Published in final edited form as:
Biol Psychiatry. 2009 March 15; 65(6): 455–463. doi:10.1016/j.biopsych.2008.09.017.

Extinction memory is impaired in schizophrenia

Daphne. J. Holt[1,2,3], **Kelimer Lebron-Milad**[1,2,3], **Mohammed R. Milad**[1,2,3], **Scott L. Rauch**[2,4], **Roger K. Pitman**[1,2,3], **Scott P. Orr**[1,2,3,5], **Brittany S. Cassidy**[1,3], **Jared P. Walsh**[1], and **Donald C. Goff**[1,2]

[1]Psychiatry Department, Massachusetts General Hospital, Boston, MA

[2]Harvard Medical School, Boston, MA

[3]Athinoula A. Martinos Center for Biomedical Imaging, Charlestown, MA

[4]McLean Hospital, Belmont, MA

[5]Department of Veterans Affairs Medical Center, Manchester, NH

Abstract

Background—Schizophrenia is associated with abnormalities in emotional processing and social cognition, which may 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—28 schizophrenia and 18 demographically-matched control subjects underwent a two-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 controls 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 controls. Within the responder group, there was no difference between the patients and controls in levels of extinction learning; however, the schizophrenia patients showed significant impairment, relative to the controls, in context-dependent recall of the extinction memory. In addition, delusion severity in the patients correlated with baseline skin conductance levels.

To whom correspondence should be addressed: Daphne J. Holt, MD, PhD, Massachusetts General Hospital East, Psychiatric Neuroimaging Research Program, Room 2662, 149 13th St. Charlestown, MA 02129, dholt@partners.org, tel: (617) 726-7618, fax: (617) 726-4078.

FINANCIAL DISCLOSURES

Scott Rauch received funds for research through MGH for Brain Stimulation Therapy from Medtronics, Inc.; through MGH for VNS from Cyberonics; and through MGH on anxiolytic action from Cephalon. Dr. Rauch also received honoraria from Novartis for consultation on emerging treatments; Neurogen for his participation as a consultant on emerging trends in anxiety associated with insomnia; Sepracor for his consultation on fear/conditioning/extinction and from Primedia for his participation in developing a CE activity and Medtronics, Inc for his attendance of the Advisory Board meeting on the Anatomy and Neuroscience of anxiety and depression. Dr. Rauch is also a trustee at McLean Hospital and also serves on the Board at Massachusetts Society for Medical Research (MSMR) as well as on the National Foundation of Mental Health (NFMH) Board.

Donald Goff received funds for research from Pfizer, Cephalon, and Janssen; speaking honoraria from Pfizer, Lilly, BristolMyerSquib, VerusMed, Letters and Science, Primedia, SG Cowen, Vista Research, Organon, Xytis, UCLA, Wyeth, Forest Laboratories, Loma Linda University, Psychiatric Times, Ohio State University, Genactics, Van Andel Research Institute; consulting honoraria from Xenoport, Dainippon Sumitomo Pharma America, Inc, and Genactics; honoraria for serving on an advisory board from Solvay/Wyeth, BristolMyerSquib, Proteus, Vanda Pharmaceuticals, Organon, and Xytis; and an honorarium for serving on a DSMB from Solvay/Wyeth.

Note that no direct conflict is anticipated. All relationships are listed for full disclosure.

The remaining authors have no financial disclosures.

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.

Keywords

schizophrenia; fear; conditioning; extinction; emotion; memory

INTRODUCTION

It has been recently recognized that impaired emotional function may 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 using 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, mis-assignment 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. A type of emotional memory, called extinction memory, has been studied extensively in rodents and humans using 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 controls. These inconsistencies may 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 which found that one third to one half of the patients exhibited no learning at all, while 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 two-day, classical Pavlovian fear conditioning and extinction paradigm which had been previously adapted for use in humans (22, 23). On the first day of this 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). Following 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. Based on previous studies (22, 42, 43), we predicted 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 controls, in context-dependent retrieval of extinction memory.

METHODS AND MATERIALS

Participants

28 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 MGH Schizophrenia Clinical and Research Program (see 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 three 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 prior to enrollment in accordance with the guidelines of the Partners Healthcare Institutional Review Board. Each patient's symptoms were evaluated by a trained rater using the Positive and Negative Symptom Scale (45).

