Behavioral Neuroscience

# Effects of Postretrieval-Extinction Learning on Return of Contextually Controlled Cued Fear

Shira Meir Drexler, Christian J. Merz, Tanja C. Hamacher-Dang, Veronica Marquardt, Nathalie Fritsch, Tobias Otto, and Oliver T. Wolf

Online First Publication, May 19, 2014. http://dx.doi.org/10.1037/a0036688

Behavioral Neuroscience


0735-7044/14/$12.00 http://dx.doi.org/10.1037/a0036688

BRIEF COMMUNICATION

# Effects of Postretrieval-Extinction Learning on Return of Contextually Controlled Cued Fear

Shira Meir Drexler, Christian J. Merz, Tanja C. Hamacher-Dang, Veronica Marquardt, Nathalie Fritsch, Tobias Otto, and Oliver T. Wolf
Ruhr-University Bochum

Reactivation of an already consolidated memory makes it labile for a period of several hrs, which are required for its reconsolidation. Evidence suggests that the return of conditioned fear through spontaneous recovery, reinstatement, or renewal can be prevented by blockading this reconsolidation process using pharmacological or behavioral interventions. Postretrieval-extinction learning has been shown to prevent the return of cued fear in humans using fear-irrelevant stimuli, as well as cued and contextual fear in rodents. The effects of postretrieval extinction on human contextually controlled cued fear to fear-relevant stimuli remain unknown, and are the focus of the present study. The experimental design was based on 3 consecutive days: acquisition, reactivation and extinction, and re-extinction. For the fear conditioning, 2 zoo frames served as different contexts, 5 fear-relevant stimuli (aversive animal pictures) served as conditioned stimuli (CS), electric shocks served as unconditioned stimuli (UCS). Expectancy ratings and skin-conductance response (SCR) were used as measures of fear responses; spontaneous recovery and renewal were used as indicators of the return of fear. The expectancy ratings and SCR results indicated spontaneous recovery on the third day, regardless of retrieval prior to extinction. No robust renewal effect was seen. It is suggested that the use of fear-relevant stimuli, the context salience, or reactivation context may explain the lack of reconsolidation effect. Our study indicates that the beneficial effects of postretrieval-extinction learning are sensitive to subtle methodological changes.

*Keywords:* fear learning, fear relevant, extinction, reconsolidation, skin conductance response (SCR)



In the fear conditioning paradigm, a contingency is made between a neutral stimulus serving as a predictor (conditioned stimulus, or CS) and an aversive event that naturally leads to a fear response (unconditioned stimulus, or UCS; Rescorla, 1988). Once conditioning occurs, the CS is able to elicit a conditioned fear response (CR) by itself. The fear conditioning paradigm is a very commonly used model for anxiety disorders such as phobias, which are related to past experience with an aversive event. The extinction training—a repeated exposure to CS without UCS—is a very common intervention for treating learned fears. However, as it does not erase the original fear memories but creates a new safety memory, a substantial proportion of participants experiences relapse (Bouton, 2002; Craske, 1999; Myers & Davis, 2007). Recovery of fear can occur either spontaneously after passage of time (spontaneous recovery; Rescorla, 2004), after changing the context in which the extinction learning took place (renewal; Bouton & King, 1983), or after unsignaled exposure to the UCS (reinstatement; Rescorla & Heth, 1975). To avoid the return of fear, a recent line of intervention aims to target the fear memory itself.

In contrast to the traditional view on memory, which has suggested a full stability of the memory trace upon its consol-

Shira Meir Drexler, Department of Cognitive Psychology, Institute of Cognitive Neuroscience, and International Graduate School of Neuroscience, Ruhr-University Bochum; Christian J. Merz, Department of Cognitive Psychology, Institute of Cognitive Neuroscience, Ruhr-University Bochum; Tanja C. Hamacher-Dang, Department of Cognitive Psychology, Institute of Cognitive Neuroscience, and International Graduate School of Neuroscience, Ruhr-University Bochum; Veronica Marquardt, Department of Cognitive Psychology, Institute of Cognitive Neuroscience, Ruhr-University Bochum; Nathalie Fritsch, Laboratory of Experimental Psychology, Ruhr-University Bochum, Germany; Tobias Otto, Department of Cognitive Psychology, Institute of Cognitive Neuroscience, Ruhr-University Bochum; Oliver T. Wolf, Department of Cognitive Psychology, Institute of Cognitive Neuroscience, and International Graduate School of Neuroscience, Ruhr-University Bochum.

Funding for this study was provided by Project P5 (WO 733/13-1; 13-2) of the German Research Foundation (DFG) Research Unit 1581, "Extinction Learning: Neural Mechanisms, Behavioral Manifestations, and Clinical Implications." The DFG had no role in study design, collection, analysis or interpretation of data, writing of the manuscript, or in the decision to submit the paper for publication. We thank Christoph Fraenz for his assistance with the manuscript.

