ORIGINAL ARTICLE

Midbrain Activation During Pavlovian Conditioning and Delusional Symptoms in Schizophrenia

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Context: Recent theories have suggested that the inappropriate activation of limbic motivational systems in response to neutral stimuli may underlie the development of delusions in schizophrenia.

Objective: To investigate the activation of the amygdala, midbrain, and ventral striatum during an aversive pavlovian conditioning task in patients with schizophrenia and healthy control participants using functional magnetic resonance imaging.

Design: Cross-sectional case-control functional neuroimaging study.

Setting: Academic medical center.

Participants: Twenty patients with *DSM-IV*–diagnosed schizophrenia or schizoaffective disorder and 20 healthy control participants.

Main Outcome Measures: Regional brain activation as assessed by functional magnetic resonance imaging blood oxygen level–dependent responses, and delusional symptom severity on the Positive and Negative Syndrome Scale.

Results: Patients with schizophrenia showed abnormal activation of the amygdala, midbrain, and ventral striatum during conditioning. Activation of the midbrain in response to neutral rather than aversive cues during conditioning was correlated with the severity of delusional symptoms in the patient group (corrected $P=.04$).

Conclusion: Inappropriate activation of the midbrain in response to neutral stimuli during conditioning is associated with the severity of delusional symptoms in patients with schizophrenia.

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SCHIZOPHRENIA TYPICALLY PRESENTS with the onset of psychotic symptoms in the third decade of life. The exact cause of these symptoms remains unknown, but abnormal learning about the significance of environmental stimuli has been suggested to lead to the development of psychosis.[1-13] In particular, recent theories have suggested that the inappropriate activation of motivational brain systems in response to neutral stimuli may underlie the development of delusional beliefs,[1,3,4,6,7,10] a hypothesis we sought to test.

We investigated the activation of motivational brain regions during associative learning in patients with schizophrenia using an aversive pavlovian conditioning procedure. During aversive pavlovian conditioning, a previously neutral stimulus (the conditioned stimulus [CS]) is repeatedly paired with an aversive outcome (the unconditioned stimulus [US]) and comes to elicit a characteristic response (the conditioned response), which often resembles the response to the US presented alone. Animal studies have demonstrated a key role for the amygdala in aversive pavlovian conditioning,[14,15] which has been confirmed in human neuroimaging studies.[16,17]

The learning of new CS-US associations during conditioning drives changes in the firing of midbrain dopaminergic neurons.[18] Dopaminergic neuron firing is initially seen in response to the presentation of the US, but over the course of conditioning it comes instead to be elicited by the predictive CS.[18] Considerable evidence from animal studies supports the view that conditioned dopaminergic activity in the midbrain and target regions in the ventral striatum mediates the motivational impact, or incentive salience, of a pavlovian CS.[19-21] Furthermore, human functional magnetic resonance imaging (fMRI) studies have demonstrated a similar pattern of learning-related changes in the activation of the midbrain and ventral striatum during conditioning.[22-28]

Table. Demographic and Clinical Characteristics of the Study Participants

Characteristic	Patients With Schizophrenia (n=20)	Healthy Control Participants (n=20)	*P* Value
Age, mean (SD), y	36.4 (9.4)	35.1 (8.2)	.66
NART IQ, mean (SD)	111.6 (10.3)	116.0 (6.8)	.16
Male, No.:Female, No.	14:6	14:6	>.99
Chlorpromazine equivalent medication dosage, mean (SD), mg/d	290.4 (184.0)	. . .	. . .
PANSS score, mean (SD)			
Total	48.5 (9.3)	. . .	. . .
Positive total	10.1 (2.6)	. . .	. . .
Negative total	14.2 (3.8)	. . .	. . .
General total	24.3 (5.8)	. . .	. . .

Abbreviations: NART, National Adult Reading Test; PANSS, Positive and Negative Syndrome Scale; ellipses, not applicable.

Increasing evidence supports the view that associative learning and the associated regulation of dopaminergic neuron firing are abnormal in schizophrenia.[1,3-5,7-11] First, putative risk genes for schizophrenia have convergent effects on synaptic processes known to be required for associative learning.[8,10,29] Second, patients with schizophrenia show deficits in a range of cognitive tasks dependent on the formation of novel associations,[26-28] including impairments in human aversive conditioning procedures.[30-33] Third, neuroimaging studies have shown abnormal activation of the midbrain and ventral striatum during conditioning in schizophrenia in both appetitive and aversive conditioning procedures,[32,34,35] with evidence of inappropriately enhanced activation of these brain regions in response to neutral stimuli.[32,34] However, no previous studies have demonstrated a direct relationship between altered activation of motivational brain regions during conditioning and delusional symptoms in schizophrenia.

