ORIGINAL ARTICLE

Failure of Neural Responses to Safety Cues in Schizophrenia

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Context: Abnormalities in associative memory processes, such as Pavlovian fear conditioning and extinction, have been observed in schizophrenia. The retrieval of fear extinction memories (safety signals) may be particularly affected; although schizophrenic patients can extinguish conditioned fear, they show a deficit in retrieving fear extinction memories after a delay. The neurobiological basis of this abnormality is unknown, but clues have emerged from studies in rodents and humans demonstrating that the ventromedial prefrontal cortex (vmPFC) is a key mediator of extinction memory retrieval.

Objective: To measure autonomic and neural responses during the acquisition and extinction of conditioned fear and the delayed recall of fear and extinction memories in patients with schizophrenia and healthy control participants.

Design: Cross-sectional case control, functional magnetic resonance imaging study.

Setting: Academic medical center.

Participants: Twenty schizophrenic patients and 17 healthy control participants demographically matched to the patient group.

Main Outcome Measures: Skin conductance and blood oxygen level–dependent responses.

Results: During fear conditioning, schizophrenic patients showed blunted autonomic responses and abnormal blood oxygen level–dependent responses, relative to control participants, within the posterior cingulate gyrus, hippocampus, and other regions. Several of these abnormalities were linked to negative symptoms. During extinction learning, patients with schizophrenia and control participants showed comparable autonomic and neural responses. Twenty-four hours after the learning phases, the control subjects exhibited decreased fear and increased vmPFC responses in the extinction (safe) context as expected, indicating successful retention of the extinction memory. In contrast, the schizophrenic patients showed inappropriately elevated fear and poor vmPFC responses in the safe context.

Conclusion: Failure of extinction memory retrieval in schizophrenia is associated with vmPFC dysfunction. In future studies, abnormalities in fear learning and extinction recall may serve as quantitative phenotypes that can be linked to genetic, symptom, or outcome profiles in schizophrenia and those at risk for the disorder.

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ALTHOUGH COGNITIVE IMpairment is a central, debilitating feature of schizophrenia, recent evidence has suggested that abnormalities in emotion-related processes play an important role in the core symptoms of the disorder. For example, negative symptoms have been linked to a diminished capacity to learn information about rewards or pleasure[1-3] and to use this information to guide behavior.[4] Also, associations found between depression and anxiety and (1) elevated risk for the development of psychosis[5-7] and (2) positive symptom severity in schizophrenia[8-11] suggest that dysregulation of the neural systems mediating emotional function contributes to psychosis. Evidence for a bias to respond to neutral information as negatively valenced or threatening in delusional patients[12,13] further suggests that the encoding or retrieval of the affective values of stimuli in the environment may be impaired in psychotic patients. One possible explanation for these abnormalities is that they arise from disruptions of the mechanisms governing emotional learning and memory processes. Supporting this hypothesis is evidence for abnormalities in basic appetitive[14,15] and aversive[16-22] associative learning and memory in schizophrenia.

One commonly used model of emotional learning and memory is Pavlovian fear conditioning and extinction. In experimental paradigms based on this model, the presentation of an aversive stimulus (the unconditioned stimulus [US]), such as a loud noise or an electrical shock, follows the presentation of a neutral stimulus, such as a

tone or picture.[23] This pairing is repeated several times until the animal learns that the neutral stimulus (the conditioned stimulus [CS]) predicts the US; the animal then exhibits autonomic responses reflecting fear (such as increased heart rate, blood pressure, and sweating) before the onset of the US. In human fear conditioning studies, a second control CS is also usually presented, which is not followed by a US and does not elicit anticipatory fear (the CS–). Repeated presentations of the CS that was previously paired with the US (the CS+) without the US leads to a gradual decrease in the conditioned physiological fear responses—a process known as fear extinction learning. Importantly, it has been demonstrated that both the fear and the extinction memory trace can be retrieved independently at a later time in a context-gated manner.[24-26] The context can be the physical environment, time, or a mood or physiological state that was present at the time of learning.[27]

Studies conducted in rodents have found that both fear and extinction learning are initiated in the amygdala,[28-31] whereas the medial prefrontal cortex (mPFC) plays a key role in the retrieval of fear extinction memories.[32] The role of the mPFC in fear extinction recall was demonstrated by experiments showing that ablation[33-35] or inhibition[36] of a region within the mPFC in rats, the infralimbic cortex, reduces, abolishes, or delays extinction recall, whereas electrical stimulation[37] of the infralimbic cortex can simulate it. Recent neuroimaging studies in humans have found evidence for a human homologue of the infralimbic cortex in the perigenual and orbitofrontal cortex (the ventromedial prefrontal cortex [vmPFC]).[38-40] This region in humans responds selectively during the retrieval of extinction memories,[38,40] and its thickness has been correlated with the success of extinction memory retrieval in healthy subjects.[41,42]

Previously, we examined fear and extinction learning and memory in patients with schizophrenia by measuring skin conductance responses (SCRs) using a validated 2-day Pavlovian fear conditioning and extinction paradigm.[17] We found that both healthy control subjects and schizophrenic patients were able to successfully acquire and extinguish conditioned fear responses. Twenty-four hours following successful fear conditioning and extinction learning to a CS+, healthy control subjects exhibited lower SCRs to the CS+ presented in the extinction learning context compared with the fear conditioning context, similar to the pattern previously observed in humans[43] and rodents.[27] In contrast, the schizophrenic patients showed an excessive fear response (high SCRs) to the CS+ in the extinction (safe) context, thus failing to demonstrate appropriate context gating of extinction memory retrieval.

In the present study, we sought to identify changes in brain activity associated with deficient fear extinction recall in schizophrenia by measuring fear and extinction learning and memory while simultaneously collecting functional magnetic resonance imaging (fMRI) data. We predicted that the schizophrenic patients would show impaired delayed extinction recall and, based on the known critical role of the vmPFC in extinction memory and evidence for mPFC impairment in schizophrenia during emotional[44-48] and social[49-52] perception, that this extinction recall deficit would be associated with dysfunction of the vmPFC.

