Archival Report

Biological Psychiatry: CNNI

Probabilistic Reinforcement Learning in Patients With Schizophrenia: Relationships to Anhedonia and Avolition

Erin C. Dowd, Michael J. Frank, Anne Collins, James M. Gold, and Deanna M. Barch

ABSTRACT

BACKGROUND: Anhedonia (a reduced experience of pleasure) and avolition (a reduction in goal-directed activity) are common features of patients with schizophrenia that have substantial effects on functional outcome but are poorly understood and treated. We examined whether alterations in reinforcement learning may contribute to these symptoms in patients with schizophrenia by impairing the translation of reward information into goal-directed action.

METHODS: Thirty-eight stable outpatients with schizophrenia or schizoaffective disorder and 37 healthy control subjects underwent functional magnetic resonance imaging scans during a probabilistic stimulus selection reinforcement learning task with dissociated choice- and feedback-related activation, followed by a behavioral transfer task allowing separate assessment of learning from positive versus negative outcomes. A *Q*-learning algorithm was used to examine functional activation relating to prediction error at the time of feedback and to expected value at the time of choice.

RESULTS: Behavioral results suggested a reduction in learning from positive feedback in patients; however, this reduction was unrelated to anhedonia/avolition severity. On analysis of the functional magnetic resonance imaging scans, prediction error–related activation at the time of feedback was highly similar between patients and control subjects. During early learning, patients activated regions in the cognitive control network to a lesser extent than control subjects. Correlation analyses revealed reduced responses to positive feedback in dorsolateral prefrontal cortex and caudate among those patients higher in anhedonia/avolition.

CONCLUSIONS: These results suggest that anhedonia/avolition are as strongly related to cortical learning or higher-level processes involved in goal-directed behavior, such as effort computation and planning, as to striatally mediated learning mechanisms.

Keywords: Anhedonia, Motivation, Prediction error, Reinforcement learning, Schizophrenia, Striatum

http://dx.doi.org/10.1016/j.bpsc.2016.05.005

Negative symptoms are major contributors to disability and poor quality of life among individuals with schizophrenia but are poorly understood and treated (1,2). Anhedonia (a reduced ability to experience pleasure) and avolition (a reduced motivation to initiate or persist in goal-directed activity) together comprise a dissociable factor of negative symptomatology (3) that has garnered increasing attention for a possible association with abnormalities in reward processing. In previous work, we described several processes required for the translation of reward information into goal-directed behavior; any disruption of these processes could lead to anhedonia or avolition (4). The work described here examines one of these processes, reinforcement learning (RL), and its relationship to anhedonia and avolition in patients with schizophrenia.

Numerous behavioral studies have suggested that RL is intact in patients with schizophrenia when learning is fairly implicit [although Siegert *et al.* (5) found evidence of impaired serial reaction time task learning] but more impaired when learning tasks require explicit representations of stimulus–reward contingencies (4,6). This pattern has given rise to the theory that the striatally mediated gradual RL system may be intact in patients with schizophrenia while more rapid, on-line, cortically mediated learning systems are impaired (6,7). Support for this theory is drawn from probabilistic reversal learning studies that show intact acquisition of probabilistic reward contingencies (which are thought to be striatally mediated) coupled with impaired reversal learning (which is thought to be cortically mediated) (8,9). Similarly, several studies using the weather prediction task have shown a relatively intact learning rate but impaired asymptotic performance, which provides mixed evidence for striatal learning impairments (7,10–12). However, a study with a larger sample size found lower learning rates in patients with schizophrenia than control subjects, suggesting possible impairments in striatally mediated learning (13). The behavioral literature therefore provides a mixed picture on whether striatally mediated learning is intact in patients with schizophrenia.

Another approach to studying RL is to ask whether the pattern of functional activation in regions receiving dopaminergic projections is consistent with a prediction error (PE)

signal. PEs are thought to be coded by dopaminergic projections to the basal ganglia, which signal the difference between predicted and received rewards and drive learning by iteratively updating reward predictions (14). In the schizophrenia literature, this approach has revealed some evidence for altered striatal PE activity among patients with schizophrenia using both Pavlovian and instrumental reward-learning tasks and for both monetary and liquid rewards (15–18), with some suggestion that positive PEs may be more affected than negative PEs (19,20) and some suggestion that the effects may be more apparent in nonmedicated (21) compared with medicated patients.

The findings reviewed above suggest the hypothesis that impairments in learning from positive outcomes related to reductions in striatal signaling of positive PEs or impaired cortical learning systems may contribute to motivational deficits in patients with schizophrenia. We tested these hypotheses by examining brain activity during a probabilistic RL paradigm, allowing examination of activation during both choice execution and feedback and the separate assessment of learning from positive versus negative outcomes. We used a model of the role of dopamine in RL proposed by Frank *et al.* (22–24), which emphasizes the separate contributions of D_1 and D_2 receptors in the striatum to "Go" and "NoGo" learning, respectively. Two previous studies have used this framework to examine Go learning (i.e., learning from rewarding outcomes) and NoGo learning (i.e., learning from nonrewarding outcomes) in medicated patients with schizophrenia, and found evidence of impaired Go learning but intact NoGo learning (25,26)—although one other study found impairments in both Go and NoGo learning (27). These findings are consistent with the hypothesis that the effectiveness of phasic dopamine signals in response to positive feedback is reduced in patients with schizophrenia, thereby impairing Go learning. These studies also examined the relationship between negative symptoms and RL impairments and showed correlations between negative symptom severity and measures of rapid explicit learning, suggesting a role for deficits in cortical learning systems in negative symptomatology. In addition, in a modeling study by Gold *et al.* (28), the behavior of patients with high negative symptoms was best captured by a computational model of striatal learning only, while a model with both striatal and cortical components best captured the behavior of patients lower in negative symptoms.

METHODS AND MATERIALS

Participants

Study participants included 49 stable outpatients with schizophrenia or schizoaffective disorder as defined by the DSM-IV and 41 healthy control subjects with no personal or family history of psychosis. Both medicated and nonmedicated patients were recruited from the community, and medication status and dose was required to have been stable for at least 2 weeks. Participants were group matched on sex, age, race, parental education, handedness (29), and smoking status. Inclusion criteria included 1) patients 18 to 50 years of age and 2) the ability to give informed consent. Exclusions can be found in the Supplement and include patients who had been diagnosed with major depressive disorder or dysthymia in the past year as defined by the DSM-IV. Ten individuals with schizophrenia and four healthy control subjects were excluded for excessive movement (described below), and an additional patient was excluded for having >50% nonresponse trials, yielding a final sample size of 37 control subjects and 38 patients (29 patients with schizophrenia and nine patients with schizoaffective disorder). All procedures were approved by the Washington University Human Research Protection Office.

Diagnosis and Clinical Assessment

Participant diagnoses were based on a Structured Clinical Interview for DSM-IV-TR (30) conducted by a master's-level clinician. See Supplement for details on clinical assessments and measures, which generated both clinician-rated and self-reported measures of anhedonia/amotivation.

Task

The experimental paradigm was a modified version of the probabilistic stimulus selection task (Figure 1) (22), consisting of an acquisition phase, during which functional magnetic resonance imaging (fMRI) scanning took place, and a test phase that was completed outside of the scanner. During acquisition, participants were presented on each trial with one of three pairs of stimuli (i.e., "AB," "CD," or "EF") in pseudorandomized order and were instructed to choose the stimulus that they believed was "correct" based on feedback received over time. Stimuli were displayed for 2000 ms, during which the participant was required to choose one of the stimuli via button press. After a jittered interstimulus interval ranging from 2000 to 6000 ms, feedback consisting of the words "Correct! +$" in green text, "Incorrect $0" in red text, or "Too Slow!" were presented on screen for 2000 ms. Subjects were told that they would win money for each correct choice, up to $20 (in actuality, all subjects were paid an additional $20 upon completion). For stimulus pair AB, the choice of A was rewarded 80% of the time, while B was rewarded 20% of the time; for pair CD, C was rewarded 70% of the time and D was rewarded 30% of the time; and for pair EF, E was rewarded 60% of the time and F was rewarded 40% of the time. Feedback was followed by an intertrial interval jittered

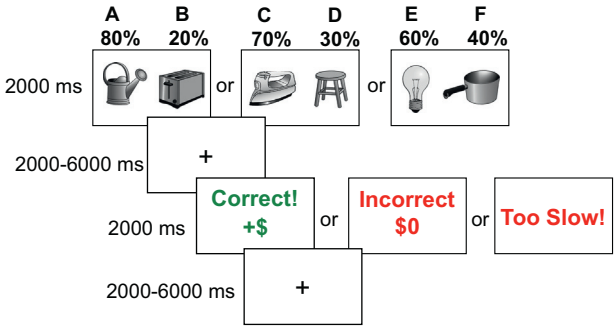

Figure 1. Experimental paradigm. The trial types and timing of the acquisition phase of the probabilistic stimulus selection task are shown. Both interstimulus and intertrial intervals were jittered to allow reconstruction of the blood oxygen level–dependent response at the time of both choice and feedback.

from 2000 to 6000 ms. Additional details can be found in the Supplement.

