Published in final edited form as:
Psychol Med. 2012 August ; 42(8): 1637–1647. doi:10.1017/S0033291711002819.

Impaired Neural Response To Internal But Not External Feedback In Schizophrenia

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Abstract

Background—Accurate monitoring and integration of both internal and external feedback is critical for guiding current and future behavior. These aspects of performance monitoring are commonly indexed by two event-related potential components: The error-related negativity (ERN) indexes internal response monitoring and is sensitive to the commission of erroneous versus correct responses, and the feedback Negativity (FN) indexes external feedback monitoring positive versus negative outcomes. Although individuals with schizophrenia consistently demonstrate a diminished ERN, the integrity of the FN has received minimal consideration.

Methods—The current research sought to clarify the scope of feedback processing impairments in schizophrenia in two studies: Study 1 examined the ERN elicited in a flankers task in 16 outpatients and 14 healthy controls; Study 2 examined the FN on a simple monetary gambling task in expanded samples of 35 outpatients and 33 healthy controls.

Results—Study 1 replicated prior reports of an impaired ERN in schizophrenia. In contrast, patients and controls demonstrated comparable FN differentiation between reward and non-reward feedback in Study 2.

Conclusions—The differential pattern across tasks suggests that basic sensitivity to external feedback indicating reward versus non-reward is intact in schizophrenia, at least under the relatively simple task conditions used in this study. Further efforts to specify intact and impaired reward-processing subcomponents in schizophrenia may help shed light on the diminished motivation and goal-seeking behavior that are commonly seen in this disorder.

Keywords

Schizophrenia; Event-Related Potentials (ERP); Error Related Negativity; Feedback Negativity; Reward Sensitivity

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1. Introduction

Schizophrenia is characterized by enduring difficulties in adaptive functioning, including diminished engagement in productive, goal-directed activities (Barch and Dowd, 2010, Blanchard *et al.*). One critical element of adaptive functioning is the accurate monitoring of responses and integration of feedback, which informs decision-making and guides behavior based on the consequences of our actions. Sensitivity to favorable versus unfavorable actions and outcomes has been extensively investigated in healthy subjects through event-related potential (ERP) measures of neural activity. The goal of the current research was to assess two aspects of response monitoring in schizophrenia, namely, sensitivity to the internal detection of errors compared to correct responses indexed by Error Related Negativity and sensitivity to external feedback that indicates good versus bad outcomes indexed by Feedback Negativity.

1.1 Error-Related Negativity (ERN)

The ERN is a response-locked ERP that reflects the activity of a neural system involved in monitoring actions and detecting errors (Falkenstein *et al.*, 1990, Gehring *et al.*, 1993, Simons, 2010). The ERN, which is typically studied using simple choice reaction time tasks (e.g., flanker tasks), differs following erroneous from correct responses: it is evident as a larger negative deflection at frontocentral sites approximately 50 msec following the commission of erroneous compared to correct responses. The size of the ERN has been shown to reflect the motivational significance errors (Hajcak *et al.*, 2005). Converging evidence from source localization, fMRI, and single unit recording studies indicates that the ERN is generated within the anterior cingulate cortex (ACC), a structure centrally involved in response monitoring and error detection (Taylor *et al.*, 2007). Prevailing reinforcement learning theories propose that the ERN reflects dopaminergic disinhibition of neurons in the ACC when actions are evaluated as worse than anticipated (Holroyd and Coles, 2002); this early error detection then recruits input from other brain regions (e.g., dorsolateral prefrontal cortex) to enhance performance and facilitate learning.

Reductions in the ERN are consistently reported in people with schizophrenia across a variety of paradigms, including Eriksen-type flanker, Go-No/Go, Stroop color-word naming, and probabilistic learning tasks (e.g., (Mathalon *et al.*, 2009, Mathalon *et al.*, 2002b, Morris *et al.*, 2008, Morris *et al.*, 2006). A reduced ERN was also recently reported in children with putative antecedent features of schizophrenia (Laurens et al., 2010), implicating reduced internal error monitoring as a trait-like feature associated with liability to this disorder. fMRI studies provide converging evidence of diminished ACC responses to errors in schizophrenia (Carter *et al.*, 2001, Koch *et al.*, 2010, Polli *et al.*, 2008).

