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

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Abstract

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

Methods—38 stable outpatients with schizophrenia or schizoaffective disorder and 37 healthy controls underwent fMRI 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 fMRI analysis, prediction error-related activation at the time of feedback was highly similar between patients and

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controls. During early learning, patients activated regions in the cognitive control network to a lesser extent than controls. Correlation analyses revealed reduced responses to positive feedback in dorsolateral prefrontal cortex and caudate among those patients higher in anhedonia/avolition.

Conclusions—Together, 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

Motivation; schizophrenia; reinforcement learning; prediction error; anhedonia; striatum

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 (reduced ability to experience pleasure) and avolition (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 have described several processes required for the translation of reward information into goal-directed behavior, disruption of any of which could lead to anhedonia and/or avolition (4). The work described here examines one of these processes, reinforcement learning, and its relationship to anhedonia and avolition in schizophrenia.

Numerous behavioral studies have suggested that reinforcement learning is intact in schizophrenia when learning is fairly implicit (though see (5) for evidence of impaired Serial Reaction Time task learning), but more impaired when learning tasks require explicit representations of stimulus-reward contingencies (see (4, 6)). This pattern has given rise to the theory that the striatally mediated gradual reinforcement learning system may be intact in 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 (thought to be striatally mediated) coupled with impaired reversal learning (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 than controls, suggesting possible impairments in striatally mediated learning (13). The behavioral literature therefore provides a mixed picture on whether striatally mediated learning is intact in schizophrenia patients as a group.

Another approach to studying reinforcement learning is to ask whether the pattern of functional activation in regions receiving dopaminergic projections is consistent with a prediction error signal. Prediction errors 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 prediction error activity among individuals with schizophrenia using both Pavlovian and instrumental reward-learning tasks, and for both monetary and liquid rewards (15–18), with

some suggestion that positive prediction errors may be more affected than negative prediction errors (19, 20) and some suggestion that the effects may be more apparent in unmedicated (21) as compared to medicated patients.

The findings reviewed above suggest the hypothesis that impairments in learning from positive outcomes, related to reductions in striatal signaling of positive prediction errors and/or impaired cortical learning systems, may contribute to motivational deficits in schizophrenia. Here, we test these hypotheses by examining brain activity during a probabilistic reinforcement learning paradigm allowing examination of activation during both choice execution and feedback, as well as the separate assessment of learning from positive versus negative outcomes. We used a model of the role of DA in RL proposed by Frank et al. (22–24), which emphasizes the separate contributions of D1 and D2 receptors in the striatum to “Go” and “NoGo” learning respectively. Two prior studies have used this framework to examine Go learning (learning from rewarding outcomes) and NoGo learning (learning from nonrewarding outcomes) in medicated patients with schizophrenia, and found evidence of impaired Go learning but intact NoGo learning (25, 26), though one other study found impairments in both Go and NoGo learning (27). These findings are consistent with the hypothesis that the effectiveness of phasic DA signals in response to positive feedback is reduced in schizophrenia, thereby impairing Go learning. These studies also examined the relationship between negative symptoms and reinforcement learning 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. Further, in a modeling study by Gold and colleagues, 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 (28).

Methods & Materials

Participants

Participants were 49 stable outpatients with DSM-IV schizophrenia or schizoaffective disorder and 41 healthy controls with no personal or family history of psychosis. Both medicated and unmedicated patients were recruited from the community, and medication status and dose was required to have been stable for at least two weeks. Participants were group matched on sex, age, race, parental education, handedness (29), and smoking status. Inclusion criteria were 1) age 18–50 years and 2) ability to give informed consent. See Supplemental Materials for exclusions, which included exclusion for DSM-IV major depressive disorder or dysthymia in the past year. Ten individuals with schizophrenia and 4 healthy controls were excluded for excessive movement (described below), and an additional patient was excluded for having more than 50% nonresponse trials, yielding a final sample size of 37 controls and 38 patients (29 schizophrenia, 9 schizoaffective). 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 Masters-level clinician. See Supplemental Materials 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 fMRI scanning took place, and a test phase that was completed outside the scanner. During acquisition, participants were presented on each trial with one of three pairs of stimuli (“AB”, “CD”, or “EF”), in pseudorandomized order, and were instructed to choose the stimulus that they believe is “correct” based on feedback received over time. Stimuli were displayed for 2000ms, during which the participant was required to choose one of the stimuli via button press. After a jittered inter-stimulus interval ranging from 2000–6000ms, feedback consisting of the words “Correct! +\$” in green text, “Incorrect \$0” in red text, or “Too Slow!” were presented on screen for 2000ms. Subjects were told that for each “Correct” choice, they would win money, up to \$20 (in actuality, all subjects were paid an additional \$20 upon completion). For stimulus pair AB, choice of A was rewarded 80% of the time, while B was rewarded 20% of the time; pair CD was 70:30, and pair EF was 60:40. Feedback was followed by an inter-trial interval jittered from 2000–6000ms. For additional details, see Supplemental Materials.

