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Use of a Brief Fear Memory Reactivation Procedure for Enhancing Exposure Therapy

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Abstract
We tested postretrieval extinction as an augmentation strategy for enhancing in vivo exposure therapy for naturally acquired pathological fear. Participants displaying marked phobic responding to either spiders or snakes were randomized to receive a standard one session in vivo exposure therapy protocol under one of two conditions. The experimental group (RFM-EXP) completed a 10-s fear reactivation procedure 30 min prior to initiating exposure therapy. Controls (EXP-RFM) completed the reactivation procedure after completing exposure therapy. Expected and peak during confrontation with live spiders or snakes were collected at pretreatment, posttreatment, and 1-month follow-up. RFM-EXP participants displayed significantly lower phobic responding at the 1-month follow-up relative to EXP-RFM controls. Unexpectedly, RFM-EXP participants showed more rapid fear attenuation during exposure relative to controls. Results provide preliminary support for further investigation of this exposure augmentation strategy across a wider range of anxiety-related disorders.

Keywords
exposure therapy, exposure augmentation, fear memory retrieval, fear reactivation, specific phobias

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Exposure therapy is a well-established set of psychotherapeutic strategies that have stood the test of time in demonstrating robust effects across the full spectrum of anxiety disorders (Hofmann & Smits, 2008). Over the past four decades, research on exposure therapy has shifted from demonstrating therapeutic efficacy to the study of change mechanisms and augmentation strategies to improve short-term efficacy and reduce return of fear (Telch, Cobb, & Lancaster, 2014). Significant advances in cognitive and behavioral neuroscience have led to a better understanding of fear extinction and have ushered in a new era of "translational" research focusing on the integration of findings from these basic science disciplines to improve extinction-based therapies for anxiety disorders (Craske et al., 2008; Craske, Treanor, Conway, Zbozinek, & Vervliet, 2014; Kindt, 2014; McNally, 2007).

Efforts to enhance exposure-based treatments have been the focus of considerable experimental investigations. Over the past three decades, two primary approaches have lead the research on exposure therapy enhancement—parametric strategies and augmentation strategies (Telch, Cobb, & Lancaster, 2014). Parametric approaches focus on testing variations in one or more exposure parameters. Examples include exposure dosing (Öst, Hellstrom, & Kåver, 1992), spacing of exposure sessions (Chambless, 1990), modality of exposure delivery, that is, imaginal, in vivo, virtual reality (García-Palacios, Botella, Hoffman, & Fabregat, 2007), exposure context (Mystkowski, Echiverri, & Labus, 2006), and level of therapist involvement (Gloster et al., 2011). In contrast, the augmentation approach involves combining exposure therapy with one or more nonexposure treatment elements such as cognitive strategies (Kamphuis & Telch, 2000), relaxation-based strategies (Murphy, Michelson, Marchione, Marchione, & Testa, 1998), fading of safety behaviors (Telch & Lancaster, 2012), having the patient engage in antagonistic actions during exposure (Wolitzky & Telch, 2009), and administration of cognitive enhancing drugs either immediately before or after an exposure

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therapy session (Hofmann, Smits, Asnaani, Gutner, & Otto, 2011; Telch, Bruchey, et al., 2014).

More recently, advances in the neurobiology of fear and fear attenuation have led to a resurgence of interest in the application of basic research on fear extinction as a vehicle for tackling the most widely cited limitation of existing exposure-based therapies—return of fear (Craske et al., 2008; Kindt, 2014). There is a growing consensus that extinction-based therapies do not erase fear memories but rather create competing context-specific inhibitory safety memories that attenuate fear responding but leave one vulnerable to a reemergence of fear responding over time (spontaneous recovery), when faced with a change in context (fear renewal), or following exposure to a stressful stimulus (reinstatement; Bouton, 2002).

The assumption that memories are carved in stone once encoded has been challenged by researchers since the pioneering work of Müller and Pilzecker (1900). Consolidation theory asserts that memories are labile during a limited window after encoding, but undergo a process of consolidation whereby they become resistant to change (McGaugh, 2000). Compelling evidence across species and research paradigms suggests that *reactivation* of a previously consolidated memory returns the memory to a temporary labile state in which it must undergo a protein synthesis-dependent process of memory reconsolidation (Nader & Hardt, 2009; Nader, Schafe, & Le Doux, 2000). During this temporary reconsolidation window, integration of new experiences creates an updated "version" of the original memory, although some data suggest that fear memory updating through memory reactivation occurs only if there is something to be learned during memory retrieval, that is, violation of expectation based on prior learning (Sevenster, Beckers, & Kindt, 2012).

Significant work in both rodents (Debiec & LeDoux, 2004; Duvarci & Nader, 2004; Jarome, Ferrara, Kwapis, & Helmstetter, 2016; J. L. C. Lee, Milton, & Everitt, 2006; Nader et al., 2000) and humans (Kindt, Soeter, & Vervliet, 2009; Soeter & Kindt, 2010; Soeter, & Kindt, 2011) has shown that fear memories acquired in the laboratory can be significantly weakened by first reactivating the memory and then administering a reconsolidation-disrupting drug that either directly or indirectly blocks the molecular cascade required for memory reconsolidation. Preliminary evidence suggests that this same approach may show promise in the treatment of those with posttraumatic stress disorder or other pathological fear states acquired outside of the laboratory (Brunet et al., 2008; Soeter & Kindt, 2015; but see Wood et al., 2015).