In our study, we have used a novel aversive pavlovian conditioning procedure to investigate amygdala, midbrain, and ventral striatal activation during aversive conditioning in patients with schizophrenia and healthy control participants using functional MRI. We additionally investigated the relationship of these measures to delusional symptoms in patients with schizophrenia. Our primary hypotheses were that we would observe abnormal conditioned activation of the amygdala in schizophrenia, reflecting impaired associative learning in the disorder, and a related dysregulation of activation of the dopaminergic midbrain and ventral striatum associated with the severity of delusional beliefs.[10]

METHODS

SUBJECTS

The study was approved by the Lothian National Health Service Research Ethics Committee, and all participants provided written informed consent before taking part. Twenty patients meeting *DSM-IV* criteria for schizophrenia (n=14) or schizoaffective disorder (n=6) took part in the study (**Table**). Diagnoses were confirmed at structured interview using the Structured Clinical Interview for *DSM-IV*, and psychotic symptoms were additionally assessed using the Positive and Negative Syndrome Scale (PANSS). Mood symptoms were rated using the Hamilton Depression Rating Scale and the Young Mania Rating Scale. Exclusion criteria for this study included any history of neurological disease, dependence on nonprescribed drugs, the presence of any MRI-incompatible implants, pregnancy, and excessive motion during the scan. Twenty matched control participants with no personal or family history of a psychotic illness or other major mental illness were also recruited and assessed using the same instruments (Table). Control participants were additionally subject to the same exclusion criteria as the patient group. Both groups completed the National Adult Reading Test as a measure of premorbid IQ.[36] Groups were matched for age, sex, IQ, and cannabis use.

EXPERIMENTAL TASK

An aversive pavlovian conditioning procedure was used with visual stimuli on a 50% reinforcement schedule (**Figure 1**). The use of a 50% reinforcement schedule allowed acquired responses to the CS to be examined in the absence of the confounding effects of US presentation.[16] The CSs were screens displaying a single color (blue or yellow). The USs were images drawn from the International Affective Picture System (IAPS) collection.[37] Two CSs were used, both of which were followed on 50% of trials by pictures from the IAPS library. One CS (CS_{av}) was paired on 50% of trials with the presentation of an aversive IAPS picture (US_{av}). The second (CS_{neu}) was paired on 50% of trials with an emotionally neutral IAPS picture (US_{neu}). The pictures changed on each trial such that the participant saw any given picture only once during scanning. Further details of the pictures used in the study are given in the eAppendix (available at http://www.archgenpsychiatry.com). The CSs were presented for 2±0.25 seconds, and on reinforced trials they were immediately followed by a 2-second presentation of the US. The mean interstimulus interval was 11 seconds, and the onset and order of individual trials were optimized for the experimental contrasts of interest using the genetic algorithm toolbox.[38] Twelve trials of each of the 4 conditions were presented per run, and 3 runs were completed per participant. The color-valence contingencies were counterbalanced across participants. Participants were asked to indicate as quickly as possible which color screen was shown during the scanning via button presses, providing behavioral measures of both response accuracy and latency. To introduce additional prediction error–related variance (see "Temporal Difference Modeling" subsection), the contingency between color and valence was reversed for the third run. Following scanning completion, participants were asked to rate the USs for emotional intensity on a scale of low, medium, or high.