Image Acquisition and Processing

Imaging was performed on a 3T Siemens TIM TRIO system with a 12-channel head coil. High-resolution structural images were acquired using a sagittal magnetization-prepared rapid acquisition gradient echo (MP-RAGE) sequence (TR=2.4s, TE=3.08ms, inversion time=1s, flip=8°, 176 slices, 1 mm³ voxels). Functional images were collected in 10 runs of 213 frames each using a gradient echo echo-planar sequence (TR=2030ms, TE=27ms, flip=90°, 36 slices). For details, see supplementary materials.

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 GLM Based Analyses

For these analyses, at the time of stimulus presentation, 6 choice types were modeled (A, B, C, D, E, and F), and at the time of feedback, 12 feedback types were modeled (positive and negative feedback for each choice). Non-response trials were coded as a variable of no interest. The analyses was conducted based on the general linear model (GLM) (31) using in-house software (32). The GLM for each subject included time as a 9-level regressor, made up of the 9 MR frames following each event (a finite-impulse response function approach -

FIR). An FIR approach was used rather than a canonical HRF approach because of the mixed evidence in the literature for the integrity of the HRF function in schizophrenia (33, 34). With an HRF approach, changes in the timing of responses can lead to artifactually altered magnitudes estimates (35, 36), while an FIR allows examination of the nature and pattern of the BOLD response patterns across groups (see (35, 36) for comparison of approaches). Activation at the time of stimulus presentation and at the time of feedback were modeled separately. Parameter estimates from the GLMs for each subject, including time (the 9 time points of the response), were entered into ANOVAs 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 Supplemental Materials.

Model-based fMRI Analyses

Behavioral data was modeled using a Q-learning algorithm with separate learning rates from positive feedback (“gains”; α_G) and negative feedback (“losses”, α_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 Supplemental Materials. Model-based fMRI analyses were conducted by including trial-by-trial, subject specific, values of Q (expected value) and prediction error as parametric regressors in a GLM that included choice and feedback events (collapsed across stimulus type) with the (Q value) modulate 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, including time (the 9 time points of the response for either the choice or feedback event), were entered into ANOVAs using subject as a random factor. 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). ROI analyses were conducted using mean activation within 6 regions including 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 .05 across all 6 regions.

We also conducted correlation analyses within the patient group between BOLD signal and anhedonia/avolition scores. Activation at time points 4 and 5 (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 in Supplemental Materials.

Results

Demographic and Clinical Characteristics

Participant demographic and clinical characteristics are shown in Table 1.

Behavioral Analysis

Acquisition Phase—The acquisition phase data was divided into 5 blocks of 72 trials (24 per stimulus pair), which were used in a repeated measures ANOVA with Block and Pair (AB, CD, EF) as within-subjects factors and Group (CON, SCZ) 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 proportion of high-probability choices for AB pairs, followed by CD, then EF. 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 controls, whereas patients performed more poorly than controls on the AB and EF pairs.

Test Phase—Test phase choice data is shown in Figure 2b. For the original AB, CD, and EF pairs that had been presented during acquisition, a Pair X 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 X 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 controls. 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 controls. To avoid this problem, an equivalent transfer measure was created that relies on the CD pair, performance on which was very closely matched between groups: ChooseC (CE, CF) vs. AvoidD (DE, DF). ANOVA analysis of this measure revealed a significant ChooseC/AvoidD X 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 controls ($t(72) = 2.40$, $p = .02$), while performance on the AvoidD measure did not differ significantly between groups ($p > .5$).