The ERN deficit in schizophrenia does not appear to simply reflect general reductions in response accuracy or a generalized decrease in neural activation during response monitoring. ERN impairments are present regardless of whether patients differ from controls in accuracy rates, and patients demonstrate a normal or even enhanced “Correct Response Negativity” (CRN) (Alain *et al.*, 2002, Mathalon *et al.*, 2002a, Morris *et al.*, 2008), a corresponding but smaller ERP 50 msec following correct responses. Furthermore, a later response-locked ERP component, the error positivity (Pe), consistently appears unaffected in schizophrenia (Alain *et al.*, 2002, Mathalon *et al.*, 2002a, Morris *et al.*, 2008). The Pe is a positive deflection in the waveform at more posterior midline sites that typically peaks around 300 ms and is larger following erroneous responses than the corresponding ERP that follows correct responses (“Pc”). This component is hypothesized to index conscious evaluation or a P3-like response to infrequent errors of commission (Overbeek *et al.*, 2005, Ridderinkhof *et al.*, 2009, van Veen and Carter, 2006). Thus, the diminished differentiation between ERN and CRN in schizophrenia has been interpreted to reflect impaired early self-monitoring and

internal error processing, whereas later response evaluation (i.e., differentiation between Pe and Pc) appears intact.

1.2 Feedback Negativity (FN)

A related ERP component, the FN, is sensitive to favorable versus unfavorable external feedback. This FN has been extensively studied using simple gambling or guessing paradigms (Simons, 2010). The FN is apparent as a relative negativity at frontocentral recording sites approximately 300 ms following outcomes indicating relatively unfavorable outcomes, such as monetary loss or negative performance feedback, compared to a favorable outcome, such as monetary gains or positive performance feedback. It has been interpreted to reflect an early binary evaluation of outcomes as either favorable or unfavorable, and appears to be insensitive to reward magnitude (Hajcak *et al.*, 2006, Sato *et al.*, 2005, Yeung and Sanfey, 2004). Importantly, the FN is typically elicited in tasks or trials in which subjects must rely on external feedback to evaluate the veracity of their responses. The FN and the ERN have often been described as reflecting common error monitoring processes subserved by the ACC (Holroyd and Coles, 2002). However, recent evidence suggests important functional and source localization differences between these components. For instance, some studies suggest that the FN might actually reflect reward-related activity of the striatum, rather than error-related activity in the ACC (Carlson *et al.*, 2011, Foti *et al.*, in press, Holroyd *et al.*, 2008). Indeed, a decreased FN is found in psychiatric conditions associated with altered reward sensitivity, such as depression and anxiety (Simons, 2010). The FN may also be useful in delineating the scope of reward-related feedback sensitivity impairments in schizophrenia, but has thus far received only limited attention in this disorder.

The literature on reward sensitivity and feedback-based learning in schizophrenia provides a mixed picture. On the one hand, individuals with schizophrenia consistently show normal levels of self-reported pleasure and physiological responses to pleasant or rewarding evocative stimuli (Horan *et al.*, 2010, Kring and Moran, 2008). On the other hand, although patients usually show intact performance on relatively simple reinforcement learning tasks, they show substantial impairment on more complex tasks involving implicit probabilistic habit learning, reversal learning, or value computation (Barch and Dowd, 2010, Gold *et al.*, 2008). In the one prior study of the FN in schizophrenia, patients showed diminished differentiation between correct versus incorrect feedback in one condition of a complex probabilistic learning task that manipulated the validity of feedback information (Morris et al., 2008), which could result from deficient learning, reward insensitivity, or both. It remains to be determined whether individuals with schizophrenia show a diminished FN in simpler paradigms that do not require learning and integration of feedback under varying task conditions.

1.3 The current research

Two ERP studies were conducted to clarify the scope of feedback processing impairments in schizophrenia. In Study 1, we compared the ERN of patients and healthy controls during a flankers task. We expected to replicate findings of a diminished ERN in schizophrenia. Study 2 considered the unexplored area of the FN during a simple monetary gambling task using larger samples of patients and controls, including all participants from Study 1. Existing literature did not support a clear directional hypothesis for this task, though one prior study (Morris et al., 2008) pointed toward diminished FN in schizophrenia.

2. Methods

2.1 Participants

Thirty-five outpatients with schizophrenia and 33 healthy control subjects participated in this research. A subset of 16 patients and 14 controls completed Study 1 and all participants completed Study 2. Patients met criteria for schizophrenia based on the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID; (First *et al.*, 1996). Patients with schizoaffective disorder were excluded and none of the patients were in a major depressive or manic episode at the time of testing. Additional exclusion criteria for patients included: substance abuse or dependence in the last six months; IQ < 70 based on chart reviews; a history of loss of consciousness for more than one hour; an identifiable neurological disorder; or insufficient fluency in English. Regarding substance use history diagnoses: 3 patients had alcohol abuse, 11 had drug dependence, 5 had other substance abuse, and 14 had other substance dependence. All patients were medicated at clinically determined dosages with 30 receiving atypical antipsychotic medications, three receiving typical antipsychotic medications, and two receiving both types of medication. Medication dosages were converted to chlorpromazine equivalents (Andreasen *et al.*, 2010) for supplemental analyses. All patients were clinically stable, which was defined as follows: no hospitalizations in the past three months, no medication changes in the past six weeks, and no changes in living status in the past two months.