Psychophysiological Procedures

A Coulbourn Instruments Lablink V System (Allentown, PA) was used to record skin conductance level via a Coulbourn Isolated Skin Conductance Coupler (71–23). Electrodes were placed on the palm of the participant's non-dominant hand. Electrodes were also attached to the second and third fingers of the dominant hand for the purpose of delivering the US (a 500 ms 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 which contained lamps that appeared on the computer screen (see 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 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 seconds: 6 seconds alone, followed by 12 seconds in combination with the CS+ or CS−. Skin conductance was recorded for 5 seconds prior to the presentation of the CX, during the 6-second presentation of the CX alone, and during the 12-second presentation of the CX plus the CS. The US occurred during the last 500 ms of the CS+. The average inter-trial interval was 16 seconds.

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 5 CS+ and 5 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-minute rest period. Each sub-phase included 5 CS+ and 5 CS− trials, all presented within the CX−. The electrical 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 5 CS+ and 5 CS− presented within the CX− without any US. During the Renewal phase, 5 CS+ and 5 CS− were presented within the CX+, and again no US was delivered. In half the participants, the Renewal phase preceded the Recall phase.

Instructions to Participants

Prior to 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. Prior to all subsequent phases of the study, participants were instructed that they “may or may not receive electrical stimulations.”

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

Skin Conductance Level and Response Values and Data Analysis

Baseline SCL was calculated as the mean skin conductance values during the 5 seconds prior to the presentation of the context during the Habituation phase.

The SCR magnitude for each CS trial was calculated by subtracting the mean skin conductance level during the 2 seconds immediately prior to CS onset (during which the context alone was being presented) from the highest skin conductance level recorded during the 12-second CS duration. Thus, all SCRs to the CS+ and CS− reflect changes in skin conductance levels 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). SCRs were square-root transformed prior to analysis. Since SCRs to the CS+ can only be extinguished after successful acquisition of those responses, extinction learning and recall were examined only

in participants who showed SCRs during the Acquisition phase (with SCRs ≥ 0.03 microseimens in two 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 using 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 using 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 using Student's *t*-test (α = 05, two-tailed). Differential fear acquisition (SCRs to the CS+ compared to 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 to SCRs to the CS+ during the first two trials of the Renewal phase) were assessed within each group using 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 standard errors of the mean.

RESULTS

Characteristics of the participants

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

Baseline SCL and Fear Acquisition

The mean SCL at baseline was non-significantly higher in the controls than the patients (controls: 3.55 ± .84; patients: 1.97 ± .37 microseimens; 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 towards 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−) (controls: .29 ± .11; patients: .10 ± .07 microseimens; t (44) = 1.46, p=. 15) or in magnitude of SCRs to the CS+ trials (controls: .09 ± .08; patients: .12 ± .06 microseimens; t (44) = .38, p=.71). However, the patients exhibited a significantly larger mean SCR to the CS− trials compared to the controls (controls: −.20 ± .09; patients: .02 ± . 04 microseimens; t (44) = 2.62, p=.01).

Examination of the acquisition data of each subject revealed that 83% of the controls (15/18) and 57% of the patients (16/28) exhibited autonomic responsivity (≥ 2 trials with SCR ≥ .03 microseimens) during the Acquisition phase ('responders'). Within this responder cohort, the controls again exhibited a non-significantly higher mean SCL than the patients (controls = 4.13 ± .94; patients = 2.49 ± .52 microseimens; t (29) = 1.55, p=.13). The responder patient and control groups did not differ in levels of fear acquisition (CS+ minus CS−) (controls: .33 ± .13; patients: .20 ± .12 microseimens; t (29) = .75, p=.46) or in magnitude of SCRs to the CS+ trials (controls: .10 ± .10; patients: .22 ± .10 microseimens; t (29) =.80, p=. 43). However, within the responder group, the patients again showed a significantly larger

mean SCR to the CS− trials compared to the controls (controls: −.22 ± .10; patients: .02 ± .06 microseimens; 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 controls, 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 (controls: .07 ± .09; patients: .03 ± .05 microseimens; t (29) = .66, p=.51) (Figure 2B) and their mean Extinction Learning Index (controls: 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 (controls: 74.2 % ± 8.0; patients: 33.7 % ± 16; t (29) = 2.23; p=.034) (Figure 3A). Further, the controls showed normal context-sensitivity during retrieval, with significantly lower SCRs to the CS+ in the extinction, compared to 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 while the schizophrenia patients and controls 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 controls (Fisher's Exact Test, p=.02).