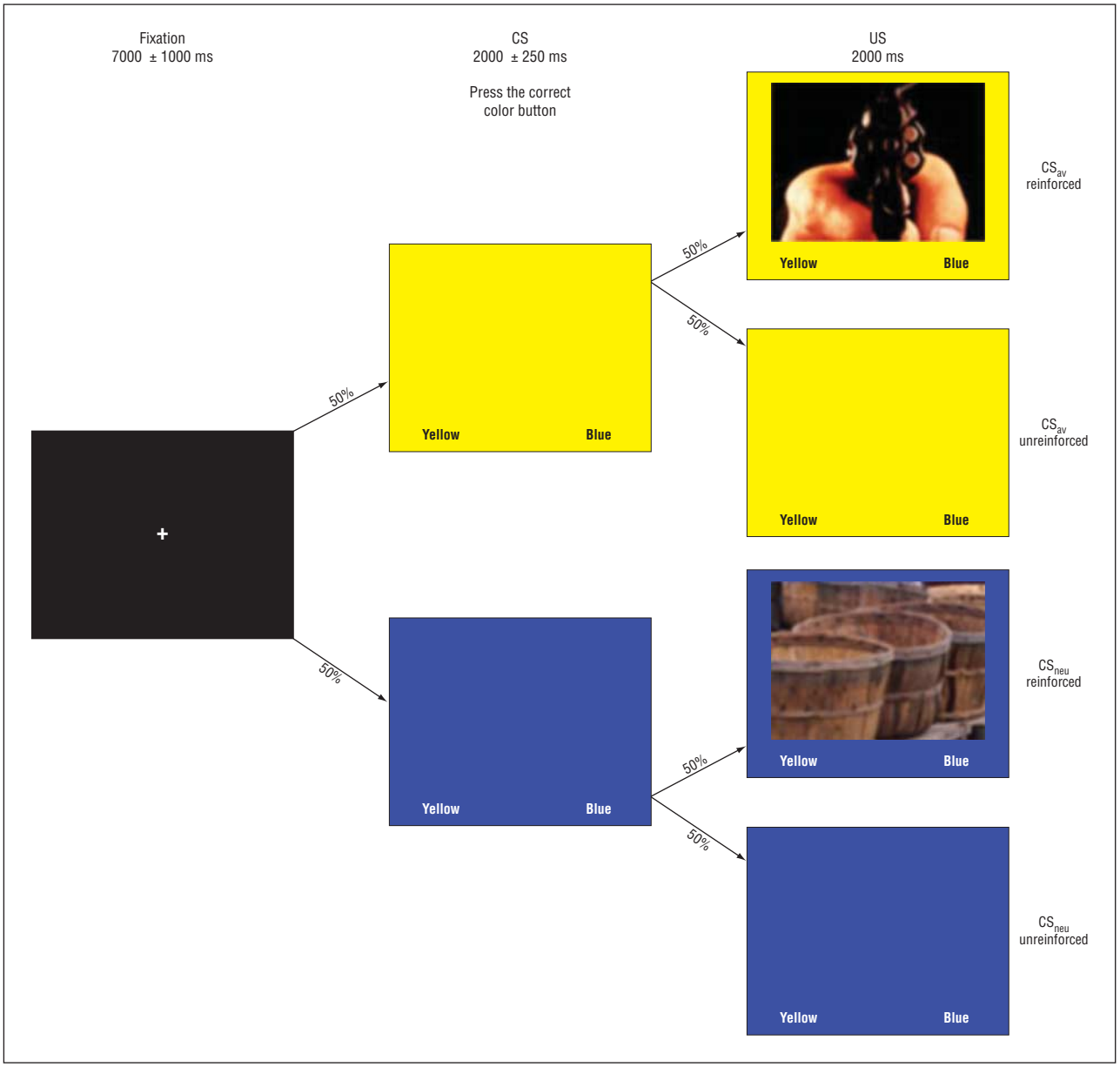

Figure 1. Schematic of the design of the functional magnetic resonance imaging pavlovian conditioning task. CS indicates conditioned stimulus; US, unconditioned stimulus; CS_{av}, aversive CS; and CS_{neu}, neutral CS.

BEHAVIORAL ANALYSIS

Previous studies of conditioning have shown that responses to an aversively associated CS are speeded during acquisition of the CS-US association.[39,40] Reaction times (RTs) were therefore analyzed using a repeated-measures analysis of variance with valence and session as within-subjects factors and group as a between-subjects factor. Paired *t* tests were used to determine whether the difference of $CS_{av} > CS_{neu}$ varied between sessions for each group.

SKIN CONDUCTANCE RESPONSE ACQUISITION AND ANALYSIS

Skin conductance responses (SCRs) were measured during scanning to provide a second measure of conditioning. Galvanic skin conductance was logged using a BIOPAC MP100 data acquisition system equipped with a GSR100C amplifier, MR-compatible carbon electrodes, and the AcqKnowledge software package (BIOPAC Systems, Inc, Goleta, California; http://www.biopac.com). Full details of the methods and analysis are given in the eAppendix.

IMAGE ACQUISITION AND PREPROCESSING

Brain imaging was performed using a GE 1.5-T Signa scanner (GE Medical, Milwaukee, Wisconsin) at the SFC Brain Imaging Research Centre, Edinburgh, Scotland. Axial gradient-echo echo-planar whole-brain images oriented parallel to the anterior commissure–posterior commissure line were acquired with an echo time of 40 milliseconds, a repetition time of 2000 milliseconds, a 64×64 matrix, and a 240-mm field of view, giving an in-plane resolution of 3.75 mm. Volumes comprised 27 interleaved, contiguous, 5-mm slices. All subjects completed 3 runs of 538 seconds each, producing 269 volumes per run, the first 4 of which were discarded to avoid T1-weighted saturation ef-

fects. A high-resolution structural T1-weighted volume was obtained using a coronal magnetization-prepared rapid-acquisition gradient-echo sequence having 128 slices and the following parameters: inversion time, 600 milliseconds; echo time, 3.4 milliseconds; flip angle, 15°; field of view, 22 cm; slice thickness, 1.7 mm; and 256 × 192 matrix.

