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Learning-related changes in brain activity following errors and performance feedback in schizophrenia

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Abstract

In previous studies of self-monitoring in schizophrenia, patients have exhibited reductions in the amplitude of the error-related negativity (ERN), a component of the event-related brain potential (ERP) elicited most prominently immediately following the execution of incorrect responses. In the current study, we examined the ERN and a related component, the feedback negativity (FBN) in 26 schizophrenia outpatients and 27 psychiatrically healthy comparison subjects during a probabilistic learning task in which participants could learn stimulus–response pairs by attending to feedback indicating response accuracy. The validity of the feedback varied in three conditions. In one condition, accuracy feedback was entirely consistent (i.e., a left response to one of the stimuli in this condition was always correct and a right response was always incorrect). In the second condition, feedback was valid on only 80% of the trials, and in the third condition, accuracy feedback was random. Changes in ERP amplitudes accompanying learning of stimulus–response pairs were examined. Schizophrenia patients exhibited reduced ERN amplitude compared to healthy subjects in all conditions. This finding extends the previously reported impairment to include disruption of self-monitoring on a task in which participants learn stimulus–response mappings by trial and error, rather than being told the mappings explicitly. Schizophrenia patients also exhibited reduced FBN amplitude compared to healthy subjects in the 100% condition during early trials when the feedback was essential for accurate performance. These findings suggest that reward-related brain activity is weakened in schizophrenia, perhaps reflecting diminished sensitivity to whether ongoing events are better or worse than expected.

Keywords: Schizophrenia; Event-related potentials; Error-related negativity; Feedback negativity; Learning

1. Introduction

Prior studies have examined schizophrenia patients' ability to evaluate the adequacy of their actions in response to environmental demands by studying the error-related negativity (ERN, or error negativity, Ne). The ERN (or, more generally, the response negativity, or RN) is a medial-frontally distributed component of the event-related brain potential (ERP) that is related to performance

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monitoring. It is elicited most prominently approximately 60–100 ms after subjects execute erroneous responses in choice response time tasks (Falkenstein, 1990; Gehring et al., 1993) and appears to have its source in the anterior cingulate cortex (ACC; Dehaene et al., 1994; Gehring and Willoughby, 2002; Holroyd et al., 1998, 2004), an area that is sensitive to reward and error information (Amador et al., 2000; Shidara and Richmond, 2002) and is involved in the neuropathology of schizophrenia (Benes et al., 1987, 1991). A related ERP component, the feedback negativity (FBN), is observed when participants receive feedback about erroneous responding or poor outcomes and has also been localized to the ACC (Gehring and Willoughby, 2002; Miltner et al., 1997; Ruchsow et al., 2002).

Schizophrenia patients exhibit diminished ERN amplitude relative to healthy subjects in a variety of experimental tasks, including Erikson-type flanker tasks (Kopp and Rist, 1999; Morris et al., 2006), Stroop color–word naming (Alain et al., 2002), go/no–go (Bates et al., 2002, 2004) and picture–word naming (Mathalon et al., 2002). This deficit in the generation of the ERN does not appear to be due to group differences in response accuracy since it is present regardless of whether patients and controls differ in accuracy rates. Furthermore, ERN amplitude reduction in schizophrenia does not appear to reflect generalized diminishment of response-related brain activity because schizophrenia patients exhibit *enhanced* RN amplitude compared to controls following correct responses in some studies (Alain et al., 2002; Mathalon et al., 2002; Morris et al., 2006, but see Bates et al., 2002, 2004).

In the current study, we examined the RN and FBN in schizophrenia patients and healthy comparison subjects during a probabilistic learning task in which stimulus–response pairs were learned by the use of feedback following each response. This represents an extension of the existing literature in two respects: First, in contrast to previous studies in which response accuracy was determined entirely by stimulus characteristics, participants' judgment of response accuracy in the present study was possible only after they learned the stimulus–response mappings by trial and error. Second, we examined brain activity following feedback indicating the accuracy of the executed response, allowing for a comparison of learning-related changes in both the RN and FBN during performance of a single task.

This work was motivated, in large part, by the dopamine model of reinforcement learning proposed by Holroyd and Coles (2002). According to this model, the RN following errors and the FBN following negative feedback reflect the functioning of a dopamine-mediated reward system in which motor-related neurons in the ACC use signals carried by the DA system for the adaptive modification of behavior (Holroyd and Coles, 2002). This model builds upon findings from studies of transient changes in mesencephalic DA neurons in primates learning to perform simple delayed response tasks (Schultz, 1998, 2002). In primates, after stimulus-reward contingencies are learned, the midbrain DA system becomes active in anticipation of a forthcoming reward and quiescent when an expected reward is not delivered (Schultz et al., 1993). Schultz and colleagues proposed that the phasic increases and decreases in DA cell firing can be understood as coding changes in the prediction of the "goodness" of ongoing events, respectively. Several investigators have noted similarities between the phasic activity of midbrain DA neurons and an error signal associated with a reinforcement learning algorithm called the "Method of Temporal Differences" (see Suri, 2002 for review). In neural network models, temporal difference errors (TDEs) are computed by an "adaptive critic" that attributes a value to ongoing events and outputs an error when it changes its own prediction. Specifically, positive (+) TDEs indicate that ongoing events are "better" than expected, and negative (−) TDEs indicate that ongoing events are "worse" than expected. Like the phasic changes in DA cell activity, TDEs "propagate back in time" from the reward to the conditioned stimulus during learning. This same basic TDE signal may be used as a learning signal by different DA target areas in order to optimize their performance (Schultz et al., 1995).