Image Acquisition and Processing

Imaging was performed on a 3T TIM TRIO system (Siemens, Berlin, Germany) with a 12-channel head coil. High-resolution structural images were acquired using a sagittal magnetization prepared rapid acquisition gradient-echo sequence (repetition time = 2.4 s, echo time = 3.08 ms, inversion time = 1 s, flip = 8°, 176 slices, and 1 mm^3 voxels). Functional images were collected in 10 runs of 213 frames each using a gradient echo planar sequence (repetition time = 2030 ms, echo time = 27 ms, flip = 90°, and 36 slices). Details can be found in the Supplement.

fMRI Analysis

Statistical analysis of fMRI data used two complementary approaches: a more traditional analysis approach, categorizing events in terms of specific choices (e.g., AB/CD/EF) to make contact with the existing literature using such approaches, and a computational model–based approach.

Traditional General Linear Model–Based Analyses

For these analyses, at the time of stimulus presentation, six choice types were modeled (i.e., A, B, C, D, E, and F), and at the time of feedback, 12 feedback types were modeled (i.e., positive and negative feedback for each choice). Nonresponse trials were coded as a variable of no interest. The analyses were conducted based on the general linear model (GLM) (31) using in-house software (32). The GLM for each subject included time as a nine-level regressor, made up of the nine MR frames after each event [i.e., a finite-impulse response (FIR) function approach). A FIR approach was used rather than a canonical hemodynamic response function approach because of the mixed evidence in the literature for the integrity of the hemodynamic response function approach in patients with schizophrenia (33,34). With a hemodynamic response function approach, changes in the timing of responses can lead to artifactually altered magnitude estimates (35,36), while an FIR allows for examination of the nature and pattern of the blood oxygen level–dependent response patterns across groups [Lindquist *et al.* (35) and Lindquist and Wager (36) provide a comparison of these approaches]. Activation at the time of stimulus presentation and at the time of feedback was modeled separately. Parameter estimates from the GLMs for each subject, including time (the nine time points of the response), were entered into analysis of variance (ANOVA) models, using subject as a random factor. In these analyses, a significant main effect of time for a voxel or region indicates activation or deactivation, and a significant interaction of any other factor with time indicates that the hemodynamic response varies across that factor. Analyses using this approach for choice-related activation are presented below, and additional details and results of these analyses are presented in the Supplement.

Model-Based fMRI Analyses

Behavioral data were modeled using a Q-learning algorithm with separate learning rates from positive feedback (i.e., "gains"; $\propto_G$) and negative feedback (i.e., "losses"; $\propto_L$) (24). This algorithm models subjects' choices by calculating a *Q* value, which is an estimate of expected reward value, for each stimulus (A–F). This value is modified on each trial according to the reward *r(t)* received, where *r(t)* = 1 for positive feedback and *r(t)* = 0 for negative feedback. For additional details, see the Supplement. Model-based fMRI analyses were conducted by including trial-by-trial, subject-specific values of *Q* (expected value) and PE as parametric regressors in a GLM that included choice and feedback events (collapsed across stimulus type) with the *Q* value modulating the choice events and predictions error modulating the feedback events. As with the traditional analyses described above, parameter estimates from the GLMs for each subject were entered into ANOVA models using subject as a random factor, including time (i.e., the nine time points of the response for either the choice or feedback event). In these analyses, a significant main effect of time for a voxel or region indicates activation or deactivation as a function of that regressor, and a significant interaction of any other regressor with time indicates that the hemodynamic response varies across that regressor. Whole-brain analyses were corrected for multiple comparisons using a *p* value/cluster size threshold of $p < .003$ (two-tailed) and 13 voxels, as determined by Monte Carlo simulations to provide a whole-brain false-positive rate of $p < .05$ (37,38). Region of interest (ROI) analyses were conducted using mean activation within six regions, including the bilateral caudate, putamen, and nucleus accumbens. These regions were defined anatomically (39) and were applied at the group level in Talairach atlas space. Significance levels in ROI analyses were false discovery rate–corrected for multiple comparisons using the Benjamini–Hochberg procedure (40) to yield an alpha of 0.05 across all 6 regions.

We also conducted correlation analyses within the patient group between blood oxygen level–dependent signal and anhedonia/avolition scores. Activation at time points 4 and 5 (i.e., the peak of the hemodynamic response) was averaged and correlated with clinical and questionnaire-based anhedonia/avolition scores. These correlations were conducted using the same voxelwise whole-brain and regionwise ROI procedures described above. Analyses as a function of antipsychotic dose are also shown in the Supplement.

RESULTS

Demographic and Clinical Characteristics

Participant demographic and clinical characteristics are shown in Table 1.

Behavioral Analysis

Acquisition Phase. The acquisition phase data were divided into five blocks of 72 trials (24 per stimulus pair), which were used in a repeated measures ANOVA with block and pair (i.e., AB, CD, and EF) as within-subjects factors and group (i.e., control subjects and patients with schizophrenia) as a between-subjects factor (Figure 2A). This analysis revealed significant main effects of block ($F_{4,292} = 8.74$; $p < .001$), with increasing proportions of high-probability choices over time, and pair ($F_{2,146} = 22.00$; $p < .001$), with the greatest

Table 1. Demographic and Clinical Characteristics

	CON (n = 37)		SCZ (n = 38)	
	Mean	SD	Mean	SD
Age, Years	36.43	8.44	35.00	9.25
Education, Years	14.14	2.1	12.95	2.3
Highest Parental Education, Years	13.78	1.65	14.00	4.3
Sex, Male (%)	43.2		63.2	
Race, White (%)	29.7		42.1	
Smokers (%)	43.2		57.9	
Fagerstrom Test for Nicotine Dependence	7.4	5.5	9.2	4.0
Handedness	4.31	0.95	4.97	0.19
SAPS/SANS Positive	0.03	.16	3.5	2.64
SAPS/SANS Negative	1.49	2.09	7.92	2.97
SAPS/SANS Disorganization	2.38	1.30	2.63	2.65
BNSS Total Anhedonia	0.68	2.15	1.05	1.91
BNSS Total Avolition	5.76	3.48	5.38	2.44
Chapman Social Anhedonia	8.92	6.26	15.39	7.98
Chapman Physical Anhedonia	11.78	6.12	18.53	10.13
Snaith–Hamilton Pleasure Scale	52.38	3.21	48.45	8.21
TEPS Anticipatory Pleasure	48.22	5.69	46.05	8.31
TEPS Consummatory Pleasure	38.41	5.64	35.03	7.37
Apathy Scale	22.19	3.57	26.11	7.26
No. of Subjects With Episodes of Major Depressive Disorder (Not in Past Year)	2		7	7
No. of Subjects With Past Substance Dependence	2		7	
No. of Subjects Taking Antipsychotic Medications	—		35[a]	
Antipsychotic Dose (Chlorpromazine Equivalent)	—		717.78	474.25
No. of Subjects Taking Antidepressant Medication	—		17	
No. of Subjects Taking Antianxiety Medication	—		6	
No. of Subjects Taking Mood Stabilizers	—		9	
No. of Subjects Taking Anticholinergic Medication	—		12	

There were no significant differences between patients and control subjects in age, sex, race, or handedness. Personal education was higher among control subjects than patients, an expected finding given the effects of schizophrenia on function, but parental education (a surrogate for premorbid socioeconomic status) was similar between groups. Smoking status also did not differ significantly between groups, both in terms of the number of participants who smoke and the Fagerstrom nicotine dependence scores among smokers. SAPS/SANS scores for positive and negative symptoms were higher among patients than control subjects, though disorganization scores were low in patients and did not differ between groups. Anhedonia and avolition scores were higher among patients than control subjects on all clinical and self-reported measures except the TEPS anticipatory pleasure score.

BNSS, Brief Negative Symptom Scale; CON, control subjects; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; SCZ, patients with schizophrenia; TEPS, Temporal Experience of Pleasure Scale.

[a]Typical only, n = 4; atypical only, n = 29; typical plus atypical, n = 2; clozapine only, n = 2; and clozapine plus other, n = 3.

proportion of high-probability choices for AB pairs, followed by CD and then EF pairs. The main effect of group was not significant, nor were any interactions with group (p values $>$ .1). However, planned simple effects tests revealed trend-level group differences within the AB ($F_{1,73}$ = 3.45; p = .07) and EF ($F_{1,73}$ = 3.22; p = .08) pairs but not the CD pair (p $>$ .8). As shown in Figure 2A, performance for the CD pair was similar between patients and control subjects, whereas patients performed more poorly than control subjects on both the AB and EF pairs.

