Extinction Memory Is Impaired in Schizophrenia

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Background: Schizophrenia is associated with abnormalities in emotional processing and social cognition, which might result from disruption of the underlying neural mechanism(s) governing emotional learning and memory. To investigate this possibility, we measured the acquisition and extinction of conditioned fear responses and delayed recall of extinction in schizophrenia and control subjects.

Methods: Twenty-eight schizophrenia and 18 demographically matched control subjects underwent a 2-day fear conditioning, extinction learning, and extinction recall procedure, in which skin conductance response (SCR) magnitude was used as the index of conditioned responses.

Results: During fear acquisition, 83% of the control subjects and 57% of the patients showed autonomic responsivity ("responders"), and the patients showed larger SCRs to the stimulus that was not paired with the unconditioned stimulus (CS−) than the control subjects. Within the responder group, there was no difference between the patients and control subjects in levels of extinction learning; however, the schizophrenia patients showed significant impairment, relative to the control subjects, in context-dependent recall of the extinction memory. In addition, delusion severity in the patients correlated with baseline skin conductance levels.

Conclusions: These data are consistent with prior evidence for a heightened neural response to innocuous stimuli in schizophrenia and elevated arousal levels in psychosis. The finding of deficient extinction recall in schizophrenia patients who showed intact extinction learning suggests that schizophrenia is associated with a disturbance in the neural processes supporting emotional memory.

Key Words: Conditioning, emotion, extinction, fear, memory, schizophrenia

It has been recently recognized that impaired emotional function might play an important role in the symptoms and the overall functional disability associated with schizophrenia (1–5). Empirical studies have reported at least two types of emotional processing abnormalities in schizophrenia patients. First, patients with schizophrenia demonstrate deficits in emotion recognition across multiple sensory domains (6–12). Second, a bias to misassign emotional meaning to neutral, innocuous stimuli has been identified in schizophrenia patients with a wide range of experimental paradigms (13–16). In some studies, emotion recognition deficits in schizophrenia have been linked to impairments in cognition or overall functioning (5,17). In contrast, misassignment of emotional meaning to neutral stimuli has been associated with psychotic symptoms (13,15,18,19).

One possibility is that one or both of these abnormalities in emotional function arise from a disruption of the basic neuronal mechanism(s) that are responsible for encoding and retrieving the emotional value or meaning of a stimulus—emotional memory processes. One type of emotional memory, called extinction memory, has been studied extensively in rodents and humans with adaptations of Pavlovian fear conditioning paradigms (20–23). Pavlovian fear conditioning involves pairing an innocuous stimulus (the conditioned stimulus [CS]) with an aversive sensation (the unconditioned stimulus [US]), such as a shock, air puff, or loud noise, which leads to the formation of a memory indicating that the CS signals danger (a "danger" memory) (24–26). If the CS is subsequently presented several times without the US (extinction learning), a second, "safety" memory is formed, linking the CS with the absence of the US. It has been shown that these two memories of a given CS can exist simultaneously and can be retrieved independently at a later time (27–29). Importantly, the safety (extinction) memory is linked to the particular context in which it was formed; the extinction memory is retrieved only if the context in which it was encoded is present at retrieval (30,31).

Studies of aversive conditioning in schizophrenia have produced mixed results, with findings of facilitated (32,33), diminished (16,34,35), as well as normal (34,36) aversive conditioning in schizophrenia patients relative to control subjects. These inconsistencies might be due in part to methodological differences among studies (for example, the absence of a non-aversive comparison condition [CS−] in some investigations) as well as to heterogeneity within patient samples. Heterogeneity was evident in several studies that found that one-third to one-half of the patients exhibited no learning at all, whereas the remaining patients showed normal acquisition of aversive conditioning (34,36). These findings are consistent with evidence for the existence of a subpopulation of patients with schizophrenia with abnormally low or absent autonomic responses to salient stimuli (37).

To date, extinction memory has not been studied in schizophrenia. Although it has been established that patients with schizophrenia have difficulty using contextual information during cognitive (38,39) and social cognitive (40,41) processing, it is not known whether these deficits are related to abnormalities in context-dependent emotional memory processes.

In the current study, we sought to determine whether schizophrenia is associated with impairment in learning or memory of conditioned fear responses. We used a 2-day, classical Pavlovian fear conditioning and extinction paradigm that had been previously adapted for use in humans (22). On the first day of this

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paradigm, participants undergo fear conditioning during which one neutral stimulus is paired (CS+) and another is not paired (CS−) with an aversive electrical tactile stimulus (US). After acquisition of conditioned fear responses, participants then undergo an extinction learning phase during which the CS+ is presented without the US. These two phases occur in distinct visual contexts (the acquisition context and the extinction context). Twenty-four hours later, participants are again exposed to the CS+ without the US, in the extinction context and in the acquisition context, and responses to the CS+ in the two contexts are measured within and across groups. We predicted, on the basis of previous studies (22,42,43), that on the second day of the study healthy control participants would show minimal SCRs to the CS+ in the extinction context, indicating successful retrieval of the extinction memory (i.e., the memory that the CS+ no longer predicts the US). We also hypothesized that patients with schizophrenia would demonstrate impairment, relative to control subjects, in context-dependent retrieval of extinction memory.

Methods and Materials

Participants

Twenty-eight patients with DSM-IV–diagnosed schizophrenia and 18 control subjects, between 18 and 65 years old, were studied. Clinically stable, medicated patients with schizophrenia were recruited through the Massachusetts General Hospital (MGH) Schizophrenia Clinical and Research Program (Table 1). Healthy control subjects were recruited via advertisement. The healthy control subjects did not have any psychiatric, neurologic, or severe medical disorders or history of substance abuse during the previous 3 months, as determined by phone screening, questionnaires, and the SCID (44). Capacity to provide informed consent was evaluated for each subject, and written informed consent was obtained from all subjects before enrollment in accordance with the guidelines of the Partners Healthcare Institutional Review Board. Each patient's symptoms were evaluated by a trained rater with the Positive and Negative Syndrome Scale (45).

Psychophysiological Procedures

A Coulbourn Instruments Lablink V System (Allentown, Pennsylvania) was used to record skin conductance level (SCL) via a Coulbourn Isolated Skin Conductance Coupler (71–23). Electrodes were placed on the palm of the participant's nondominant hand. Electrodes were also attached to the second and third fingers of the dominant hand for the purpose of delivering the US (a 500-msec electrical stimulus). The US was generated by a Coulbourn Transcutaneous Aversive Finger Stimulator (E13-22). The intensity of the electrical US was set by each participant before the start of the procedure at a level that was "highly annoying but not painful."

Fear Conditioning and Extinction Procedures

The fear conditioning and extinction procedures used in this study were similar to those previously described (22,42). During both days of the procedure, participants sat in a comfortable chair in front of a computer monitor. After the electrodes were attached, participants were asked to passively view digital photographs of two rooms containing lamps that appeared on the computer screen (Figure 1).