METHODS

PARTICIPANTS

For all subjects, exclusion criteria included severe medical illness, significant head trauma, neurologic illness, substance abuse during the past 6 months, and contraindications for MRI scanning (eg, implanted metal objects, claustrophobia). We limited our cohort to males to avoid introducing heterogeneity into our measures related to sex differences.[53] Seventeen healthy male subjects were recruited via advertisement and screened for psychiatric illness using the structured clinical interview for *DSM-IV* (SCID)[54]; subjects with past or present psychiatric diagnoses were excluded. Twenty male patients who met *DSM-IV* criteria for schizophrenia (12 treated and 8 untreated with antipsychotic medication; **Table 1**) according to the SCID were recruited and characterized by the Massachusetts General Hospital Schizophrenia Program. The schizophrenia and control groups were matched with respect to age, mean parental education, and handedness (Table 1). Written informed consent was obtained from all subjects prior to enrollment in accordance with the guidelines of the Partners HealthCare institutional review board. Levels of positive and negative symptoms of schizophrenia were evaluated in each patient by a trained rater (D.J.H.) using the Positive and Negative Syndrome Scale[55] on the first day of the experimental protocol. Also, symptoms of anxiety and depression were measured on day 1 of the protocol in all subjects using the Spielberger State and Trait Anxiety Inventory[56] and the Beck Depression Inventory,[57] respectively.

FEAR CONDITIONING AND EXTINCTION PROCEDURE

A 2-day fear conditioning and extinction protocol used by our group in previous studies[40,58,59] was administered during fMRI data collection. The protocol consisted of 3 phases on day 1 (habituation, fear conditioning, and extinction learning) and 2 phases on day 2 (extinction recall and fear renewal). During both days, recording electrodes were placed on the palm of the participant's nondominant hand. Electrodes were also attached to the second and third fingers of the participant's dominant hand for the purpose of delivering the US (a 500-millisecond mild electrical stimulus). The intensity of the US was set by each participant before the beginning of the procedure to a level that was "annoying but not painful." Electrical stimulations were only delivered during the fear conditioning phase, but participants were told that they "may or may not receive electrical stimulations" before every phase other than habituation. The visual stimuli consisted of digital photographs of 2 rooms that contained lamps (**Figure 1**) that were presented via a projector in the magnet bore. The 2 rooms (a library and an office) comprised the 2 virtual contexts. Three colors of the lit lampshade of the lamp (blue, red, or yellow) comprised the 3 conditioned stimuli (CS). During the fear conditioning phase, 2 of the CS were paired at a 60% reinforcement rate with the US (CS+) and 1 was not paired with the US (CS–). The US occurred during 500 milliseconds following the offset of the CS+. During the extinction learning phase, only 1 of the 2 CS+ was presented again, without being followed by the US (the extinguished CS+ [CS+E]). The other CS+ never underwent extinction (the unextinguished CS+ [CS+U]). All phases of the experiment included 16 CS+ (all phases except extinction learning: 8 CS+E, 8 CS+U; extinc-

tion learning: 16 CS+E) and 16 CS– trials (eFigure 1; http://www.archgenpsychiatry.com). For the 3 phases that included both the CS+E and CS+U, these 2 trial types were presented sequentially in an order that was counterbalanced across participants. The CS– trials were intermixed among the CS+ trials. For each trial, the context was presented for 9 seconds: 3 seconds alone, followed by 6 seconds in combination with a CS+ or CS–. The trials of the fear conditioning and fear renewal runs included the conditioning context. The trials of the extinction learning and extinction recall runs included the extinction context. The selection of the CS colors and contexts was counterbalanced across participants. The design of the paradigm was event related; the mean intertrial interval was 15 seconds (range, 12-18 seconds).

Throughout the procedure, participants passively viewed the stimuli, and each participant's attention to the stimuli was monitored by study staff via the ISCAN fMRI Remote Eye Tracking Laboratory. Functional runs during which subjects closed their eyes were excluded from the analyses. At the end of day 1 and at the start of day 2, each participant was asked whether he could recall the color of the light and describe the room that was or was not associated with the electrical stimulation.

SKIN CONDUCTANCE DATA COLLECTION AND ANALYSES

During the procedure just described, skin conductance was recorded for 5 seconds before the presentation of the context, during the 3-second presentation of the context alone, and during the 6-second presentation of the context plus the CS. The SCR magnitude for each CS was calculated by subtracting the mean skin conductance during the 2 seconds immediately before CS onset (ie, the response to the context alone) from the highest skin conductance recorded during the 6-second CS duration. Skin conductance responses were square root transformed prior to analysis. Differential fear conditioning was calculated as the mean SCR for the CS+ trials minus the mean SCR for the CS– trials during fear conditioning (early conditioning: first 4 trials; late conditioning: last 4 trials). Extinction learning was calculated as the mean SCR for the last 4 CS+ trials minus the mean SCR for the last 4 CS– trials during extinction learning. The success of extinction recall was measured using an Extinction Retention Index: 100 – ([the average SCR for the first 4 trials of extinction recall divided by the largest SCR of fear conditioning] × 100). The direction of the effect for within-group differential fear conditioning (CS+ > CS–), extinction recall context dependence (CS+U > CS+E),[17,43] and the reduction in the Extinction Retention Index in the schizophrenic patients[17] were each predicted a priori; thus, 1-tailed *t* tests were planned for those comparisons. Two-tailed *t* tests were used for all other comparisons.

fMRI DATA ACQUISITION AND ANALYSES

Scanning occurred in a 3-T MR scanner (Siemens TIM Trio; Siemens Medical Systems) with echoplanar imaging capability and a 12-channel gradient head coil. For each functional run, T2-weighted echoplanar images were acquired (45 × 3-mm thick slices, 3.1 × 3.1 × 3-mm in-plane resolution) using a gradient echo sequence (repetition time = 3000 milliseconds; echo time = 30 milliseconds; flip angle = 90°). The fMRI data were processed using the FreeSurfer functional analysis stream (https://surfer.nmr.mgh.harvard.edu/fswiki). Each functional run was motion corrected, spatially smoothed (full width at half maximal = 5 mm) with a 3-dimensional Gaussian filter, and intensity normalized. Functional runs were excluded from the fMRI analyses if greater than 15 instances of more than 1 mm of head movement between repetition times occurred during the run. The following conditions were included in the general linear model for the day 1 experimental phases: a blank screen/fixation period (which included the electrical stimulations), the context presented alone, early CS+, late CS+, early CS–, and late CS– (eFigure 1). Conditions for the day 2 phases included a blank screen/fixation period, the context presented alone, early CS+E, late CS+E, early CS+U, late CS+U, and CS–. Data collected during the fixation periods and the context presented alone were not included in the subsequent analyses. Statistical maps of group averaged data and between-group differences were created in Talairach space by calculating a *t* statistic at each voxel for