Modeling Results

Model fits as measured by LLH 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 AIC 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 controls and 26 patients). The learners were higher than the non-learners on self-reported anhedonia/amativation ($t(1,36) = -3.07, p = .004$), lower on WAIS Vocabulary scores ($t(1,36) = -2.42, p = .02$), but did not differ significantly on clinician-rated anhedonia/amativation ($t(1,36) = -0.48, p = .64$), 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 Prediction Error Analysis

Within the striatal ROIs, all regions demonstrated significant prediction error effects (all p s $< .007$) with positive modulation (greater activation with greater prediction error), with no significant group differences. These regions were also identified by the whole-brain analysis, (Tables 3/4 and Figure 4). A set of regions demonstrating activation that was positively modulated (Table 3, Figure 4A,B) included bilateral ventral striatum and amygdala. As can be seen in graphs to the right in Figure 4B, in these regions, activity in response to outcomes was more positive with high prediction errors. Further, as can be seen in graphs to the left in Figure 4B, both patients and controls showed greater activation when they received positive feedback, regardless of whether it was for a high probability choice or a low probability choice. A second subset of regions demonstrated activation with negative modulation, such that activation was greater for smaller positive (or larger negative) prediction errors (Table 4). These regions included cognitive control regions such as bilateral DLPFC, PPC, anterior insula, and preSMA. Examples of each type of activation pattern are shown in Figure 4B. Another third set of regions, including rostral ACC and medial frontal gyrus, demonstrated deactivation that was positively modulated (i.e., less deactivation for more positive prediction errors).

There were two regions that demonstrated an interaction between prediction error and group: right inferior frontal gyrus (+47,+15,+7; 26 voxels) and right superior temporal gyrus (+60,-60,+26; 20 voxels). Right inferior frontal gyrus showed activation that was negatively modulated in controls (reduced activation with higher prediction errors), but no significant modulation in patients. Superior temporal gyrus showed activation that was decreased for larger positive prediction errors in controls, but increased for larger positive prediction errors in patients. No significant group differences in prediction error activity were found in striatal regions.

fMRI Q-value Analysis

Striatal ROI analysis of Q value-related activity revealed robust positive modulation in bilateral nucleus accumbens (L: $F(8,416) = 6.92, p < 10^{-7}$), R: $F(8,416) = 5.89, p < 10^{-8}$), indicating greater activation when choosing stimuli with 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 timecourses are shown in Figure 5. Similar to the ROI analysis results, in the whole brain analyses, right ventral striatum demonstrated 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 bilateral DLPFC, posterior parietal cortex, anterior insula, and ACC/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 controls for all of these regions (Figure 5C).

Several regions showed a significant Time X Group interaction in the Q value effect (Table 5). Regions in brainstem, bilateral cerebellum, and left superior frontal gyrus displayed activation that was negatively modulated in controls but positively modulated in patients. Similarly, left parahippocampal gyrus was modulated positively in patients, but not in controls, and right superior parietal lobule was modulated negatively in controls, but not in patients. Finally, precuneus showed deactivation that was negatively modulated in patients, but not controls. 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. Thus, we conducted analyses only with early learning (Blocks 1–3). On ROI analysis, a Choice X Time (i.e., time within trial for a FIR analysis) X Group 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 demonstrated Choice X Time interactions in which activity was greater for high than low-probability choices in both groups, including regions in bilateral caudate, left inferior frontal gyrus, and right anterior insula (Supplemental Table S6 and Figure S6). Similar to the full Q value analysis, greater activation for low- than high-probability choices was seen in left DLPFC and precentral gyrus. A Time x Group interaction was present in a number of cognitive control regions including bilateral posterior parietal cortex, right DLPFC, preSMA, thalamus, and right anterior insula/inferior frontal gyrus (Table S6 and Figure S6a). All of these regions activated more strongly in controls than patients during early learning at the time of choice, regardless of which stimulus was ultimately chosen. Choice x Time x 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 high-probability choices among controls, with the opposite pattern among patients (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 prediction errors in the striatum using the ROI analyses (all $ps > .1$, see 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 left caudate and bilateral posterior DLPFC (Brodmann areas 44/6) (Figure 6 and 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 prediction error or positive feedback related activity.

Discussion

Behavioral results using transfer measures sensitive to Go vs. NoGo learning suggested some evidence for impairments in learning from positive, but not negative, feedback in patients as compared to controls. However, while the behavioral results demonstrated some impairment in Go learning, we found little evidence in the neuroimaging results for reduced striatal responses among patients as compared to controls. We had hypothesized that Go learning impairments would be associated with reduced positive prediction error activity, and with 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 prediction errors when examining the full acquisition phase.