Imaging data preprocessing and analysis were performed using the Statistical Parametric Mapping 5 program (Wellcome Department of Imaging Neuroscience, London, England; http://www.fil.ion.ucl.ac.uk/spm/software/spm5/). Functional data were realigned and coregistered to their respective T1-weighted structural image. This was then segmented, with subsequent normalization parameters applied to the mutually aligned functional volumes. Finally, functional images were smoothed using an 8-mm full-width at half-maximum gaussian filter and resampled at a resolution of 3 mm isotropic. Temporally, data were high-pass filtered at a period of 128 seconds, and serial correlations were estimated using a first-order autoregressive model.

IMAGE ANALYSIS

All 4 conditions were modeled at the first level: CS_{av} reinforced, CS_{neu} reinforced, CS_{av} unreinforced, and CS_{neu} unreinforced. Trials for which the subject produced no behavioral response and each subject's motion parameters were included as nuisance regressors. Events were modeled as δ functions synchronized to the onset of the CS, convolved with a canonical hemodynamic function. The primary analysis was to establish an effect of conditioning using the contrast of $CS_{av} > CS_{neu}$ as well as the reverse contrast. To avoid the confounding influence of the US, only the 50% of trials that had not been reinforced were included. Previous work has indicated that conditioning effects are more pronounced during the early stages of training[16]; therefore, this analysis was initially constrained to the first run. First-level *t* tests were used within random-effects second-level analyses: 1-sample *t* tests were used to determine within-group effects, whereas group differences were assessed with a 2-sample *t* test.

As we had a clear set of a priori hypotheses concerning the amygdala, ventral striatum, and dopaminergic midbrain, small volume correction was then applied within these regions of interest (ROIs) at a voxel level of $P < .05$, familywise error (FWE) corrected for multiple comparisons. The amygdala ROI was derived directly from the automated anatomical labeling atlas. The ventral striatum was defined as the ventral half of a union between the automated anatomical labeling caudate nucleus and putamen (Montreal Neurological Institute [MNI] z cutoff at –3 mm). The dopaminergic midbrain was defined as a union between the Brodmann area–defined substantia nigra and a 10-mm-diameter sphere located at 0, –20, –10.[34]

As these areas are believed to mediate association formation in the context of aversive conditioning, it was predicted that dysfunctional activation of these regions in patients would be associated with delusional symptoms. To investigate this, the patients' contrasts of interest for session 1 were regressed according to their PANSS scores for item P1 (delusions) and item P6 (suspiciousness or persecution), with both PANSS items included in the regression. As a rigorous test of this hypothesis, we also tested the correlation of brain activation with hallucination scores from the PANSS (item P3), which we predicted would not show an association with brain activation in the hypothesized regions during conditioning. We conducted ROI analysis for the amygdala, ventral striatum, and midbrain as previously described. In addition, where significant results were found, analyses were rerun with the chlorpromazine equivalent antipsychotic medication dosage included as a covariate to establish whether any of the observed effects were attributable to antipsychotic medication.

TEMPORAL DIFFERENCE MODELING

We next investigated whether conditioning-related activation of the midbrain, ventral striatum, and amygdala conformed to the pattern of firing of dopaminergic neurons predicted by temporal difference (TD) models.[18,22,41] The TD model describes mathematically the learning processes that occur during pavlovian conditioning and closely relates to the observed changes in dopaminergic neuron firing seen in animals.[18] It is derived from the prediction in reinforcement learning theory that learning occurs when outcomes deviate from expectations. For each trial, a prediction error is calculated corresponding to the difference between the expected and observed outcomes. Previous studies have shown that midbrain and ventral striatal responses in fMRI correlate with prediction errors calculated using the TD model in healthy subjects.[22,25,34,42] We assessed the degree to which brain activation in the midbrain, ventral striatum, and amygdala correlated with prediction errors in both control and patient groups across all 3 training runs in our study (see eAppendix for full methods). In addition, we determined the accumulated value attributed to the CS_{av} and CS_{neu} across the conditioning paradigm, representing the degree to which each CS acquired motivational salience (eAppendix). Finally, we investigated whether patients inappropriately attributed motivational salience to neutral stimuli over the course of learning by repeating the TD model with neutral rather than aversive stimuli modeled as salient (eAppendix).