Table 1. Demographic Characteristics of All Participants[a]

	Mean (SD)	
	Control Group (n = 17)	Schizophrenia Group (n = 20)
Age, y	34.2 (9.9)	34.7 (9.8)
Premorbid IQ[b]	111.1 (7.1)	106.1 (9.8)
Parental education, y	14.7 (2.0)	13.7 (3.2)
Trait anxiety[c,d]	28.6 (9.9)	42.3 (12.4)
State anxiety[c,d]	25.4 (4.7)	37.5 (12.0)
Depression[d,e]	1.3 (2.0)	9.5 (9.4)
Intensity of electrical stimulation[d]	2.0 (1.0)	1.3 (0.5)
Subjects who learned the CS identities, %[d]	88	50
Subjects who recalled the CS identities, %	82	65
Subjects who learned the context identities, %	100	90
Subjects who recalled the context identities, %[d]	100	75
PANSS total score		52.7 (13.8)
PANSS positive symptoms subscale score		13.5 (5.7)
PANSS negative symptoms subscale score		13.9 (6.3)
PANSS general symptoms subscale score		25.3 (5.9)
Duration of illness, y		12.9 (9.4)
Chlorpromazine equivalents		301.0 (347.5)

Abbreviations: CS, conditioned stimulus; PANSS, Positive and Negative Syndrome Scale.

[a] A group of schizophrenic patients (n = 20) and a group of healthy control subjects (n = 17) matched for age, parental education, and IQ were enrolled in the study. One of the patients and one of the control subjects were left-handed; the remaining subjects were right-handed. Eleven patients were taking second-generation antipsychotics (aripiprazole [n = 3]; risperidone [n = 2]; clozapine [n = 2]; olanzapine [n = 1]; quetiapine [n = 1]; clozapine and aripiprazole [n = 1]; paliperidone [n = 1]). One patient was taking haloperidol and 8 were not taking any antipsychotic medication. Within the patient group, scores on all subscales of the PANSS (negative, positive, and general) were correlated with one another ($R > .46$; $P < .02$), and state anxiety levels correlated with trait anxiety levels ($R = .67$; $P = .002$), depressive symptoms ($R = .60$; $P < .006$), and positive symptoms ($R = .54$; $P = .01$). Mean levels of electrical stimulation set by each subject were lower in the schizophrenic patients than in the control subjects ($P = .004$). Also, the schizophrenic patients showed lower levels of explicit learning of the CS identities at the end of day 1 ($P = .01$) and lower levels of explicit recall of the context identities at the beginning of day 2 ($P = .03$) compared with the control subjects.

[b] Premorbid IQ was measured using the American National Adult Reading Test.

[c] Trait and state anxiety levels were measured using the Spielberger State and Trait Anxiety Inventory.

[d] Significant difference between schizophrenic patients and control subjects ($P < .05$).

[e] Symptoms of depression were measured using the Beck Depression Inventory.

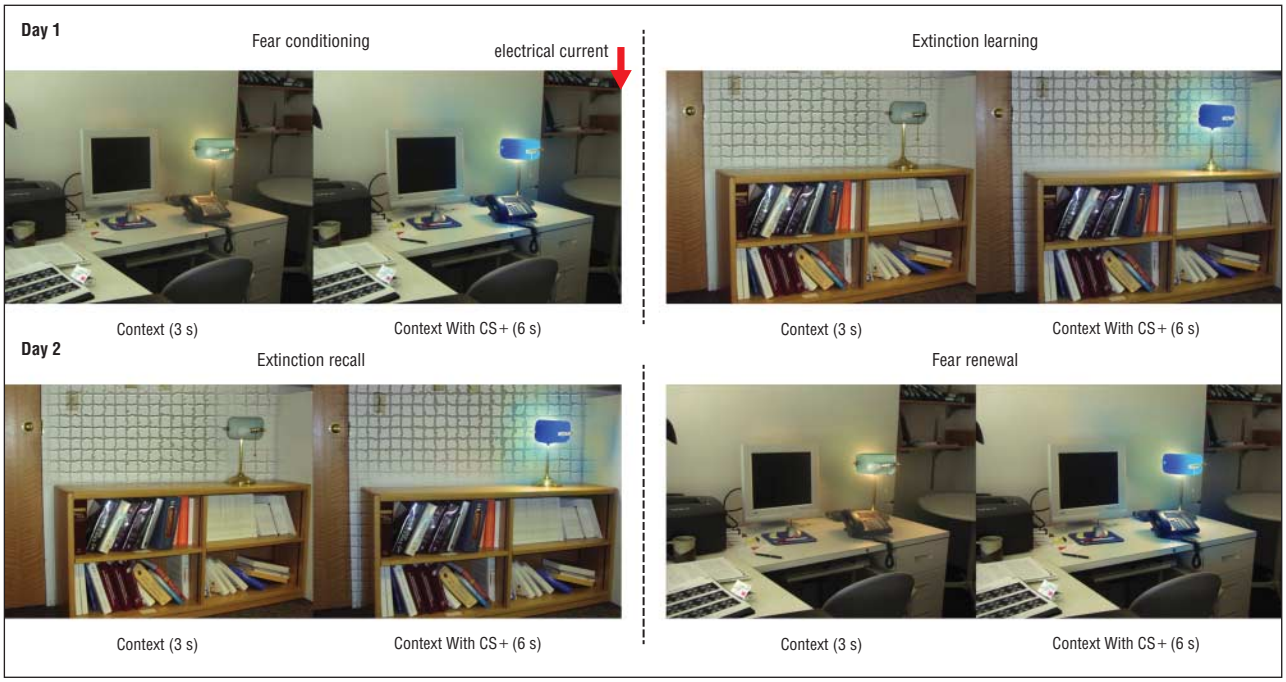

Figure 1. The 2-day experimental paradigm. In this example, the blue light is the conditioned stimulus (CS) that was paired during fear conditioning with the electrical stimulation and was later presented during the extinction learning phase (CS+E). The fear learning context here is the office, whereas the extinction learning context is the library.