Our findings of significant striatal activation at the group level in schizophrenia during learning, with no significant differences from controls, contrast with the findings of several studies in the literature demonstrating reduced striatal prediction errors in patients (41–43). However, other studies have found intact striatal prediction errors in schizophrenia patients (44–48). A possible source of these differences across studies are clinical differences in the populations examined (medicated versus 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 prediction error activity is related to positive symptoms in schizophrenia (49). Further, we also excluded patients and controls with evidence of major depression in the past year to help de-confound depression versus psychosis effects on reinforcement learning. Given that depression is also associated with altered striatal activation in response to reward (50) and to prediction error (51), it is possible that this difference from many previous studies reduced the evidence for altered prediction error signals in the striatum among our sample of individuals with schizophrenia.

The lack of significant relationships between anhedonia/avolition scores and striatal responses specifically to prediction error differs from some reports in the literature (17, 52), 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 reinforcement learning 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 controls. This procedure introduced a practice mismatch between groups, but mismatches in

the amount of practice given are not unusual in prediction error 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 as compared to 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 prediction error responses reflected in part the small sample of participants with good model fits, though the magnitudes of the correlations between prediction error 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 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 contributed as well. Our behavioral data provides some evidence for this. At both acquisition and test, we found reduced performance on the AB pair in patients as compared to controls, while performance on the CD and EF pairs (at test) did not differ between groups, though the group differences in the EF pair might have achieved significance with sample sizes larger than 38 and 37. 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 (6).

There were also some imaging results consistent with the hypothesis of impaired cortical learning in this group. In both the prediction error and Q-value analyses, we saw evidence for altered activation in frontal cortex, with right inferior frontal modulation in patients in response to prediction errors, and altered superior frontal gyrus modulation in patients in the Q value analysis. Further, during the early learning phase, several regions involved in cognitive control demonstrated reduced overall choice-related activation in patients as compared to controls, which is consistent with a reduction in explicit learning during the early learning phase. As noted above, analyses of both positive versus negative feedback and prediction error 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 controls as a group do not differ in striatal prediction error activity), and we could potentially have seen differences from controls 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 controls at the group

level were very small. We did have to exclude more non-learners from the patients than the controls, which could have biased the results in favor of seeing strong PE responses in the striatum in patients. However, Figure S1 illustrates 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 antipsychotics. As presented in Supplemental Materials, correlations with dose equivalents revealed increased NoGo learning in patients with higher medication doses, but no significant relationships between dose and brain activity. Interestingly, increased NoGo learning is what the Frank model predicts for greater levels of D2R antagonism, meaning that this relationship is actually consistent with the model (23, 53). Perhaps surprisingly, studies examining striatal activation in schizophrenia tend to find reduced striatal activation for unmedicated patients, with intact activation for patients taking atypical antipsychotics, including some direct evidence of a normalizing effect of starting these medications (54). The present study lends further support to these findings by demonstrating intact striatal activation in a population of patients primarily taking atypical antipsychotics.

In conclusion, this study demonstrated some behavioral evidence of impaired learning from positive versus negative feedback, as well as impaired learning of stimuli with high versus low reinforcement ratios, among medicated patients with chronic schizophrenia. Striatal activation was intact in the patient group at the time of choice and feedback, including intact prediction error activity. At the time of choice, patients failed to recruit cognitive control regions to the same extent as controls during early learning. These findings are suggestive of alterations in cortical, but not basal ganglia, reinforcement learning mechanisms in the patient group as a whole. However, severity of anhedonia and avolition in patients were 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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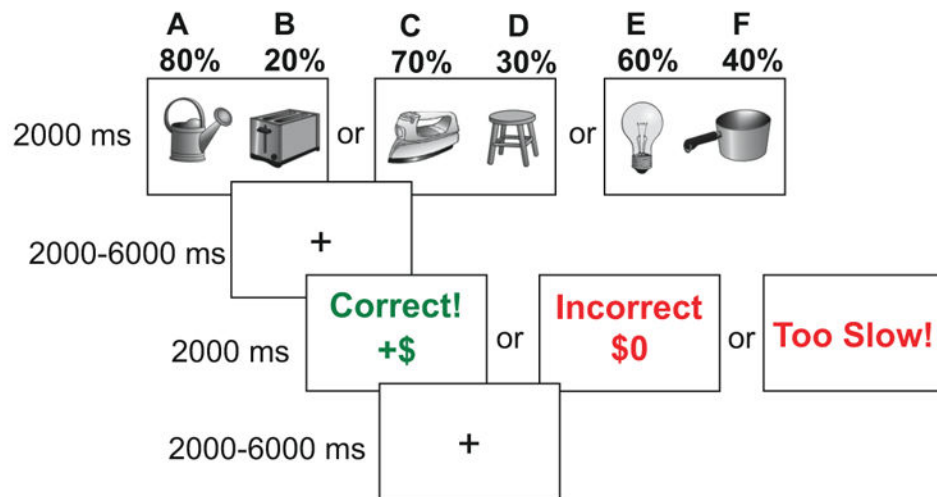