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 (Rho=−.69; p=.004; n=15). Also, there were no significant correlations between magnitudes of fear acquisition, extinction learning or extinction memory recall and the PANSS total and subscale scores within the patient group. However, a significant correlation was found between SCL and the PANSS Positive subscale scores (Rho = .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 (Rho = .80; p=.0002; n=16) (Figure 4B) and also levels of suspiciousness and persecution (Rho=.55; p=.027; n=16). No other items within the PANSS Positive subscale were significantly correlated with skin conductance levels. Also, there were no significant correlations between the reported findings and age, I.Q., 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 controls; 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 controls, and baseline skin conductance levels in the responder patient group correlated with delusion severity.

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 to the 5–10% of nonresponders found in healthy and non-schizophrenia 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 hyporesponsivity is intrinsic to the disorder (49–54).

The discrepancies among the results of studies of aversive conditioning in schizophrenia (16, 32–36) may 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 between the mean levels of fear acquisition between the schizophrenia and control groups did not reach significance, the effect size was 0.41 (Cohen's d) (in the full cohort of subjects), suggesting that the failure to find a significant difference between the groups in fear acquisition may have reflected a Type II error.

The trend towards a reduction in differential fear acquisition in the schizophrenia group was at least in part due 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 towards 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 (18, 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 controls) (data not shown) were the same as the findings for the responders, with impaired extinction recall, following intact extinction learning, in the patients in comparison to the controls. Thus extinction recall may be impaired in a substantial proportion of patients with schizophrenia.

The retrieval of extinction memory relies on a network of limbic brain regions which includes the medial prefrontal cortex, hippocampus and amygdala (20, 21, 23, 26, 43, 58–60), areas which show abnormal levels of activity during emotional processing in schizophrenia (19, 55, 57, 61–64). An fMRI 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 post-mortem evidence for structural and functional abnormalities of the hippocampus in schizophrenia (65–68).

Because schizophrenia is characterized by deficits in episodic memory and in other cognitive processes (69), it is possible that general cognitive abnormalities in the patients may 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 I.Q. (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 which 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 (70, 71). 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 (72, 73). 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 (74–77). Because an extinction recall impairment in schizophrenia may have greater biological ‘proximity’ to neuronal dysfunction than conventional measures of psychopathology, future trials of such agents may benefit from targeting quantifiable NMDA-dependent processes such as extinction memory recall.

Elevated skin conductance levels in delusions

The correlation between severity of delusional ideation and baseline skin conductance levels is in line with previous studies which have found elevated levels of spontaneous skin conductance responding in patients with high levels of positive symptoms (50, 78) and with findings of elevated skin conductance levels in schizotypal individuals (79). Elevated arousal during delusional states could account for the presence of attentional and memory biases towards threatening (81, 82), generally emotional (83) or affectively ambiguous (13, 84) 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 controls 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 may be underestimated by the present study.

Acknowledgments

This work was funded by NIMH (K23 MH076054 (DJH) and K24 MH002025 (DCG)) and the National Alliance for Research in Schizophrenia and Depression (NARSAD) with the Sidney J. Baer Trust. We are grateful to Dr. Eric Maclin for valuable assistance with the statistical analyses.