Photographs of the two rooms (a conference room and an office) constituted the two virtual contexts (CX). During the procedure, one context was associated (CX+) and one was not associated (CX−) with receiving the electrical stimulus. Each room CX contained a lamp. Two colors of the lit lampshade (blue

Table 1. Demographic Characteristics of the Full Cohort of Subjects and the Responders

	Full Cohort		Responders	
	Control Subjects $n = 18$: 7 Female	Patients $n = 28$: 5 Female	Control Subjects $n = 15$: 5 Female	Patients $n = 16$: 5 Female
Age (yrs)	42.8 (3.4)	43.6 (2.0)	41.2 (3.8)	42.8 (3.0)
Mean Parental Education (yrs)	13.2 (.7)	13.4 (.5)	13.2 (.9)	13.1 (.6)
Mean Parental SES[a]	2.7 (.2)	2.5 (.2)	2.8 (.3)	2.6 (.3)
Verbal IQ[b]	110.0 (1.6)	104.2 (2.0)	111.8 (1.2)	101.6 (3.0
Stimulation Level	2.6 (.3)	2.3 (.2)	2.7 (.3)	2.2 (.3)
PANSS Total		56.5 (2.1)		58.9 (2.7)
PANSS Positive Scale		14.6 (1.0)		15.1 (1.1)
PANSS Negative Scale		13.8 (.7)		13.7 (1.0)
PANSS General Scale		28.5 (1.2)		30.1 (1.4)
PANSS Delusion Item		2.9 (.3)		3.1 (.4)
Duration of Illness (yrs)		18.7 (2.0)		18.6 (2.8)
Chlorpromazine Equivalents		441.4 (70.6)		347.8 (68.8)

Demographic characteristics of the full cohort of subjects ($n = 46$) and the responders (participants with ≥ 2 trials with skin conductance responses (SCRs) ≥ .03 μS during the Acquisition phase) ($n = 31$). Means are presented, with SEM in parentheses. Antipsychotic medications taken by the patients, with the number of patients taking them in parentheses: clozapine (12), risperidone (5), olanzapine (5), aripiprazole (6), quetiapine (2), ziprazadone (1), perphenazine (1), haloperidol (1), and no antipsychotic medication (3). Only one patient was taking an anticholinergic medication (benztropine). Although the proportion of responders was 26% higher in the control than in the patient group, this difference did not reach statistical significance (Fischer's Exact Test, $p = .11$). Within the patient group, there were no significant differences between the responders ($n = 15$) and nonresponders ($n = 12$) on any clinical or outcome measure, although there was a trend toward a higher mean SCR to the CS+ trials during the Acquisition phase in the responders compared with the nonresponders ($p = .09$) and a trend toward a higher verbal IQ in the nonresponders compared with the responders ($p = .09$). Also, within the responder cohort, there were no significant differences between the control subjects ($n = 16$) and patients ($n = 15$) in demographic characteristics or selected level of electrical stimulation, with the exception that, as in the full cohort, mean verbal IQ was higher in the control subjects than in the patients ($p = .004$).

SES, socioeconomic status; PANSS, Positive and Negative Syndrome Scale; CS+, the stimulus that was paired with the unconditioned stimulus.

[a]SES, measured with the Hollingshead index.

[b]Verbal IQ, measured with the North American Reading Test.

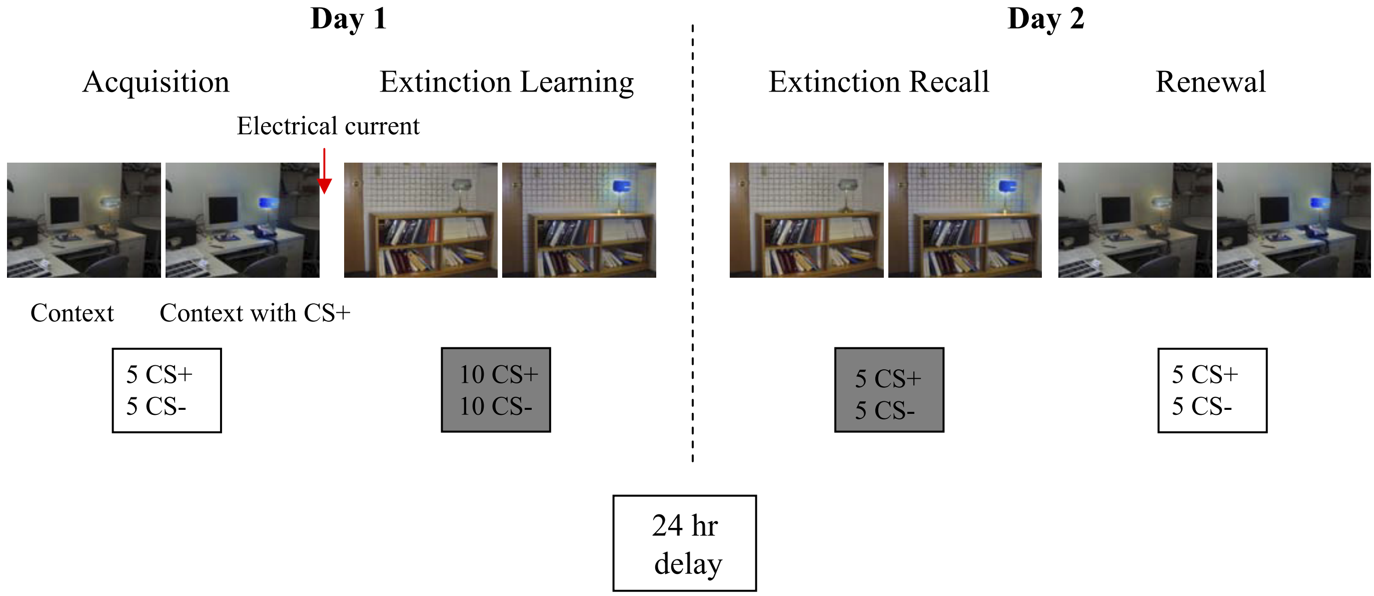

Figure 1. Schematic of experimental protocol. Photographs of the visual contexts (CX), within which conditioned stimuli (CS) were presented, are shown. In this example, a photograph of an office is the conditioning context (CX+) and a photograph of a conference room is the extinction context (CX−). The blue light is the conditioned stimulus that was paired with the electrical current (CS+) and later extinguished. The conditioned stimulus that was not paired with the electrical current, the CS− (which, in this example, would be a yellow light), is not shown here. Six seconds after the onset of the presentation of the room photograph, the lampshade in the room turns yellow or blue for 12 sec (total stimulus duration for the room photograph: 18 sec). The numbers of each stimulus type presented during each phase is indicated. The Extinction Learning phase was divided into an early and late phase that each included 10 trials (5 CS+ and 5 CS−), all presented within the CX−. Electrical current was delivered only during the Acquisition phase. Gray shading indicates the CX−. The Habituation phase is not shown for simplicity. The order of the phases on Day 2, Extinction Recall and Renewal, were counterbalanced across subjects. Reprinted from *Biological Psychiatry*, volume 62, Milad et al., Recall of fear extinction in humans activates the ventromedial prefrontal cortex and hippocampus in concert, pages 446–454, 2007, with permission from Elsevier.

or yellow) constituted the CSs. One CS was paired (CS+) and one was not paired (CS−) with presentations of the electrical stimulus. The selection of the CS+ and CS− colors and the CX+ and CX− rooms was counterbalanced across participants.