According to Holroyd and Coles' theory, the RN and FBN are associated with the impact on ACC of phasic decreases, but not increases, in DA activity. Thus, this position holds that the RN and FBN are elicited when the system first determines that an error has occurred, such that a RN is elicited when the error is detected immediately following the response, and an FBN is elicited when the error is detected because of the feedback. In trial-and-error learning tasks participants gradually learn the stimulus–response mappings, which they can then utilize to judge the accuracy of their responses. Concomitantly, the performance feedback becomes redundant, and so this ERP component propagates with learning from the time of feedback presentation (where it is seen as the FBN) to the time of response generation (where it is seen as the RN). Based on previous findings of diminished RN amplitude in schizophrenia and on the relationship between RN and FBN described by Holroyd and Coles (2002), we hypothesized that the amplitude of these components would be reduced and that learning-related changes in

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these components would be smaller in schizophrenia patients compared to healthy comparison subjects.

2. Method

2.1. Participants

Twenty-seven schizophrenia outpatients and twenty-seven healthy comparison subjects participated in the study. Data from one patient were excluded because he failed to respond on more than one third of the trials. Demographic and clinical characteristics of the groups are summarized in Table 1. The groups did not differ in age, $F(1, 51)=.49$, $p=.48$, gender, χ^2 $(1, N=53)=.57$, $p=.45$, or ethnicity, χ^2 $(2, N=53)=1.68$, $p=.43$. Schizophrenia patients had fewer years of education than comparison subjects, $F(1, 51)=8.31$, $p=.006$, but reported greater parental education, $F(1, 51)=5.66$, $p=.02$. Except for one comparison subject, all subjects reported that they were right-handed.

Patient participants were recruited from outpatient psychiatric clinics at the Maryland Psychiatric Research Center and the Baltimore Veterans' Affairs Medical Center. They were diagnosed using a best-estimate approach combining information from medical records, collateral information (when available) and the Structured Clinical Interview for DSM-IV (SCID; First et al., 1994). Twenty-five of the patients were diagnosed with schizophrenia and one was diagnosed with schizoaffective disorder. Patients were medicated with second-generation antipsychotic medication ($n=21$), traditional antipsychotic medication ($n=3$) or both ($n=2$). On the day of testing, symptom ratings were obtained using the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham, 1962) and the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1982).

Healthy comparison subjects were recruited via newspaper advertisements, fliers, or random-digit dialing of local phone numbers. They were assessed with the SCID and had no personal or family history of schizophrenia or schizoaffective disorder, and no personal history of bipolar disorder, major depressive disorder, or alcohol or substance dependence in the last three months. All participants provided written informed consent.

2.2. Experimental task

Subjects performed a probabilistic learning task (Holroyd and Coles, 2002; Nieuwenhuis et al., 2002) in which participants' goal was to learn stimulus–response pairings via feedback. The stimuli were color photographs, presented individually for 500 ms on a video monitor. Responses were button presses made with either the right or left thumb using a hand-held response box. Three feedback probability conditions were included. In the 100% condition, accuracy feedback was entirely consistent (i.e., a left response to one of the stimuli in this condition was always correct and a right response was always incorrect). In the second condition, feedback was consistent on 80% of the trials and reversed on the remaining trials. For example, a left response to a stimulus in this condition was rewarded as a correct response 80% of the time but was penalized as incorrect on the remaining trials. In the third condition, accuracy feedback was random. There were, thus, three classes of stimuli (100%, 80%, and 50%) and eight types of feedback (i.e., correct and incorrect feedback for 100%, 80% valid, 80% invalid, and 50% trials). Two stimuli for each condition were included in each block of trials, such that there was one stimulus from each of the conditions for each hand and a total of six stimuli to be learned during each block. A unique set of six stimuli were presented in random order in each block.

Participants received a bonus of two cents for each correct response, were penalized two cents for each incorrect response, and were penalized four cents for each response that was slower than 1100 ms. This modest time pressure insured that most participants would be able to learn the stimulus–response pairings in the 100% and 80% conditions but would also make a sufficient number of errors due to impulsive responding or lapses in recall. Participants began the task with a one dollar bonus and were told that they could win a bonus of up to $10. Accuracy and bonus/penalty feedback (e.g., "Correct +2 cents") were displayed for 500 ms beginning 1000 ms after each response. Bonus/penalty amounts for each block and cumulative bonus/penalty amounts were displayed following each block of trials. Participants completed 60 practice trials followed by 4 blocks of 300 trials each.

2.3. Psychophysiological recording, data reduction and analyses

Electroencephalography (EEG) recordings were obtained using 32 Ag/AgCl electrodes in International 10/20 system positions. Electrooculographic activity was recorded from electrodes placed above and below the left eye and at the outer edge of both eyes. EEG and EOG were recorded using Synamps amplifiers and Scan 4.3 software (Compumedics/Neuroscan, El Paso, TX). Scalp EEG data were recorded at a rate of 500 Hz with an online 100 Hz low-pass filter and referenced to linked earlobe electrodes. For each response and feedback

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Table 1
Demographic and clinical status data for schizophrenia patients and healthy comparison participants

	Comparison participants		Schizophrenia patients	
	M	SD	*M*	SD
Age (years)	43.3	11.3	45.0	6.3
Education (years) [a]	15.2	3.0	12.9	2.9
Parent's highest education (years) [b]	13.0	3.2	15.3 [c]	3.7
Gender				
Male	16		18	
Female	11		8	
Ethnicity				
European American	18		14	
African American	9		11	
Asian American			1	
BPRS 20-item total score			37.0	10.5
SANS 22-item total score			33.1	17.6

Note: BPRS = Brief Psychiatric Rating Scale; SANS = Scale for the Assessment of Negative Symptoms.
[a] Group difference $p=.006$.
[b] Group difference $p=.02$.
[c] $n=24$.

stimulus, an epoch beginning 200 ms before the event was created. Vertical and horizontal eye movement artifacts were corrected offline (Gratton et al., 1983; Miller et al., 1988). A 1–10 Hz 24 dB filter was applied and a 100 ms baseline was subtracted from each epoch.