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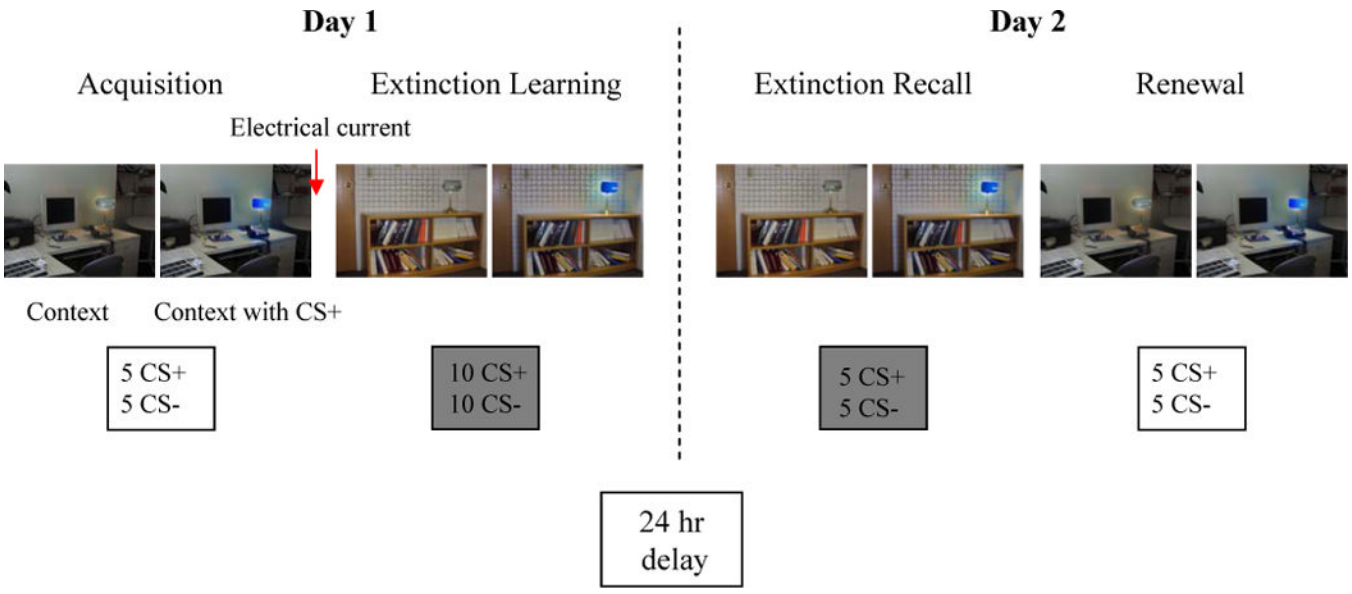

Figure 1.

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 seconds (total stimulus duration for the room photograph: 18 seconds). 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. Note that the order of the phases on Day 2, Extinction Recall and Renewal, were counterbalanced across subjects.