the the contrasts of interest, including a weighted least squares adjustment, using random effects analyses. Responses during fear conditioning and extinction learning were measured by comparing responses during the first (early) or last (late) 4 CS+ trials to the accompanying 4 CS– trials. Because we did not have a strong a priori basis for making predictions about neural responses during fear conditioning and extinction learning in schizophrenia (since our previous study did not demonstrate between-group differences for these phases[17]), for these 2 phases, we used a conservative whole brain–cluster correction calculated using a Monte Carlo simulation (10 000 iterations, height threshold of $P < .005$) to identify voxels showing significant within-group responses or between-group differences in activation. Extinction recall and fear renewal–associated activations were measured by comparing responses during the first 4 trials of the CS+E to responses during the first 4 trials of the CS+U.[40] Activation for this contrast during extinction recall was considered significant if clusters of voxels within the vmPFC (Brodmann areas [BAs] 25, 11, and 10) met a threshold of 10 or more contiguous activated voxels at $P < .001$. Locations of activation peaks were identified using the Talairach atlas.[60]

ASSOCIATIONS WITH CLINICAL VARIABLES

Correlations (Spearman Rho) between skin conductance measures and symptom levels were deemed significant if they met a statistical threshold of $P < .05$, Bonferroni corrected. A whole brain–regression analysis, with a cluster correction calculated using a Monte Carlo simulation (10 000 iterations, height threshold of $P < .005$), was used to identify significant correlations (Pearson R) between activation magnitudes and symptom levels. Secondary, exploratory analyses comparing the antipsychotic treated vs untreated patients, and the patients with active delusions vs those without (score on the Positive and Negative Syndrome Scale delusion item ≥ 3 or ≤ 2, respectively) were also conducted because of (1) concern about the potential confounding effects of antipsychotic treatment on our outcomes[61,62] and (2) prior evidence for abnormal affective processing in delusional patients.[12,13,44,47,63]

RESULTS

FEAR CONDITIONING AND EXTINCTION LEARNING

SCRs

Both the control subjects and schizophrenic patients showed differential fear conditioning (CS+ > CS–) during early (controls subjects: $t_{16} = 4.6$, $P = 2 \times 10^{-4}$; schizophrenic patients: $t_{19} = 2.05$, $P = .03$) and, to a lesser extent, late (control subjects: $t_{16} = 1.9$, $P = .04$; schizophrenic patients: $t_{19} = 1.6$, $P = .06$) fear conditioning (**Figure 2**A). At a trend level, control subjects showed a greater magnitude of differential fear conditioning than schizophrenic patients during early ($t_{35} = 1.8$, $P = .07$), but not late, fear conditioning.

Both the control subjects and the schizophrenic patients were able to successfully extinguish conditioned fear responses (CS+ minus CS– in late extinction learning; control subjects vs schizophrenic patients: $t_{29} = 0.41$, $P = .96$; Figure 2B).

BOLD Responses

During early fear conditioning, the control subjects showed greater responses to the CS+ compared with the CS– in limbic (hippocampus, entorhinal cortex, amygdala, insula, thalamus, brainstem, and superior temporal sulcus) and visual (fusiform and lateral occipital cortices) areas (**Table 2**). During late fear conditioning, the con-

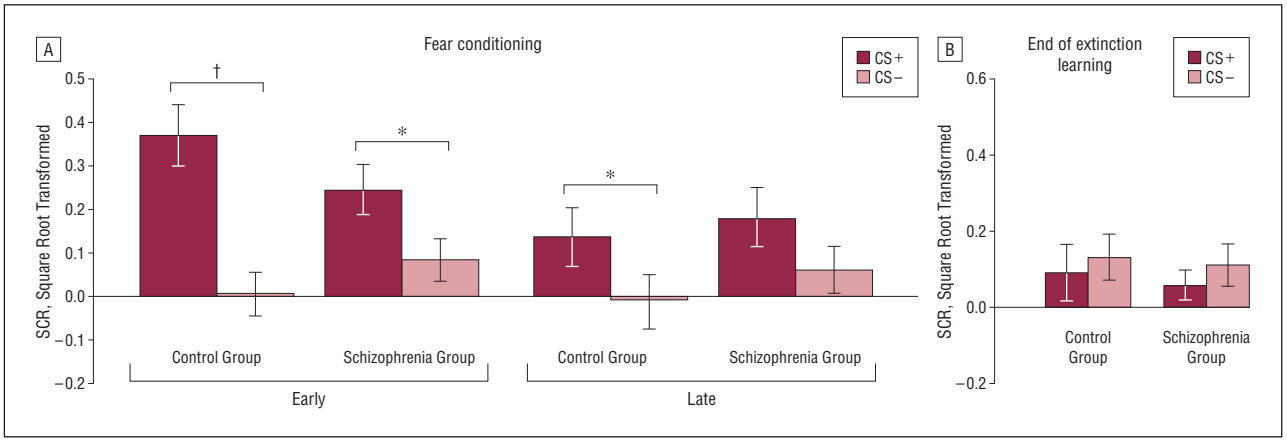

Figure 2. Skin conductance responses (SCR) on day 1 of the experiment. Mean SCRs for the fear conditioning (A) and extinction learning (B) phases are plotted. Means for each phase (early and late conditioning and end of extinction learning) are calculated using 4 CS+ and 4 CS− trials. Because it is only possible to measure levels of fear extinction and delayed fear extinction memory in participants who show some fear conditioning, participants who did not have 2 or more trials with a response magnitude of 0.3 μS or greater during the fear conditioning phase were excluded from the SCR analyses for all of the phases that followed (2 control subjects and 3 schizophrenic patients).[17] One additional control subject was excluded from the extinction learning analysis because of poor electrode contact during data collection. Thus, the fear conditioning SCR analyses include data of 17 control subjects and 20 schizophrenic patients, and the extinction learning SCR analysis includes data of 14 control subjects and 17 schizophrenic patients. Both the control and schizophrenia groups acquired differential conditioned fear responses (CS+ > CS) during early conditioning. Although there was a trend toward a difference between the 2 groups in differential early fear conditioning ($P = .07$), there were no significant differences between the 2 groups in SCRs to the CS+ and CS− alone. *$P < .05$; † $P < .0005$, for the results of the within-group paired *t* tests.