Figure 1. Experimental paradigm. Shown are the trial types and timing of the acquisition phase of the Probabilistic Stimulus Selection task. Both inter-stimulus intervals and inter-trial intervals were jittered to allow reconstruction of the BOLD response at the time of both choice and feedback.

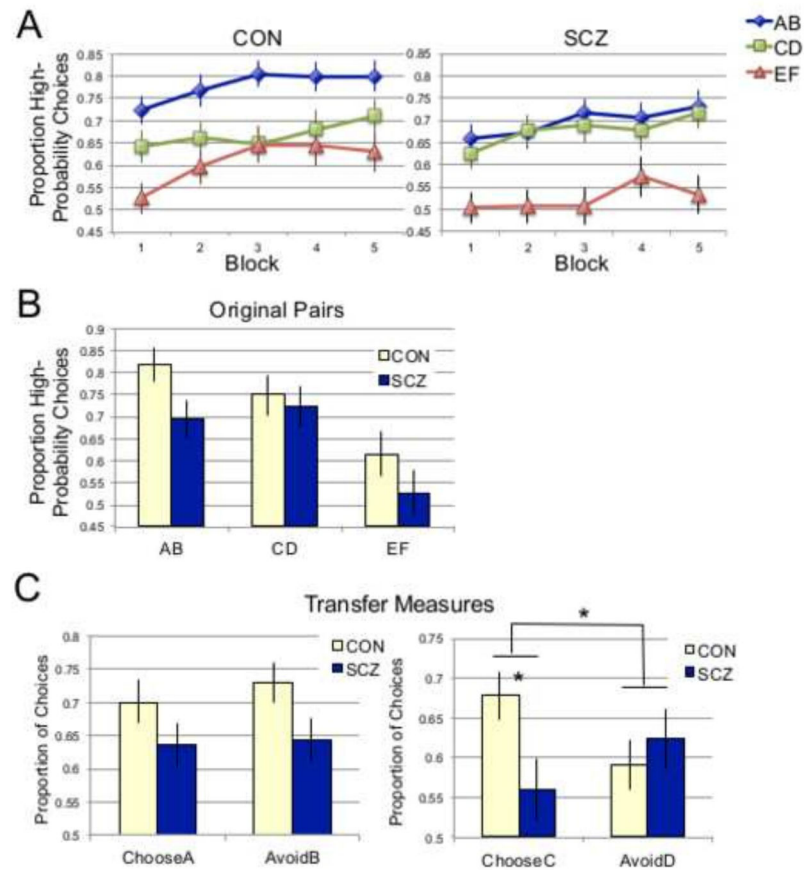


Figure 2. Behavioral results. (A) Acquisition phase performance. Proportion of high-probability choices (A/C/E) per 24-trial block. (B) Test-phase performance for original AB, CD, and EF pairs. (C) Test-phase performance for ChooseA/AvoidB and ChooseC/AvoidD transfer measures.