For each trial during the experiment, the CX was presented for 18 sec: 6 sec alone, followed by 12 sec in combination with the CS+ or CS−. Skin conductance was recorded for 5 sec before the presentation of the CX, during the 6-sec presentation of the CX alone, and during the 12-sec presentation of the CX plus the CS. The US occurred during the last 500 msec of the CS+. The average inter-trial interval was 16 sec.

The experimental protocol was administered over two separate days. There were three phases on Day 1: Habituation, Acquisition, and Extinction Learning. The Habituation phase included trials in which the CS+ and CS− (4 trials of each) were presented in a counterbalanced manner within either the acquisition context (CX+) or the extinction context (CX−). The Acquisition phase included five CS+ and five CS− trials, all presented within the CX+. The Extinction Learning phase was divided into two sub-phases: early and late, which were separated by a 1-min rest period. Each sub-phase included five CS+ and five CS− trials, all presented within the CX−. The US was not delivered during the Extinction Learning phase.

On Day 2, there were two phases: Extinction Recall and Renewal. The Extinction Recall phase included five CS+ and five CS− presented within the CX− without any US. During the Renewal phase, five CS+ and five CS− were presented within the CX+, and again no US was delivered. In one-half the participants, the Renewal phase preceded the Recall phase.

Instructions to Participants

Before the Habituation phase, participants were instructed that the purpose of this phase was to show them all the possible pictures that they would see throughout the study and that no electrical current would be delivered. Before all subsequent phases of the study, participants were instructed that they "may or may not receive electrical stimulations."

After the Acquisition phase and at the start of Day 2, each participant was asked whether they could recall the color of the light that was paired with the electrical stimulation and to describe the room that contained the light that was paired with the stimulation.

SCL and SCR Values and Data Analysis

Baseline SCL was calculated as the mean skin conductance values during the 5 sec before the presentation of the context during the Habituation phase.

The SCR magnitude for each CS trial was calculated by subtracting the mean SCL during the 2 sec immediately before CS onset (during which the context alone was being presented) from the highest SCL recorded during the 12-sec CS duration. Thus, all SCRs to the CS+ and CS− reflect changes in SCLs above any changes produced by the context. To minimize the impact of individual variation in fear acquisition on the extinction learning and extinction recall measures, the measures of extinction learning and extinction recall were normalized in each individual to their largest SCR during fear acquisition (22,42). Also, SCRs were square-root transformed before analysis. Because SCRs to the CS+ can only be extinguished after successful acquisition of those responses, extinction learning and recall were examined

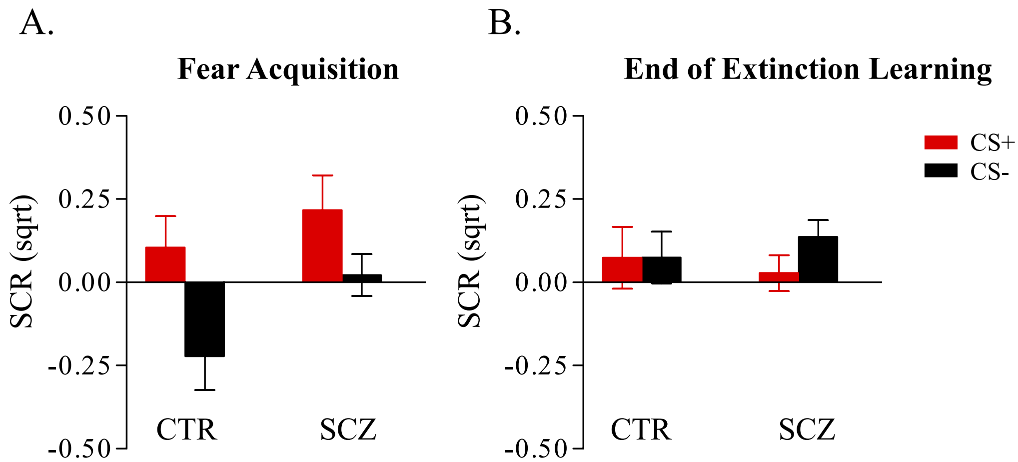

Figure 2. Plots of mean skin conductance responses (SCRs) ± SEM during the last two trials of the CS+ (red bars) and CS− (black bars) during the Acquisition phase **(A)** and the Extinction Learning phase **(B)** in the control subjects (CTR) (n = 15) and schizophrenia patients (SCZ) (n = 16) within the responder cohort. For the responders, within-group analyses revealed that the CTR demonstrated acquisition of differential fear conditioning to the CS+ versus CS− [$t(14)$ = 2.57, p = .011), and the patients showed a trend toward acquisition of differential fear responses [$t(15)$ = 1.61, p = .064), similar to the findings in the full cohort. There were no differences between the control and patient responder groups in overall fear acquisition and extinction learning (see text). Sqrt, square-root transformed; other abbreviations as in Figure 1.

only in participants who showed SCRs during the Acquisition phase (with SCRs ≥ .03 μS in 2 or more of the 10 trials of the Acquisition phase), consistent with previous studies (22,46).

Fear acquisition was calculated as the mean SCR for the last two trials of the CS+ minus the mean SCR for the last two trials of the CS− during the Acquisition phase. Extinction learning was calculated with an Extinction Learning Index, representing extinction learning success on Day 1: 100 − ([the average SCR for the last two trials of the Extinction Learning phase divided by the largest SCR for the Acquisition phase] × 100). Extinction memory was calculated with an Extinction Retention Index, representing extinction recall success on Day 2, with the same formula as the Extinction Learning Index except that SCRs for the first two trials of the Extinction Recall phase were used.

Our a priori hypothesis regarding extinction recall was tested with Student t test (α = .05, two-tailed). Differential fear acquisition (SCRs to the CS+ compared with SCRs to the CS− during the last two trials of the Acquisition phase) and differential context sensitivity (SCRs to the CS+ during the first two trials of the Extinction Recall phase compared with SCRs to the CS+ during the first two trials of the Renewal phase) were assessed within each group with paired t tests (α = .05, one-tailed).

Fisher's Exact Test was used to assess between-group differences in explicit recall of CS and CX identities (α = .05, two-tailed). Means are presented with SEM.

Results

Characteristics of the Participants

There were no differences between the patients and control subjects in age, mean parental education, socioeconomic status, or in level of electrical stimulation chosen (Table 1). Mean verbal IQ was lower in the patients than in the control subjects [$t(43)$ = 2.07, p = .04].

Baseline SCL and Fear Acquisition

The mean SCL at baseline was nonsignificantly higher in the control subjects than in the patients [control subjects: 3.55 ± .84 μS; patients: 1.97 ± .37 μS; $t(29)$ = 1.93, p = .06].