Table 2. Neural Responses During Fear Conditioning and Extinction Learning[a]

Region	BA	Area, mm³	Talairach (x,y,z)	Peak *P* Value	*Z*
Control Subjects					
Early fear conditioning (CS+ > CS−)					
L thalamus, brainstem		84 392	−10, −21, −7	4×10^{-8}	5.51
R lateral occipital cortex	18	3784	42, −85, −8	2×10^{-7}	5.21
L entorhinal cortex, hippocampus, amygdala	28	6304	−20, −14, −24	6×10^{-6}	4.53
L superior temporal sulcus	22	4808	−50, −55, −17	9×10^{-6}	4.44
R fusiform gyrus	37	3592	32, −56, −12	5×10^{-5}	4.06
L insula		3760	−38, 13, −1	3×10^{-4}	3.62
Late fear conditioning (CS+ > CS−)					
R hippocampus		2792	20, −34, −1	1×10^{-4}	3.89
Early extinction learning (CS+ > CS−)					
R brainstem, thalamus		6432	4, −18, −20	1×10^{-5}	4.42
Schizophrenic Patients					
Early fear conditioning (CS− > CS+)*	31, 39	5552	−32, −58, 22	3×10^{-5}	4.17
L posterior cingulate gyrus, inferior parietal cortex					
R posterior cingulate gyrus, precuneus, inferior parietal cortex	23, 40	23,40	30, −52, 27	8×10^{-5}	3.95
Control > Schizophrenia Groups					
Early fear conditioning (CS+ > CS−)					
L posterior cingulate gyrus	23	53 632	−8, −42, 27	4×10^{-7}	5.08
Thalamus, brainstem		4880	−8, −19, −3	3×10^{-5}	4.17
Late fear conditioning (CS+ > CS−)					
R hippocampus, thalamus		2968	18, −34, −1	5×10^{-5}	4.06

Abbreviations: BA, Brodmann area; CS, conditioned stimulus; L, left; R, right.

[a]Peak activations during fear conditioning and extinction learning in the control and schizophrenia groups, as well as clusters of activation that showed significantly greater activation in the control group compared with the schizophrenia group, are listed. There were no regions that showed significantly greater activation in the schizophrenia group compared with the control group. Within-group or between-group differences for the CS+ > CS− contrast are listed, except in the case of early fear conditioning for the schizophrenia group, for which only clusters of CS− > CS+ activation were found (indicated with *). There was no significant activation found for the CS− > CS+ contrast in the control group. Seventeen control participants and 18 schizophrenic patients are included in these analyses (2 patients were excluded owing to excessive head movement; see "Methods").

trol subjects showed greater responses to the CS+ compared with the CS− in the right hippocampus. In contrast, the schizophrenic patients showed a reversal of the expected pattern of response during early fear conditioning, with greater response to the CS− compared with the CS+ in the inferior parietal cortex, precuneus, and posterior cingulate gyrus. Direct comparisons between the responses of the 2 groups revealed that the control subjects showed significantly greater activation (CS+ > CS−) of the thalamus (early and late fear conditioning), brainstem and left

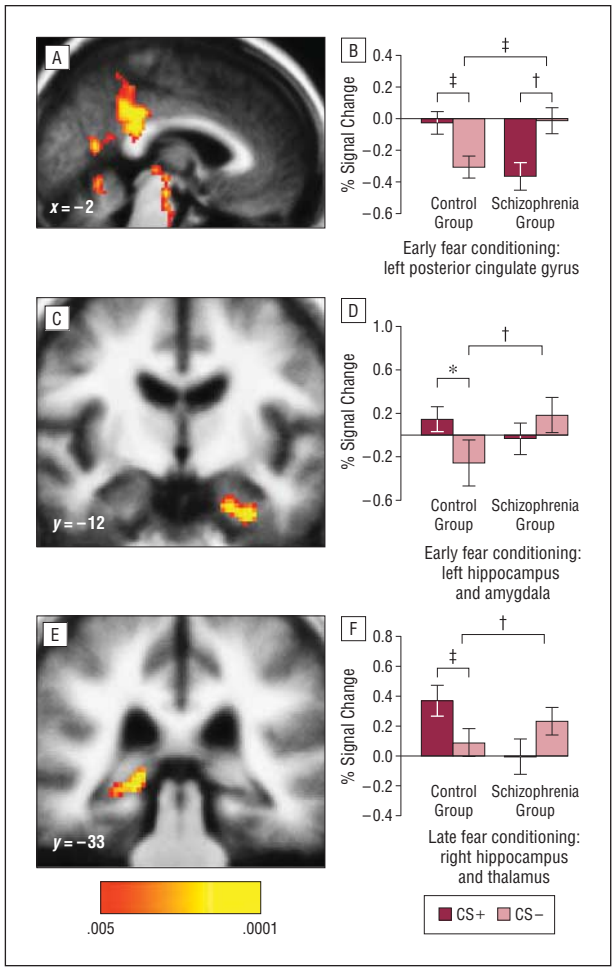

Figure 3. Neural responses during fear conditioning. Voxelwise maps (A, C, and E) and bar plots (B, D, and F) showing responses of regions with significantly greater activation for the CS+ minus CS− contrast in the control subjects (n = 17) compared with the schizophrenic patients (n = 18) during fear conditioning: the left posterior cingulate gyrus (A and B), left hippocampus and amygdala (C and D) during early fear conditioning, and the right hippocampus and thalamus (E and F) during late fear conditioning. Percent signal change values, relative to a low-level baseline condition, were extracted using 3-mm radius spheres centered on the coordinate of the voxel showing the peak between-group difference (see Table 2 for coordinates and *P* values). The low-level baseline condition consisted of the average signal intensity over the functional magnetic resonance imaging run. * $P < .05$; † $P < .005$; ‡ $P < .0005$. Symbols that are closest to the bar plots represent *P* values for the within-group paired *t* tests, while those that are further from the plots represent *P* values for between-group comparisons. The *P* values of the between-group comparison at each voxel in A, C, and E are indicated by the colored bar (values less than .0001 are represented by the same color).

posterior cingulate gyrus (early fear conditioning), and the right hippocampus (late fear conditioning) than the schizophrenic patients (**Figure 3**). Also, below the whole brain–corrected level of significance, there was greater activation in the control compared with the schizophrenia group during early fear conditioning in the left medial temporal lobe (amygdala, hippocampus, and entorhinal cortex) (Talairach coordinates [x, y, z] of peak difference: –30, –12, –27; $z = 4.1$; $P = 5 \times 10^{-5}$).