RESULTS

BEHAVIORAL ANALYSIS

Groups were matched for color naming accuracy for both aversive (Mann-Whitney $U = 147$; $P = .16$) and neutral (Mann-Whitney $U = 136$; $P = .30$) trials, indicating that they similarly performed and attended to the task (eFigure 1). The groups did not differ in terms of their arousal ratings for the neutral or aversive USs (aversive: Mann-Whitney $U = 129$; $P = .14$; neutral: Mann-Whitney $U = 158$, $P = .51$), in line with previous findings.[43,44]

Analysis of RT changes across the 3 runs provided behavioral evidence of the effect of conditioning in both groups, with a relative speeding of RTs seen in response to the CS_{av} in both run 1 and run 3 (**Figure 2**A). Significant effects were found for session ($F_{2,76} = 4.3$; $P = .02$), group ($F_{1,38} = 4.6$; $P = .04$), and the interaction between valence and session ($F_{2,76} = 3.7$; $P = .03$). The patient group responded slightly more slowly overall; however, RTs were equivalently modulated by learning in both groups (Figure 2A).

PHYSIOLOGICAL RESPONSE ANALYSIS

Conditioning was also assessed by measuring SCRs (Figure 2B). Analysis of SCRs revealed a main effect of session ($F_{2,76} = 5.7$; $P = .005$) and a main effect of group ($F_{1,39} = 4.7$; $P = .04$). The session × group interaction was also significant ($F_{1,37} = 6.0$: $P = .02$). This interaction derived from a relatively greater SCR to aversive stimuli in control subjects in run 1 and a relatively greater SCR to

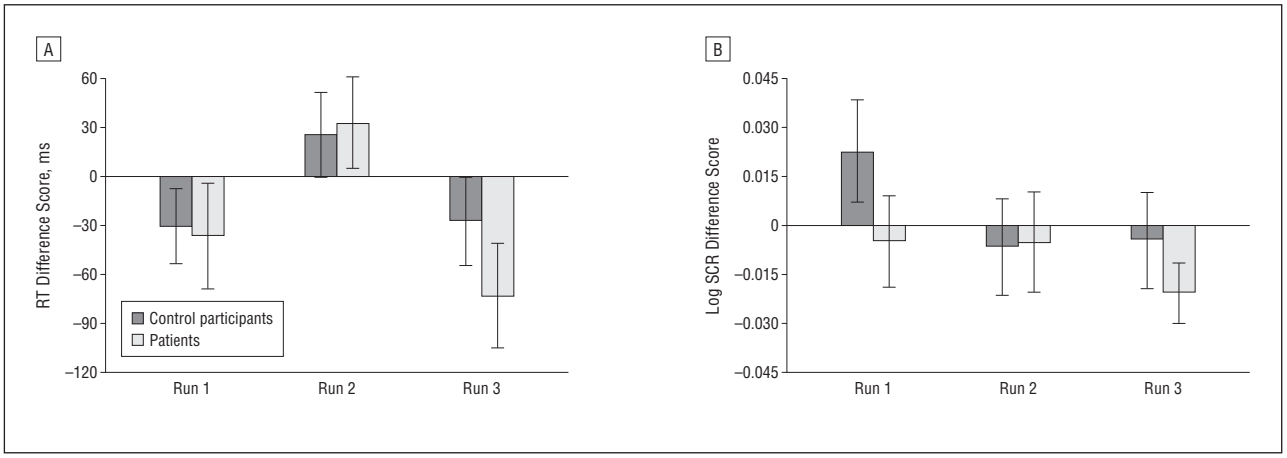

Figure 2. Behavioral measures of conditioning in patients and control participants. A, Reaction time (RT) difference scores (aversive minus neutral). B, Logarithm of the skin conductance response (SCR) difference scores (aversive minus neutral). Error bars indicate ±1 SE.

neutral stimuli in patients in run 3. Further examination of the data demonstrated that the relative impairment in SCRs in patients in run 1 was in part derived from a failure of habituation of SCRs to the neutral stimuli in the patient group.

PATIENTS SHOW ABNORMAL CONDITIONED ACTIVATION OF THE AMYGDALA

Previous studies have demonstrated a rapid acquisition of conditioned responses within the amygdala during aversive conditioning, with subsequent response habituation.[16] We similarly found amygdala activation to be greatest during the first run of conditioning in the present task (eFigure 2) and therefore focused our initial analysis of conditioning-related brain responses on the first run of training.

