a slightly different orientation in the left anterior cingulate (residual variance was 5.58%).

Discussion
Results from the present study provide converging behavioral and neurophysiological evidence for a deficit in error detection and response correction in patients with schizophrenia. The amplitude of the ERN was dramatically attenuated in individuals with schizophrenia relative to controls, and patients demonstrated reduced error-related slowing of response time. These results suggest that deficits in response monitoring in patients with schizophrenia result primarily from a disruption of processes supporting error detection.

It was recently demonstrated (Carter et al., 1998) that similar patterns of neural activity in the anterior cingulate are associated
with errors and trials where there is response conflict. These data lead to the suggestion that the ERN may provide a more general index of conflict processing rather than an index of error detection. A recent study (Gehring and Fencsik, 2001) found that the ERN amplitude was larger in situations where correct and incorrect responses involved similar movement features as compared to dissimilar movement features. This finding seems consistent with the hypothesis that the ERN indexes conflict processing rather than error detection. In the current study, incongruent trials could be thought to result in the activation of two competing responses, one for the color of the stimulus and one for the word that was presented. Thus, the electrophysiological data could be interpreted as reflecting a disturbance of conflict processing in schizophrenia. However, the behavioral results are difficult to reconcile with a deficit in conflict processing, since the proportion of intrusion errors was similar in controls and patients and a disturbance of conflict processing could be expected to increase the probability of intrusion errors. Therefore, together our results appear to be more consistent with a deficit of error detection in individuals diagnosed as schizophrenic.

Patients with schizophrenia generated a negative wave on correct trials that resembled the neural response observed for intrusion errors. This finding is consistent with those of Mathalon et al. (Mathalon et al., 2002), who observed a ‘correct-response negativity’ in patients with schizophrenia. This result also bears some similarity to data obtained in patients with damage to the DLPFC. Gehring and Knight observed that a post-response negativity was elicited for both correct and error trials in patients with damage to the DLPFC (Gehring and Knight, 2000). Although the functional significance of the ‘correct-response negativity’ is unclear, this finding suggests that deficits in response monitoring in individuals with schizophrenia involve dysfunction within a distributed neural network that likely includes the DLPFC and anterior cingulate gyrus.

The amplitude of the Pe component was similar in patients and controls. This finding replicates that of Mathalon et al. (Mathalon et al., 2002) and provides evidence that the ERN and Pe index distinct aspects of response monitoring that are differentially affected in patients with schizophrenia. The absence of an effect of schizophrenia on the Pe is interesting given the reduction in error-related slowing of response time observed in patients, as both of these effects have been interpreted as reflecting the activity of error-compensation.
net the roles of the DLPFC and anterior cingulate are somewhat dissociable. Damage to the DLPFC results in the generation of a response-related negativity on both correct and error trials (Gehring and Knight, 2000), while dysfunction of the anterior cingulate results in a reduction in the amplitude of neural activity that is elicited on error trials (Carter et al., 2001). Together, this evidence may indicate that dysfunction of the anterior cingulate, rather than the DLPFC or medial temporal lobe, may be a primary cause of disruptions in error monitoring — and goal-directed behavior more generally — in schizophrenia. The reductions of ERN amplitude and error-related slowing of response time are also consistent with Frith’s theory related to deficits of willed action in patients with schizophrenia (Frith, 2000). In this model, generation of the ERN could be seen as being dependent upon the activity of a mechanism that supports the comparison of a prospective model of the intended action to the actual response of the individual. The ERN would therefore be generated when there is a discrepancy between willed and realized action (Gehring et al., 1993). Given this model, the reduction in ERN amplitude and error-related slowing of response time in schizophrenia could be understood as resulting from a reduced ability to maintain an integrated representation of the prospective model (Frith et al., 2000), or possibly a disruption of the comparison process. However, it seems unlikely that the reduced ERN in patients with schizophrenia resulted from an impairment of the ability to represent the prospective model, as such an impairment would be expected to result in an increase in the probability of intrusion errors when the goal of naming the color rather than reading the word became degraded (West, 1999; West and Alain, 2000). Therefore, the present results may be more consistent with a deficit of the comparison process.

Notes
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