During early extinction learning, the control subjects showed activation of the right brainstem and thalamus; however, there were no significant differences between the 2 groups in the magnitude of responses during early or late extinction learning.

CONTEXT-DEPENDENT EXTINCTION RECALL

SCRs

Twenty-four hours after the fear conditioning and extinction learning phases, the control subjects showed a mean Extinction Retention Index of 76.6%, whereas the schizophrenic patients showed significant impairment in extinction memory, with a mean Extinction Retention Index of 42.9% ($t_{24} = 2.06$, $P = .03$; **Figure 4**A). In addition, the healthy control subjects demonstrated context gating of extinction memory retrieval, showing significantly lower SCRs (ie, less fear) to the CS+E presented with the extinction context compared with the fear context (extinction recall vs fear renewal: $t_{12} = 2.16$, $P = .03$; Figure 4B and eFigure 2). However, the patients with schizophrenia failed to show the expected pattern of context gating of memory retrieval; in fact, they showed greater SCRs to the CS+E with the extinction compared with the fear context ($t_{12} = 3.38$, $P = .003$).

BOLD Responses

As expected, the control subjects successfully recruited the vmPFC (BA 25/BA 11 [2, 16, –17]; $z = 4.16$; $P = 3 \times 10^{-5}$) during extinction recall. The schizophrenic patients failed to show this response. Moreover, the vmPFC response during extinction recall was significantly larger in the control group compared with the schizophrenia group (peak difference: BA 25 [0, 12, –18]; $z = 3.98$; $P = 8 \times 10^{-5}$; Figure 4C). In addition, the responses of the vmPFC were modulated by context in the control but not the schizophrenia group (Figure 4D and eFigure 2); in the control group, the portion of the vmPFC showing significant activation during extinction recall showed no responses during fear renewal ($t_{13} = 2.57$; $P = .01$).

Associations With Symptoms and Potential Confounds

In the schizophrenia group, negative symptom severity was inversely correlated with (1) skin conductance ($R = –0.59$; $P = .006$; **Figure 5**A) and (2) posterior cingulate gyrus ($P = 7 \times 10^{-5}$; Figure 5B) responses during early fear conditioning. There were no significant correlations between the abnormalities found in the schizophrenia group just described and levels of positive symptoms, anxiety, depression, electrical stimulation level, antipsychotic medication dosage, or duration of illness. Secondary analyses revealed no significant differences between the antipsychotic-treated and untreated patients (eFigure 3) or between the delusional and nondelusional patients (eFigure 4) in skin conductance or neural responses during any phase. However, the delusional patients showed significantly lower vmPFC responses than the healthy control subjects during extinction recall (BA 25 [–4, 1, –11]; $z = 3.14$; $P = .002$), whereas the nondelusional patients and control subjects did not differ in vmPFC response magnitude during this phase.

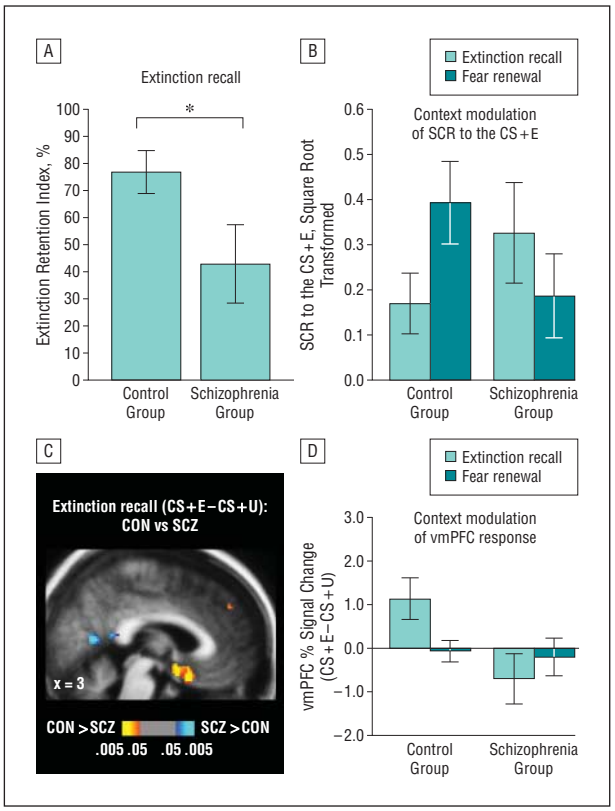

Figure 4. Skin conductance and neural responses during retrieval of extinction and fear memories. A, Bar plots showing mean Extinction Retention Index values for the control (n = 13) and schizophrenia (n = 13) groups (an additional 2 control subjects and 4 schizophrenic patients were excluded from the day 2 skin conductance response (SCR) analyses because of poor electrode contact during data collection). B, Bar plots showing the expected pattern of context dependence of SCRs during day 2 to the CS+ presented during extinction learning (CS+E) in the control group (n = 13): lower SCRs (ie, less fear) to the CS+E in the extinction compared with the fear context. In contrast, the schizophrenic patients (n = 13) showed an aberrant pattern of responses on day 2, showing lower SCRs to the CS+E in the fear compared with the extinction context. C, A voxel-wise map of the results of the comparison between the mean activation levels (for the CS+E minus CS+U contrast) during extinction recall in the control (n = 17) and schizophrenia (n = 15) groups showed that the ventromedial prefrontal cortex (vmPFC) exhibited significantly greater activation in the control subjects compared with the schizophrenic patients. The *P* values of the between-group comparison at each voxel in C are indicated by the colored bar (values less than .005 are represented by the same color). D, Bar plots showing the expected context gating of vmPFC responses in the control group: greater responses to CS+E (vs CS+U) in the extinction compared with the fear context. In contrast, the schizophrenic patients failed to recruit the vmPFC in either context. Percent signal change data were extracted using a 3-mm radius sphere centered on the voxel showing the peak between-group difference in the vmPFC during extinction recall. Five schizophrenic patients were excluded from the day 2 functional magnetic resonance imaging analyses because of excessive head motion. Light blue bars indicate skin conductance (B) or blood oxygen level–dependent (D) responses during extinction recall; dark blue bars, skin conductance (B) or blood oxygen level–dependent (D) responses during fear renewal. CON indicates control group; SCZ, schizophrenia group. * $P = .03$.