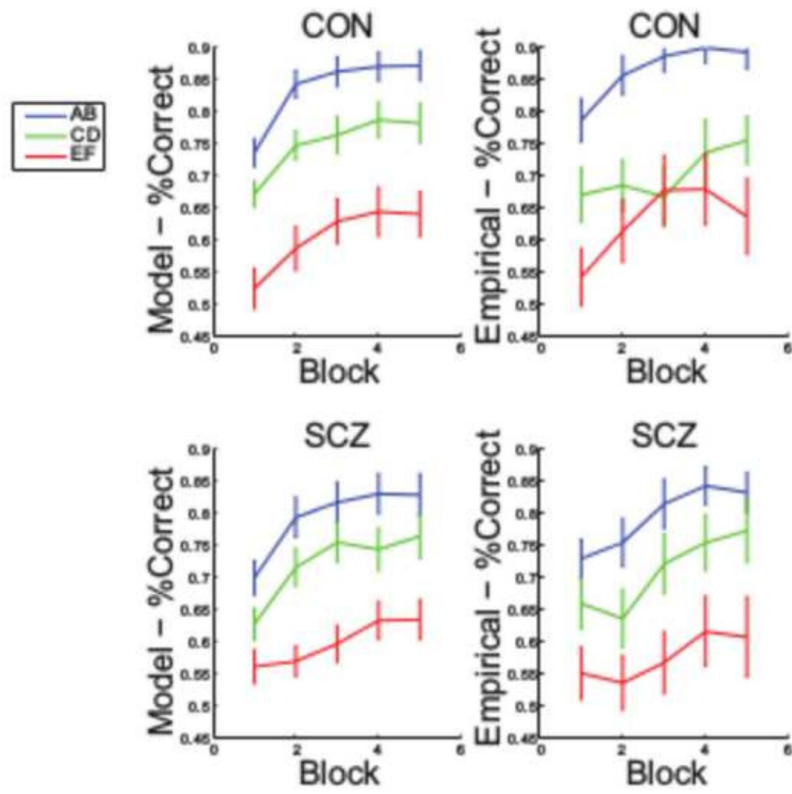


Figure 3. Modeling results. Comparison between empirical behavior and model-predicted learning curves.