Alternatives to pharmacological blockade of memory reconsolidation have also shown promise in attenuating trauma memories. James et al. (2015) recently found that reactivation of a laboratory-induced trauma memory followed by a competing working memory task (playing the game Tetris) was successful in markedly reducing the subsequent occurrence of intrusive memories of the trauma. Monfils, Cowansage, Klann, and LeDoux (2009) provided the first demonstration that strategic reactivation of a fear memory can be used in conjunction with classic Pavlovian fear extinction to modify a conditioned fear memory in rodents. Rats that underwent reactivation of the fear memory via a brief retrieval trial during the reconsolidation window (10 min prior to initiating extinction training) showed significantly less spontaneous recovery, fear renewal, and fear reinstatement relative to controls that did not undergo fear reactivation prior to extinction, or animals that received fear reactivation followed by an extinction session outside of the reconsolidation window (6 hr postretrieval). Moreover, compared to controls, rodents that underwent the retrieval-extinction procedure showed plasticity-related changes in the lateral amygdala consistent with a reconsolidation update mechanism as opposed to a facilitation of extinction learning (Monfils et al., 2009). Replications of these findings in rodents have appeared (Clem & Huganir, 2010; Flavell, Barber, & Lee, 2011; Jones, Ringuet, & Monfils, 2013; H. J. Lee, Haberman, Roquet, & Monfils, 2015; Olshavsky et al., 2013; Rao-Ruiz et al., 2011; Shumake & Monfils, 2015; Tedesco, Roquet, DeMis, Chiamulera, & Monfils, 2014), but others have failed to replicate (Baker, McNally, & Richardson, 2013; Chan, Leung, Westbrook, & McNally, 2010; Ishii et al., 2012).

Using a Pavlovian shock-conditioning paradigm, Schiller and colleagues (2010) replicated these effects in humans by showing that postretrieval extinction training administered 10 min after a reactivation cue (i.e., during the reconsolidation window) prevented spontaneous recovery and reinstatement of fear, as compared to controls that either did not receive a reactivation cue or underwent extinction 6 hr after reactivation (well outside the reconsolidation window). In addition, the authors found that the blockade of fear return was cue-specific, extended to reinstatement as well as recovery of fear, and persisted for up to a year after extinction training (Schiller et al., 2010). As in the case with rodents, some attempts to replicate these effects have been successful (Agren et al., 2012; Oyarzún et al., 2012; Schiller, Kanen, LeDoux, Monfils, & Phelps, 2013) whereas others have not (Golkar, Bellander, Olsson, & Öhman, 2012; Kindt & Soeter, 2013; Meir Drexler et al., 2014; Shiban, Brütting, Pauli, & Mühlberger, 2015; Soeter & Kindt, 2011). Note that differences in specific study parameters could reasonably account for the discrepancies noted across experiments, that is, the fear measure used (skin conductance versus startle response), the absence or presence of online contingency measures, and the fear relevance/irrelevance of the conditioned stimuli that are reminded or not. In their recent meta-analysis, Kredlow, Unger, and Otto (2016) reported that postretrieval

extinction demonstrated a small-to- moderate effect (g = 0.40) for preventing return of fear in humans relative to standard extinction.

The Present Study

Based on the mounting evidence that pharmacological and behavioral manipulations are capable of disrupting the reconsolidation of conditioned fear memories under some conditions, we sought to test the translational utility of postretrieval extinction as an augmentation strategy for enhancing the clinical efficacy of standard in vivo exposure therapy for naturally acquired pathological fear. In the experimental condition, participants displaying a marked fear of spiders or snake phobia received a brief fear memory reactivation procedure designed to render the fear memory labile and thus receptive to reconsolidation update. After a 30-min rest period, participants then received a standard one-session in vivo exposure treatment designed to provide corrective learning (i.e., disconfirmation of the belief that the spider/snake is harmful). Participants in the control group were provided an identical, one-session exposure treatment with the brief fear memory network reactivation procedure administered outside of the reconsolidation window (i.e., at the conclusion of exposure therapy). We hypothesized that compared to controls, participants who underwent reactivation of their fear memory network prior to starting exposure therapy would show enhanced fear attenuation at a 1-month follow-up.

Method

Study design

See Figure 1 for an overview of the study design and the sequencing of procedural elements over the course of the study for each of the two experimental conditions.