Healthy controls were recruited through flyers posted in the local newspapers, websites, and posted advertisements. An initial screening interview excluded potential controls with identifiable neurological disorder or head injury, psychotic disorder in a first-degree relative, or insufficient fluency in English. Potential controls were then screened with the SCID and excluded for history of psychotic disorder, bipolar disorder, recurrent depression, lifetime history of substance dependence, or substance abuse in the last 6 months. Controls were also administered portions of the Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II; (First *et al.*, 1994) and excluded if they had avoidant, paranoid, schizoid, or schizotypal personality disorder.

All participants had the capacity to give informed consent and provided written informed consent in accordance with Institutional Review Board-approved procedures.

2.2 Symptom ratings

For all patients, psychiatric symptoms during the previous month were rated using the expanded 24-item UCLA version of the Brief Psychiatric Rating Scale (BPRS (Lukoff *et al.*, 1986, Overall and Gorham, 1962). Ratings from the positive and negative symptom subscales, as well as total scores, were examined (Kopelowicz *et al.*, 2008). Data from two patients were missing due to scheduling conflicts. All SCID and BPRS interviewers were trained through the Treatment Unit of the Department of Veterans Affairs VISN 22 Mental Illness Research, Education, and Clinical Center based on established procedures (Ventura *et al.*, 1993, Ventura *et al.*, 1998). All interviewers had a masters or doctoral-level degree. The process included formal didactics, achieving a minimum level of reliability (minimum kappa = .75) for key psychotic and mood items using an extensive library of videotaped interviews, as well as live, co-rated interviews conducted with faculty members. After certification, all raters participated in a continuous quality assurance program that involved periodic reliability checks and corated live interviews with faculty.

2.3 ERP paradigms

2.3.1 Study 1: ERN flanker task—An arrow version of the anker task (Eriksen and Eriksen, 1974) was administered following procedures used by Hajcak *et al* (2005). On each

trial, ve horizontally aligned arrowheads were presented. Half of all trials were compatible ("≪≪<" or "≫≫>") and half were incompatible ("≪>≪" or "≫<≫"); the order of compatible and incompatible trials was random. All stimuli were presented for 200 ms followed by an ITI that varied randomly from 2300 to 2800 ms.

Participants were instructed to press the right mouse button if the center arrow was facing to the right and to press the left mouse button if the center arrow was facing to the left. Participants performed a practice block containing 30 trials during which they were instructed to be both as accurate and fast as possible. The actual task consisted of 11 blocks of 30 trials (330 trials total) with each block initiated by the participant. To encourage both fast and accurate responding, participants received feedback based on their performance at the end of each block. If performance was 75% correct or lower, the message "Please try to be more accurate" was displayed; performance above 90% correct was followed by "Please try to respond faster"; otherwise, the message "You're doing a great job" was displayed.

2.3.2 Study 2: FN gambling task—To assess processing of feedback indicating good versus bad outcomes, a simple gambling paradigm was employed (Foti and Hajcak, 2010, Foti *et al.*, in press). On each trial, participants were shown a graphic displaying two doors horizontally adjacent and were told to choose which door they wanted to open. They were told to press the left mouse button to choose the left door or the right mouse button to choose the right door. Following each choice, a feedback stimulus appeared on the screen informing the participants whether they won or lost money on that trial. A green '↑' indicated a correct guess and a gain of $.80, whereas a red '↓' indicated an incorrect guess and a loss of $.40. A fixation mark (+) was presented prior to the onset of each stimulus. At the end of each trial, participants were presented with the instruction to 'Click for the next round'. The order and timing of all stimuli were as follows: (i) the graphic of two doors was presented indefinitely until a response was made, (ii) a fixation mark was presented for 1000 ms, (iii) a feedback arrow was presented for 2000 ms, (iv) a fixation mark was presented for 1500 ms, and (v) "Click for the next round" was presented until a response was made. Participants were told that they would gain $.80 each time they opened a door that hid a prize and lose $.40 each time they opened a door without a prize, and that they would earn between $0 and $20 total. In actuality, participants completed 50 trials with exactly 25 wins and 25 losses, for a net sum of $10.00; feedback order was randomized across participants.

2.4 EEG recording and processing

Participants had their EEG activity continuously recorded in Studies 1 and 2 using the same procedure. The EEG was recorded using a custom cap (Cortech Solutions, Wilmington, North Carolina, USA) and the ActiveTwo BioSemi system (BioSemi, Amsterdam, Netherlands). The signal was preamplified at the electrode with a gain of one; the EEG was digitized at 24-bit resolution with a sampling rate of 512 Hz using a low-pass fifth order sinc filter with a half-power cutoff of 104 Hz. Recordings were taken from 64 scalp electrodes based on the 10/20 system, as well as two electrodes placed on the left and right mastoids. The electrooculogram was recorded from four facial electrodes: two 1 cm above and below the left eye, one 1 cm to the left of the left eye, and one 1 cm to the right of the right eye. Each electrode was measured online with respect to a common mode sense electrode that formed a monopolar channel.