Correspondence concerning this article should be addressed to Oliver T. Wolf, Department of Cognitive Psychology, Institute of Cognitive Neuroscience, Ruhr-University Bochum, Universitätsstr. 150, D-44780 Bochum, Germany. E-mail: oliver.t.wolf@ruhr-uni-bochum.de

idation, recent studies have shown that reactivation of an already consolidated memory item (via its retrieval) makes it once again fragile and susceptible to interruption until it reconsolidates (Nader, Schafe, & LeDoux, 2000). In other words, memory consolidation is not a one-time event (Lewis, 1979). Postreactivation reconsolidation shares several similar mechanisms with initial memory consolidation (e.g., the dependency on protein synthesis and noradrenergic activity), and can be affected by similar pharmacological interventions. In rodents, postretrieval administration of protein-synthesis inhibitors has been found to impair memory reconsolidation in various tasks (Alberini, 2008; Dudai, 2004; Duvarci & Nader, 2004). β-Blockers have shown similar effects on reconsolidation of conditioned fear (Kindt, Soeter, & Vervliet, 2009; Soeter & Kindt, 2011), emotional episodic memory (Schwabe, Nader, Wolf, Beaudry, & Pruessner, 2012), and even traumatic memories (Brunet, Orr, Tremblay, & Robertson, 2008) in humans.

As pharmacological interventions bear a certain degree of risk, recent studies have aimed to find a potent and safe behavioral intervention for impairing unwanted memories. Indeed, animal and human studies have shown that new learning postretrieval can interfere with the original memory in declarative (Forcato et al., 2007; Hupbach, Gomez, Hardt, & Nadel, 2007; Strange, Kroes, Fan, & Dolan, 2010; Schwabe & Wolf, 2009; Wichert, Wolf, & Schwabe, 2011) and procedural memory tasks (Walker, Brakefield, Hobson, & Stickgold, 2003) and cued (Clem & Huganir, 2010; Monfils, Cowansage, Klann, & LeDoux, 2009; Schiller et al., 2010) and contextual (Rao-Ruiz et al., 2011) fear conditioning. For example, Schiller et al. (2010) showed that postretrieval-extinction learning blocks spontaneous recovery of the fear response to fear-irrelevant CS. The effect was highly selective to the reactivated stimulus, and lasted one year. Postretrieval-extinction learning can also disrupt the renewal of fear in rodents (Monfils, Cowansage, Klann, & LeDoux, 2009). Some human studies have successfully replicated Schiller et al.'s (2010) results (Agren et al., 2012; Oyarzún et al., 2012), but others failed (Golkar, Bellander, Olsson, & Öhman, 2012; Kindt & Soeter, 2013; Soeter & Kindt, 2011). None of them, however, examined renewal of contextually controlled cued fear using fear-relevant stimuli. The current study aims to fill in this gap.

This study used a contextually controlled cued fear-conditioning paradigm (Ungör & Lachnit, 2006, 2008) with fear-relevant stimuli aimed to enhance acquisition (Kindt, Soeter, & Vervliet, 2009). Skin conductance responses (SCRs, representing autonomic responses; Schiller et al., 2010) and expectancy ratings (representing declarative contingency knowledge; Kindt & Soeter, 2013) served as measures of fear. Spontaneous recovery and renewal effects served as measures of the return of fear. If postretrieval-extinction learning could indeed have impaired the fear memory itself, we expected it to lead to a stronger and more lasting effect on fear (weaker or even absent spontaneous recovery and renewal), compared with extinction learning without reactivation. As sex effects on reconsolidation are mainly unknown, this factor was examined in an exploratory manner.

## Materials and Method

### Participants

Participants ($N = 39$; 20 men, 19 women) aged 19–30 years volunteered for the study. None of the participants had a somatic/endocrine disease or a history of psychiatric/neurological treatment. Apart from hormonal contraceptives (used by all the women in the sample), participants didn't take any regular medication. Participants were recruited via announcements on bulletin boards at the campus of Ruhr-University Bochum, Germany, and received a financial reward for participation. The study was approved by the local ethics committee. All participants signed an informed consent. Participants were randomly assigned to two groups: reactivation plus extinction and extinction only (control group).

### Stimuli

Five aversive animal pictures (dog, spider, shark, snake, and tiger) with similar values for valence, dominance, and arousal were chosen from the International Affective Picture System (IAPS; Lang, Bradley, & Cuthbert, 2005) and served as CS. They were presented (8 s) in two distinguishable zoo frames with different names, colors, and textures, serving as two different contexts (A and B). Electric shock (100 ms) to the left shin served as the UCS and coterminated with the CS+. A constant voltage stimulator (STM100C; BIOPAC Systems, Goleta, CA) provided the transcutaneous electrical stimulation through two silver/silverchloride (Ag/AgCl) electrodes (0.5 $cm^2$ surface each). Stimulus intensity was set for each participant individually using a gradually increasing rating procedure to an "unpleasant, but not painful" level. The individual settings were used in all three experimental days.