Test Phase. Test phase choice data are shown in Figure 2B. For the original AB, CD, and EF pairs that had been presented during acquisition, a pair $\times$ group ANOVA revealed a main effect of pair ($F_{2,144}$ = 13.81; p $<$ .001) but no main effect of group ($F_{1,72}$ = 2.67; p $>$ .1) or pair $\times$ group interaction ($F_{2,144}$ = 0.86; p $>$ .42). However, planned simple effects tests revealed a significant group difference for the AB pair only ($F_{1,72}$ = 4.44; p = .04), in which patients performed more poorly than control subjects. To examine whether learning from positive versus negative feedback differed between groups, we compared ChooseA (learn positive) and AvoidB (avoid negative) using a repeated measures ANOVA with group as a between-subjects factor, which revealed only a trend-level main effect of group ($F_{1,72}$ = 3.61; p = .07) (Figure 2B). However, while the ChooseA/AvoidB measure has been the transfer measure of interest in previously published versions of this task, its appropriateness in this sample is called into question by the fact that patients performed more poorly on the AB pair than control subjects. To avoid this problem, an equivalent transfer measure was created that relies on the CD pair, performance on which was closely matched between groups: ChooseC (i.e., CE and CF) versus AvoidD (i.e., DE and DF). ANOVA of this measure

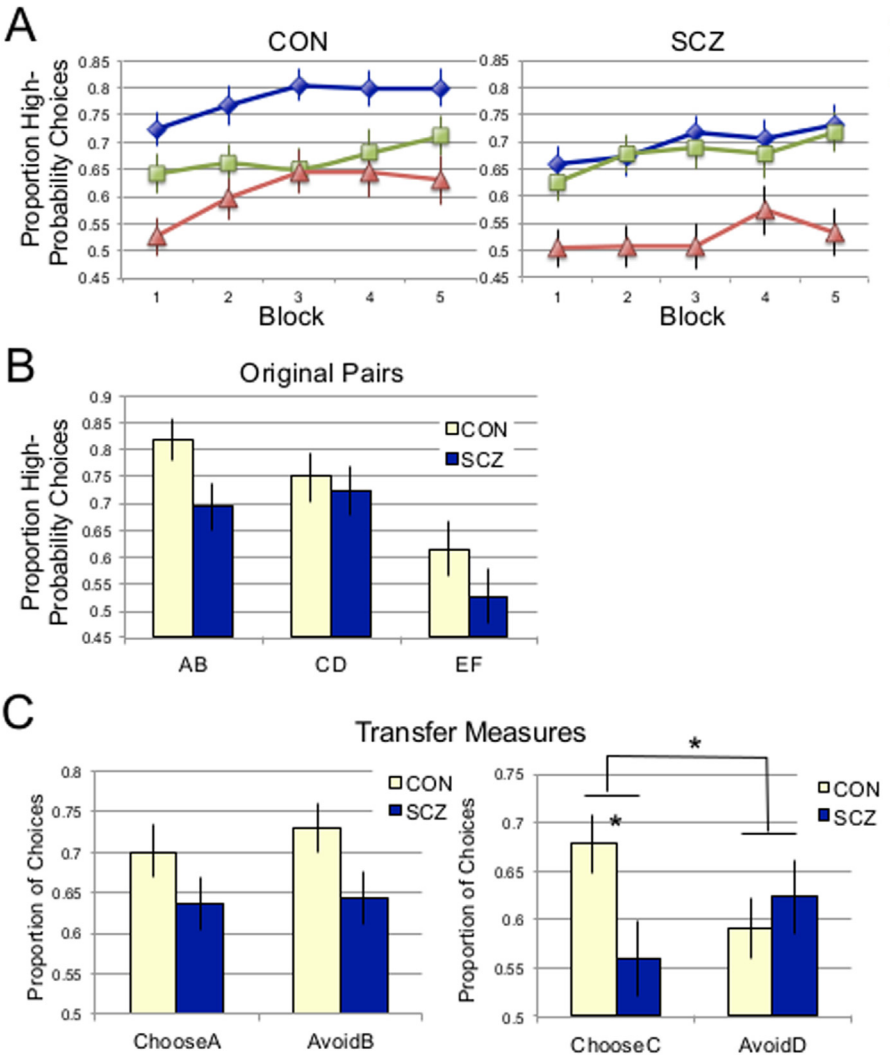

Figure 2. Behavioral results. **(A)** Acquisition phase performance. Proportion of high-probability choices (A/C/E) per 24-trial block. **(B)** Test phase performance for original AB, CD, and EF pairs. **(C)** Test phase performance for ChooseA/AvoidB and ChooseC/AvoidD transfer measures. CON, control subjects; SCZ, patients with schizophrenia.

revealed a significant ChooseC/AvoidD × group interaction ($F_{1,72}$ = 5.21; p = .03), with no significant main effects (p values > .2). As shown in Figure 2C, ChooseC performance was significantly lower in patients than control subjects (t_{72} = 2.40; p = .02), while performance on the AvoidD measure did not differ significantly between groups (p > .5).

Modeling Results

Model fits as measured by log-likelihood did not differ significantly between groups (Table 2). However, there were a number of subjects who showed no appreciable learning and for whom model fits were poor. To restrict the modeling analysis to those subjects whose choices were well described by the model, a subset of "nonlearners" was excluded (Table 2). We used Akaike information criterion to verify that the model with gain and loss learning rates fit better than a single learning rate model [this was true for 54 subjects (28 control subjects and 26 patients)]. The learners were higher than the nonlearners on self-reported anhedonia/amotivation ($t_{1,36}$ = –3.07; p = .004) and lower on Wechsler Adult Intelligence Scale Vocabulary scores ($t_{1,36}$ = –2.42; p = .02), but did not differ significantly on clinician-rated anhedonia/amotivation ($t_{1,36}$ = –0.48; p = .64), positive symptoms ($t_{1,36}$ = 0.13; p = .90), and chlorpromazine equivalents ($t_{1,36}$ = 0.77; p = .44). Model simulations showed that fit parameters were able to appropriately predict subjects' choices (Figure 3). Gain and loss learning rates are shown in Table 2. Independent sample t tests indicated a trend for patients to show lower gain learning rates (t_{52} = 1.63; p = .055, 1-tailed) but not loss learning rates (t_{52} = 0.56; p = .96, 1-tailed).

fMRI PE Analysis

Within the striatal ROIs, all regions showed significant PE effects (all p values < .007) with positive modulation (i.e., greater activation with greater PE), with no significant group differences. These regions were also identified by the whole-brain analysis (Tables 3 and 4 and Figure 4). A set of regions showing activation that was positively modulated (Table 3 and Figure 4A, B) included bilateral ventral striatum and amygdala. As can be seen in graphs to the right in Figure 4B, in these

Table 2. Model Fit and Parameter Data

Sample	Criterion/Value	CON	SCZ
Full Sample (38 CON, 37 SCZ)	LLH	–173.13 (57.6)	–184.68 (52.9)
	BIC	363.83 (115.1)	386.89 (105.9)
	Gain Learning Rate	0.279 (0.30)	0.173 (0.24)
	Loss Learning Rate	0.275 (0.33)	0.215 (0.33)
Learners Only (28 CON, 26 SCZ)	LLH	–154.6 (53.0)	–171.62 (53.8)
	BIC	326.78 (106.0)	360.83 (107.6)
	Gain Learning Rate	0.268 (.25)	0.165 (0.21)
	Loss Learning Rate	0.218 (.28)	0.213 (0.31)

BIC, Bayesian information criterion; CON, control subjects; LLH, log-likelihood; SCZ, patients with schizophrenia.

regions, activity in response to outcomes was more positive with high PEs. In addition, as can be seen in graphs to the left in Figure 4B, both patients and control subjects showed greater activation when they received positive feedback, regardless of whether it was for a high- or a low-probability choice. A second subset of regions showed activation with negative modulation, such that activation was greater for smaller positive (or larger negative) PEs (Table 4). These regions included cognitive control regions, such as the bilateral dorsolateral prefrontal cortex (DLPFC), posterior parietal cortex, anterior insula, and pre-supplementary motor area (preSMA). Examples of each type of activation pattern are shown in Figure 4B. Another third set of regions, including the rostral anterior cingulate cortex and medial frontal gyrus, showed deactivation that was positively modulated (i.e., less deactivation for more positive PEs).