Off-line analysis was performed using Brain Vision Analyzer software (Brain Products, Munich, Germany). All EEG data was re-referenced to the average of the two mastoids. Filtering, segmenting, and averaging parameters for each task are described separately below. For both tasks, each trial was corrected for blinks and eye movements using the method developed by Gratton and colleagues (Gratton *et al.*, 1983). Specific channels were

rejected in each trial using a semi-automated procedure, with physiological artifacts identified by the following criteria: a step of more than 50 μV between sample points, a difference of 300 μV within a trial, and a maximum difference of less than 0.5 μV within 100-ms intervals. Additional physiological artifacts were identified using visual inspection.

For the flanker task, the data were band-pass filtered with cutoffs of 0.1 and 30 Hz. The EEG was segmented for each trial beginning 400 ms before each response onset and continuing for 1000 ms (i.e., until 600 ms after response onset). Response-locked ERPs were averaged separately for error and correct trials. The ERN was evaluated as the average activity on error trials from response onset to 100 ms (i.e. 0–100 ms) at pooling of FCz/Cz (where the effect was largest) and the CRN was evaluated in the same time window and electrodes on correct trials. The Pe and Pc were evaluated on error and correct trials, respectively, as the average activity from 200–300 ms at Cz following response onset. A 200 ms window from 400 to 200 ms prior to response onset served as the baseline. ERP activity on correct trials has been associated with response monitoring (Simons, 2010). Moreover, error-related brain activity may reflect processes common to both error and correct responses. Accordingly, it is particularly informative to examine the difference between error and correct trials in order to separate activity that is uniquely related to error-processing from activity related to response monitoring in general (Burle *et al.*, 2008). The difference wave approach can help isolate ERP components that are more readily interpreted in terms of specific cognitive functions (Luck, 2005). Difference scores for error minus correct trials were therefore calculated in the time windows of the ERN/CRN, as well as the Pe/Pc – we refer to these as the ΔERN and ΔPe. Based on the literature (Olvet and Hajcak, 2009), participants who made fewer than six errors were excluded from all analyses (schizophrenia = 3; controls = 4), resulting in final sample sizes of 16 patients and 14 controls.

For the gambling task, the EEG data were band-pass filtered with cutoffs of 0.1 and 30 Hz. The EEG was segmented for each trial, beginning 200 ms before feedback onset and continuing for 800 ms following feedback onset. Stimulus-locked responses were averaged separately for non-rewards and rewards, and the activity in the 200-ms window before feedback onset served as the baseline. The FN was quantified as mean activity from 250 – 350 ms at a pooling of FCz/Cz for non-reward and reward trials, as well as the difference between non-reward and reward trials (ΔFN). A difference wave approach is particularly relevant in studies of the FN, insofar as non-reward and reward are thought to elicit phasic decreases and increases in dopamine, respectively (Holroyd and Coles, 2002). One outlier in the control group (ERPs > 3 standard deviations above group mean) was excluded from all analyses for this task, resulting in final sample sizes of 35 patients and 32 controls.

3. Results

3.1 Sample characteristics

As shown in Table 1, the groups did not significantly differ in sex, age, ethnicity, or marital status. The patients had lower personal education levels than controls but the groups did not differ in parental education, which was the variable intended to control for family socioeconomic status, as opposed to personal education, which can be influenced by the illness itself. The schizophrenia group had a typical age of onset, was chronically ill, and showed mild to moderate levels of clinical symptoms at the time of testing. For antipsychotic medications, patients were taking an average of 305.50 chlorpromazine equivalents.

There were no significant differences on any demographic or clinical variables (all p's > .05) between the subgroups of schizophrenia (n = 16) and control (n = 14) participants included in study 1 versus those participants not in study 1.

3.2 Study 1: Flankers task

3.2.1 Behavioral data—Behavioral measures included both the number of error trials for each subject, as well as accuracy expressed as a percentage. Average reaction time (RT) on error and correct trials were also calculated separately. To reduce the influence of outliers, trials were removed from the analysis of reaction times that were faster than 200 ms or slower than 1200 ms. The number of trials removed for the schizophrenia (14.13 [27.49]) and control (3.50 [10.21]) groups did not significantly differ, $t(28) = .18$, $p > .05$.