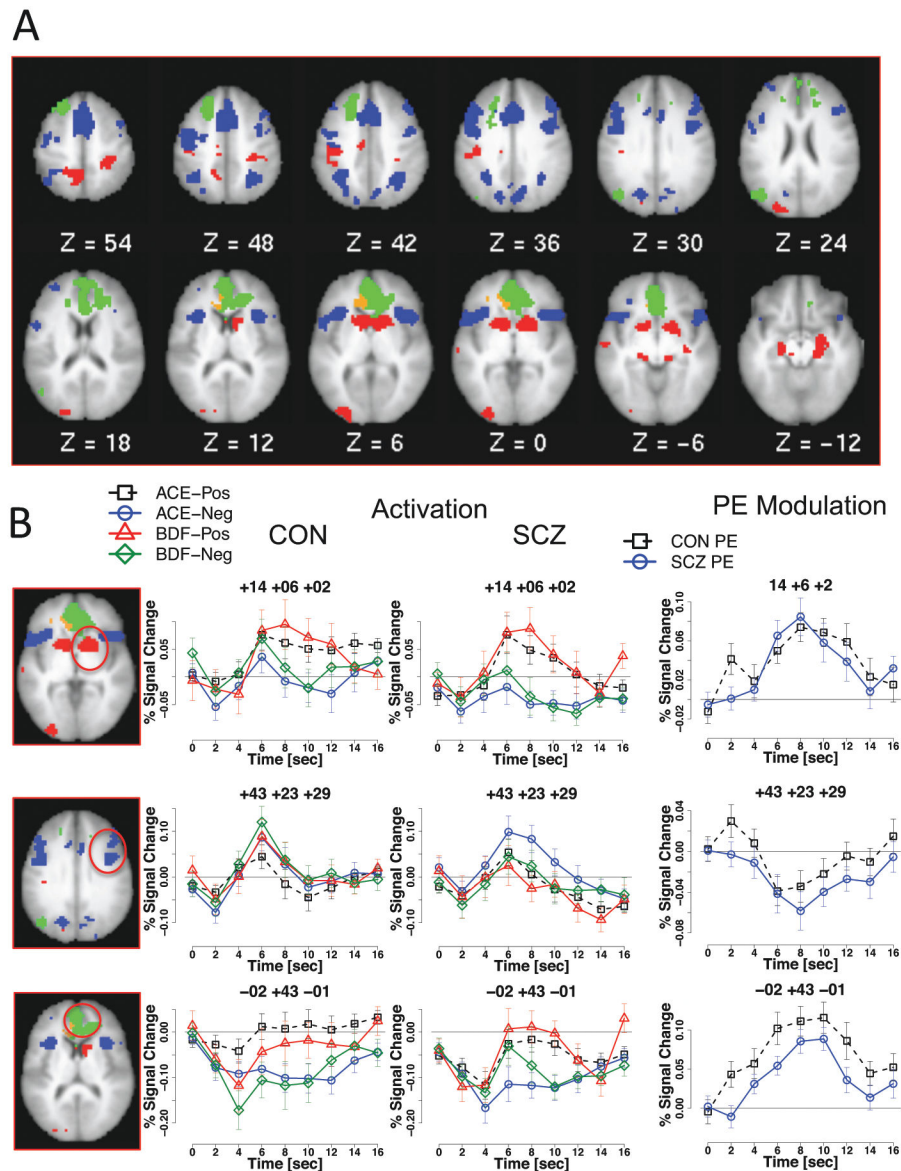


Figure 4. Prediction error analysis: Prediction Error x Time interactions. (A) Regions with significant prediction error effects in both groups. Red = activation with positive modulation; blue = activation with negative modulation; green = deactivation with positive modulation; orange = deactivation with negative modulation. (B) Example timecourses for each activation pattern. ACE: High-probability choice (A, C, or E), BDF: low-probability choice (B, D, or F), Pos: Positive feedback, Neg: Negative feedback, CON: Control, SCZ: Schizophrenia, PE: Prediction Error. Regions shown were significant at whole brain threshold of $Z = 3.0$, $N = 13$ voxels.

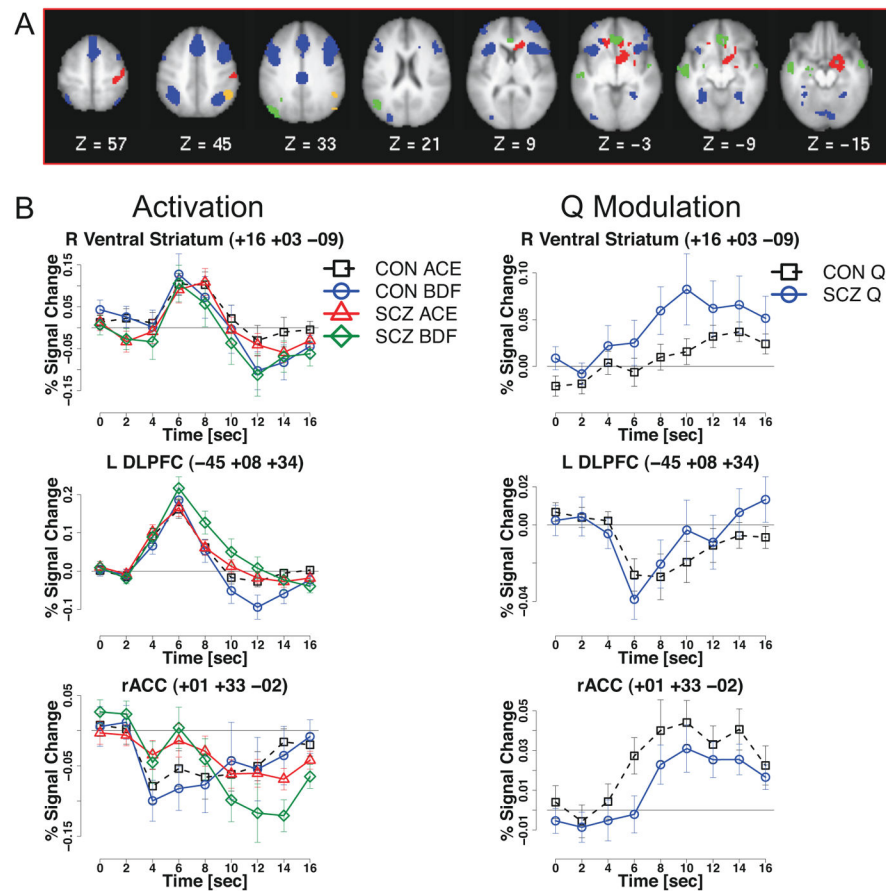


Figure 5.

Q value effects. (A) Regions demonstrating significant Q-value modulation. Red = activation with positive modulation; blue = activation with negative modulation; green = deactivation with positive modulation; orange = deactivation with negative modulation. (B) Timecourse for right ventral striatum showing activation with positive modulation. (C) Timecourse for DLPFC showing activation with negative modulation. (D) Timecourse for rACC showing deactivation with positive modulation. ACE: high-probability choice (A, C, or E), BDF: low-probability choice (B, D, or F), CON: control, SCZ: schizophrenia, Q = Q-value (expected value). Regions shown were significant at whole brain threshold of $Z = 3.0$, $N = 13$ voxels.