There were two regions that showed an interaction between PE and group: the right inferior frontal gyrus (+47, +15, +7; 26 voxels) and the right superior temporal gyrus (+60, –60, +26; 20 voxels). The right inferior frontal gyrus showed activation

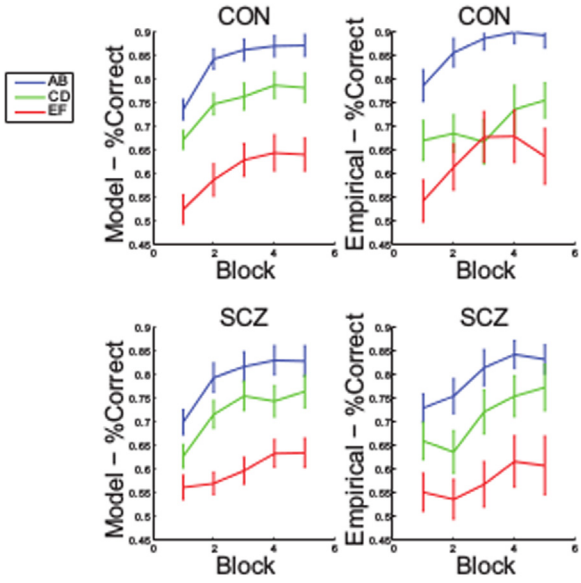

Figure 3. Modeling results. Comparison between empirical behavior and model-predicted learning curves. CON, control subjects; SCZ, patients with schizophrenia.

that was negatively modulated in control subjects (i.e., reduced activation with higher PEs) but no significant modulation in patients. Superior temporal gyrus showed activation that was decreased for larger positive PEs in control subjects but increased for larger positive PEs in patients. No significant group differences in PE activity were found in striatal regions.

fMRI *Q* Value Analysis

Striatal ROI analysis of *Q* value–related activity revealed a robust positive modulation in the bilateral nucleus accumbens (left: $F_{8,416} = 6.92$ [$p < 10^{-7}$]; right: $F_{8,416} = 5.89$ [$p < 10^{-8}$]), indicating greater activation when choosing stimuli with a higher expected value. These effects did not interact with group and were strongly present within each group. Similar regions were identified in the whole-brain analysis (Table 5), and example time courses are shown in Figure 5. Similar to the ROI analysis results, in the whole-brain analyses, the right ventral striatum showed activation that was modulated positively by *Q* value, as did regions in right caudate, right postcentral gyrus, and left inferior frontal gyrus (Figure 5B). Cognitive control network regions, including the bilateral DLPFC, posterior parietal cortex, anterior insula, and anterior cingulate cortex/preSMA, showed activation with negative modulation, meaning that the lower the *Q* value of the chosen stimulus, the greater the activation in these regions. The activation patterns and magnitudes were highly similar between patients and control subjects for all of these regions (Figure 5C).

Several regions showed a significant time × group interaction in the *Q* value effect (Table 5). Regions in the brainstem, bilateral cerebellum, and left superior frontal gyrus showed activation that was negatively modulated in control subjects but positively modulated in patients. Similarly, the left parahippocampal gyrus was modulated positively in patients but not in control subjects, and the right superior parietal lobule was modulated negatively in control subjects but not in patients. Finally, the precuneus showed deactivation that was negatively modulated in patients but not in control subjects. No group differences in *Q* value effects were seen in striatal regions.

ANOVA Analysis: Choice-Related Activity Early in Learning

As shown in Figure 2A, group-level performance began to plateau during block 3. Therefore, we conducted analyses only with early learning (i.e., blocks 1–3). On ROI analysis, a choice × time (i.e., time within trial for a FIR analysis) × group

Table 3. Regions Showing Positive Modulation of Activity for Prediction Errors

Hemisphere	Region	BA	X	Y	Z	No. of Voxels	Z	Activation	PE Modulation
L	Ventral striatum	—	−11	9	2	167	5.94	Activation	Positive
L	Cingulate gyrus	24	−11	−19	40	27	4.16	Activation	Positive
R	Ventral striatum	—	14	6	2	198	6.71	Activation	Positive
R	Hippocampus	—	29	−15	−9	60	4.87	Activation	Positive
L	Inferior parietal lobule	40	−42	−32	41	102	4.53	Activation	Positive
L	Middle occipital gyrus	18	−26	−95	4	77	5.17	Activation	Positive
L	Middle occipital gyrus	18	−22	−88	22	45	4.10	Activation	Positive
L	Middle temporal gyrus	21	−61	−19	−3	15	4.23	Activation	Positive
R	Amygdala	—	18	−28	−9	46	5.57	Activation	Positive
L	Amygdala	—	−15	−27	−9	57	5.19	Activation	Positive
R	Postcentral gyrus	3	29	−34	55	107	4.58	Activation	Positive
R	Postcentral gyrus	3	18	−37	69	43	4.13	Activation	Positive
L	Precuneus	7	−13	−48	54	100	4.87	Activation	Positive
L	Anterior cingulate	32	−2	43	−1	254	8.12	Deactivation	Positive
R	Anterior cingulate	32	18	34	14	224	4.62	Deactivation	Positive
R	Anterior cingulate	25	6	19	−5	120	558	Deactivation	Positive
R	Anterior cingulate	24	2	25	14	224	4.62	Deactivation	Positive
R	Anterior cingulate	32	−19	33	23	32	3.90	Deactivation	Positive
L	Medial frontal gyrus	9	−3	53	15	177	6.38	Deactivation	Positive
L	Middle frontal gyrus	8	−25	12	39	53	4.56	Deactivation	Positive
L	Middle temporal gyrus	39	44	−72	25	77	4.29	Deactivation	Positive
L	Superior frontal gyrus	8	-21	28	46	148	6.00	Deactivation	Positive
L	Superior frontal gyrus	8	-33	23	54	28	4.26	Deactivation	Positive

BA, Brodmann area; L, left; PE, prediction error; R, right.

ANOVA again revealed no significant effects of choice or group in striatal regions. On whole-brain analysis, the patterns of activation for high- versus low-probability (of reward) choices within early learning showed overlap with the *Q* value analysis described above. Several regions showed choice × time interactions in which activity was greater for high than low-probability choices in both groups, including regions in the bilateral caudate, left inferior frontal gyrus, and right anterior insula (Supplemental Table S6 and Supplemental Figure S6). Similar to the full *Q* value analysis, greater activation for low- than for high-probability choices was seen in the left DLPFC and precentral gyrus. A time × group interaction was present in a number of cognitive control regions, including the bilateral posterior parietal cortex, right DLPFC, preSMA, thalamus, and right anterior insula/inferior frontal gyrus (Supplemental Table S6 and Supplemental Figure S6A). All of these regions activated more strongly in control subjects than in patients during early learning at the time of choice, regardless of which stimulus was ultimately chosen. Choice × time × group interactions were also seen in a few regions; among these were midbrain and right cerebellar crus I, which activated more strongly for low- than for high-probability choices among control subjects, with the opposite pattern among patients (Supplemental Table S6).

Individual Differences Analyses

There were no significant relationships between higher clinician-rated or self-reported anhedonia/amotivation scores and impairments in either Choose C performance (Go learning), gain learning rates, activity during high-probability responses to positive or negative feedback, or positive or negative PEs in the striatum using the ROI analyses (all p values $> .1$; Supplemental Table S7). However, whole-brain analysis revealed significant negative relationships between the self-reported anhedonia/avolition scores and responses to positive feedback in several regions, including the left caudate and bilateral posterior DLPFC (Brodmann areas 44/6) (Figure 6 and Supplemental Table S8). These regions showed reduced activation in response to positive feedback in those patients who were higher in self-reported anhedonia/avolition. We did not find any regions that survived whole-brain correction for the relationship between greater positive feedback related activity and either lower clinician-rated anhedonia/amotivation scores or better performance in either Choose C performance (Go learning) or gain learning rates for either PE or positive feedback–related activity.

DISCUSSION

Behavioral results using transfer measures sensitive to Go versus NoGo learning suggested some evidence for impairments in learning from positive, but not negative, feedback in patients compared with control subjects. However, while the behavioral results showed some impairment in Go learning, we found little evidence in the neuroimaging results for reduced striatal responses among patients compared with control subjects. We hypothesized that Go learning impairments would be associated with reduced positive PE activity and