Within-group analyses revealed that the control group demonstrated acquisition of differential fear conditioning to the CS+ versus CS− [$t(17)$ = 2.65; p = .008], and the patients showed a trend toward acquisition of differential fear responses [$t(27)$ = 1.61, p = .08]. There were no statistically significant differences between the two groups in mean levels of fear acquisition (CS+ minus CS−) [control subjects: .29 ± .11 μS; patients: .10 ± .07 μS; $t(44)$ = 1.46, p = .15] or in magnitude of SCRs to the CS+ trials [control subjects: .09 ± .08 μS; patients: .12 ± .06 μS; $t(44)$ = .38, p = .71]. However, the patients exhibited a significantly larger mean SCR to the CS− trials compared with the control subjects [control subjects: −.20 ± .09 μS; patients: .02 ± .04 μS; $t(44)$ = 2.62, p = .01].

Examination of the acquisition data of each subject revealed that 83% of the control subjects (15 of 18) and 57% of the patients (16 of 28) exhibited autonomic responsivity (≥ 2 trials with SCR ≥ .03 μS) during the Acquisition phase ("responders"). Within this responder cohort, the control subjects again exhibited a nonsignificantly higher mean SCL than the patients [control subjects = 4.13 ± .94 μS; patients = 2.49 ± .52 μS; $t(29)$ = 1.55, p = .13]. The responder patient and control groups did not differ in levels of fear acquisition (CS+ minus CS−) [control subjects: .33 ± .13 μS; patients: .20 ± .12 μS; $t(29)$ = .75, p = .46] or in magnitude of SCRs to the CS+ trials [control subjects: .10 ± .10 μS; patients: .22 ± .10 μS; $t(29)$ =.80, p = .43]. However, within the responder group, the patients again showed a significantly larger mean SCR to the CS− trials compared with the control subjects [control subjects: −.22 ± .10 μS; patients: .02 ± .06 μS; $t(29)$ = 2.06, p = .048] (Figure 2A). Because we planned to measure fear extinction and extinction memory only in participants who displayed SCRs during acquisition (see Methods), further analyses were limited to the responders (15 control subjects, 16 patients).

Extinction Learning

The patient and control groups demonstrated equivalent levels of extinction learning, as reflected by their responses to the CS+ at the end of the Extinction Learning phase [control subjects: .07 ± .09 μS; patients: .03 ± .05 μS; $t(29)$ = .66, p = .51] (Figure 2B) and their mean Extinction Learning Index [control subjects:

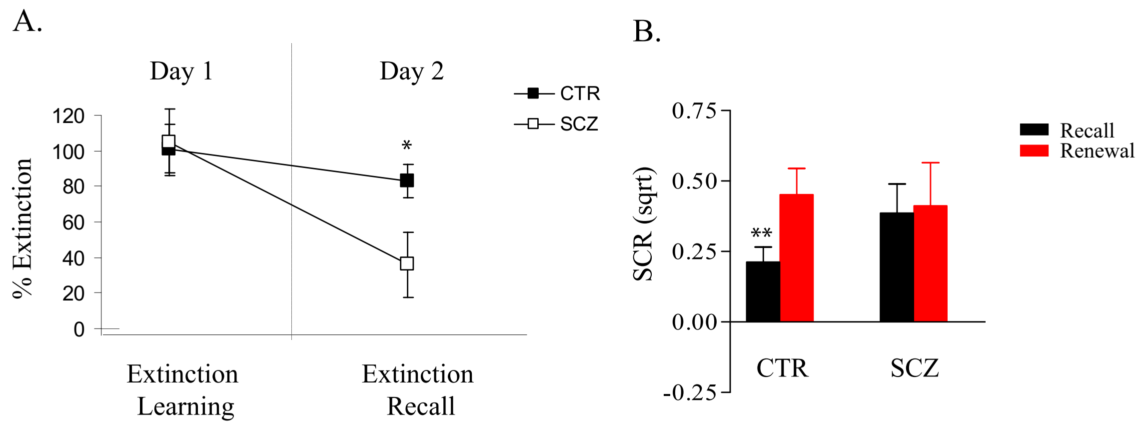

Figure 3. (A) A plot of mean percent extinction ± SEM of the two groups during the Extinction Learning (Day 1) and Extinction Recall (Day 2) phases. Extinction learning and extinction recall are each normalized to the highest levels of fear (SCR) attained during the Acquisition phase and are expressed as a percentage of that maximal fear response that is extinguished (the mean Extinction Learning Index and Extinction Retention Index are shown on the left and right of this plot, respectively; see Methods). The two groups do not differ with respect to extinction learning, but extinction recall is significantly lower in the patients than in the control subjects. Note that because measurements of SCRs to the conditioned stimuli are normalized to the SCRs to the context (see Methods), SCRs at the end of extinction can have negative values, which can lead to a value of the Extinction Learning Index that exceeds 100%. **(B)** A plot of mean SCRs ± SEM to the CS+ of the two groups during the Extinction Recall (black bars) and Renewal (red bars) phases on Day 2, showing that SCRs to the CS+ are modulated by context in the control subjects (n = 15) but not in the patients (n = 16). CTR, n = 15; SCZ, n = 16; $*p$ = .034; $**p$ = .008. Abbreviations as in Figures 1 and 2.

89.5 ± 11.9%; patients: 92.5 ± 16.1%; $t(29) = .15$, $p = .88$] (Figure 3A).

Extinction Recall After 24 Hours

Despite the comparable levels of extinction learning shown by the schizophrenia and control groups, the patients with schizophrenia demonstrated impaired recall of the extinction memory, with a significantly lower Extinction Retention Index than the control subjects [control subjects: 74.2 ± 8.0%; patients: 33.7 ± 16%; $t(29) = 2.23$, $p = .034$] (Figure 3A). Furthermore, the control subjects showed normal context-sensitivity during retrieval, with significantly lower SCRs to the CS+ in the extinction compared with the acquisition context [$t(14) = 2.77$, $p = .008$]; in contrast, the schizophrenia patients did not demonstrate a significant effect of context on SCRs to the CS+ on Day 2 [$t(15) = .22$, $p = .41$] (Figure 3B).

Explicit Learning

There was no difference between the two groups in explicit learning on Day 1 (see Table 2). However, debriefing at the beginning of Day 2 revealed that, although the schizophrenia patients and control subjects were equally likely to correctly recall the identities of the CS+ and CS−, the patients were less likely to recall the identities of the CX+ and CX− than the control subjects (Fisher's Exact Test, $p = .02$).

Table 2. Percentage of Subjects Within Each Group Demonstrating Successful Recall of the Identities of the CS+ and CX+

	Control	Schizophrenia	p
% recalled CS+ on Day 1	86.7	75.0	.65
% recalled CX+ on Day 1	100.0	92.9	.48
% recalled CS+ on Day 2	86.7	68.8	.39
% recalled CX+ on Day 2	100.0	62.5	.02

Percentage of subjects within each group demonstrating successful recall of the identities of the CS+ (vs. CS−) and CX+ (vs. CX−) with the p values of the corresponding statistical comparisons (Fisher's Exact Test).