A threshold of three consecutive correct responses to both items in a probability condition was used to classify each trial as "pre-" or "post-learning." For example, all trials occurring up until the point at which the participant responded correctly on three consecutive presentations of both 100% stimuli in a block were identified as "pre-learning" and all remaining trials in that probability condition were considered to be "post-learning." Using trials from all four blocks, response and feedback averages for correct and incorrect trials in each probability condition were computed separately for trials before and after this threshold was met. In the 50% condition, trials from the first half of the block were included in the "pre-learning" averages and trials from the second half of the block were included in the "post-learning" averages and response-locked epochs were sorted according to the type of feedback received on the trial.

Response- and feedback-related negativities were quantified at Fz, FCz, Cz, CPz, and Pz electrode sites using the following steps: For RN and FBN separately, the condition in which the negativity was maximal was determined by visual examination of the group average waveforms. For both groups, the FBN was maximal following error feedback in the 80% invalid post-learning condition. The RN was largest following erroneous responses in the 100% post-learning condition for controls and following errors in the 80% post-learning waveform for schizophrenia patients. Both the RN and FBN were maximal at FCz for both groups in these conditions. The latency of the RN and FBN were then determined for these conditions for each participant individually by identifying the most negative peak occurring within 140 ms after the response and between 200 and 400 ms following the feedback in the FCz channel. Finally, for each of the five electrodes, the mean amplitude in a 50-ms period centered on each participant's latency was computed for each average.

Mixed-model analysis of variance (ANOVA) was used to compare the effects of probability condition, accuracy, and learning in the two groups. The Greenhouse–Geisser adjustment for repeated measures was used and an alpha level of .05 was adopted. Corrected F, p and effect size (partial eta squared, or η^2_p) values and uncorrected degrees of freedom are reported. Simple-effects ANOVAs

Table 2
Behavioral data

Probability condition		Percent correct		Trials to criterion [a]		Response time (ms)			Percentage of missed RT deadline trials [b]		
		80%	100%	80%	100%	50%	80%	100%	50%	80%	100%
Comparison subjects	Mean	70.8	82.5	26.1	14.5	572.9	562.1	555.2	3.4	2.9	2.0
	SD	9.3	10.1	7.0	5.0	80.8	70.9	75.9	3.3	3.3	2.2
Schizophrenia patients	Mean	71.0	77.6	24.2	18.5	614.2	603.6	594.1	6.8	5.1	4.4
	SD	12.7	15.0	6.9	6.6	91.8	85.9	80.1	5.0	3.9	3.7
t value		.05	−1.41	−1.00	2.50	1.74	1.92	1.81	2.89	2.16	2.95
P value		.96	.17	.32	.02	.09	.06	.08	.006	.04	.005

SD: Standard deviation.
[a] Computed as the percentage of the total number of trials of the condition completed before learning threshold (defined in the text) was achieved. Trials on which no response occurred within the RT limit were omitted from threshold determinations.
[b] Includes trials in which a response occurred after the 1100 ms deadline and trials on which there was no response.

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with the Bonferroni correction were used for post-hoc comparisons on between-group measures. Spearman's rho (ρ) was used for correlational analyses.

3. Results

3.1. Behavioral data

Behavioral data are presented in Table 2. Schizophrenia patients and comparison subjects had equivalent accuracy rates in the 80% condition, $F(1, 51)=.003$, $p=.96$, but comparison subjects were somewhat more accurate than patients in the 100% condition, $F(1, 51)=1.98$, $p=.17$; Group × Probability condition interaction, $F(1, 51)=7.14$, $p=.01$, $\eta^2_p=.12$. Schizophrenia patients took more trials than comparison subjects to reach criterion in the 100% condition, $F(1, 51)=6.28$, $p=.015$, but not in the 80% condition, $F(1, 51)=1.00$, $p=.32$; Group × Probability condition interaction, $F(1, 51)=9.52$, $p=.003$, $\eta^2_p=.16$. Schizophrenia patients missed the RT deadline on more trials, $F(1, 51)=6.49$, $p=.01$, $\eta^2_p=.12$, and tended to respond more slowly overall, $F(1, 51)=3.40$, $p=.07$, $\eta^2_p=.06$, compared to control subjects.

3.2. ERP data

3.2.1. Response negativity

The hypothesis that schizophrenia patients would fail to exhibit normal learning-related potentiation of the RN was tested by comparing RN amplitude following correct and incorrect responses occurring before and after the learning threshold in the 80% and 100% conditions. Valid and invalid trials in the 80% condition were combined for these analyses since these two types of trials are indistinguishable at the time the response is made, and RN data from the 50% condition was not included because accuracy was random in this condition. This four-way interaction (Group × Probability condition × Accuracy × Learning) was significant, $F(1, 51)=10.63$, $p=.002$, $\eta^2_p=.17$ (Figs. 1 and 2). In the 100% condition, comparison subjects showed the expected pattern of larger RN amplitude following errors in the post-learning trials than in the pre-learning trials, $F(1, 26)=15.16$, $p=.001$, $\eta^2_p=.37$, but patients did not show this learning-related change, $F(1, 25)=1.25$, $p=.28$; Group × Accuracy × Learning interaction, $F(1, 51)=11.74$, $p=.001$, $\eta^2_p=.19$. Consistent with previous reports of diminished ERN amplitude in schizophrenia, the RN following errors in the 100% condition was reduced in schizophrenia patients compared to healthy subjects in post-learning trials, $F(1, 51)=14.55$, $p=.001$, $\eta^2_p=.22$. Larger RN amplitudes following errors after learning were correlated with higher accuracy rates in this condition in the healthy subjects, $\rho(27)=-.57$, $p=.002$, but not in schizophrenia patients, $\rho(26)=.14$, $p=.48$.