Participants and procedures

Participants (N = 32) reporting marked fear of snakes or spiders were recruited from a large subject pool of undergraduates through a two-stage screening process and then randomized to one of two exposure therapy conditions: (a) brief reactivation of the fear memory network administered 30 min before exposure therapy (RFM-EXP)[1] or (b) brief reactivation of the fear memory administered after the completion of exposure therapy (EXP-RFM control). In Stage 1, potential participants (N = 1,163) completed an online assessment battery. Those who were 18 or older, who reported no use of psychotropic medication or history of exposure treatment, and who scored 54 or higher on the Fear of Spiders/Snakes Questionnaire (Szymanski & O'Donohue, 1995) were invited to the laboratory for a face-to-face behavioral assessment (Stage 2). During this screening, participants completed two consecutive behavioral approach tests involving two different live snakes or spiders (see Assessments[AQ: 3]). Of the 54 participants who underwent Stage 2 screening, 9 were excluded due to insufficient fear as indexed by a subjective peak fear rating of less than 50 out of 100 on at least one of the two behavioral approach tests. Of the 45 eligible participants, 13 refused treatment. The remaining 32 randomized participants ranged in age from 18 to 40 (M = 21.31, SD = 4.40) and were predominantly female (87.5%) and non-Caucasian (53.2%). In all, 18 participants (56.2%) were assessed and treated for snake phobia and 14 participants (43.8%) were assessed and treated for spider phobia. All study procedures were approved by the Institutional Review Board of the Office of Research Support at the University of Texas at Austin. All participants provided informed consent.

Fig. 1. Overview of the study design and the sequencing of procedural elements over the course of the study for each of the two experimental conditions.[AQ: 8]
Note: RFM-EXP = reactivation of the fear memory network followed by 30 min of exposure therapy; EXP-RFM = exposure therapy followed by reactivation of the fear memory network outside the reconsolidation update window; SPQ = Spider/Snake Phobia Questionnaire; BATs = behavioral approach tests.

Experimental manipulation of fear memory network reactivation

After arriving for their treatment visit, participants randomized to the RFM-EXP condition completed a 10-s procedure designed to reactivate the fear memory network and initiate the reconsolidation update mechanism. In preparation for this procedure, the treatment animal

(snake or spider) was placed on a white, 30.5 cm by 30.5 cm (12 in. by 12 in.)[AQ:] mid on the floor. Participants were escorted to the treatment room and provided the following instructions:

> Now we are going to have you enter this room with me and position yourself within one square (12 inches) of the snake/spider. Once in position, I would like you to focus all your attention on the snake/spider for the next 10 seconds. While focusing on the snake/spider, it is important that you do your best to call forth from memory an actual or imagined fear encounter with a snake or spider. Do you have any questions?

The 10-s duration was selected based on the assumption that it was sufficient to activate multiple facets of the fear memory network (i.e., episodic memory of an imagined/anticipated encounter or direct encounter) but too brief for fear attenuation to occur. Following the RFM procedure and before beginning exposure therapy, participants completed a 30-min rest period during which they completed survey questions unrelated to their target fear. The 30-min duration was selected because prior research has established that a period of 10 to 60 min between retrieval and extinction training is sufficient for activation of the reconsolidation update mechanism in both rodents (e.g., Monfils et al., 2009) and humans (Kredlow et al., 2016).

Participants randomized to the EXP-RFM control group underwent the identical procedure as those in the RFM-EXP experimental group, except that the RFM procedure was completed 30 min *after* completing exposure therapy.

Exposure therapy protocol

The exposure therapy protocol consisted of six 3-min in vivo exposure trials with a 2-min interval between each trial. Prior to starting, participants were provided a treatment rationale emphasizing that phobias are maintained by avoidance and false perceptions of threat and that repeatedly confronting the feared object has proven to be an effective method for overcoming many different types of phobias. Following the presentation of the treatment rationale, participants were provided detailed information about the exposure procedures. In brief, participants were escorted to the treatment room measuring 310 cm by 284 cm. Placed on the floor in the center of the room was a plastic white mat measuring 213 cm by 152 cm marked with a series of equally spaced black squares measuring 30.5 by 30.5 cm.

Participants were instructed to remove their shoes and stand at the doorway of the treatment room while a staff member placed the live feared animal (snake or spider) on the floor mat in the center of the room. Participants were further instructed that if the animal begins to move further from them, they are to reposition themselves to remain within 30.5 cm (12 in.) of the animal's head at all times. Prior to entering the room, participants were asked to rate their expected fear on a 0 to 100 scale. The participant was then instructed to enter the room unaccompanied and stand within 30.5 cm (one square) of the animal's head until the staff member signaled the end of the 3-min exposure trial. If the participant's distance from the animal exceeded 30.5 cm, the experimenter paused the timer and instructed the participant to move closer to the animal. Upon achieving the 3-min criterion, the participant was instructed to exit the room. At that point, participants provided ratings of peak fear during the trial using the same 0 to 100 scale. This sequence was repeated for all six exposure trials.

Assessment of phobic responding

In vivo fear responding to behavioral approach tests (BATs). At each of the three assessment periods (pre, post, and follow-up), Participants completed two consecutive BATs with animals that matched their primary phobia (snake or spider). The animals used in the BATs were two Chilean rose tarantulas of differing colors (species: *Grammostola rosea*; measuring approximately 4.5 cm. in length and 2.5 cm in width), one African ball python (species: *Python regius*; body length approximately 85 cm; body width approximately 12 cm), and one American corn snake (species: *Elaphe guttata guttata*; body length approximately 122 cm; body width approximately 7.6 cm). Animal care was provided in accordance with guidelines set forth by the University of Texas at Austin's Institutional Animal Care and Use Committee.