Abbreviations as in Figure 1.

Correlations

There were no correlations among the four primary outcome measures within either group, with the exception of an inverse correlation between mean SCL and the extinction learning index within the control group only (P = −.69; $p = .004$; $n = 15$). Also, there were no significant correlations between magnitudes of fear acquisition, extinction learning, or extinction memory recall and the positive and negative syndrome scale (PANSS) total and subscale scores within the patient group. However, a significant correlation was found between SCL and the PANSS Positive subscale scores (P = .69; $p = .0028$; $n = 16$) (Figure 4A). Additional analyses revealed that the correlation between SCL and positive symptom severity was due to an association between baseline SCL and severity of delusional thinking (P = .80; $p = .0002$; $n = 16$) (Figure 4B) and also levels of suspiciousness and persecution (P = .55; $p = .027$; $n = 16$). No other items within the PANSS Positive subscale were significantly correlated with SCLs. Also, there were no significant correlations between the reported findings and age, IQ, duration of illness, or dose of antipsychotic medication.

Discussion

Summary of Findings

In this study, a substantial proportion (43%) of the patients with schizophrenia displayed minimal autonomic responsivity, consistent with previous findings (37). The patients who had intact autonomic responses (responders) demonstrated levels of fear acquisition and extinction learning that were comparable to the control subjects; however, these patients showed impairment and loss of context sensitivity in delayed recall of extinction. Moreover, the reduction in extinction recall manifested by abnormal SCRs in the patients was accompanied by a parallel reduction in explicit recall of the identities of the safe and dangerous contexts.

In addition, during fear acquisition, the patients showed higher SCRs to the CS− than the control subjects, and baseline SCLs in the responder patient group correlated with delusion severity.

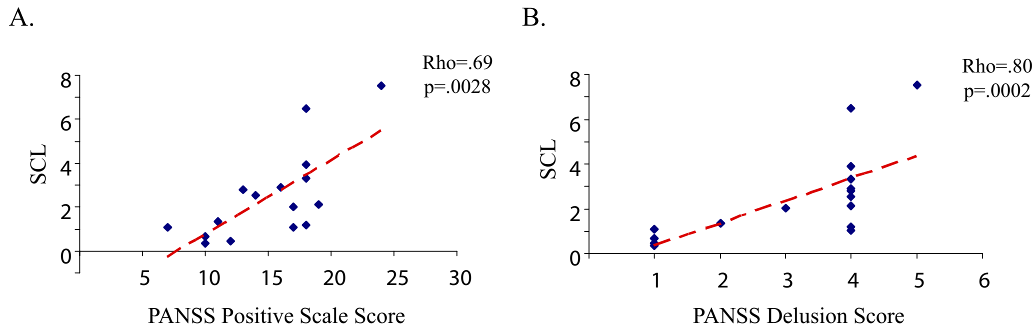

Figure 4. Scatter plots of the correlations between baseline skin conductance level (SCL) and the positive and negative syndrome scale (PANSS) Positive Scale score **(A)** and the PANSS delusion score **(B)** within the schizophrenia group ($n = 16$).

Reduced Autonomic Responsivity and Abnormal Responses to the CS− During Fear Acquisition

The finding of a population of schizophrenia patients with minimal or absent autonomic responses to sensory stimuli has been repeatedly replicated (37,47,48). The average proportion of patients with schizophrenia classified as nonresponders in previous studies is approximately 40%, compared with the 5%–10% of nonresponders found in healthy and nonschizophrenia psychiatric samples (37), consistent with the rates found in the current study. It has been demonstrated in studies of unmedicated schizophrenia patients that some degree of autonomic hypo-responsivity is intrinsic to the disorder (49–54).

The discrepancies among the results of studies of aversive conditioning in schizophrenia (16,32–36) might be due in part to this heterogeneity in autonomic responsivity. In the current study, we found some evidence for an impairment in the acquisition of conditioned fear responses in schizophrenia; although the difference in the mean levels of fear acquisition between the schizophrenia and control groups did not reach significance, the effect size was .41 (Cohen's d) in the full cohort of subjects, suggesting that the failure to find a significant difference between the groups in fear acquisition might have reflected a Type II error.

The trend toward a reduction in differential fear acquisition in the schizophrenia group was due at least in part to an abnormally elevated response to the CS−, replicating a previous similar finding (16). These results are consistent with the increasing evidence for the presence of a behavioral and neural bias toward misattributing emotional meaning to innocuous, emotionally neutral stimuli in individuals with schizophrenia (13,15,18,55). Functional neuroimaging studies have detected abnormally elevated activity in response to neutral, nonaversive stimuli in patients with schizophrenia in the amygdala (56,57), parahippocampal gyrus (18), ventral striatum (16), cingulate gyrus (55), and lateral prefrontal cortex (15). Taken together, the consistent replication of this overall finding and its relationship to abnormal fear conditioning and dysfunction of emotional learning and memory circuitry suggest that aberrant neural responses to neutral stimuli in schizophrenia arise from disruption of a basic emotional memory mechanism.

Extinction Recall Deficit

The finding of abnormally reduced recall of extinction memory in patients with intact autonomic responsivity suggests that some patients with schizophrenia are impaired in a specific type of emotional memory, namely the retrieval of a "safety signal" (58). Although our finding is limited to a subgroup of schizophrenia patients with intact autonomic responsivity, results of an exploratory analysis of the data from the full cohort of subjects (28 patients, 18 control subjects) (data not shown) were the same as the findings for the responders, with impaired extinction recall, after intact extinction learning, in the patients in comparison with the control subjects. Thus extinction recall might be impaired in a substantial proportion of patients with schizophrenia.

The retrieval of extinction memory relies on a network of limbic brain regions that includes the medial prefrontal cortex, hippocampus, and amygdala (20,21,23,26,43,58–60), areas that show abnormal levels of activity during emotional processing in schizophrenia (19,55,57,61–66). A functional magnetic resonance imaging study of extinction recall in healthy humans found that the success of extinction recall was predicted by the magnitude of both medial prefrontal and hippocampal activation (43). The hippocampus is thought to mediate the effects of context on Pavlovian fear conditioning and extinction (58); the loss of context-sensitivity in the schizophrenia patients during the retrieval phases of this study suggests that impaired extinction recall in schizophrenia could reflect dysfunction of the hippocampus. This hypothesis is supported by a large body of neuroimaging and postmortem evidence for structural and functional abnormalities of the hippocampus in schizophrenia (67–70).

Because schizophrenia is characterized by deficits in episodic memory and in other cognitive processes (71), it is possible that general cognitive abnormalities in the patients might have contributed to the impairment in explicit recall of the identities of the contexts on Day 2, the deficit in extinction recall, or both. We could not address this question directly in this study, because we did not measure explicit memory capacity or other aspects of cognitive function, except IQ (which did not predict extinction recall success in either group). Because the relationship between explicit episodic memory processes and implicit automatic ones such as extinction recall is not fully understood, studies that formally measure both types of memory in the same subjects will shed further light on this question.