As expected, learning-related changes in RN amplitude were less pronounced in the 80% condition. There was a marginal Accuracy × Learning interaction, $F(1, 51)=3.75$, $p=.06$, $\eta^2_p=.07$. Response negativity following errors increased from early to later trials, $F(1, 51)=6.28$, $p=.015$, $\eta^2_p=.11$, and no learning-related changes occurred in the RN following correct responses, $F(1, 51)=0.02$, $p=.89$. In this condition, comparison subjects exhibited larger RN than schizophrenia patients following errors, $F(1, 51)=6.13$, $p=.02$, $\eta^2_p=.11$, and correct responses, $F(1, 51)=5.33$, $p=.03$, $\eta^2_p=.10$. Larger post-learning RN amplitude following errors was associated with greater accuracy in healthy subjects, $\rho(27)=-.46$, $p=.02$, and modestly related in schizophrenia patients, $\rho(26)=-.37$, $p=.06$.

In the 50% condition, patients exhibited a diminished RN compared to controls, $F(1, 51)=7.34$, $p=.009$, $\eta^2_p=.13$.

3.2.2. Feedback negativity

To test the hypothesis that the generation of the FBN would be disrupted in schizophrenia, FBN following correct and incorrect feedback was compared in the four FB probability conditions for the two groups. A Group × Probability condition (50%, 80% invalid, 80% valid, 100%) × Feedback type (Correct, Incorrect) × Learning (pre-threshold, post-threshold) mixed-model ANOVA revealed an interaction between probability condition, feedback type and learning, $F(3, 153)=6.65$, $p=.001$, $\eta^2_p=.12$ (Figs. 3 and 4). Because it is likely that the sample size yielded insufficient power to detect the complex 4-way interaction, we examined each probability condition separately. In the 100% condition, a Group × Feedback type × Learning interaction, $F(1, 51)=9.10$, $p=.004$, $\eta^2_p=.15$, was present. In healthy subjects, a large Feedback type × Learning interaction was present, $F(1, 26)=35.86$, $p<.001$, $\eta^2_p=.58$, characterized by the expected decrease in amplitude following error feedback as learning progressed, $F(1, 26)=12.03$, $p=.002$, $\eta^2_p=.32$, and an unexpected increase in FBN following correct feedback in later compared to earlier trials, $F(1, 26)=34.09$, $p<.001$, $\eta^2_p=.57$. It appears that this increase was due to component overlap involving the positivity following the FBN. A broad, posterior-maximal positivity was prominent following correct feedback in early trials and following error feedback, but was reduced following correct feedback in later trials. The interaction of

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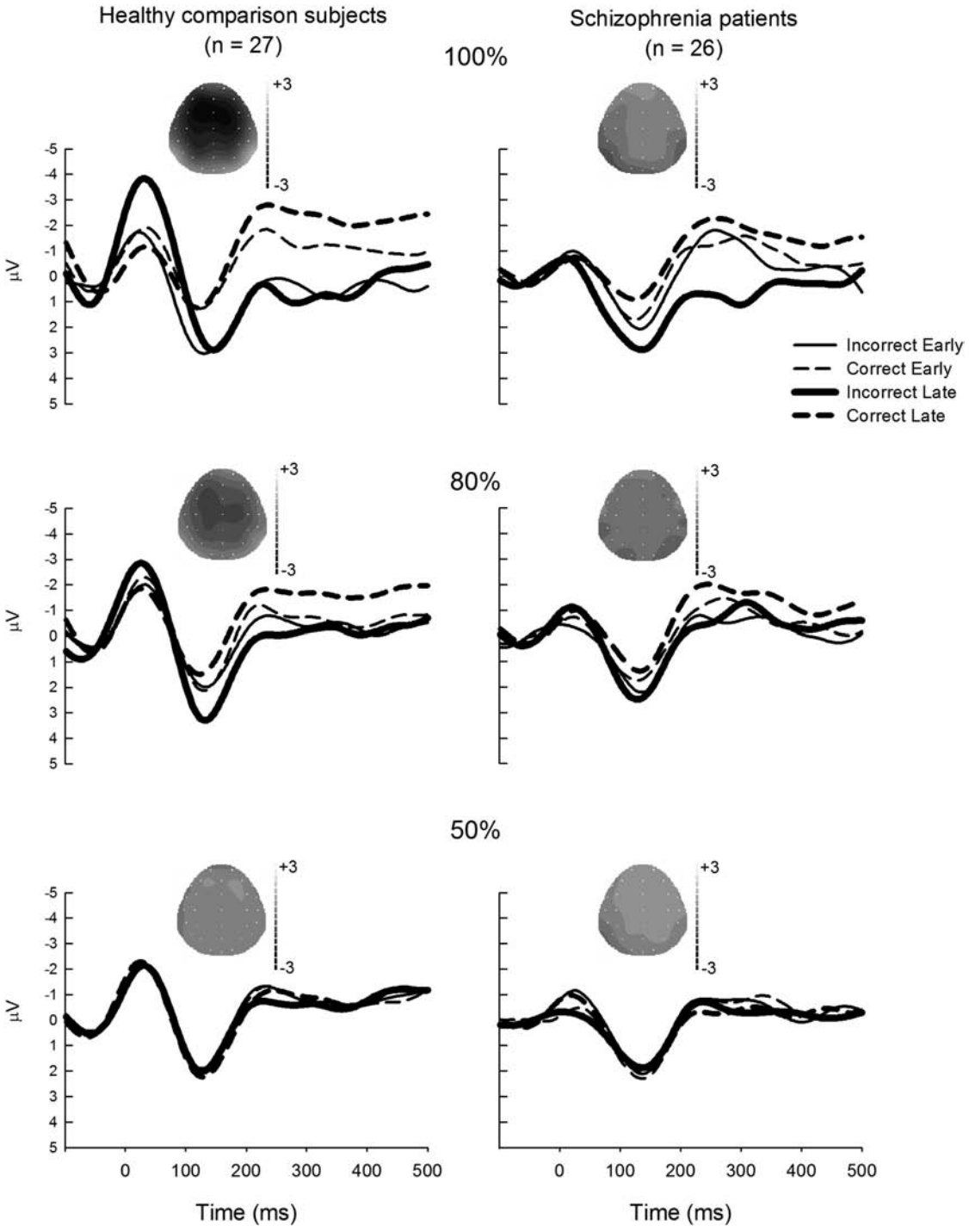