For BAT 1 (treatment context), participants were escorted to a room measuring 3.10 m by 2.84 m that contained a plastic white mat marked with 30.48 cm black squares placed on the floor in the middle of the room. Participants were instructed to remove their shoes and stand at the doorway of the treatment room while a staff member placed the live feared animal (American corn snake or Chilean rose tarantula) on the floor mat in the center of the room. The animal used during BAT 1 was the same animal used during exposure therapy and the RFM procedure. Prior to entering, participants were asked to rate their expected fear on a 0 to 100 scale. Participants were then instructed to approach the animal and stand facing the animal within 30.5 cm (12 in.; one square) of its head for a maximum of 2 min. Upon exiting the room, participants rated their actual peak fear on a 0 to 100 scale.

The procedures for BAT 2 (generalization context) were identical in all respects to those of BAT 1 with two exceptions. First, unlike in BAT 1, the animal used in BAT 2 was not used during the RFM procedure or exposure

therapy. Second, the floor mat was green cloth instead of white plastic.

Fear of Spiders/Snakes Questionnaire (FSQ). All participants completed the FSQ (Szymanski & O'Donohue, 1995) at pretreatment and 1-month follow-up. This 18-item instrument presents statements such as "If I saw a spider now, I would think it will harm me" and "If I saw a spider now I would feel very panicky," tapping cognitive, behavioral, physiological, negative attitudes, and fear of harm related to fear of spiders. Respondents are asked to indicate the extent to which they agree with each statement on a scale from 0 (*strongly disagree*) to 6 (*strongly agree*). The FSQ has adequate internal consistency (Cronbach's $\alpha = .92$), split-half reliability ($r = .89$), and test–retest reliability over a 1-month period ($r = .63$ to .97; Szymanski & O'Donohue, 1995). Minor modifications of the instrument (i.e., replacing the word *spider* with *snake*) were made for the subset of study participants whose target phobia was snakes.

Statistical analysis

Outcome analyses. All data were modeled using version 22 of SPSS Statistics. Treatment groups (RFM-EXP vs. EXP-RFM) were compared at baseline, 1-day posttreatment, and 1-month follow-up using independent samples *t* tests when data were normally distributed, and nonparametric Mann–Whitney *U* tests when data were not normally distributed. Distribution normality within both experimental groups was assessed using Shapiro–Wilk tests ($p < .05$). Our primary outcomes were expected and peak fear during BAT 2 (the generalization context test). Secondary outcomes included expected and peak fear during BAT 1 (the treatment context test). Data were missing for two participants at posttreatment (1 in each of the two groups), and four participants at follow-up (3 in EXP-RFM and 1 RFM-EXP). Missing data for these four participants were imputed with series means (Little & Rubin, 2002).

Fear decline during treatment. Growth curve modeling (GCM; Raudenbush & Bryk, 2002) was used to investigate potential between group differences in the fear decline slopes. GCM offers several advantages over repeated measures ANOVA including greater flexibility in modeling change over time, more accurate effect estimates, and less susceptibility to Type I error (Raudenbush & Byrk, 2002). In addition, simulation studies have demonstrated that under realistic data conditions, GCM results in greater statistical power and more accurate estimates than a traditional repeated measures ANOVA (Quené & van den Bergh, 2004).

Reported fear for each of six 3-min exposure therapy trials (Level 1) was nested within individuals (Level 2). Separate GCMs were performed for each of the two fear expression indices: (a) expected fear reported before each exposure trial and (b) peak fear reported at the end of each trial.

To identify the best functional form each of the two growth models, we first tested the fixed and random effects of time (linear and quadratic). We retained statistically significant ($p \leq .05$) fixed and random effects of time in accordance with *t* tests and Wald-*Z* tests, respectively. We then added the fixed effects of pretreatment severity and treatment condition as predictors of the intercept and growth trajectory. The pretreatment severity measure consisted of the pretreatment level of the outcome of interest (peak or expected fear) during the treatment context BAT (BAT 1). To simplify interpretation of coefficients, pretreatment severity was *z*-transformed and treatment groups were dummy coded (EXP-RFM/control = 0, RFM-EXP/experimental = 1). We removed nonsignificant, higher-order, fixed effects using a backward elimination procedure to produce the final GCM. Because the sample was fairly small for this exploratory pilot study, higher-order effects with $p \leq .1$ were retained in the model when they improved model fit based on the Akaike information criterion (AIC). When a statistically significant interaction ($p \leq .05$, or trend at $p \leq .1$) between trial (linear or quadratic) and treatment condition was identified in the final conditional GCM, we tested simple effects of condition at each time point by recentering the model at each of six treatment trials.

Treatment process data for one participant (in the EXP-RFM group) were missing from the final data set, so this individual was excluded from the treatment process analysis. All initial models were constructed using maximum likelihood (ML) regression to allow for comparison of deviation statistics between models with differing fixed effects. We used an unstructured variance–covariance matrix to model the relationships between the random effects because this model produced significantly lower deviance, according to chi-squared tests of model fit using the −2 log likelihood statistic. After the final conditional GCM model was selected, we used restricted maximum likelihood (REML) regression to produce estimates because REML provides superior estimates for a smaller number of Level 2 units (Raudenbush & Bryk, 2002). The effect size for each predictor in the models was estimated by calculating Cohen's *d* based on the *t* test statistics for that predictor ($2t / \sqrt{\text{degrees freedom}}$).