Control participants demonstrated significant conditioned activation of the right amygdala for the contrast $CS_{av} > CS_{neu}$ (**Figure 3**A) (MNI coordinates: 24, 3, –18, $P = .005$, FWE corrected for multiple comparisons within the a priori ROI). Activation of the left amygdala was also observed in this contrast at slightly lower statistical thresholds (Figure 3A). No other brain regions showed this pattern of conditioning-related activation. In contrast, patients failed to show conditioned amygdala activation, with between-group comparisons revealing lower amygdala activation bilaterally in patients compared with control participants (Figure 3B) (MNI coordinates: 18, 0, –18, $P = .03$, and –18, 0, –12, $P = .04$, FWE corrected within the amygdala ROI). This between-group difference remained significant after covarying for antipsychotic medication dosage ($P = .02$ for the right amygdala and $P = .31$ for the left amygdala) and did not derive from differential responses to the US per se as additional analyses synchronized to US onset demonstrated that control participants and patients did not differ in their response to the USs (eFigure 3). There was no evidence of an association between amygdala activation and the severity of delusions or hallucinations. No significant effects were seen in the reverse contrast.

MIDBRAIN ACTIVATION IN PATIENTS CORRELATES WITH DELUSIONAL SYMPTOMS

We next investigated the relationship between blood oxygen level–dependent responses during conditioning and delusional and persecutory symptoms as rated by the PANSS (PANSS items P1 and P6). There was a significant correlation between midbrain activation during conditioning and delusional symptom severity (PANSS item P1) in the contrast of $CS_{neu} > CS_{av}$ (MNI coordinates: –9, –24, –12, $P = .04$, FWE corrected within the midbrain ROI), which remained significant after covarying for antipsychotic medication dosage ($P = .049$). This correlation derived from increased midbrain activation in response to neutral vs aversive CSs in subjects with higher delusion scores (**Figure 4**). There was no equivalent correlation of midbrain activation or other brain region activation with severity of hallucinations (PANSS item P3), and no correlation was seen between nucleus accumbens activation and psychotic symptoms.

TD MODELING REVEALS ALTERED MIDBRAIN AND VENTRAL STRIATAL RESPONSES IN PATIENTS

Temporal difference modeling, performed across all 3 runs of conditioning, revealed significant prediction error–related brain activation in the control group in the midbrain and the right ventral striatum (midbrain MNI coordinates: 3, –27, –12, $P = .03$, FWE corrected within the midbrain ROI; striatum MNI coordinates: 27, 6, –6, $P = .03$, FWE corrected within the ventral striatum ROI). Patients did not show TD signals in either of these brain regions, and direct between-group comparisons confirmed that patients had a significantly lower TD signal in the midbrain than control participants (MNI coordinates: 12, –12, –15, $P = .04$, FWE corrected within the midbrain ROI), which remained the case after covarying for medication dosage ($P = .04$). Notably, examination of parameter estimates in the midbrain suggested that patients showed a reversed pattern of TD responses, potentially indicating a greater TD response to neutral stimuli

than to aversive stimuli.[34] There was no significant correlation between TD signals in the accumbens and midbrain and the severity of delusions or hallucinations in the patient group.

PATIENTS INAPPROPRIATELY ENCODE NEUTRAL TRIAL VALUE WITHIN NUCLEUS ACCUMBENS

We further investigated the inappropriate response of patients to neutral stimuli by performing an additional TD analysis in which neutral USs were treated as motivationally salient (with an outcome value of +1) and aversive USs were modeled as being motivationally irrelevant (with an outcome value of 0). Control participants showed no significant prediction error–related or value-related activation for neutral trials in this analysis, suggesting that these stimuli were correctly dismissed as being irrelevant. Patients, on the other hand, showed a significant relationship between neutral trial value and activity within the left nucleus accumbens (MNI coordinates: −9, 15, −9, $P=.03$, FWE corrected within the striatum ROI), the significance of which was strengthened after covarying for medication ($P=.004$). These findings demonstrate that patients with schizophrenia inappropriately encode value for neutral stimuli in the nucleus accumbens.

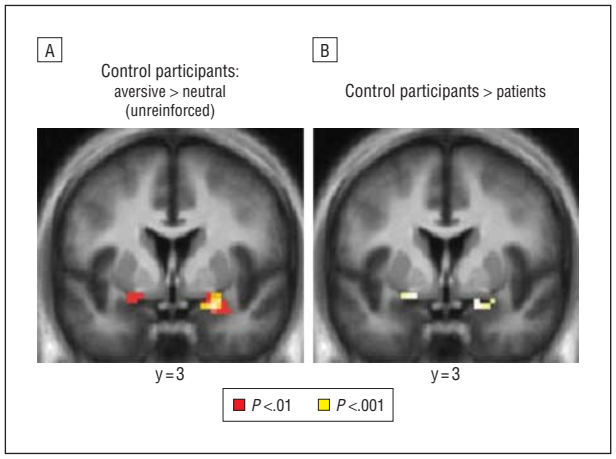

Figure 3. Conditioning effects on amygdala activation. A, Amygdala activation as a function of conditioning in the control group (aversive conditioned stimulus > neutral conditioned stimulus, run 1). B, Between-group comparison showing relatively lower amygdala activation during conditioning in the patient group than in the control group. Significant effects are shown at $P<.001$ or $P<.01$ (uncorrected voxel level). Results are displayed on the mean normalized structural image of the study's 40 participants.