Fig. 1. Response-locked waveforms for correct and incorrect responses occurring before ("early") and after ("late") the behavioral learning threshold was met. Data shown in waveforms are from FCz channel. Incorrect–correct difference activity on post-learning trials at the latency of peak RN activity is shown on topographical maps.

feedback type and learning was also present for schizophrenia patients in the 100% probability condition, although to a reduced degree, $F(1, 25)=5.85$, $p=.02$, $\eta^2_p=.19$. Comparing patients' FBN following correct and incorrect feedback separately, there were no effects of learning for either type of feedback ($p=.19$

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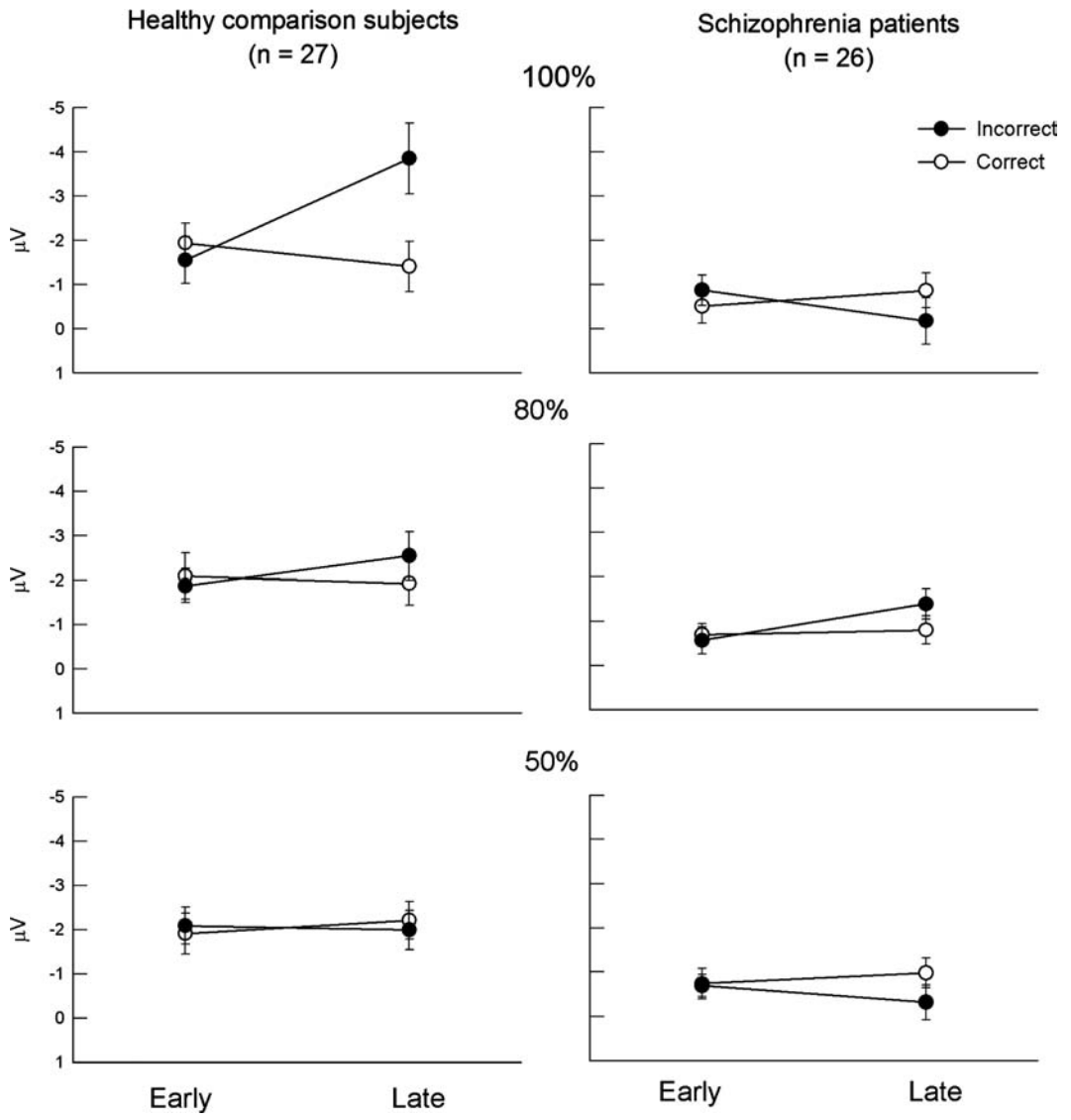

Fig. 2. Mean RN amplitude for correct and incorrect responses occurring before ("early") and after ("late") the behavioral learning threshold was met. Data shown are from FCz channel. Error bars indicate standard error.

and .17 respectively). The amplitude of the FBN following error feedback in early trials was reduced in schizophrenia patients compared to control subjects, $F(1, 51)=6.02$, $p=.02$, $\eta^2_p=.10$[2].