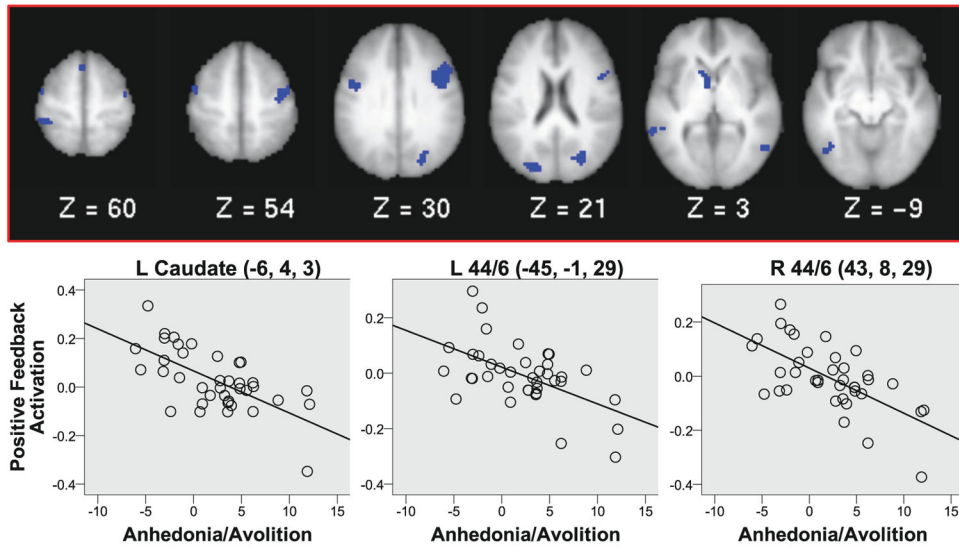


Figure 6. Correlation analyses: Regions with significant negative correlations between responses to positive feedback and self-reported anhedonia/avolition among patients. Regions shown were significant at whole-brain threshold of $Z = 3.0$, $N = 13$ voxels.

Table 1

Demographic and clinical characteristics

	CON (N = 37)		SCZ (N = 38)	
	Mean	SD	Mean	SD
Age	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 (% Caucasian)	29.7		42.1	
Smoking Status (% 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
Past Major Depressive Disorder (#)(not in past year)	2		7	7
Past Substance Dependence (#)	2		7	
Antipsychotic Medication (# Taking)	--		35 ^a	
Antipsychotic Dose (CPZ equivalent)	--		717.78	474.25
Antidepressant Medication (# Taking)	--		17	
Antianxiety Medication (# Taking)	--		6	
Mood Stabilizer Medication (# Taking)	--		9	
Anticholinergic Medication (# Taking)	--		12	

Notes: There were no significant differences between patients and controls in age, sex, race, or handedness. Personal education was higher among controls 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 controls, though disorganization scores were low in patients and did not differ between groups. Anhedonia and avolition scores were higher among patients than controls on all clinical and self-report measures except the TEPS anticipatory pleasure score.

^aTypical only $n = 4$; atypical only $n = 29$; typical + atypical $n = 2$; clozapine only $n = 2$; clozapine + other $n = 3$.

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	.279 (.30)	.173 (.24)
	Loss Learning Rate	.275 (.33)	.215 (.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	.268 (.25)	.165 (21)
	Loss Learning Rate	.218 (.28)	.213 (.31)

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Table 3

Regions demonstrating positive modulation of activity for prediction errors

	Region	BA	X	Y	Z	# 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	-03	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

Table 4

Regions demonstrating negative modulation of activity for prediction errors

	Region	BA	X	Y	Z	# 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	01	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

Table 5

Regions demonstrating a significant parametric effect of Q values

Effect	Region	BA	X	Y	Z	# Voxels	Z	Activation Pattern		
								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	

Effect	Region	BA	X	Y	Z	# Voxels	Z	Activation Pattern	
								Choice vs Baseline	Q Value Modulation
	R	24	1	33	-2	129	6.60	Deactivation	Positive
	R	40	49	-54	35	127	4.80	Deactivation	Negative
Q X Group	R	7	30	-65	57	13	4.01	Activation	CON: Neg; SCZ: None
	R	--	1	-32	-38	26	4.13	Activation	CON: Neg; SCZ: Pos
	L	--	-28	-48	-47	71	4.84	Activation	CON: Neg; SCZ: Pos
	R	--	28	-60	-42	57	4.53	Activation	CON: Neg; SCZ: Pos
	L	10	-11	63	18	22	4.93	Activation	CON: Neg; SCZ: Pos
		23	0	-20	28	14	3.82	Activation	CON: None; SCZ: Neg
	L	7	-5	-70	47	18	3.57	Activation	CON: None; SCZ: Neg
	L	36	-22	-40	-15	32	4.8	Activation	CON: None; SCZ: Pos
		7	0	-53	38	15	3.94	Deactivation	CON: None; SCZ: Pos