Results

Outcome analyses

Means and standard deviations for outcome measures at baseline, 1-day posttreatment, and 1-month follow-up are included in Table 1 and Figure 2. At baseline, between-group comparisons revealed no differences on expected or peak fear for both BATs (all ps $\geq .28$), and no differences on

Table 1. Means and Standard Deviations for Outcome Measures at Pretreatment, 1-Day Posttreatment, and 1-Month Follow-Up

	RFM-EXP (n = 15)			EXP-RFM (n = 17)		
Measure	PreTx	PostTx	Follow-up	PreTx	PostTx	Follow-up
BAT 1 expected fear						
M	81.33	27.70	16.15	81.18	27.45	23.87
SD	16.09	21.82	17.53	16.44	18.81	15.85
BAT 1 peak fear						
M	76.33	18.87	11.29	82.06	21.06	17.00
SD	15.17	17.22	17.46	16.40	16.18	13.53
BAT 2 expected fear						
M	80.33	33.82	26.73	81.76	40.25	34.57
SD	15.06	19.43	18.21	12.11	25.95	18.75
BAT 2 peak fear						
M	83.00	29.06	14.79	82.71	28.64	24.20
SD	15.79	24.38	20.99	15.97	18.51	17.00
FSQ						
M	83.20	—	53.15	84.29	—	49.51
SD	16.41	—	28.96	12.22	—	22.77

Note: RFM-EXP = reactivation of the fear memory network 30 min before exposure therapy; EXP-RFM = exposure therapy before reactivation of the fear memory network; BAT 1 = Behavioral Approach Test 1/Treatment Context Test; BAT 2 = Behavioral Approach Test 2/Generalization Context Test; FSQ = Fear of Snakes/Spiders Questionnaire; PreTx = pretreatment; PostTx = 1-day post-treatment; follow-up = 1-month follow-up. Missing data were imputed with means. All paired-sample t tests were statistically significant (all ps < .001) indicating improvement within each treatment group from pretreatment to posttreatment, and pretreatment to follow-up.

the phobia questionnaire (FSQ; p = .74). At 1-day posttreatment, there again were no differences in expected or peak fear for either BAT (all ps ≥ .44). (The questionnaire was not completed at posttreatment.) However, at 1-month follow-up, the RFM-EXP group reported lower peak fear in the training context (at a trend level; *Mdn* = 0 vs. 14; U = 81.00, p = .08, moderate effect size/r = .32) and in the generalization context (*Mdn* = 5 vs. 20; U = 74.50; p = .04, moderate effect size/r = .36). At 1-month follow-up, there were no differences in expected fear on either BAT (ps = .13) or on the self-report questionnaire (p = .69).

Fear decline during treatment

Peak fear across exposure therapy trials. Attenuation of peak fear across the six 3-min exposure therapy trials for each experimental group is presented in Figure 3. The fully unconditional mean model (ML) revealed an intraclass correlation within participants of .47 (T_{00} = 283.16, Wald Z = 3.31, p = .001). The unconditional linear growth ML model showed a significant fixed effect for trial, ß = −3.62, t(31) = −3.55, p = .001, and random effect for trial (T_{11} = 20.69, Wald Z = 2.49, p = .01). The unconditional quadratic model was not significant, ß = 0.72, t(31) = 1.58, p = .12, nor was the random effect of trial squared (T_{22} = 1.42, Wald Z = 0.80, p = .42), so these effects were not included in the conditional growth model.

The conditional linear growth model with all predictors showed that the trial by pretreatment severity interaction was not significant, ß = −1.26, t(31) = −1.32, p = .20, indicating that pretreatment severity did not explain individual variation in linear growth. After this term was removed from the model, all predictors in the ML model were statistically significant (p < .05). The final REML model is reported in Table S1 in the Supplemental Material available online. To probe the trial by treatment interaction, we examined the main effect of treatment after recentering the REML model at each of the 6 treatment trials. This analysis revealed that RFM-EXP participants reported significantly lower peak fear for the first trial, had a trend for lower levels of peak fear for second trial, and statistically equivalent levels of peak fear for Trials 3 through 6 (see Fig. 2 and Table S2).