FBN amplitude was larger following error feedback compared to correct feedback in the 50%, $F(1, 51)=61.10$, $p<.001$, $\eta^2_p=.54$, 80% valid, $F(1, 51)=12.24$, $p<.01$, $\eta^2_p=.54$, and 80% invalid, $F(1, 51)=72.88$, $p<.001$, $\eta^2_p=.59$, conditions. In both the 80% invalid condition, $F(1, 51)=2.89$, $p=.09$, $\eta^2_p=.05$, and the 50% condition, $F(1, 51)=3.96$, $p=.05$, $\eta^2_p=.07$, schizophrenia patients tended to have a reduced FBN following error feedback in later trials compared to comparison subjects. FBN amplitude was larger following invalid error feedback than valid error feedback both before, $F(1, 51)=12.06$, $p=.001$, $\eta^2_p=.19$, and after, $F(1, 51)=23.61$, $p=.001$, $\eta^2_p=.32$, the learning threshold.

Larger FBN amplitude in post-learning trials in the 80% invalid condition was associated with improved

[2] To examine whether diminished sensory processing might contribute to diminished RN and FBN amplitude, N170 following the imperative stimulus and the FB was analyzed. Schizophrenia patients had diminished N170 amplitude compared to healthy comparison subjects at P3/P4 electrodes, but N170 amplitude was generally uncorrelated or negatively correlated with the amplitude of the corresponding RN or FBN.

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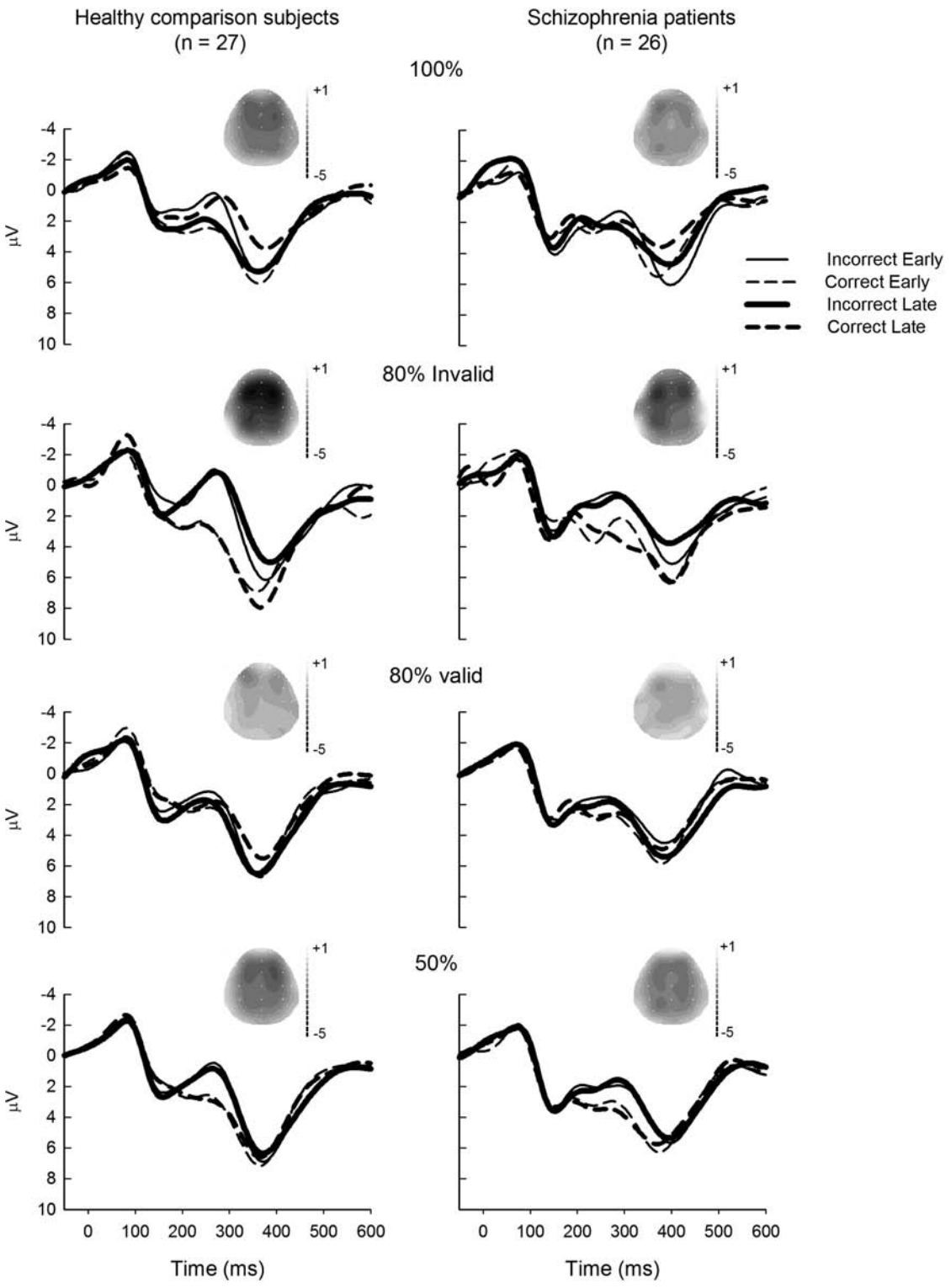

Fig. 3. Feedback-locked waveforms for correct and incorrect feedback occurring before ("early") and after ("late") the behavioral learning threshold was met. Data shown in waveforms are from FCz channel. Incorrect–correct difference activity on pre-learning trials at the latency of peak FBN activity is shown on topographical maps.