These results have some implications for studies of the treatment of schizophrenia. Extinction recall in rodents depends upon N-methyl-D-aspartate (NMDA) glutamate receptor activity (72,73). In basic investigations of the pathophysiology of schizophrenia, antagonism of the NMDA receptor has been used as a pharmacological model of schizophrenia symptoms, primarily because of the striking similarities between the psychological effects of NMDA receptor antagonists and both the negative and positive symptom clusters of schizophrenia (74,75). Clinical trials have found mixed evidence for efficacy of agonists at the glycine modulatory site of the NMDA receptor in the treatment of cognitive deficits and negative symptoms in schizophrenia patients (76–79). Because an extinction recall impairment in schizophrenia might have greater biological "proximity" to neuronal dysfunction than conventional measures of psychopathology, future trials of such agents might benefit from targeting quantifiable NMDA-dependent processes such as extinction memory recall.

Elevated SCL in Delusions

The correlation between severity of delusional ideation and baseline SCL is in line with previous studies that have found elevated levels of spontaneous skin conductance responding in patients with high levels of positive symptoms (50,80) and with findings of elevated SCLs in schizotypal individuals (81). Elevated arousal during delusional states could account for the presence of attentional and memory biases toward threatening (82,83), generally emotional (84), or affectively neutral or ambiguous (13,85) information in delusional patients.

Limitations

The interpretation of our results is limited by the fact that we did not examine our data for the potential confounding effects of gender, subclasses of antipsychotic medication, caffeine, and nicotine, due to power constraints imposed by the modest number of subjects. Another important limitation of this study is that we cannot exclude the possibility that antipsychotic treatment influenced our results, although we found no evidence for such an effect. Studies conducted in animals have found that D2 dopamine receptor blockade diminishes the acquisition of Pavlovian (86,87) and operant (88–90) aversive conditioning. However, in the current study, normalizing the primary outcome measures to the maximal acquired fear response within individuals likely eliminated or minimized this potential confound, and we found no evidence for differences between the patients and control subjects within the responder group in responses to the CS+ or in overall levels of fear acquisition. Interestingly, D2 dopamine receptor antagonists have been shown to facilitate extinction learning (88,91) and recall of extinction (91) in animals. Thus, if antipsychotic treatment improves extinction recall, the intrinsic impairment in schizophrenia might be underestimated by the present study.

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1. Sergi MJ, Rassovsky Y, Widmark C, Reist C, Erhart S, Braff DL, *et al.* (2007): Social cognition in schizophrenia: Relationships with neurocognition and negative symptoms. *Schizophr Res* 90:316–324.
2. Smith B, Fowler DG, Freeman D, Bebbington P, Bashforth H, Garety P, *et al.* (2006): Emotion and psychosis: Links between depression, self-esteem, negative schematic beliefs and delusions and hallucinations. *Schizophr Res* 86:181–188.
3. Penn DL, Corrigan PW, Bentall RP, Racenstein JM, Newman L (1997): Social cognition in schizophrenia. *Psychol Bull* 121:114–132.
4. Kapur S (2003): Psychosis as a state of aberrant salience: A framework linking biology, phenomenology, and pharmacology in schizophrenia. *Am J Psychiatry*; 160:13–23.
5. Hooker C, Park S (2002): Emotion processing and its relationship to social functioning in schizophrenia patients. *Psychiatry Res* 112:41–50.
6. Moberg PJ, Arnold SE, Doty RL, Kohler C, Kanes S, Seigel S, *et al.* (2003): Impairment of odor hedonics in men with schizophrenia. *Am J Psychiatry* 160:1784–1789.
7. Addington J, Saeedi H, Addington D (2006): Facial affect recognition: A mediator between cognitive and social functioning in psychosis? *Schizophr Res* 85:142–150.
8. Crespo-Facorro B, Paradiso S, Andreasen NC, O'Leary DS, Watkins GL, Ponto LL, Hichwa RD (2001): Neural mechanisms of anhedonia in schizophrenia: A PET study of response to unpleasant and pleasant odors. *JAMA* 286:427–435.
9. Leitman DI, Hoptman MJ, Foxe JJ, Saccente E, Wylie GR, Nierenberg J, *et al.* (2007): The neural substrates of impaired prosodic detection in schizophrenia and its sensorial antecedents. *Am J Psychiatry* 164:474–482.
10. Malaspina D, Coleman E (2003): Olfaction and social drive in schizophrenia. *Arch Gen Psychiatry* 60:578–584.
11. Hoekert M, Kahn RS, Pijnenborg M, Aleman A (2007): Impaired recognition and expression of emotional prosody in schizophrenia: Review and meta-analysis. *Schizophr Res* 96:135–145.
12. Edwards J, Jackson HJ, Pattison PE (2002): Emotion recognition via facial expression and affective prosody in schizophrenia: A methodological review. *Clin Psychol Rev* 22:789–832.
13. Holt DJ, Titone D, Long LS, Goff DC, Cather C, Rauch SL, *et al.* (2006): The misattribution of salience in delusional patients with schizophrenia. *Schizophr Res* 83:247–256.
14. Kohler CG, Turner TH, Bilker WB, Brensinger CM, Siegel SJ, Kanes SJ, *et al.* (2003): Facial emotion recognition in schizophrenia: Intensity effects and error pattern. *Am J Psychiatry* 160:1768–1774.
15. Corlett PR, Murray GK, Honey GD, Aitken MR, Shanks DR, Robbins TW, *et al.* (2007): Disrupted prediction-error signal in psychosis: Evidence for an associative account of delusions. *Brain* 130:2387–2400.
16. Jensen J, Willeit M, Zipursky RB, Savina I, Smith AJ, Menon M, Crawley AP, Kapur S (2008): The formation of abnormal associations in schizophrenia: Neural and behavioral evidence. *Neuropsychopharmacology* 33:473–479.
17. Kerr SL, Neale JM (1993): Emotion perception in schizophrenia: Specific deficit or further evidence of generalized poor performance? *J Abnorm Psychol* 102:312–318.
18. Surguladze S, Russell T, Kucharska-Pietura K, Travis MJ, Giampietro V, David AS, Phillips ML (2006): A reversal of the normal pattern of parahippocampal response to neutral and fearful faces is associated with reality distortion in schizophrenia. *Biol Psychiatry* 60:423–431.