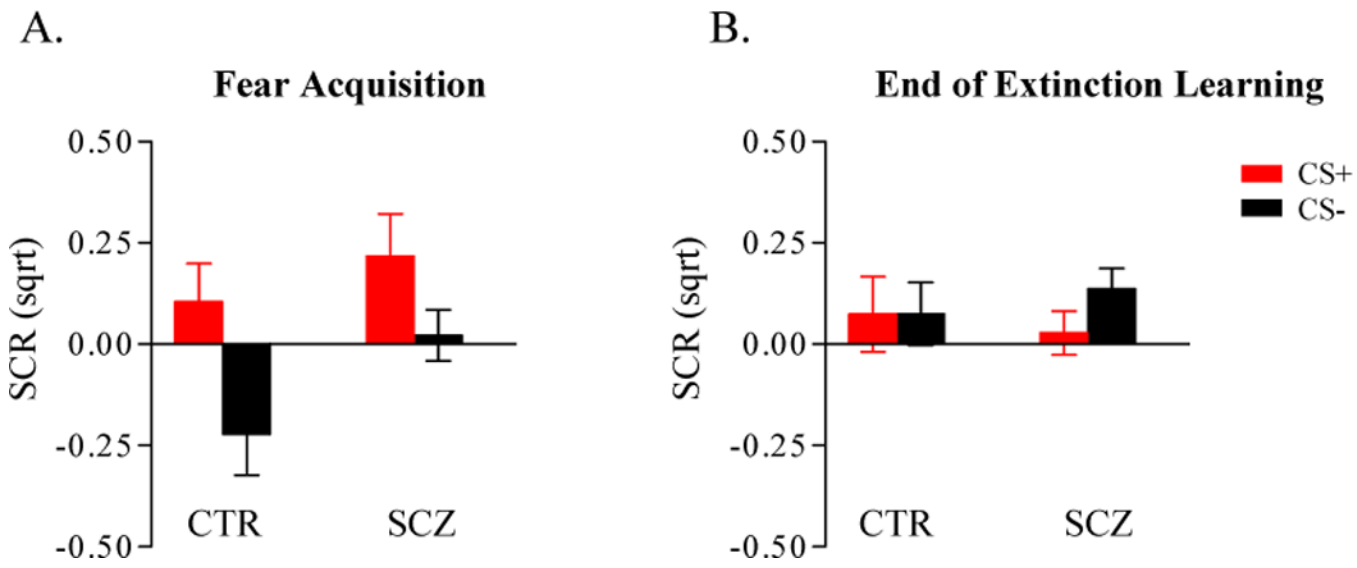

Figure 2.

Plots of mean SCRs ± SEM during the last two trials of the CS+ (red bars) and CS− (black bars) during the Acquistion phase (A) and the Extinction Learning phase (B) in the controls (CTR, n = 15) and schizophrenia patients (SCZ, n = 16) within the responder cohort. For the responders, within-group analyses revealed that the controls demonstrated acquisition of differential fear conditioning to the CS+ versus CS− (t (14) = 2.57; p=.011), and the patients showed a trend towards 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). 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%. Sqrt: square-root transformed.

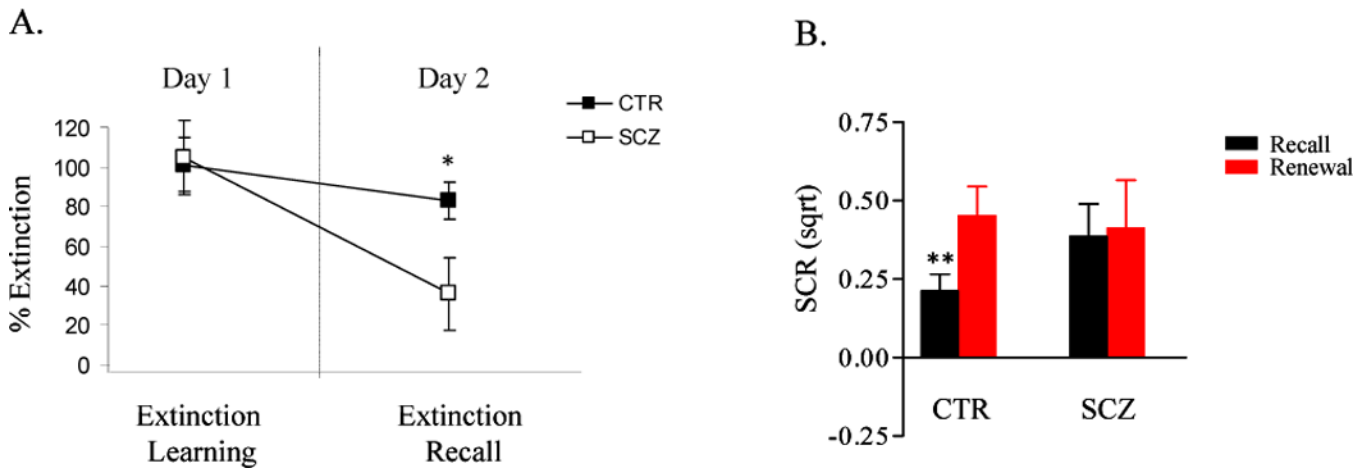

Figure 3.

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 controls. CTR: control group, n=15; SCZ: schizophrenia group, n=16; *p = .034. Sqrt: square-root transformed.

B. A plot of mean SCRs ± SEM to the CS+ of the two groups during the Extinction Retention (black bars) and Renewal (red bars) phases on Day 2, showing that SCRs to the CS+ are modulated by context in the controls (n=15) but not in the patients (n=16). **p = .008.