Table 4. Regions Showing Negative Modulation of Activity for Prediction Errors

Hemisphere	Region	BA	X	Y	Z	No. of Voxels	Z	Activation	PE Modulation
R	Cingulate gyrus	32	5	18	41	214	5.67	Activation	Negative
L	Cingulate gyrus	32	−10	19	33	82	4.79	Activation	Negative
L	Inferior frontal gyrus	9	047	7	32	201	4.50	Activation	Negative
L	Anterior insula	13	−34	17	6	171	5.69	Activation	Negative
R	Anterior insula	13	40	16	6	185	6.23	Activation	Negative
R	Middle frontal gyrus	9	43	23	29	143	5.18	Activation	Negative
R	Middle frontal gyrus	6	37	8	53	72	4.43	Activation	Negative
L	Precentral gyrus	4	−40	−11	52	192	5.10	Activation	Negative
R	Precentral gyrus	6	40	2	35	130	4.77	Activation	Negative
L	Precentral gyrus	9	−42	25	37	95	4.68	Activation	Negative
R	Precuneus	7	7	−72	38	94	4.02	Activation	Negative
L	Precuneus	7	−20	−71	38	94	4.02	Activation	Negative
L	Superior frontal gyrus	6	−3	10	51	250	7.22	Activation	Negative
R	Superior frontal gyrus	6	5	1	64	157	6.25	Activation	Negative
L	Superior frontal gyrus	6	−14	−1	66	78	5.23	Activation	Negative
R	Superior frontal gyrus	6	12	14	62	77	4.83	Activation	Negative
L	Superior frontal gyrus	10	−34	49	21	32	4.37	Activation	Negative
R	Superior parietal lobule	7	31	−55	43	142	5.21	Activation	Negative
L	Superior parietal lobule	40	−35	−52	48	159	4.50	Activation	Negative
L	Superior temporal gyrus	22	−49	10	2	127	6.05	Activation	Negative
R	Superior temporal gyrus	38	46	12	−8	79	6.38	Activation	Negative
L	Anterior cingulate	32	−14	29	8	97	4.79	Deactivation	Negative

BA, Brodmann area; L, left; PE, prediction error; R, right.

reduced anticipatory reward responses at the time of choice in striatal regions among patients. Instead, we found that striatal activity was intact in patients at the time of both choice and feedback. We found no group differences in striatal activity for positive versus negative choices or feedback, expected values, or PEs when examining the full acquisition phase.

Our findings of significant striatal activation at the group level in patients with schizophrenia during learning, with no significant differences from control subjects, contrast with the findings of several studies in the literature showing reduced striatal PEs in patients with schizophrenia (17,21,41). However, other studies have found intact striatal PEs in patients with schizophrenia (16,42–45). One possible source of these differences across studies is clinical differences in the populations examined (medicated vs. unmedicated); among other possible differences, our patients had lower positive symptom severity than many published reports, and there is evidence in the literature that aberrant PE activity is related to positive symptoms in patients with schizophrenia (46). We also excluded patients and control subjects with evidence of major depression in the past year to help deconfound depression versus psychosis effects on RL. Given that depression is also associated with altered striatal activation in response to reward (47) and to PE (48), it is possible that this difference from many previous studies reduced the evidence for altered PE signals in the striatum among our sample of patients with schizophrenia.

The lack of significant relationships between anhedonia/avolition scores and striatal responses specifically to PE differs from some reports in the literature (17,44), although at least one other study did not find such relationships (16) and we did see a relationship of anhedonia/avolition to positive feedback responses in the caudate. Behavioral studies have also reported relationships between RL and negative symptom severity (26,28), which we did not find. We speculate that these differences may have been influenced by the specifics of the experimental design. One important difference between our task and many in the literature is that patients received additional practice on the task, with different stimuli, before the scanning session. This was done to avoid an influence of confusion about task procedures, which was common among patients but not control subjects. This procedure introduced a practice mismatch between groups, but mismatches in the amount of practice given are not unusual in PE studies, which sometimes have subjects train to criterion before entering the scanner. It is possible that this additional practice in patients contributed to the relative lack of group differences in our study compared with others in the literature, which has implication for our understanding of the mechanisms driving such impairments in patients. However, it is also possible that the lack of significant correlation with PE responses reflected in part the small sample of participants with good model fits, although the magnitudes of the correlations between PE activity in the striatum and amotivation/anhedonia scores were low and we did not see additional significant associations if we included subjects who did not have good model fits.

Regions such as the orbitofrontal cortex, prefrontal cortex, and medial temporal lobe are commonly associated with more rapid, explicit forms of learning. This task was designed to rely heavily on the basal ganglia slow learning system, but it is likely that these explicit systems also contributed. Our

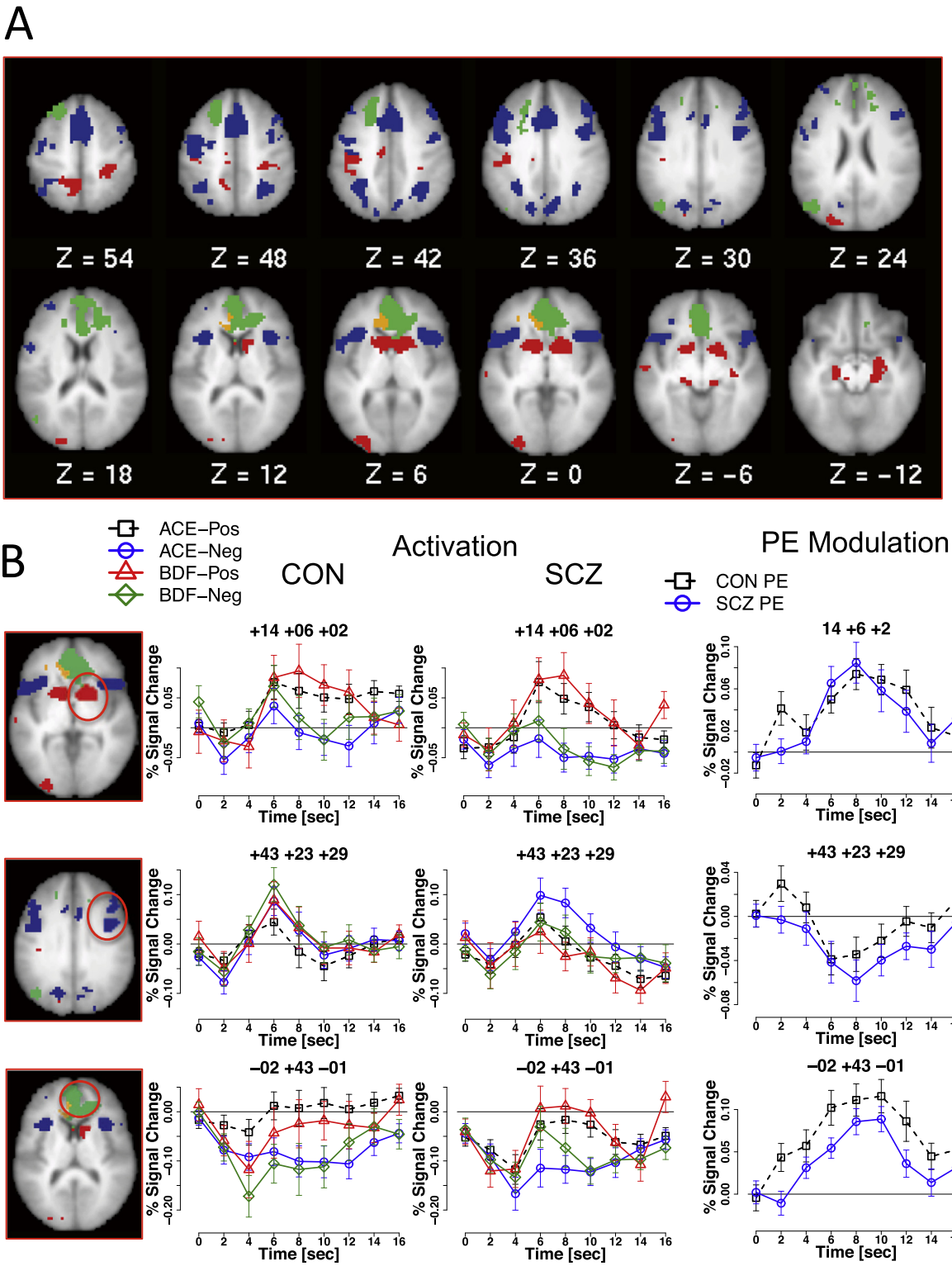

Figure 4. Prediction error analysis (prediction error × time interactions). **(A)** Regions with significant prediction error effects in both groups. Red indicates activation with positive modulation, blue indicates activation with negative modulation, green indicates deactivation with positive modulation, and orange indicates deactivation with negative modulation. **(B)** Example time courses for each activation pattern. Regions shown were significant at whole-brain threshold of $Z \geq 3.0$, $N \geq 13$ voxels. ACE, high-probability choice (A, C, or E); BDF, low-probability choice (B, D, or F); CON, control; Neg, negative feedback; PE, prediction error; Pos, positive feedback; SCZ, patients with schizophrenia.