Accuracy and RT data are presented in Table 2. An independent samples t-test indicated that the schizophrenia and control groups made a comparable number of errors, $t(28) = -.02$, $p > .05$, and had a comparable % correct, $t(28) = -.01$, $p > .05$. For RT, a 2 (Trial Type) X 2 (Group) mixed model ANOVA revealed a significant Trial Type effect, $F(1,28) = 24.44$, $p < .001$, $\eta_p^2 = .446$, indicating that participants were faster on error than on correct trials. There was also a significant Group effect, $F(1,28) = 10.51$, $p < .005$, $\eta_p^2 = .273$, reflecting the typical finding of generally slower RTs in schizophrenia, but the Trial Type X Group interaction was not significant, $F(1,28) = .05$, $p > .05$, $\eta_p^2 = .002$. Thus, the groups showed similar accuracy levels and patterns of RT differences across trial types.

3.2.2 ERPs—For the ERN, grand average response-locked ERPs are presented in Figure 1 and average ERP values are presented in Table 2. A 2 (Trial Type) X 2 (Group) mixed model ANOVA revealed non-significant effects for Trial Type, $F(1,28) = 1.66$, $p > .05$, $\eta_p^2 = .056$, and Group, $F(1,28) = .43$, $p > .05$, $\eta_p^2 = .179$. However, a significant Trial Type X Group interaction indicated that the difference between the ERN and CRN was smaller in the schizophrenia group than in the control group, $F(1,28) = 6.10$, $p < .05$, $\eta_p^2 = .015$. A post-hoc interaction contrast comparing error minus correct trials (i.e., ΔERN) in the two groups confirmed that patients showed less discrimination between the ERN and CRN than controls, $t(28) = 2.47$, $p < .05$, $d = .90$.

For the Pe, grand average response-locked ERPs are presented in Figure 2 and average ERP values are presented at the bottom of Table 2. A 2 (Trial Type) X 2 (Group) mixed model ANOVA revealed a significant Trial Type effect, $F(1,28) = 39.25$, $p < .001$, $\eta_p^2 = .584$, indicating that the Pe was significantly more positive than the Pc. There were no significant effects for Group, $F(1,28) = .38$, $p > .05$, $\eta_p^2 = .013$, or the Trial Type X Group interaction, $F(1,28) = 1.33$, $p > .05$, $\eta_p^2 = .045$. Consistent with these results, the ΔPe between correct versus error trials did not significantly differ across groups, $t(28) = 1.16$, $p > .05$, $d = .43$. In summary, the ERP data for the Flankers task indicated a smaller ΔERN in the schizophrenia than the control group, but a comparable ΔPe for both groups.

3.3 Study 2: Gambling task

For the FN, grand average response-locked ERPs are presented in Figure 3 and average ERP values are presented in Table 3. A 2 (Trial Type) X 2 (Group) mixed model ANOVA revealed a significant Trial Type effect, indicating that the FN was significantly more negative for non-reward than for reward trials across groups, $F(1,65) = 32.57$, $p < .001$, $\eta_p^2 = .334$. However, both the effect of Group, $F(1,65) = 2.47$, $p > .05$, $\eta_p^2 = .037$, and the Group X Trial Type interaction, $(1,65) = .03$, $p > .05$, $\eta_p^2 = .001$, did not reach significance, indicating that the difference in the FN for reward versus non-reward trials was comparable across groups. Consistent with these results, the ΔFN between reward versus non-reward trials did not differ between groups, $t(65) = .19$, $p > .05$, $d = .05$.[1,2,3]

3.4 Supplemental analyses

Exploratory analyses examined Spearman rank-order correlations between the ΔERN, ΔPe, and ΔFN difference wave scores and BPRS positive, negative, and total symptoms, as well as chlorpromazine equivalents, within the schizophrenia group. We were particularly interested in whether the ΔFN during the gambling task related to individual differences in negative symptoms. Of the nine correlations computed, only one was marginally significant and the direction of the correlation was counter-intuitive. For the gambling task, higher positive symptoms were associated with more negative ΔFN scores (i.e., greater FN differentiation between reward versus non-reward trials), $r = -.35$, $p = .05$. There were no significant or trend-level correlations for negative symptoms. Finally, there were no significant or trend-level correlations between chlorpromazine equivalents and any of the ERP variables (all r's < .20, p's > .10)

4. Discussion

Individuals with schizophrenia showed a reduced ΔERN accompanied by an intact ΔPe, indicating deficient early error monitoring. In contrast, sensitivity to external feedback during a simple gambling task was intact - the ΔFN significantly differentiated feedback indicating monetary reward from non-reward to a comparable degree in patients and controls. It has been suggested that the ΔERN and ΔFN reflect common activity of an error monitoring system that is sensitive to internal and external feedback, respectively (Holroyd & Coles, 2002). Within this context, the differential pattern for the ΔERN and ΔFN suggests that error monitoring is not universally impaired in schizophrenia, and that the processing of external feedback may be relatively unaffected. Taken together, these findings help clarify components of error monitoring and reward processing that are differentially impaired and intact in schizophrenia.