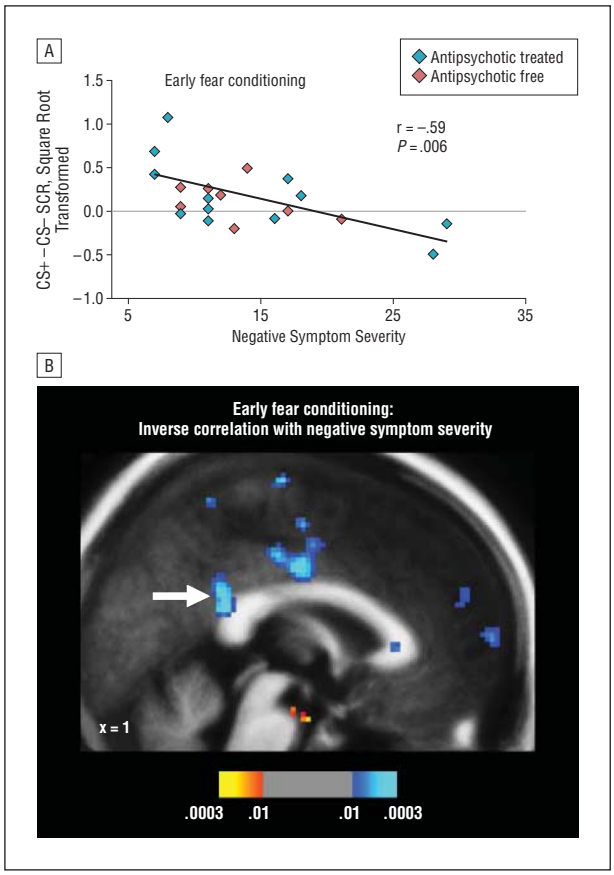

Figure 5. Correlations between skin conductance and neural responses during fear conditioning and negative symptom levels. A, Scatterplot illustrating the relationship between negative symptom severity, as measured by the Positive and Negative Syndrome Scale (PANSS) negative symptom subscale score, and early differential fear conditioning (CS+ minus CS– skin conductance responses [SCRs]). Values for antipsychotic-treated (n = 12) and antipsychotic-free (n = 8) schizophrenic patients are presented as blue and orange diamonds, respectively. B, A map of the clusters of voxels that showed less differential activation during early fear conditioning in patients with greater levels of negative symptoms (inverse correlations between CS+ minus CS– activation and negative symptom severity; n = 18) is shown (cluster corrected for the whole brain; $P < .005$). The Talairach coordinates and location of the voxel with the lowest *P* value for this correlation are 2, -41, -20 (Brodmann are [BA] 23), $z = 3.98$, $P = 7 \times 10^{-5}$ (white arrow). Also, the location and lowest *P* value for the more dorsal and anterior peak found in the posterior cingulate gyrus for this correlation are 0, -11, 33 (BA 23/24); $z = 3.54$, $P = 4 \times 10^{-4}$. The *P* values of the Pearson correlation at each voxel in B are indicated by the colored bar (values less than .0003 are represented by the same color). Because during early fear conditioning, the control subjects and schizophrenic patients showed opposite patterns of responses within the posterior cingulate gyrus (Figure 3B), this correlation suggested that the between-group difference in activation during this phase was driven largely by abnormal (reversed) responses of the schizophrenic patients with high levels of negative symptoms. When the contributions of the individual items of the PANSS negative symptom subscale to these 2 correlations were examined, it was found that all of the items, except social withdrawal ($r = -0.16$; $P = .51$) and emotional withdrawal, which showed only a trend ($r = -0.40$; $P = .08$), showed significant inverse correlations ($P < .05$) with SCR during early fear conditioning. Also, significant inverse correlations were found between blunted affect ($r = -0.60$; $P = .008$), poor rapport ($r = -0.47$; $P = .05$), and stereotyped thinking ($r = -0.58$; $P = .01$), and posterior cingulate gyrus responses during early fear conditioning.

COMMENT

During fear conditioning, patients with schizophrenia showed blunted autonomic responses and either absent or reversed (greater responses to the CS– than to the CS+) neural responses compared with control subjects. Several of these abnormalities were linked to negative symptoms. In contrast, autonomic and neural responses during extinction learning in the schizophrenia and control groups did not differ. Twenty-four hours following extinction learning, the control subjects exhibited the expected pattern of decreased fear and increased vmPFC responses in the extinction compared with the fear con-

text. However, the schizophrenic patients showed inappropriately elevated fear and no vmPFC activity in the extinction context, failing to retain the extinction memory encoded 1 day earlier.

FEAR CONDITIONING AND EXTINCTION LEARNING IN SCHIZOPHRENIA

The results of older studies of Pavlovian or other types of aversive conditioning in schizophrenia have been mixed,[19-22,64] possibly reflecting methodologic variation.[17] However, several recent studies have demonstrated that schizophrenic patients can successfully acquire differential conditioned fear[17,18] (also see study by Romaniuk et al[16]), but they often show lower responses to the CS+[16,18] and/or greater responses to the CS–[16,17] compared with control subjects. In the present study, this reversed pattern of responses was observed in the schizophrenia group during fear conditioning in the posterior cingulate gyrus, precuneus, and inferior parietal cortex, and to a lesser extent in the hippocampus and thalamus. This overall pattern of greater responses to nonsalient relative to salient stimuli has been observed previously in the posterior cingulate gyrus[44] and parahippocampal gyrus[65] in schizophrenic patients, as well as in the medial frontal and parietal cortices, thalamus, and hippocampus in young people at elevated risk for developing schizophrenia.[66] Given that many previous studies have reported abnormally reduced activation of limbic brain regions, particularly the amygdala,[67] in schizophrenia, the present findings support the proposal[67,68] that these findings may in fact reflect a combined effect of abnormally elevated responses to neutral stimuli and reduced responses to aversive stimuli. The present results suggest that this pattern of responses may arise from abnormalities in emotional learning.