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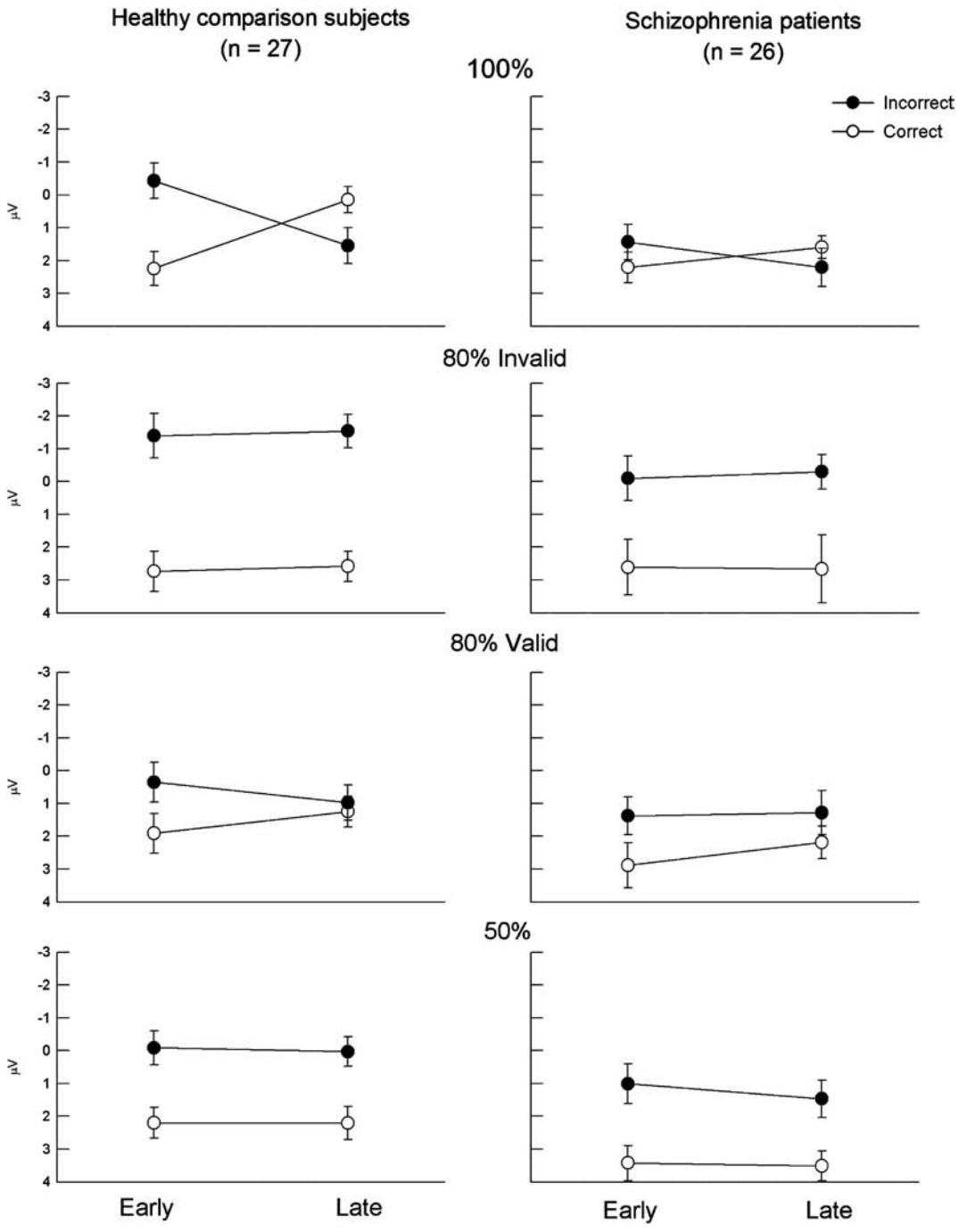

Fig. 4. Mean FBN amplitude for correct and incorrect feedback occurring before ("early") and after ("late") the behavioral learning threshold was met. Data shown are from FCz channel. Error bars indicate standard error.

accuracy on 80% trials in healthy subjects, $\rho(27)=-.46$, $p=.02$, but not in schizophrenia patients, $\rho(26)=-.29$, $p=.16$, suggesting that detection of violations of reward expectation was related to the likelihood that healthy subjects emitted the dominant response in this condition.

3.2.3. ERP/symptom relationships

Exploratory analyses of the relationships between symptom ratings and ERP measures revealed an intriguing pattern of selective correlations in which more severe reality distortion symptoms were associated

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Table 3
Correlations between symptom ratings and ERP amplitudes

		Reality distortion [a]	Negative symptoms [b]	SANS total
Response negativity	100% post-learning	.35*	.02	.14
	80% post-learning	.43**	−.03	.03
Feedback negativity	100% pre-learning	.16	.42**	.34*
	80% invalid pre-learning	.15	.42**	.33*
	80% invalid post-learning	.09	.33*	.40**
	80% valid post-learning	.13	.39*	.24
	50% post-learning	.10	.34*	.41**

**$p<.05$ (two tailed); *$p<.1$ (two tailed).
BPRS: Brief Psychiatric Rating Scale.
SANS: Scale for the Assessment of Negative Symptoms.
Note: Positive coefficients indicate that higher/more severe symptom ratings are associated with smaller/less negative ERP amplitude.
[a] Sum of BPRS ratings on suspiciousness, hallucinations, unusual thought content, and grandiosity items (range 4–17).
[b] Sum of BPRS ratings on blunted affect, emotional withdrawal, and motor retardation items (range 3–20).

with reduced RN amplitudes and more severe negative symptoms were associated with diminished FBN magnitude (see Table 3).