Expected fear across exposure therapy trials. Attenuation of expected fear across the six 3-min exposure therapy trials for each experimental group is presented in Figure 2. The unconditional mean model (ML) revealed an intraclass correlation rating within participants of 0.411 (T_{00} = 255.31, Wald Z = 3.17, p = .002). The unconditional linear growth ML model showed a significant

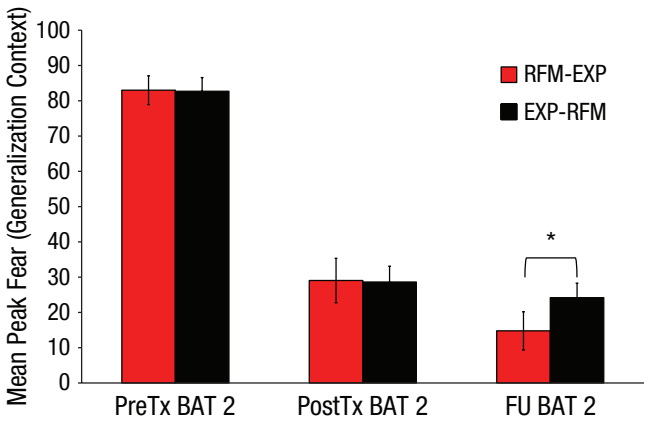

Fig. 2. Mean peak fear scores (plus or minus one standard error) for BAT 2 (generalization context) at pretreatment (PreTx BAT 2), 1-day posttreatment (PostTx BAT 2), and 1-month follow-up (FU BAT 2). Relative to controls (EXP-RFM), the RFM-EXP group showed lower peak fear scores in the generalization context (BAT 2) at the 1-month follow-up ($p = .04$).
Note: RFM-EXP = reactivation of the fear memory network followed by 30 min of exposure therapy; EXP-RFM = exposure therapy followed by reactivation of the fear memory network outside the reconsolidation update window. *$p \leq .05$.

fixed effect for trial, ß = −6.86, $t(31) = -6.72$, $p < .001$, and a significant random effect for trial ($T_{11} = 26.02$, Wald $Z = 3.16$, $p = .002$). The unconditional quadratic ML model showed a significant fixed effect of trial squared, ß = 1.50, $t(31) = 4.18$, $p < .001$, and random effect of trial squared ($T_{22} = 2.19$, Wald $Z = 2.08$, $p = .04$), so the quadratic fixed and random effects of trial squared were retained in the final model.

The conditional quadratic growth model with all predictors revealed a nonsignificant interaction of trial squared with pretreatment severity, ß = 0.44, $t(31) = 1.29$, $p = .21$. After this term was removed from the ML model, the results showed that the interaction of trial with pretreatment severity was nonsignificant, ß = −0.11, $t(31) = -0.11$, $p = .91$. After removing pretreatment severity as a predictor of quadratic and linear growth, all remaining higher-order terms were either significant ($p < .05$) or had a trend for significance ($p < .10$), so were retained in the final model (see Table S1 for final model). Though the trial-squared by treatment interaction was marginally significant in the ML model, ß = 1.23, $t(31) = 1.80$, $p = .08$, we left this interaction in the model because the AIC increased when this interaction was removed. See Table S1 for the final REML model.

To probe the treatment by time interaction, we explored the simple effects of treatment at each time point in the REML models. RFM-EXP participants reported significantly lower expected fear before Trials 1, 2, and 3; had a trend for lower levels of expected fear before Trial 4; and had statistically equivalent reports of expected fear before Trials 5 and 6 (see Fig. 2 and Table S2).

Discussion

This is the first successful demonstration of an exposure enhancement effect resulting from the use of a brief fear memory reactivation procedure prior to the start of exposure treatment. Two major findings emerged from this investigation. Consistent with expectation, we found preliminary evidence supporting the facilitative effects of administering a brief reactivation trial followed by exposure therapy during the presumed temporal window for memory reconsolidation. Even after controlling for level of fear reduction during treatment, those receiving the fear memory reactivation procedure 30 min prior to exposure treatment displayed significantly lower phobic responding at the 1-month follow-up relative to controls who received the fear memory reactivation procedure after completing exposure treatment. This finding is consistent with preclinical fear extinction studies in both rodents (Monfils et al., 2009) and humans (Schiller et al., 2010) showing greater retention of extinction for participants receiving the memory retrieval trial prior to the initiation of extinction training.

Our findings are in marked contrast to those of Shiban et al. (2015) who reported that a brief fear reactivation trial (5-s presentation of a virtual spider) did not enhance virtual reality (VR) exposure treatment of spider phobia as indexed by spontaneous recovery indices (i.e., subjective fear ratings and electrodermal responding) obtained 24 hr following treatment. Methodological differences between the current study and that of Shiban et al. are numerous and may account for the discrepant findings. These include (a) procedural differences in the fear reactivation manipulation, that is, nature of fear cue (VR spider vs. live spider), duration of reactivation trial (5 s vs. 10 s), duration of waiting period (10 min vs. 30 min), explicit instructions for participants to call forth a memory of a real or imagined encounter with a spider (no vs. yes); (b) differences in the modality of exposure treatment following reactivation (VR vs. in vivo); (c) assessment parameters, that is, assessment of fear renewal (no vs. yes), and follow-up assessment period (24 hr vs. 30 days); and (d) analytic approach (repeated measures ANOVA vs GCM).