The intact sensitivity to external reward-related feedback (ΔFN) demonstrated by the schizophrenia group is broadly consistent with considerable evidence of normal self-reported and physiological responses to pleasant or rewarding stimuli in this population (Horan *et al.*, 2010, Kring and Moran, 2008). Thus, there is converging evidence that, at a basic level, sensitivity to external reward feedback and pleasurable stimuli is essentially intact in schizophrenia. Interestingly, a similar pattern of normal FN accompanied by impaired ERN was recently reported in adolescents and young adults with autism (Larson et al., in press), a neurodevelopmental disorder that shows significant behavioral, neural, and genetic overlap with schizophrenia (Burbach and van der Zwaag, 2009, Nylander *et al.*, 2008). However, the feedback sensitivity profile shown by our patients differs from some other psychiatric conditions; people with obsessive-compulsive and generalized anxiety

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[1]The pattern of results was similar within the subset of participants who completed then flankers task, indicating a significant Trial Type effect, $F(1,28) = 37.22$, $p < .001$, $\eta_p^2 = .580$, but no significant Group, $F(1,28) = .97$, $p > .05$, $\eta_p^2 = .035$, or interaction, $F(1,28) = .55$, $p > .05$, $\eta_p^2 = .02$, effects.

[2]We performed a similar analysis for the P3 component, defined as mean activity between 350–450 msec at Cz, where the response was maximal. Results indicated no significant effects for Condition, $F(1,65) = .93$, $p > .05$, $\eta_p^2 = .014$, Group, $F(1,65) = 1.72$, $p > .05$, $\eta_p^2 = .026$, or the Condition X Group interaction, $F(1,65) = .02$, $p > .05$, $\eta_p^2 = .001$.

[3]We considered the possibility that group differences in latency jitter accounted for the group differences in ΔERN. We believe this explanation is unlikely primarily because our analyses were based on mean amplitudes. In most cases, any reduction in amplitude associated with latency jitter can be mitigated by using an area amplitude, rather than a peak amplitude, measure (Luck, 2005). Furthermore, the morphometry of the ERN and CRN waveforms appear comparable in the patients and controls (Figure 1), suggesting that the measurement window (100 msec) was sufficiently large to cover the full latency range within each group. Our confidence is bolstered by two additional sets of latency-based analyses for the main ERP variables (ΔERN, ΔPe, and ΔFN). First, we compared the groups on peak latencies. There were no significant differences for any of the ERPs (all t's < 1.20, p's > .05), indicating that there were no peak latency shifts across groups. Second, we compared the groups on mean amplitude (+/− 50 msec) around the peaks identified for each individual subject. The pattern of results was the same as in the primary analyses: the groups differed for ΔERN ($t[28] = 3.47$, $p < .01$) but not for ΔPe or ΔFN (t's < 1.0, p's > .05). Thus, the primary analyses do not appear to be strongly impacted by group differences in latency jitter.

disorders show enhanced ΔERN and diminished ΔFN (Simons, 2010), and diminished ΔFN is also associated with depressive symptoms (Foti and Hajcak, 2009).

Although schizophrenia patients show generally intact sensitivity to simple external reward feedback, the translation of reward information into adaptive, goal-directed behavior involves coordinated activity among several additional reward processing sub-components. As reviewed by Barch and Dowd (2010), in the context of intact hedonic or "liking" responses to rewarding stimuli, people with schizophrenia may experience difficulties integrating reward information in the context of learning, anticipation, and/or decision-making to guide current and future behavior. This framework may help account for a previous report of impaired FN in schizophrenia. Morris et al. (2008) examined FN during a complex probabilistic reward learning task, in which participants were required to learn the correct responses associated with a range of stimuli and were rewarded for accurate performance. Among controls, FN amplitude decreased as stimulus-response pairings were learned, whereas among patients this effect of learning on the FN was attenuated (see (Koch et al., 2010) for comparable findings in an fMRI probabilistic learning task). Differences in the FN results between the current study and Morris et al. may reflect differences in how rewards were delivered and incorporated in the paradigms used in these studies. The current study used a simple gambling task in which reward delivery was random with no additional learning or performance demands. In contrast, rewards were contingent on effective learning and accurate performance under varying reinforcement conditions in Morris et al. Although schizophrenia patients may show intact basic reward liking on tasks with minimal integrative processing demands, impairments may emerge in the context of higher-level reward learning tasks that involve more complex reinforcement contingencies or value computations.