The inverse correlations seen here between skin conductance and posterior cingulate responses during fear conditioning, and the severity of negative symptoms, although unexpected, are generally reminiscent of findings of impaired positive reinforcement learning in schizophrenic patients with prominent negative symptoms.[1-3] Together, the findings of this study and prior studies suggest that negative symptoms may be related to a general impairment in learning conditioned associations (whether linked to aversive or rewarding unconditioned stimuli).

The posterior cingulate gyrus has not been studied extensively in schizophrenia, possibly because its function is not well understood.[69,70] However, a number of recent studies have reported abnormalities in its function or connectivity in schizophrenia.[44,45,49,71] In light of evidence for its involvement in episodic memory processes,[72,73] we speculate that dysfunction of the posterior cingulate gyrus and hippocampus during fear conditioning in schizophrenia may interfere with the encoding of episodic memory traces of the CS+/US and CS–/no US associations. The reduced accuracy in encoding the CS+ and CS– identities shown here by the schizophrenic patients is consistent with this possibility (Table 1). Given that humans may rely on episodic memory processes during fear conditioning to a greater extent than other species, one possible interpretation of our findings is that nonconscious, automatic associative learning during fear conditioning is preserved (as reflected by the patients' ability to acquire some differential SCRs) in patients with schizophrenia to a greater extent than conscious, episodic learning.

The finding of relatively preserved SCRs accompanied by abnormal neural responses during fear conditioning in schizophrenia is consistent with previous reports of inconsistencies between peripheral and central nervous system measures of fear responses in schizophrenic patients.[47,48] This pattern of findings may be related to a disruption in communication between central and peripheral autonomic system centers in schizophrenia or may simply reflect a greater sensitivity of fMRI (owing to its anatomic resolution) compared with skin conductance measurements.

Although the schizophrenic patients showed aberrant neural responses during fear conditioning, their extinction learning responses were comparable with those of control subjects. This dissociation between our findings for fear and extinction learning may be partly explained by evidence for independence of the fear and extinction systems. Fear and extinction learning are mediated by distinct cell populations in the amygdala,[30] and fear and extinction memories are retrieved independently, in a context-gated manner.[27]

ABNORMALITIES IN FEAR EXTINCTION MEMORY IN SCHIZOPHRENIA

Following successful extinction learning, both peripheral (skin conductance) and central (vmPFC responses) nervous system components of extinction recall were deficient in the schizophrenic patients. Interestingly, impairment in vmPFC activity during the extinction recall phase was particularly prominent in the patients with active delusions, suggesting that deficient retrieval of safety-related information may confer a vulnerability to delusional thinking. It is not yet clear whether extinction recall impairment in schizophrenia reflects a selective derangement of the medial prefrontal–emotional memory system or one manifestation of a more global abnormality in limbic function or memory consolidation.[74-76] In a recent study that used a preference conditioning paradigm, patients with schizophrenia showed intact learning; however, 24 hours later, they failed to recall the more frequently rewarded stimulus, whereas the control subjects retained this association.[76] In light of the established role of the vmPFC in reward processing,[77,78] this previous finding and the present result suggest that inaccurate assessments of both reward and safety-related information in schizophrenia may result from disruptions of affective discrimination, memory consolidation, and retrieval processes mediated by the vmPFC.

LIMITATIONS

Most of the patients enrolled in this study were taking antipsychotic medications, which have known effects on associative learning. Treatment with dopamine D_2 receptor antagonists interferes with the expression of conditioned avoidance motor responses[79,80] and the acqui-

sition of conditioned fear responses[61] in rodents. Results of studies of the effect of antipsychotics on extinction learning and extinction memory recall in rodents have been mixed, with evidence for facilitation of extinction learning[80,81] and extinction recall,[82] as well as evidence for inhibition of extinction recall by D_2,[62] as well as D_1,[83] receptor antagonists. It is not clear whether similar effects occur in humans. Functional MRI studies have shown that treatment with first-generation antipsychotics is associated with reduced activation of the striatum during aversive[84] and reward[85-87] learning. However, to our knowledge, the effect of antipsychotic medication on emotional memory in humans has not been investigated. Here, we did not find any differences between the antipsychotic-treated and untreated schizophrenic patients in the extent of the abnormalities reported here. However, to fully resolve this issue, follow-up studies conducted in a larger number of unmedicated schizophrenic patients or individuals in the prodromal phase of the illness must be conducted.

CONCLUSION

Studies in rodents have demonstrated that fear extinction recall can be induced or augmented by stimulation of *N*-methyl-D-aspartate[36] and metabotropic[88] glutamate receptors within the medial prefrontal cortex. Other studies suggest that a partial *N*-methyl-D-aspartate–receptor agonist, D-cycloserine, can facilitate consolidation of extinction memories.[89-91] Also, it has been shown that neurotrophins, such as brain-derived neurotrophic factor, play a central role in extinction and fear memory formation in the medial prefrontal cortex.[92,93] Because schizophrenia has been associated with *N*-methyl-D-aspartate–receptor hypofunction,[94,95] reductions in serum brain-derived neurotrophic factor,[96,97] and neural changes linked to a specific brain-derived neurotrophic factor genotype,[98] it will be important to determine whether abnormalities in any of these molecular mediators play a role in deficits in fear extinction memory and vmPFC function in schizophrenia. Preliminary work by our group suggests that once-weekly treatment with D-cycloserine facilitates memory consolidation and reduces negative symptom burden in patients with schizophrenia,[99] and that D-cycloserine may also potentiate responses to cognitive treatments of delusions.[100] Follow-up studies will determine whether D-cycloserine or other therapeutic agents can selectively reverse deficits in vmPFC-mediated extinction recall and affective dysfunction in schizophrenic patients. These data also support the use of psychosocial approaches for treating schizophrenia that influence the fear and extinction memory system by reducing negative affect and arousal or by promoting consolidation of extinction memories.

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