Our second major finding—albeit unexpected—was the enhanced fear attenuation observed during the first few exposure therapy trials for participants receiving the preexposure fear network reactivation procedure. It is interesting that despite the marked acceleration of fear reduction observed during the first 6 min of exposure treatment for those in the fear reactivation group, controls "caught up" during the latter two thirds of exposure treatment and showed equivalent levels of posttreatment fear reduction in both the training and generalization contexts. This unanticipated finding is in direct contrast

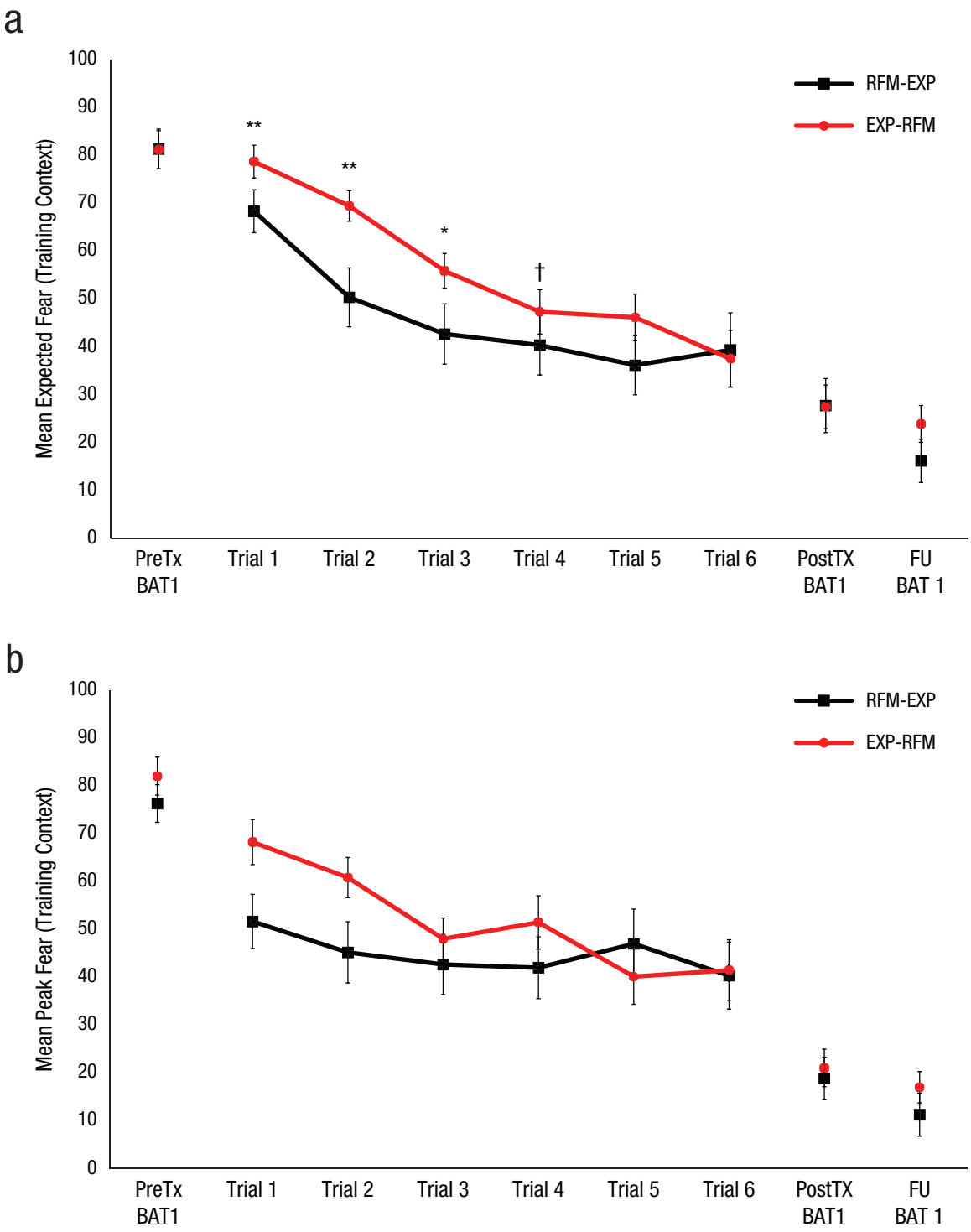

Fig. 3. Mean peak fear (top panel) and expected fear (bottom panel) during BAT 1 (treatment context) at pretreatment (PreTx BAT 1), before each of the six exposure therapy trials, and at 1-day posttreatment (PostTx BAT 1) and at 1-month follow-up (FU BAT 1).

Note: RFM-EXP = reactivation of the fear memory network followed by 30 min of exposure therapy; EXP-RFM = exposure therapy followed by reactivation of the fear memory network outside the reconsolidation update window. $^{*}p \leq .05$. $^{\dagger}p \leq 0.1$.

to research with rodents, which has showed either no facilitation of extinction training (Monfils et al., 2009) or interference with extinction training (Flavell et al., 2011).