4. Discussion

The amplitude of the RN was diminished in patients compared to controls when response accuracy was most certain (i.e., following errors on post-learning trials in the 100% probability condition), replicating previous reports and extending this finding to a task in which knowledge about response accuracy was developed via experience and feedback rather than determined solely by characteristics of the stimuli. Schizophrenia patients' RN was also diminished when response accuracy was difficult or impossible to determine (i.e., in the 80% and 50% conditions following correct and incorrect responses), suggesting that healthy subjects generate a stronger reward prediction error signal than schizophrenia patients when uncertain about the adequacy of their responding.

The second goal of this study was to determine whether there is a concomitant reduction in FBN in schizophrenia. Impaired generation of FBN was most prominent in the 100% probability condition, in which schizophrenia patients generated only a small FBN following error feedback on early trials that remained unchanged in later trials. To our knowledge, this is the first evidence of disruption of the generation of the FBN in schizophrenia patients. Further, the FBN failed to propagate to the RN in schizophrenia patients as learning of the picture–response pairs took place. This pattern of findings is especially noteworthy given that this is the condition in which the feedback was entirely unambiguous, learning was most rapid, and learning-related changes in RN and FBN were most robust in healthy subjects. Healthy participants learned the pairings in fewer trials than schizophrenia patients and exhibited a strong correlation between response-related brain activity and response accuracy. Response negativity amplitude and behavior were not correlated in the schizophrenia patients, suggesting a decoupling of brain activity from behavior that might have contributed to their diminished performance in this condition.

In the other probability conditions, the group differences in FBN were less robust, but a pattern of diminished amplitude in schizophrenia patients was consistent. Considered in the framework of the reinforcement learning model of the ERN (Holroyd and Coles, 2002), it appears that the reward prediction error signal in schizophrenia patients is weakened, reflecting diminished sensitivity to whether ongoing events are better or worse than expected. The diminished amplitude of the FBN and its relative insensitivity to the valence of feedback may reflect various possible alterations in the functioning of the phasic DA system. For example, it may be that in schizophrenia patients, the modulation of phasic DA activity according to the valence of outcomes is weakened. That is, possibly due to cytoarchitectural abnormalities in the ACC, the magnitude of the error signal is diminished and thus the differences in FNB associated with positive and negative outcomes are minimized. An alternative possibility is that the magnitude of the TDE occurring on individual trials is intact but that modulation of the signal is imprecise or non-specific, such that a combination of (+) TDEs and (−) TDEs are elicited by both positive and negative outcomes, resulting in diminished overall amplitude and lack of modulation according to valence. This weakening of the error signal following feedback appears to disrupt the propagation of the signal to the time of the response, resulting in more uniformly diminished response-related activity, perhaps reflecting a preponderance of (+) TDE signals generated by schizophrenia patients when they are uncertain about the accuracy of their responding.

The absence of learning-related changes in the FBN following error feedback in the 80% invalid condition was unexpected given previous findings of increased FBN following unexpected error feedback on trials occurring later in the sequence (Nieuwenhuis et al., 2002). We

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suggest that this absence of an effect may be due to rapid learning by participants of the S–R pairings, as evidenced by the difference in FBN amplitude following valid and invalid error feedback even on early trials. Unfortunately, there were not a sufficient number of trial blocks to allow a more fine-grained sorting of these relatively infrequent early invalid trials.

It is possible that the effects of antipsychotic medications on phasic DA activity may have contributed to the abnormalities observed in the RN and FBN in schizophrenia patients. Evidence for this type of effect of antipsychotic medication is mixed. Acute administration of haloperidol (de Bruijn et al., 2006; Zirnheld et al., 2004) and olanzapine (de Bruijn et al., 2006) to healthy participants diminishes ERN amplitude, but Kopp and Rist (1999) found medication dose to be unrelated to ERN amplitude in schizophrenia patients, and Bates et al. (2004) found that patients' ERNs increased in amplitude following hospital admission and clinical stabilization. Similarly, ACC activity increased in medication-naïve schizophrenia patients tested after treatment with antipsychotic medication (Snitz et al., 2005). The participants in the current study were medicated with several different first and second generation antipsychotic medications (and combinations of these), thus there was an insufficient sample size to detect relationships between dose/type of medication and RN/FBN amplitude. Regardless, most schizophrenia patients are treated with antipsychotic medications for years at a time, thus it remains important to understand their neurocognitive functioning while medicated.

The relationship between reality distortion symptoms and RN amplitude is inconsistent with previous work finding no such relationship (Alain et al., 2002; Bates et al., 2002) but is consistent with the theorized link between psychotic symptoms and failures in self-monitoring (Frith, 1987). The finding of correlations between negative symptoms (as measured by the BPRS and the SANS) and FBN in several of the experimental conditions is novel and suggests that these symptoms stem from diminished sensitivity to environmental contingencies.

In conclusion, these data extend the finding of reduced RN in schizophrenia patients to include responses for which accuracy judgments are based on learning and experience, and demonstrate provocative evidence of disruption of the FBN, especially in patients with negative symptoms. It will be important, in future work, to determine whether antipsychotic medications contribute to this disruption or whether abnormalities in FBN persist despite the dopaminergic effects of medication so that the viability of FBN as a marker of medication response could be investigated. Also, further study of reward-related brain activity in a rehabilitation setting could inform the development of interventions that engage this system and maximize therapeutic benefit.

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Contributors

S. Morris implemented the study procedures, assisted with and supervised data collection and processing, analyzed the ERP data and drafted the manuscript. E. Heerey assisted with subject recruitment, data collection and processing, and analyzed the behavioral data. J. Gold supervised subject recruitment, provided guidance for analysis and interpretation of data. C. Holroyd provided guidance for the implementation of the study procedures and assisted with the interpretation of the data. All authors contributed to and have approved the final manuscript.

Conflicts of interest

All other authors declare that they have no conflicts of interest.

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