The schizophrenia patients' differential pattern of performance adds to growing evidence that the ERN and the FN do not necessarily reflect functionally identical neural activity related to a general error-detection network (e.g., (Hajcak *et al.*, 2006, Hajcak *et al.*, 2005). Evidence rather consistently indicates that the ERN reflects error monitoring processes subserved by the ACC (Holroyd & Coles, 2002). In contrast, recent evidence suggests that the FN actually reflects increased neural activity to favorable outcomes—a reward-related positivity—and that this response is generated in the striatum (Carlson *et al.*, 2011, Foti *et al.*, in press, Holroyd *et al.*, 2008). This conceptualization of the FN is supported by functional differences between extensive animal and human research linking reward processing to the striatum and medial prefrontal cortex (MPFC; see (Foti et al., in press). The emerging distinction between these ERP components suggests a pattern in which schizophrenia is characterized by impaired error-related activity in the anterior cingulate cortex, but intact reward-related activity in the striatum and MPFC, at least when rewards are presented randomly without additional integrative processing demands. However, differences in the complexity of the ERN and FN tasks used in this study should also be considered when interpreting these findings. For example, the ERN task requires a representation of the actual and intended response whereas the FN task does not require any representation of the response. It could be argued that errors/unfavorable outcomes are simply more obvious and easier for patients to detect in the FN task than the ERN task – an explanation that does not require group differences in distinct neural circuits. Studies that combine ERP and fMRI (e.g., Mathalon et al., 2009) can directly address this issue.

The current study should be interpreted in the context of some limitations. First, patients were taking antipsychotic medications and their effects on feedback and reward processing are uncertain. It is possible that the patients' normal FN reflects medication benefits, as the majority of patients were taking atypical antipsychotics, which have been found to improve some components of reward processing (Juckel *et al.*, 2006a, Juckel *et al.*, 2006b,

Schlagenhauf *et al.*, 2008). Alternatively, the impaired ERN could be a consequence of prolonged exposure to antipsychotics, though evidence that ERN impairment is detectable in children with putative antecedent features of schizophrenia (Laurens et al., 2010) argues against this possibility. If medications did impact performance, they did not have a uniform effect across tasks. Second, our use of the BPRS may have limited our ability to detect an association between negative symptoms and reward processing; the BPRS negative symptom subscale focuses on expressive symptoms (e.g., blunted affect) whereas experience-related symptoms (e.g., avolition, asociality) have a stronger theoretical link to feedback and reward processing (Blanchard *et al.*, in press). Third, the patients were predominantly male and chronically ill, potentially limiting generalizability. Further efforts to specify impaired and intact reward processing subcomponents may help shed light on the underlying causes of the diminished motivation and goal-seeking seen clinically in many people with schizophrenia.

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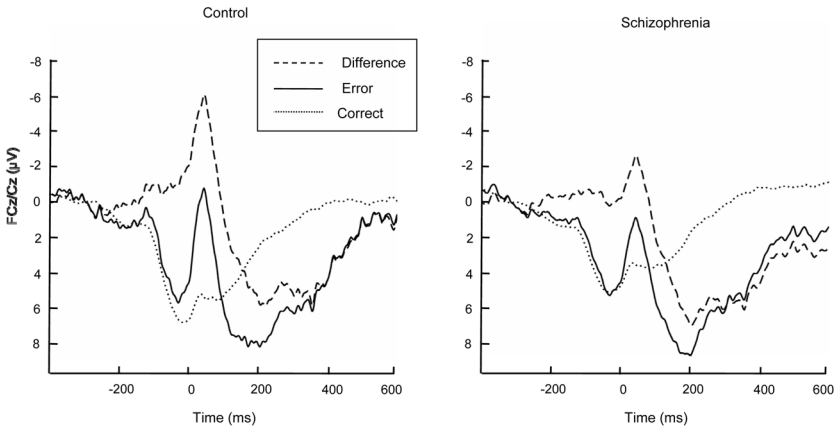

Figure 1.

Flankers task response-locked ERPs at FCz/Cz for error (ERN) and correct (CRN) trials for control (left) and schizophrenia (right) groups, as well as the difference. Response onset occurred at 0 ms and negative is plotted up.