COMPARISON OF PATIENT SUBGROUPS

We explored whether the primary results differed between patients with a *DSM-IV* diagnosis of schizophrenia and those with schizoaffective disorder. No significant differences were found between these groups for any of the main findings, even at lenient statistical thresholds.

COMMENT

We have investigated the response of the amygdala, midbrain, and ventral striatum during aversive pavlovian conditioning in healthy control participants and patients with schizophrenia. Control participants showed conditioned activation of the amygdala and learning-related activation of the midbrain and ventral striatum. Patients with schizophrenia had significantly impaired amygdala activation during conditioning and showed significantly less learning-related activation of the midbrain than control subjects. Furthermore, inappropriate activation of the midbrain in response to neutral rather than aversive cues during conditioning was correlated with the severity of delusional symptoms in the patient group. These results provide experimental support for the hypothesis that the inappropriate attribution of motivational significance to neutral stimuli underlies the development of delusional beliefs in schizophrenia.[1]

The involvement of the amygdala in aversive pavlovian conditioning has been established in rodent models and human neuroimaging studies.[14,16,17] While previous functional MRI studies of aversive conditioning have used electric shocks or very loud noise as the US, we instead used aversive pictures from the IAPS picture library as they are less liable to lead to movement in the scanner

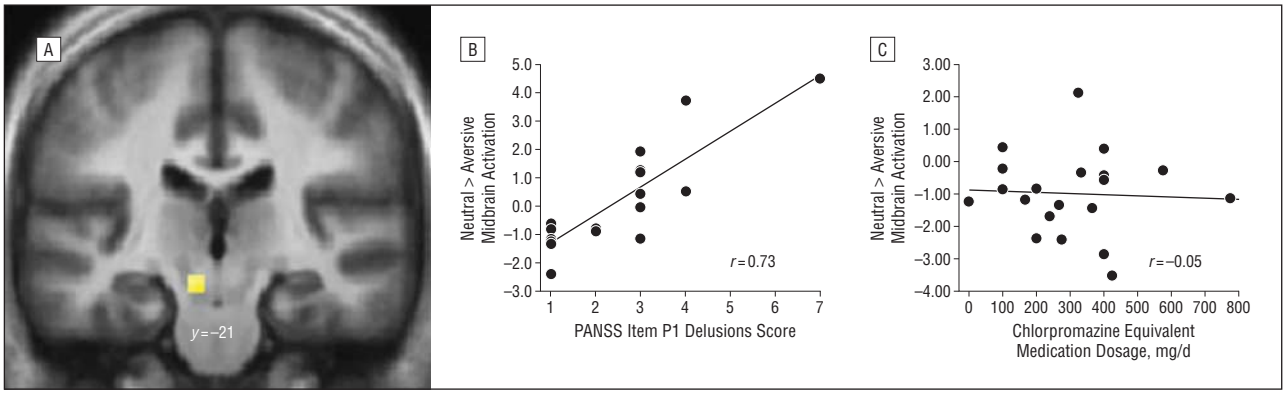

Figure 4. Patients' midbrain activation during conditioning correlates with delusional symptoms. A, A significant correlation of patients' midbrain activation was seen with respect to Positive and Negative Syndrome Scale (PANSS) item P1 delusional symptom scores ($P=.04$, familywise error corrected). Statistical parametric mapping was thresholded at an uncorrected level of $P<.001$. B, Scatterplot displaying the relationship between midbrain activation (peak voxel) and PANSS item P1 scores, covarying for item P6 scores. Patients with higher delusion scores showed an increased midbrain response to neutral stimuli relative to fearful stimuli. C, Scatterplot of medication dosage against midbrain activation showing that antipsychotic medication dosage does not account for the observed relationship with delusions.

and are generally well tolerated by patients. Aversive IAPS pictures produced robust conditioned activation of the amygdala in control participants, which was greatest early in conditioning in accordance with previous aversive conditioning studies[16,17] and which was paralleled by changes in SCRs and RTs.[45,46]