What might account for the observed facilitation of fear attenuation during the early trials of exposure therapy for those receiving the fear reactivation procedure? Two putative mechanisms may account for this finding. The first to consider is prediction error. The prediction error model—sometimes referred to as the *expectancy violation model*—posits that the disparity between what is expected and what actually occurs is crucial for learning to occur (Rescorla & Wagner, 1972). This model also predicts that greater learning occurs early in a session, because the mismatch between what is expected and what actually occurs generally becomes progressively smaller across extinction trials, thus resulting in less learning. Perhaps the pretreatment reactivation procedure led to greater prediction error thus resulting in enhanced fear attenuation during the early exposure trials.[2]

Alternatively, it is possible that the facilitating effects of preexposure reactivation are related to an endogenous boost in neurotransmitters such as noradrenaline as a result of fear activation during the pretreatment reactivation procedure. Studies in nonhuman animals have shown that extinction can be facilitated pharmacologically with a noradrenergic agonist (Cain, Blouin, & Barad, 2004). It is interesting to note that systemic noradrenergic blockade after a single reactivation trial interferes with reconsolidation and results in a persistent reduction in fear (Debiec & LeDoux, 2004). Together, the findings indicate that blocking the molecular cascade engaged after memory reactivation interferes with memory reconsolidation, but also suggest an optimally timed reactivation trial prior to an extinction session could serve to "pharmacologically" boost within-session learning.

The two proposed mechanisms are not necessarily mutually exclusive. They could operate independently or synergistically. In fact, one would expect that pharmacological boosting during reactivation might increase fear expectation for the exposure that follows (provided the timing is optimal). Therefore, the fact that no negative outcome occurs in the presence of the stimulus results in a greater negative prediction, and thus more rapid fear attenuation. Consistent with this formulation, baseline cue-dependent physiological reactivity has recently been shown to predict treatment response among PTSD patients undergoing VR exposure treatment (Norrholm et al., 2016). The authors suggest that the increased baseline activation may have led to higher expectancy violation, which in turn may have led to enhanced outcome.

It is important that greater prediction error alone does not explain the superior fear attenuation observed at the 1-month follow-up because both groups were equivalent by the end of the exposure session. It is likely that a combination of factors is at play, facilitating both updating of previous information (i.e., reconsolidation updating) and production of new inhibitory learning. A sensitive balance is required for this combination to occur. If the prediction error is large at the onset, new inhibitory learning generally takes place (as is typically the case with standard extinction/exposure). In essence, an initial minimizing of prediction error between what the participants anticipate prior to the session and the reactivation trial likely promotes updating of the fear memory network (i.e., engages a reconsolidation mode rather than an extinction mode; Gershman, Jones, Norman, Monfils, & Niv, 2013). The heightened arousal that is initiated by the preexposure reactivation next leads to a larger prediction error than what the controls experience at the beginning of exposure therapy and explains the facilitation of extinction learning at the early stage of exposure therapy. The RFM procedure intended to activate (and destabilize) a fear memory network prior to the exposure session could allow both a reconsolidation updating mechanism as well as facilitation of within-session fear extinction to take place.

Several study limitations deserve mention. First, our sample size was less than optimal, and although effect sizes were in the moderate range for our primary outcome, replication with a larger and more diverse sample is needed. Second, although our participants displayed marked naturally acquired phobic responding to spiders and snakes, further research is needed to establish the utility of the preexposure RFM procedure for enhancing exposure therapy in patients presenting with other more complex anxiety-related disorders. Third, our follow-up period was relatively brief (1 month), thus further work should examine the durability of the RFM procedure over a longer follow-up period. Finally, research on key parameters of the RFM procedure (i.e., instructional set, duration of the reactivation trial, interval between reactivation and the commencement of exposure therapy) is needed to optimize exposure enhancement effects.

In conclusion, results of this proof-of-concept study provide the first demonstration of exposure therapy enhancement through a brief pretreatment reactivation of the fear memory network and warrant additional research on RFM exposure enhancement across a wider range of anxiety-related disorders.

Author Contributions

M. J. Telch contributed to the study concept and design, supervised the exposure protocol and the implementation of the fear reactivation procedure, drafted major sections of the manuscript, and took overall scientific responsibility for all facets of the project. J. York was responsible for subject recruitment and running participants through the experimental protocol. C. L. Lancaster performed the data analysis, preparation of the tables

and figures, and manuscript preparation of the results under the supervision of M. J. Telch. M. H. Monfils contributed to the study concept and interpretation of the results and contributed to the writing of several sections of the discussion. All authors approved the final version of the submitted manuscript.

Declaration of Conflicting Interests

The authors declared that they had no conflicts of interest with respect to their authorship or the publication of this article.

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Notes

1. We prefer the term *reactivation* rather than *retrieval* because in both the rodent and human conditioned fear extinction literature, the terms *retrieval* and *reactivation* have each been used to describe the same basic strategy. It is our view that when applied to naturally acquired pathological fear (as is the case here), the term *retrieval* incorrectly implies that a specific fear memory is being *retrieved*. With some exceptions (i.e., PTSD) most forms of pathological fear expression involve a naturally acquired "fear memory network" as opposed to a discrete fear memory.
2. To examine this possible hypothesis, we constructed a relatively crude fear prediction error index for each trial by calculating the mean group difference between predicted versus actual fear at each trial (see Rachman & Bichard, 1988). Relative to controls, those who received the reactivation procedure prior to starting exposure therapy showed almost twice the level of error prediction (expected fear > actual fear).

Supplemental Material

Additional supporting information may be found at http://cpx.sagepub.com/content/by/supplemental-data.

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