19. Holt DJ, Phillips ML (in press): The human amygdala in schizophrenia. In: Phelps EA, Whalen PJ, editors. *The Human Amygdala.* New York, Guilford.
20. Sotres-Bayon F, Bush DE, Ledoux JE (2004): Emotional perseveration: An update on prefrontal-amygdala interactions in fear extinction. *Learn Mem* 11:525–535.
21. Quirk GJ, Garcia R, Gonzalez-Lima F (2006): Prefrontal mechanisms in extinction of conditioned fear. *Biol Psychiatry* 60:337–343.
22. Milad MR, Orr SP, Pitman RK, Rauch SL (2005): Context modulation of memory for fear extinction in humans. *Psychophysiology* 42:456–464.
23. Milad MR, Rauch SL, Pitman RK, Quirk GJ (2006): Fear extinction in rats: Implications for human brain imaging and anxiety disorders. *Biol Psychol* 73:61–71.
24. Quirk GJ, Mueller D (2008): Neural mechanisms of extinction learning and retrieval. *Neuropsychopharmacology* 33:56–72.
25. Ledoux JE (2000): Emotion circuits in the brain. *Annu Rev Neurosci* 23: 155–184.
26. Myers KM, Davis M (2007): Mechanisms of fear extinction. *Mol Psychiatry* 12:120–150.
27. Bouton ME, Garcia-Gutierrez A, Zilski J, Moody EW (2006): Extinction in multiple contexts does not necessarily make extinction less vulnerable to relapse. *Behav Res Ther* 44:983–994.
28. Milad MR, Quirk GJ (2002): Neurons in medial prefrontal cortex signal memory for fear extinction. *Nature* 420:70–74.
29. Quirk GJ (2002): Memory for extinction of conditioned fear is long-lasting and persists following spontaneous recovery. *Learn Mem* 9:402–407.
30. Corcoran KA, Quirk GJ (2007): Activity in prelimbic cortex is necessary for the expression of learned, but not innate, fears. *J Neurosci* 27:840–844.
31. Bouton ME, Frohardt RJ, Sunsay C, Waddell J, Morris RW (2008): Contextual control of inhibition with reinforcement: Adaptation and timing mechanisms. *J Exp Psychol Anim Behav Process* 34:223–236.
32. Sears LL, Andreasen NC, O'Leary DS (2000): Cerebellar functional abnormalities in schizophrenia are suggested by classical eyeblink conditioning. *Biol Psychiatry* 48:204–209.
33. Spain B (1966): Eyelid conditioning and arousal in schizophrenic and normal subjects. *J Abnorm Psychol* 71:260–266.
34. Kosmidis MH, Breier A, Fantie BD (1999): Avoidance learning in schizophrenia: A dissociation between the effects of aversive and non-aversive stimuli. *Schizophr Res* 38:51–59.
35. Hofer E, Doby D, Anderer P, Dantendorfer K (2001): Impaired conditional discrimination learning in schizophrenia. *Schizophr Res* 51:127–136.
36. Howe ES (1958): GSR conditioning in anxiety states, normals, and chronic functional schizophrenic subjects. *J Abnorm Psychol* 56:183–189.
37. Ohman A (1981): Electrodermal activity and vulnerability to schizophrenia: A review. *Biol Psychol* 12:87–145.
38. Barch DM, Carter CS, MacDonald AW 3rd, Braver TS, Cohen JD (2003): Context-processing deficits in schizophrenia: Diagnostic specificity, 4-week course, and relationships to clinical symptoms. *J Abnorm Psychol* 112:132–143.
39. Hemsley DR (2005): The development of a cognitive model of schizophrenia: Placing it in context. *Neurosci Biobehav Rev* 29:977–988.
40. Green MJ, Waldron JH, Simpson I, Coltheart M (2008): Visual processing of social context during mental state perception in schizophrenia. *J Psychiatry Neurosci* 33:34–42.
41. Green MJ, Waldron JH, Coltheart M (2007): Emotional context processing is impaired in schizophrenia. *Cognit Neuropsychiatry* 12:259–280.
42. Milad MR, Goldstein JM, Orr SP, Wedig MM, Klibanski A, Pitman RK, Rauch SL (2006): Fear conditioning and extinction: Influence of sex and menstrual cycle in healthy humans. *Behav Neurosci* 120:1196–11203.
43. Milad MR, Wright CI, Orr SP, Pitman RK, Quirk GJ, Rauch SL (2007): Recall of fear extinction in humans activates the ventromedial prefrontal cortex and hippocampus in concert. *Biol Psychiatry* 62:446–454.
44. First MB, Spitzer RL, Gibbon M, Williams JBW (1995): *Structured Clinical Interview for DSM-IV Axis I Disorders*. New York: The New York State Psychiatric Institute, Biometrics Research.
45. Kay SR, Fiszbein A, Opler LA (1987): The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull* 13:261–276.
46. Phelps EA, Delgado MR, Nearing KI, Ledoux JE (2004): Extinction learning in humans: Role of the amygdala and vmPFC. *Neuron* 43:897–905.
47. Gruzelier JH, Venables PH (1972): Skin conductance orienting activity in a heterogeneous sample of schizophrenics. *J Nerv Ment Dis* 155:277–287.
48. Bernstein AS, Frith CD, Gruzelier JH, Patterson T, Straube E, Venables PH, Zahn TP (1982): An analysis of the skin conductance orienting response in samples of American, British, and German schizophrenics. *Biol Psychol* 14:155–211.
49. Zahn TP, Carpenter WT Jr, McGlashan TH (1981): Autonomic nervous system activity in acute schizophrenia: I. method and comparison with normal controls. *Arch Gen Psychiatry* 38:251–258.
50. Zahn TP, Jacobsen LK, Gordon CT, McKenna K, Frazier JA, Rapoport JL (1997): Autonomic nervous system markers of psychopathology in childhood-onset schizophrenia. *Arch Gen Psychiatry* 54:904–912.
51. Gruzelier J, Connolly J, Eves F, Hirsch S, Zaki S, Weller M, Yorkston N (1981): Effect of propranolol and phenothiazines on electrodermal orienting and habituation in schizophrenia. *Psychol Med* 11:93–108.
52. Gruzelier JH, Hammond NV (1978): The effect of chlorpromazine upon psychophysiological, endocrine and information processing measures in schizophrenia. *J Psychiatr Res* 14:167–182.
53. Zahn TP (1976): On the bimodality of the distribution of electrodermal orienting responses in schizophrenic patients. *J Nerv Ment Dis* 162:195–199.
54. Straube ER (1979): On the meaning of electrodermal nonresponding in schizophrenia. *J Nerv Ment Dis* 167:601–611.
55. Holt DJ, Lakshmanan B, Freudenreich O, Goff DC, Rauch SL, Kuperberg GR (2007): Abnormal neural responses to ambiguous social information in psychosis [abstract]. *Schizophr Bull* 33:524.
56. Hall J, Whalley HC, McKirdy JW, Romaniuk L, McGonigle D, McIntosh AM, *et al.* (2008): Overactivation of fear systems to neutral faces in schizophrenia. *Biol Psychiatry* 64:70–73.
57. Holt DJ, Kunkel L, Weiss AP, Goff DC, Wright CI, Shin LM, *et al.* (2006): Increased medial temporal lobe activation during the passive viewing of emotional and neutral facial expressions in schizophrenia. *Schizophr Res* 82:153–162.
58. Corcoran KA, Quirk GJ (2007): Recalling safety: Cooperative functions of the ventromedial prefrontal cortex and the hippocampus in extinction. *CNS Spectr* 12:200–206.
59. Rauch SL, Shin LM, Phelps EA (2006): Neurocircuitry models of posttraumatic stress disorder and extinction: Human neuroimaging research—past, present, and future. *Biol Psychiatry* 60:376–382.
60. Kalisch R, Korenfeld E, Stephan KE, Weiskopf N, Seymour B, Dolan RJ (2006): Context-dependent human extinction memory is mediated by a ventromedial prefrontal and hippocampal network. *J Neurosci* 26:9503–9511.
61. Gur RE, Loughead J, Kohler CG, Elliott MA, Lesko K, Ruparel K, *et al.* (2007): Limbic activation associated with misidentification of fearful faces and flat affect in schizophrenia. *Arch Gen Psychiatry* 64:1356–1366.
62. Holt DJ, Weiss AP, Rauch SL, Wright CI, Zalesak M, Goff DC, *et al.* (2005): Sustained activation of the hippocampus in response to fearful faces in schizophrenia. *Biol Psychiatry* 57:1011–1019.
63. Gur RE, McGrath C, Chan RM, Schroeder L, Turner T, Turetsky BI, *et al.* (2002): An fMRI study of facial emotion processing in patients with schizophrenia. *Am J Psychiatry* 159:1992–1999.
64. Taylor SF, Liberzon I, Decker LR, Koeppe RA (2002): A functional anatomic study of emotion in schizophrenia. *Schizophr Res* 58:159–172.
65. Taylor SF, Welsh RC, Chen AC, Velander AJ, Liberzon I (2007): Medial frontal hyperactivity in reality distortion. *Biol Psychiatry* 61:1171–1178.
66. Williams LM, Das P, Liddell BJ, Olivieri G, Peduto AS, David AS, *et al.* (2007): Fronto-limbic and autonomic disjunctions to negative emotion distinguish schizophrenia subtypes. *Psychiatry Res* 155:29–44.
67. Heckers S, Konradi C (2002): Hippocampal neurons in schizophrenia. *J Neural Transm* 109:891–905.
68. Wright IC, Rabe-Hesketh S, Woodruff PW, David AS, Murray RM, Bullmore ET (2000): Meta-analysis of regional brain volumes in schizophrenia. *Am J Psychiatry* 157:16–25.
69. Nelson MD, Saykin AJ, Flashman LA, Riordan HJ (1998): Hippocampal volume reduction in schizophrenia as assessed by magnetic resonance imaging: A meta-analytic study. *Arch Gen Psychiatry* 55:433–440.
70. Weiss AP, Heckers S (2001): Neuroimaging of declarative memory in schizophrenia. *Scand J Psychol* 42:239–250.
71. Cirillo MA, Seidman LJ (2003): Verbal declarative memory dysfunction in schizophrenia: From clinical assessment to genetics and brain mechanisms. *Neuropsychol Rev* 13:43–77.