Patients with schizophrenia showed a bilateral deficit in amygdala activation during aversive conditioning when compared with healthy control participants. This decrease in amygdala activation could not be accounted for in terms of impaired task performance, as there was no evidence of differential task performance on the color-discrimination task conducted in the scanner, or in the modulation of RTs by conditioning. Patients with schizophrenia did, however, show decreased conditioning of SCRs, consistent with impaired regulation of autonomic arousal by the amygdala.[15] This dissociation between SCRs and RT responses in patients is consistent with previous findings that parallel neural systems (both intra-amygdala and extra-amygdala) subserve different components of pavlovian conditioning.[47,48]

Healthy control participants demonstrated learning-related activation of the midbrain during aversive conditioning as assessed by TD modeling. Previous studies have used TD modeling to demonstrate prediction error–related activations of the midbrain during appetitive conditioning,[25,34] which correlate with the response of dopaminergic neurons observed during conditioning in animal studies.[18] Animal studies have also shown conditioned dopaminergic responses during aversive learning,[49-51] suggesting a parallel role for midbrain dopaminergic neurons in aversive conditioning. However, this has not been a universal finding,[52,53] leading some authors to suggest a role for serotonergic systems in aversive prediction error signaling.[54] Our findings provide support for an aversive prediction error signal in the midbrain, paralleling that seen in appetitive conditioning.

Patients with schizophrenia showed significantly lower learning-related midbrain activation than control participants. This is in accordance with previous studies that have shown abnormal prediction error–related midbrain activation during appetitive conditioning in subjects with psychosis[34] and suggests a general abnormality in the recruitment of the midbrain during learning for both appetitive and aversive reinforcers in schizophrenia. Theorists have suggested that the abnormal regulation of midbrain dopaminergic neuron firing in relation to salient stimuli may underlie the development of delusional symptoms in schizophrenia.[1,3,4] We did not find a specific association between delusional symptoms and midbrain prediction error signals, replicating the findings of previous investigations using appetitive stimuli.[11,34] However, we did identify a strong association between inappropriate midbrain activation in response to neutral cues rather than aversive cues during conditioning and delusional symptoms. To our knowledge, these findings provide the first evidence that abnormal midbrain activation in response to neutral stimuli during conditioning is associated with the severity of delusional symptoms, providing support for theories of abnormal salience attribution in schizophrenia.[1] Furthermore, our findings suggest that TD modeling, which attempts to model the transfer of neural responses from the US to the CS over the course of associative learning, does not provide as good an account of delusional symptom formation as model-free approaches focused on the aberrant salience of the CS.[11,12,34,55]

Patients with schizophrenia also demonstrated abnormal encoding of the motivational salience, or value, of the neutral stimulus in the ventral striatum. The ventral striatum plays a central role in motivated behavior and is a major target of neuronal projections from the midbrain. Participants with schizophrenia showed a significant association of ventral striatal activity with the acquired value of neutral rather than aversive stimuli. This striking result parallels previous findings of abnormal striatal activation during aversive conditioning in schizophrenia[32] and suggests that during conditioning patients erroneously learn about neutral stimuli as though they had reinforcing (aversive) outcomes.

A number of limitations to our study should be noted. First, nearly all of the patients in the study were receiving antipsychotic medication. However, no primary findings correlated with antipsychotic medication dosage, and the relationship between delusions and inappropriate midbrain activation in response to neutral stimuli remained significant even after covarying for antipsychotic treatment. Second, although the study was relatively well powered in terms of neuroimaging studies, further studies will be required to establish the generalizability of our findings. Finally, while we obtained in-scanner measurements of RTs and SCRs, future imaging studies could usefully include additional behavioral measures to further demonstrate the abnormal attribution of motivation salience to neutral stimuli in patients with schizophrenia.[13]

Overall, our findings demonstrate abnormal responses of limbic brain regions to neutral stimuli in patients with schizophrenia during conditioning. Inappropriate activation of the dopaminergic midbrain to neutral stimuli correlated with the severity of delusional symptoms in patients. These findings support the view that the aberrant regulation of motivational systems contributes to the development of delusional symptoms in schizophrenia.[1,3,4,10]

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Online-Only Material: The eAppendix and eFigures are available at http://www.archgenpsychiatry.com.

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Correction

Figure Parts Mislabeled. In the article titled "Mitochondrial Complex I Activity and Oxidative Damage to Mitochondrial Proteins in the Prefrontal Cortex of Patients With Biopolar Disorder," by Andreazza et al, published in the April issue of the *Archives* (2010;67[4]:360-368), the first (A) and second (B) graphs of Figure 4 on page 365 should be switched. The legend is correct.