Table 5. Regions Showing a Significant Parametric Effect of *Q* Values

									Activation Pattern	
Effect	Hemisphere	Region	BA	X	Y	Z	No. of Voxels	Z	Choice vs. Baseline	Q Value Modulation
Q	R	Postcentral gyrus	3	42	–25	54	82	4.79	Activation	Positive
	R	Ventral striatum	—	16	3	–9	220	6.98	Activation	Positive
	R	Caudate	—	11	24	3	116	5.69	Activation	Positive
	L	Inferior frontal gyrus	47	–17	29	-5	60	5.11	Activation	Positive
	R	ACC/pSMA	8	1	19	44	570	7.38	Activation	Negative
	L	Anterior insula	13	–32	18	3	251	6.87	Activation	Negative
	R	Anterior insula	13	43	18	7	376	7.38	Activation	Negative
	L	Fusiform gyrus	37	–34	–56	–6	70	4.57	Activation	Negative
	R	Cerebellar crus I	—	12	–85	–17	57	5.18	Activation	Negative
	R	Cerebellar vermis	—	3	–72	–37	14	4.66	Activation	Negative
	R	Lingual gyrus	19	29	–59	–3	65	4.87	Activation	Negative
	R	Middle frontal gyrus	8	42	11	41	598	6.28	Activation	Negative
	L	Middle frontal gyrus	9	–45	8	34	232	5.03	Activation	Negative
	R	Middle frontal gyrus	10	39	49	7	155	7.41	Activation	Negative
	L	Middle frontal gyrus	10	–42	50	5	74	6.56	Activation	Negative
	L	Middle frontal gyrus	9	–47	31	27	92	4.54	Activation	Negative
	L	Middle occipital gyrus	18	–30	–87	6	85	4.54	Activation	Negative
	L	Posterior cingulate	23	–1	–26	32	82	5.43	Activation	Negative
	L	Posterior parietal cortex	40	–40	–53	47	236	6.06	Activation	Negative
	L	Posterior parietal cortex	7	32	–61	49	192	5.27	Activation	Negative
	L	Cerebellar crus II	—	–10	–87	–31	147	7.26	Activation	Negative
	L	Superior frontal gyrus	6	–2	10	68	85	5.01	Activation	Negative
	L	Middle temporal gyrus	21	–53	–17	–9	109	5.21	Deactivation	Positive
	L	Middle temporal gyrus	39	–40	–70	28	129	4.52	Deactivation	Positive
	R	Middle temporal gyrus	21	53	–8	–14	28	4.71	Deactivation	Positive
	L	Parahippocampal gyrus	28	–21	–13	–18	27	3.44	Deactivation	Positive
	R	Anterior cingulate	24	1	33	–2	129	6.60	Deactivation	Positive
	R	Inferior parietal lobule	40	49	–54	35	127	4.80	Deactivation	Negative
Q x Group	R	Inferior parietal lobule	7	30	–65	57	13	4.01	Activation	CON: negative; SCZ: none
	R	Brainstem	—	1	–32	–38	26	4.13	Activation	CON: negative; SCZ: positive
	L	Cerebellum	—	–28	–48	–47	71	4.84	Activation	CON: negative; SCZ: positive
	R	Cerebellum	—	28	–60	–42	57	4.53	Activation	CON: negative; SCZ: positive
	L	Superior frontal gyrus	10	–11	63	18	22	4.93	Activation	CON: negative; SCZ: positive
		Cingulate gyrus	23	0	–20	28	14	3.82	Activation	CON: none; SCZ: negative
	L	Precuneus	7	–5	–70	47	18	3.57	Activation	CON: none; SCZ: negative
	L	Parahippocampal gyrus	36	–22	–40	–15	32	4.8	Activation	CON: none; SCZ: positive
		Precuneus	7	0	–53	38	15	3.94	Deactivation	CON: none; SCZ: positive

ACC, anterior cingulate cortex; BA, Brodmann area; CON, control subjects; L, left; pSMA, presupplementary motor area; R, right; SCZ, patients with schizophrenia.

behavioral data provide some evidence for this. At both acquisition and test, we found reduced performance on the AB pair in patients compared with control subjects, while performance on the CD and EF pairs (at test) did not differ between groups, although the group differences in the EF pair might have achieved significance with sample sizes larger than 38 and 37 patients. We speculate that this finding may be related to impairments in explicit learning among patients, given that the AB pair had the highest probability ratio and was therefore the easiest to learn via explicit mechanisms. Higher ratios require fewer trials to be held in working memory for explicit representations of reward contingencies to be formed, while lower ratios require integration over many more trials and are better suited to the gradual, implicit learning system of the basal ganglia. This interpretation is consistent with the hypothesis in the literature that cortical learning is impaired in patients with schizophrenia (6).

There were also some imaging results consistent with the hypothesis of impaired cortical learning in this group. In both the PE and *Q* value analyses, we saw evidence for altered activation in the frontal cortex, with right inferior frontal modulation in patients in response to PEs and altered superior frontal gyrus modulation in patients in the *Q* value analysis. In addition, during the early learning phase, several regions involved in cognitive control showed reduced overall choice-related activation in patients compared with control subjects, which is consistent with a reduction in explicit learning during the early learning phase. As noted above, analyses of both

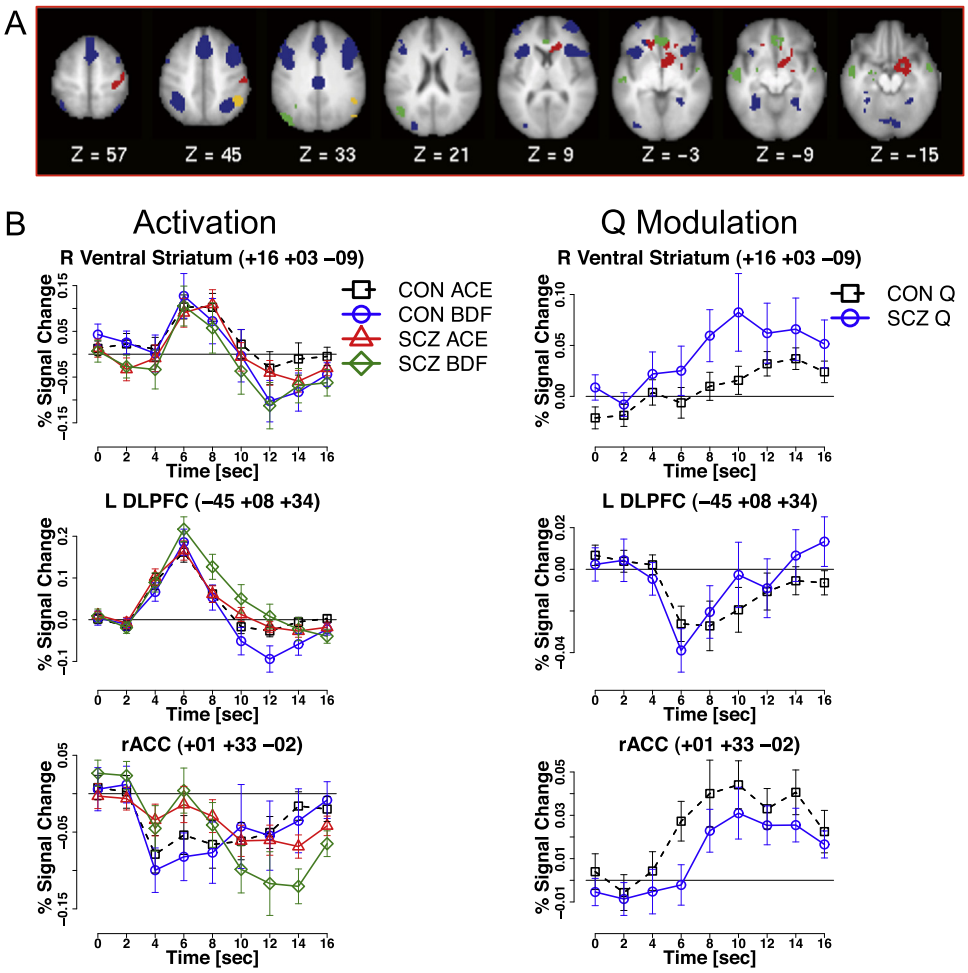

Figure 5. *Q* value effects. **(A)** Regions showing significant *Q* value modulation. Red indicates activation with positive modulation, blue indicates activation with negative modulation, green indicates deactivation with positive modulation, and orange indicates deactivation with negative modulation. **(B)** Time course for right ventral striatum showing activation with positive modulation. **(C)** Time course for dorsolateral prefrontal cortex (DLPFC) showing activation with negative modulation. **(D)** Time course for rostral anterior cingulate cortex (rACC) showing deactivation with positive modulation. Regions shown were significant at whole-brain threshold of $Z \geq 3.0$, $N \geq 13$ voxels. ACE, high-probability choice (A, C, or E); BDF, low-probability choice (B, D, or F); CON, control; L, left; Q, *Q*-value (expected value); R, right; SCZ, patients with schizophrenia.

positive versus negative feedback and PE analyses revealed intact activity in patients. However, despite the largely intact group activation, activation in response to positive feedback correlated with anhedonia/avolition in the patient group in both striatal and cortical regions. This finding is consistent with the hypothesis that deficits in responses to positive feedback in both cortical and striatal regions may contribute to these symptoms.