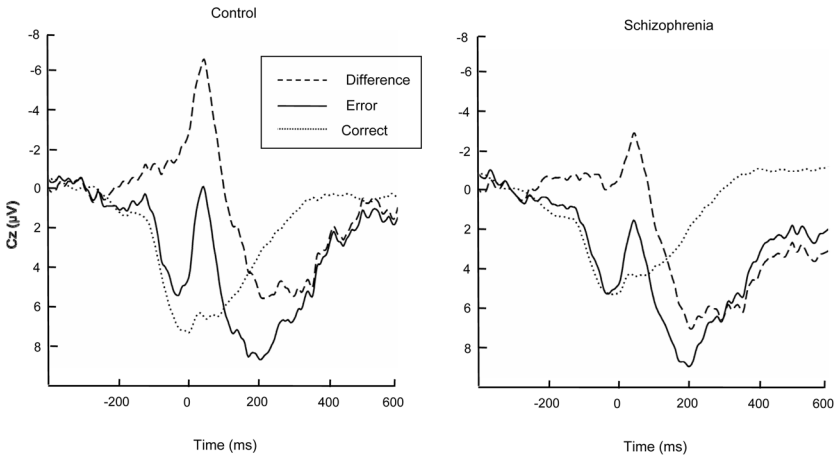

Figure 2.
Flankers task response-locked ERPs at Cz for error (Pe) and correct (Pc) trials for control (left) and schizophrenia (right) groups, as well as the difference. Response onset occurred at 0 ms and negative is plotted up.

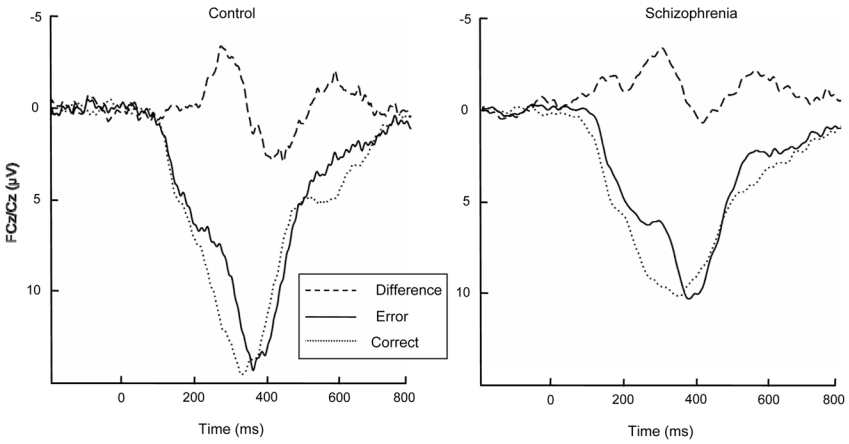

Figure 3.

Gambling task feedback-locked FN at FCz/Cz for non-reward and reward trials for control (left) and schizophrenia (right) groups, as well as the difference. Feedback onset occurred at 0 ms and negative is plotted up.

Table 1

Demographic and Clinical Data

	Schizophrenia (N = 35)	Controls (N = 33)	Statistic
Sex (% male)	74.3	75.8	X^2 (1,68) = .89
Age (SD)	46.9 (7.6)	43.5 (9.3)	t(66) = 1.65
Ethnicity			
White	41.2	45.5	X^2 (1,68) = .89
African American	38.2	36.4	
Asian	8.8	9.1	
Hispanic	11.8	3.0	
Other	0.0	6.1	
Marital status			
Never married	60.0	66.7	X^2 (2,68) = 4.85
Currently married	5.7	18.2	
Ever married	34.3	15.2	
Education (SD)	13.1 (1.5)	14.6 (1.6)	t(66) = 4.01***
Parental education (SD)	14.1 (3.4)	14.8 (2.6)	t(66) = .96
Age of onset (SD)	21.6 (5.5)		
Duration of illness (SD)	25.3 (8.6)		
Chlorpromazine equivalent units	305.50 (189.2)		
BPRS			
Positive symptoms (SD)	2.1 (0.8)		
Negative symptoms (SD)	1.7 (0.9)		
Total (SD)	41.6 (10.5)		

Notes: BPRS = Brief Psychiatric Rating Scale;

*** $p < .001$.

Table 2

Behavioral and ERP Data for the Flankers Task

	Schizophrenia (N = 16)	**Controls (N = 14)**
Accuracy		
No. of errors	28.06 (21.24)	28.21 (16.66)
% correct	90.96 (.08)	90.96 (.05)
Reaction time		
Error trials	452.34 (129.77)	340.30 (37.70)
Correct trials	582.18 (150.53)	459.06 (125.04)
ERPs		
ERN	2.24 (4.49)	2.00 (4.82)
CRN	3.36 (4.15)	5.58 (6.05)
ΔERN	−1.13 (3.91)	−3.59 (6.41)
Pe	7.44 (7.57)	7.55 (8.05)
Pc	−0.13 (2.33)	2.33 (5.47)
ΔPe	7.57 (6.32)	5.22 (4.57)

Table 3

ERP Data for the Gambling Task

	Schizophrenia (N = 35)	**Controls (N = 33)**
FN (Non-reward)	7.26 (6.10)	9.55 (5.42)
FN (Reward)	10.19 (7.38)	12.69 (7.27)
Δ FN	−2.93 (4.29)	−3.13 (4.41)