72. Burgos-Robles A, Vidal-Gonzalez I, Santini E, Quirk GJ (2007): Consolidation of fear extinction requires NMDA receptor-dependent bursting in the ventromedial prefrontal cortex. *Neuron* 53:871–880.
73. Santini E, Muller RU, Quirk GJ (2001): Consolidation of extinction learning involves transfer from NMDA-independent to NMDA-dependent memory. *J Neurosci* 21:9009–9017.
74. Goff DC, Coyle JT (2001): The emerging role of glutamate in the pathophysiology and treatment of schizophrenia. *Am J Psychiatry* 158:1367–1377.
75. Krystal JH, D'Souza DC, Mathalon D, Perry E, Belger A, Hoffman R (2003): NMDA receptor antagonist effects, cortical glutamatergic function, and schizophrenia: Toward a paradigm shift in medication development. *Psychopharmacology (Berl)* 169:215–233.
76. Duncan EJ, Szilagyi S, Schwartz MP, Bugarski-Kirola D, Kunzova A, Negi S, *et al.* (2004): Effects of D-cycloserine on negative symptoms in schizophrenia. *Schizophr Res* 71:239–248.
77. Goff DC, Tsai G, Levitt J, Amico E, Manoach D, Schoenfeld DA, *et al.* (1999): A placebo-controlled trial of D-cycloserine added to conventional neuroleptics in patients with schizophrenia. *Arch Gen Psychiatry* 56:21–27.
78. Goff DC, Tsai G, Manoach DS, Flood J, Darby DG, Coyle JT (1996): D-cycloserine added to clozapine for patients with schizophrenia. *Am J Psychiatry* 153:1628–1630.
79. Buchanan RW, Javitt DC, Marder SR, Schooler NR, Gold JM, McMahon RP, *et al.* (2007): The Cognitive and Negative Symptoms in Schizophrenia Trial (CONSIST): The efficacy of glutamatergic agents for negative symptoms and cognitive impairments. *Am J Psychiatry* 164:1593–1602.
80. Maina G, Barzega G, Bellino S, Bogetto F, Ravizza L (1995): Type I and type II schizophrenia: Relations between tonic electrodermal activity and clinical ratings before and after haloperidol treatment. *Psychiatry Res* 57:49–56.
81. Raine A, Venables PH, Mednick S, Mellingen K (2002): Increased psychophysiological arousal and orienting at ages 3 and 11 years in persistently schizotypal adults. *Schizophr Res* 54:77–85.
82. Bentall RP, Kaney S (1989): Content specific information processing and persecutory delusions: An investigation using the emotional Stroop test. *Br J Med Psychol* 62:355–364.
83. Fear C, Sharp H, Healy D (1996): Cognitive processes in delusional disorders. *Br J Psychiatry* 168:61–67.
84. Kinderman P (1994): Attentional bias, persecutory delusions and the self-concept. *Br J Med Psychol* 67:53–66.
85. Phillips ML, Senior C, David AS (2000): Perception of threat in schizophrenics with persecutory delusions: An investigation using visual scan paths. *Psychol Med* 30:157–167.
86. Greba Q, Gifkins A, Kokkinidis L (2001): Inhibition of amygdaloid dopamine D2 receptors impairs emotional learning measured with fear-potentiated startle. *Brain Res* 899:218–226.
87. Inoue T, Tsuchiya K, Koyama T (1996): Effects of typical and atypical antipsychotic drugs on freezing behavior induced by conditioned fear. *Pharmacol Biochem Behav* 55:195–201.
88. Li M, Parkes J, Fletcher PJ, Kapur S (2004): Evaluation of the motor initiation hypothesis of APD-induced conditioned avoidance decreases. *Pharmacol Biochem Behav* 78:811–819.
89. Blackburn JR, Pfaus JG, Phillips AG (1992): Dopamine functions in appetitive and defensive behaviours. *Prog Neurobiol* 39:247–279.
90. Salamone JD, Cousins MS, Bucher S (1994): Anhedonia or anergia? Effects of haloperidol and nucleus accumbens dopamine depletion on instrumental response selection in a T-maze cost/benefit procedure. *Behav Brain Res* 65:221–229.
91. Ponnusamy R, Nissim HA, Barad M (2005): Systemic blockade of D2-like dopamine receptors facilitates extinction of conditioned fear in mice. *Learn Mem* 12:399–406.