The conclusions from this study are limited by the fact that one cannot prove the null hypothesis (i.e., that patients and control subjects as a group do not differ in striatal PE activity), and we could potentially have seen differences from control subjects if the sample sizes were larger. However, Figure 4B shows that the patients with schizophrenia did show strong PE responses in the striatum and the effect sizes of any difference from control subjects at the group level were small. We did have to exclude more nonlearners from the patient group than from the control group, which could have biased the results in favor of seeing strong PE responses in the striatum in patients. However, Supplemental Figure S1 shows strong striatal responses to positive feedback even in the whole sample of patients in the traditional GLM analyses. Another limitation was that the majority of patients examined here were taking antipsychotic medications. As presented in the Supplement, correlations with dose equivalents revealed increased NoGo learning in patients with higher medication doses, but there were no significant relationships between dose and brain activity. Interestingly, increased NoGo learning is what the Frank model predicts for greater levels of D_2 receptor antagonism, meaning that this relationship is actually consistent with the model (23). Perhaps surprisingly, studies examining striatal activation in patients with schizophrenia tend to find reduced striatal activation for unmedicated patients, with intact activation for patients taking atypical antipsychotic medications, including some direct evidence of a normalizing effect of starting these medications (49). The present study lends additional support to these findings by showing intact striatal activation in a population of patients who are primarily taking atypical antipsychotic medications.

Conclusions

This study showed some behavioral evidence of impaired learning from positive versus negative feedback and impaired learning of stimuli with high versus low

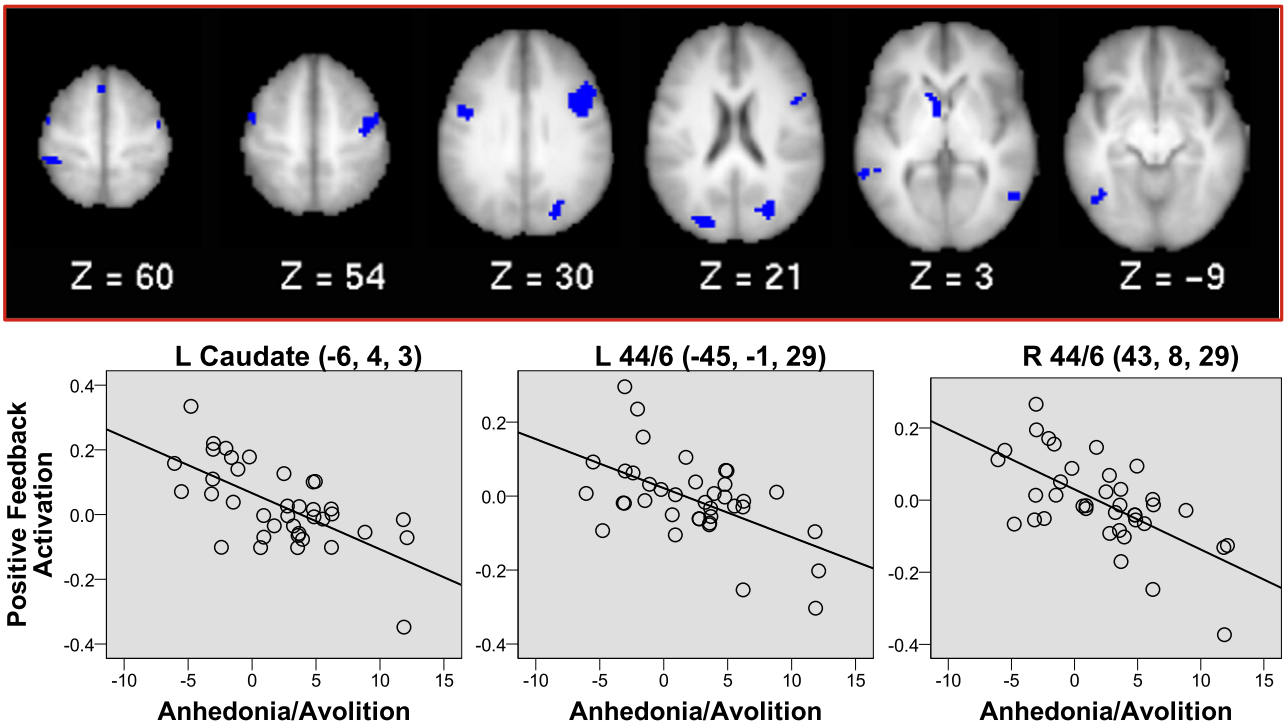

Figure 6. Correlation analyses. Regions with significant negative correlations between responses to positive feedback and self-reported anhedonia/avolition among patients. Regions shown were significant at whole-brain threshold of $Z \geq 3.0$, $N \geq 13$ voxels. L, left; R, right.

reinforcement ratio among medicated patients with chronic schizophrenia. Striatal activation was intact in the patient group at the time of choice and feedback, including intact PE activity. At the time of choice, patients failed to recruit cognitive control regions to the same extent as control subjects during early learning. These findings are suggestive of alterations in cortical but not basal ganglia and RL mechanisms in the patient group as a whole. However, severity of anhedonia and avolition in patients was associated with reduced responses to positive feedback in caudate and bilateral DLPFC, suggesting a relationship between these symptoms and altered processing of positive feedback in patients in both cortical and striatal regions.

ACKNOWLEDGMENTS AND DISCLOSURES

This work was supported by a National Institute of Mental Health Grant (Grant No. MH066031 to DMB).

DMB is a consultant for Pfizer, Amgen, and Takeda on studies related to the treatment of negative symptoms in schizophrenia. JMG is a consultant for Amgen, Roche, Pfizer, Merck, AstraZeneca, Solvay, and GlaxoSmithKline on studies related to the treatment of negative symptoms in schizophrenia. JMG also receives royalty payments from the Brief Assessment of Cognition in Schizophrenia. MJF and AC are consultants for Roche on studies related to the treatment of negative symptoms in schizophrenia. ECD reports no biomedical financial interests or potential conflicts of interest.

We thank the participants in this study who gave generously of their time.

ARTICLE INFORMATION

From the Division of Biology and Biomedical Sciences (ECD), Neuroscience Program, and the Departments of Psychological & Brain Sciences, Psychiatry, and Radiology (DMB), Washington University in St. Louis, St. Louis, Missouri; Department of Psychology (MJF), Brown University, Providence, Rhode Island; Department of Psychology (AC), University of California at Berkeley, Berkeley, California; and Department of Psychiatry (JMG), Maryland Psychiatric Research Center, Catonsville, Maryland.

Address correspondence to Deanna M. Barch, Ph.D., Washington University in St. Louis, Box 1125, One Brookings Drive, St. Louis, MO 63130; E-mail: dbarch@artsci.wustl.edu.

Received Jan 26, 2016; revised Apr 30, 2016; accepted May 27, 2016.

Supplementary material cited in this article is available online at http://dx.doi.org/10.1016/j.bpsc.2016.05.005.

REFERENCES

1. Milev P, Ho BC, Arndt S, Andreasen NC (2005): Predictive values of neurocognition and negative symptoms on functional outcome in schizophrenia: A longitudinal first-episode study with 7-year follow-up. Am J Psychiatry 162:495–506.
2. Kirkpatrick B, Fenton WS, Carpenter WT Jr, Marder SR (2006): The NIMH-MATRICS consensus statement on negative symptoms. Schizophr Bull 32:214–219.
3. Messinger JW, Tremeau F, Antonius D, Mendelsohn E, Prudent V, Stanford AD, *et al*. (2011): Avolition and expressive deficits capture negative symptom phenomenology: Implications for DSM-5 and schizophrenia research. Clin Psychol Rev 31:161–168.
4. Barch DM, Dowd EC (2010): Goal representations and motivational drive in schizophrenia: The role of prefrontal-striatal interactions. Schizophr Bull 36:919–934.
5. Siegert RJ, Weatherall M, Bell EM (2008): Is implicit sequence learning impaired in schizophrenia? A meta-analysis. Brain Cogn 67:351–359.
6. Gold JM, Waltz JA, Prentice KJ, Morris SE, Heerey EA (2008): Reward processing in schizophrenia: A deficit in the representation of value. Schizophr Bull 34:835–847.