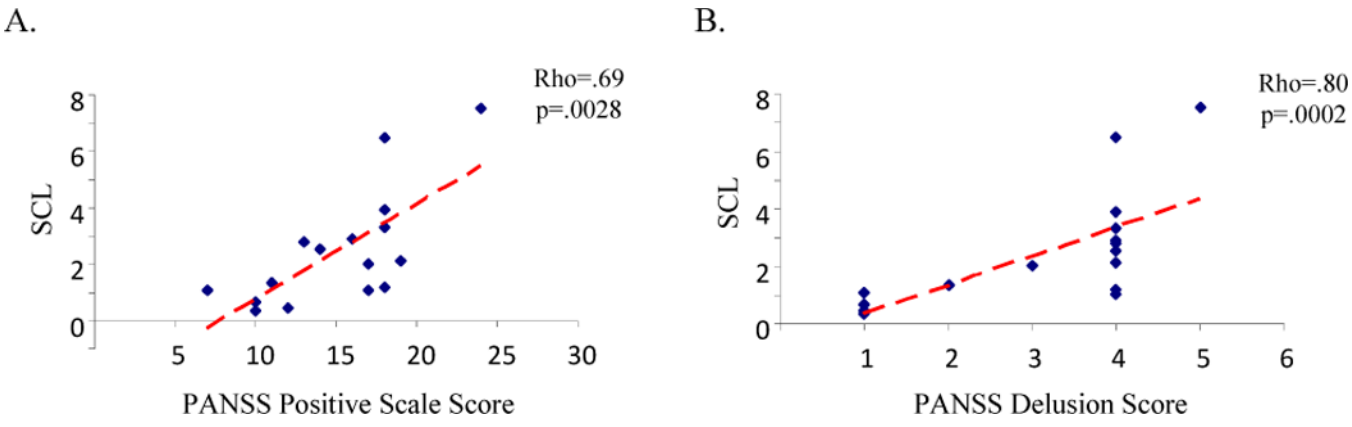

Figure 4.
Scatter plots of the correlations between baseline skin conductance level (SCL) and the PANSS Positive Scale score (A) and the PANSS delusion score (B) within the schizophrenia group (n =16).

Table 1

Demographic characteristics of the full cohort of subjects (n = 46) and the responders (participants with ≥ 2 trials with SCRs ≥ .03 microseimens during the Acquisition phase) (n=31). Means are presented, with standard errors of the mean 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 non-responders (n=12) on any clinical or outcome measure, although there was a trend towards a higher mean SCR to the CS+ trials during the Acquisition phase in the responders compared to the nonresponders (p=.09) and a trend towards a higher verbal I.Q. in the nonresponders compared to the responders (p=.09). Also, within the responder cohort, there were no significant differences between the controls (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 I.Q. was higher in the controls than in the patients (p=.004). a: Socioeconomic status, measured using the Hollingshead index; b: Verbal I.Q., measured using the North American Reading Test.

	Full cohort		**Responders**	
	Controls n=18: 7 female	**Patients n=28: 5 female**	**Controls n=15: 5 female**	**Patients n=16: 5 female**
Age (years)	42.8 (3.4)	43.6 (2.0)	41.2 (3.8)	42.8 (3.0)
Mean parental education (years)	13.2 (0.7)	13.4 (0.5)	13.2 (0.9)	13.1 (0.6)
Mean parental SES[a]	2.7 (0.2)	2.5 (0.2)	2.8 (0.3)	2.6 (0.3)
Verbal I.Q.[b]	110.0 (1.6)	104.2 (2.0)	111.8 (1.2)	101.6 (3.0
Stimulation level	2.6 (0.3)	2.3 (0.2)	2.7 (0.3)	2.2 (0.3)
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 (0.7)		13.7 (1.0)
PANSS General scale		28.5 (1.2)		30.1 (1.4)
PANSS delusion item		2.9 (0.3)		3.1 (0.4)
Duration of illness (years)		18.7 (2.0)		18.6 (2.8)
Chlorpromazine equivalents		441.4 (70.6)		347.8 (68.8)

Table 2

Percentage of subjects within each group (15 controls, 16 patients with schizophrenia) 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).

	Control	Schizophrenia	P value
% recalled CS+ on Day 1	86.7	75	.65
% recalled CX+ on Day 1	100	92.9	.48
% recalled CS+ on Day 2	86.7	68.8	.39
% recalled CX+ on Day 2	100	62.5	.02