7. Weickert TW, Terrazas A, Bigelow LB, Malley JD, Hyde T, Egan MF, *et al*. (2002): Habit and skill learning in schizophrenia: Evidence of normal striatal processing with abnormal cortical input. Learn Mem 9:430–442.
8. Waltz JA, Gold JM (2007): Probabilistic reversal learning impairments in schizophrenia: Further evidence of orbitofrontal dysfunction. Schizophr Res 93:296–303.
9. Weiler JA, Bellebaum C, Brune M, Juckel G, Daum I (2009): Impairment of probabilistic reward-based learning in schizophrenia. Neuropsychology 23:571–580.
10. Beninger RJ, Wasserman J, Zanibbi K, Charbonneau D, Mangels J, Beninger BV (2003): Typical and atypical antipsychotic medications differentially affect two nondeclarative memory tasks in schizophrenic patients: A double dissociation. Schizophr Res 61:281–292.
11. Keri S, Kelemen O, Szekeres G, Bagoczky N, Erdelyi R, Antal A, *et al*. (2000): Schizophrenics know more than they can tell: Probabilistic classification learning in schizophrenia. Psychol Med 30:149–155.
12. Keri S, Nagy O, Kelemen O, Myers CE, Gluck MA (2005): Dissociation between medial temporal lobe and basal ganglia memory systems in schizophrenia. Schizophr Res 77:321–328.
13. Weickert TW, Goldberg TE, Egan MF, Apud JA, Meeter M, Myers CE, *et al*. (2010): Relative risk of probabilistic category learning deficits in patients with schizophrenia and their siblings. Biol Psychiatry 67: 948–955.
14. Schultz W (2007): Multiple dopamine functions at different time courses. Annu Rev Neurosci 30:259–288.
15. Murray GK, Corlett PR, Clark L, Pessiglione M, Blackwell AD, Honey G, *et al*. (2008): Substantia nigra/ventral tegmental reward prediction error disruption in psychosis. Mol Psychiatry 13(239):267–276.
16. Gradin VB, Kumar P, Waiter G, Ahearn T, Stickle C, Milders M, *et al*. (2011): Expected value and prediction error abnormalities in depression and schizophrenia. Brain 134:1751–1764.
17. Morris RW, Vercammen A, Lenroot R, Moore L, Langton JM, Short B, *et al*. (2012): Disambiguating ventral striatum fMRI-related bold signal during reward prediction in schizophrenia. Mol Psychiatry 17(235): 280–289.
18. Segarra N, Metastasio A, Ziauddeen H, Spencer J, Reinders NR, Dudas RB, *et al*. (2015): Abnormal frontostriatal activity during unexpected reward receipt in depression and schizophrenia: Relationship to anhedonia. Neuropsychopharmacology 2016(41): 2001–2010.
19. Walter H, Kammerer H, Frasch K, Spitzer M, Abler B (2009): Altered reward functions in patients on atypical antipsychotic medication in line with the revised dopamine hypothesis of schizophrenia. Psychopharmacology (Berl) 206:121–132.
20. Waltz JA, Schweitzer JB, Ross TJ, Kurup PK, Salmeron BJ, Rose EJ, *et al*. (2010): Abnormal responses to monetary outcomes in cortex, but not in the basal ganglia, in schizophrenia. Neuropsychopharmacology 35:2427–2439.
21. Schlagenhauf F, Huys QJ, Deserno L, Rapp MA, Beck A, Heinze HJ, *et al*. (2014): Striatal dysfunction during reversal learning in unmedicated schizophrenia patients. Neuroimage 89:171–180.
22. Frank M, Seeberger LC, O'Reilly RC (2004): By carrot or by stick: Cognitive reinforcement learning in parkinsonism. Science 306: 1940–1943.
23. Frank MJ, O'Reilly RC (2006): A mechanistic account of striatal dopamine function in human cognition: Psychopharmacological studies with cabergoline and haloperidol. Behav Neurosci 120: 497–517.
24. Frank MJ, Moustafa AA, Haughey HM, Curran T, Hutchison KE (2007): Genetic triple dissociation reveals multiple roles for dopamine in reinforcement learning. Proc Natl Acad Sci U S A 104: 16311–16316.
25. Waltz J, Frank M, Robinson B, Gold J (2007): Selective reinforcement learning deficits in schizophrenia support predictions from computational models of striatal-cortical dysfunction. Biol Psychiatry 62: 756–764.
26. Waltz JA, Frank MJ, Wiecki TV, Gold JM (2011): Altered probabilistic learning and response biases in schizophrenia: Behavioral evidence and neurocomputational modeling. Neuropsychology 25: 86–97.
27. Fervaha G, Agid O, Foussias G, Remington G (2013): Impairments in both reward and punishment guided reinforcement learning in schizophrenia. Schizophr Res 150:592–593.
28. Gold JM, Waltz JA, Matveeva TM, Kasanova Z, Strauss GP, Herbener ES, *et al*. (2012): Negative symptoms and the failure to represent the expected reward value of actions: Behavioral and computational modeling evidence. Arch Gen Psychiatry 69:129–138.
29. Oldfield RC (1971): The assessment and analysis of handedness: The Edinburgh inventory. Neuropsychologia 9:97–113.
30. First MB, Spitzer RL, Gibbon M, Williams JB (2001): Structured clinical interview for DSM-IV-TR axis I disorders, research version, patient edition. New York: Biometrics Research, New York State Psychiatric Institute.
31. Friston KJ, Holmes AP, Worsley KJ, Poline J-P, Frith CD, Frackowiak RSJ (1995): Statistical parametric maps in functional imaging: a general linear approach. Hum Brain Mapp 2:189–210.
32. Miezin FM, Maccotta L, Ollinger JM, Petersen SE, Buckner RL (2000): Characterizing the hemodynamic response: Effects of presentation rate, sampling procedure, and the possibility of ordering brain activity based on relative timing. Neuroimage 11:735–759.
33. Barch DM, Mathews JR, Buckner RL, Maccotta L, Csernansky JG, Snyder AZ (2003): Hemodynamic responses in visual, motor, and somatosensory cortices in schizophrenia. Neuroimage 20:1884–1893.
34. Ford JM, Johnson MB, Whitfield SL, Faustman WO, Mathalon DH (2005): Delayed hemodynamic responses in schizophrenia. Neuroimage 26:922–931.
35. Lindquist MA, Meng Loh J, Atlas LY, Wager TD (2009): Modeling the hemodynamic response function in fMRI: Efficiency, bias and mismodeling. Neuroimage 45(suppl 1):S187–S198.
36. Lindquist MA, Wager TD (2007): Validity and power in hemodynamic response modeling: a comparison study and a new approach. Hum Brain Mapp 28:764–784.
37. McAvoy MP, Ollinger JM, Buckner RL (2001): Cluster size thresholds for assessment of significant activation in fMRI. Neuroimage 13:S198.
38. Forman SD, Cohen JD, Fitzgerald M, Eddy WF, Mintun MA, Noll DC (1995): Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): Use of a cluster-size threshold. Magn Reson Med 33:636–647.
39. Mamah D, Wang L, Barch D, de Erausquin GA, Gado M, Csernansky JG (2007): Structural analysis of the basal ganglia in schizophrenia. Schizophr Res 89:59–71.
40. Benjamini Y, Hochberg Y (1995): Controlling the false discovery rate: A practical and powerful approach to multiple testing. J Royal Stat Soc 57:289–300.
41. Murray G, Corlett P, Clark L, Pessiglione M, Blackwell A, Honey G, *et al*. (2007): Substantia nigra/ventral tegmental reward prediction error disruption in psychosis. Mol Psychiatry 13:267–276.
42. Koch K, Schachtzabel C, Wagner G, Schikora J, Schultz C, Reichenbach JR, *et al*. (2010): Altered activation in association with reward-related trial-and-error learning in patients with schizophrenia. Neuroimage 50:223–232.
43. Walter H, Kammerer H, Frasch K, Spitzer M, Abler B (2009): Altered reward functions in patients on atypical antipsychotic medication in line with the revised dopamine hypothesis of schizophrenia. Psychopharmacology 206:121–132.
44. Waltz JA, Schweitzer JB, Gold JM, Kurup PK, Ross TJ, Salmeron BJ, *et al*. (2009): Patients with schizophrenia have a reduced neural response to both unpredictable and predictable primary reinforcers. Neuropsychopharmacology 34:1567–1577.
45. Wolf DH, Satterthwaite TD, Kantrowitz JJ, Katchmar N, Vandekar L, Elliott MA, *et al*. (2014): Amotivation in schizophrenia: Integrated assessment with behavioral, clinical, and imaging measures. Schizophrenia Bull 40:1328–1337.

46. Kapur S (2003): Psychosis as a state of aberrant salience: A framework linking biology, phenomenology, and pharmacology in schizophrenia. Am J Psychiatry 160:13–23.
47. Zhang WN, Chang SH, Guo LY, Zhang KL, Wang J (2013): The neural correlates of reward-related processing in major depressive disorder: A meta-analysis of functional magnetic resonance imaging studies. J Affect Disord 151:531–539.
48. Chen C, Takahashi T, Nakagawa S, Inoue T, Kusumi I (2015): Reinforcement learning in depression: A review of computational research. Neurosci Biobehav Rev 55:247–267.
49. Nielsen MO, Rostrup E, Wulff S, Bak N, Broberg BV, Lublin H, *et al*. (2012): Improvement of brain reward abnormalities by antipsychotic monotherapy in schizophrenia. Arch Gen Psychiatry 69: 1195–1204.