### Expectancy Ratings

During the first 5 s following each stimulus onset, participants had to predict whether they would receive an electric shock or not, using an 11-step scale appearing on the screen together with the CS. The scale ranged from −5 (*no shock*) to + 5 (*shock*) with 0 representing complete uncertainty.

### Skin Conductance Responses

SCRs were sampled using Ag/AgCl electrodes filled with an isotonic electrolyte medium (Synapse Conductive Electrode Cream, Kustomer Kinetics Inc., Arcadia, CA), placed at the hypothenar of the nondominant hand. SCR amplitudes to the CS and UCS served as measures of the CRs and unconditioned responses (UCRs), respectively. The level of SCR was determined by taking the base-to-peak difference for the largest waveform during 5–8.5 s (CR, upon completion of expectancy rating) and 8.5–13 s (UCR) after CS onset.

### Learning Procedure

The study consisted of three consecutive stages conducted 24 hr apart: acquisition, reactivation and extinction, and re-extinction. The 24-hr breaks were inserted to allow memory consolidation (Dudai, 2004).

**Day 1: Acquisition.** On the first day, two animal pictures serving as CS+ were presented in context A or B and were paired with an electric shock, CS1+ (A), CS3+ (B); two different pictures were presented in context A or B and served as CS– : CS2– (A), CS4– (B) without electric shock. A 75% reinforcement rate was chosen to prevent a quick extinction on the second day. When reinforced, the CS+ coterminated with the UCS. Intertrial intervals (ITIs) between offset of one stimulus and onset of the next were 8–12 s; each of the CSs was presented 16 times in a pseudorandomized order. To enhance CS–UCS contingency retention on the following days, participants were instructed to remember what they learned during this phase (Norrholm et al., 2006).

**Day 2: Reactivation and extinction.** As mere retrieval is not sufficient to trigger memory reconsolidation (Sevenster, Beckers, & Kindt, 2012), all participants were attached to shock and skin conductance electrodes. Afterward, participants from the reactivation + extinction group were presented with the CS1+ (unreinforced) for 30 s, without acquisition context (the specific zoo frame). Following a 10-min break (Schiller et al., 2010), during which they watched a recorded TV show, participants started the extinction training. Participants from the extinction-only group started the extinction training immediately after electrodes attachment and watching the TV-show, without prior CS1+ presentation. The extinction training comprised presentation of four stimuli in context A or B, CS1+ (B), CS2– (A), CS4– (B), CS5– (A), unreinforced, eight times each, in a pseudorandomized order (ITI 8–12 s). Most critically, the CS1+, which had been acquired in context A, was now extinguished in context B.

**Day 3: Re-extinction.** On this day, all participants were presented with eight trials for each CS1+ and CS3 + in context A or B, CS1+ (A), CS3+ (A), CS1+ (B), CS3+ (B; unreinforced, pseudorandomized order, ITI 8–12 s). Spontaneous recovery of fear was tested by comparing end of extinction (Day 2) to beginning of re-extinction (Day 3) for CS1+ in extinction context, CS1+ (B). Possible ABA renewal effects were tested by comparing first trial of CS1+ in acquisition (A) and extinction (B) contexts. In addition, percent of SCR recovery for CS1+ in context A or B was calculated as SCR level on the first trial of re-extinction (Day 3) divided by the largest SCR on acquisition (Day 1, context A; Milad, Orr, Pitman, & Rauch, 2005).

## Results

### Expectancy Ratings

For the acquisition phase, analysis of variance (ANOVA) with the within-subjects factors CS (CS+, CS–), context (A, B) and time (trials 1–16), and the between-subjects factors group and sex showed a significant effect of CS ($F_{1, 37} = 310.06$, $p < .001$) and of time ($F_{15, 23} = 12.19$, $p < .001$). In addition, a significant interaction CS x time was found ($F_{15, 37} = 26.11$, $p < .001$), showing a differential responding pattern to the CS+ and CS– over time. Neither context ($F_{1, 37} = 0.5$, *ns*), group ($F_{1, 37} = 0.5$, *ns*) nor sex ($F_{1, 34} = 0.28$, *ns*) had a significant effect. Figure 1A presents the differential expectancy ratings for the two CSs+, CS1+ (A), CS3+ (B) compared with the two CSs–, CS2– (A), CS4– (B) along 16 trials of acquisition.

For the extinction phase, ANOVA with the within-subjects factors CS [CS1+ (B), CS2– (A), CS4– (B), CS5– (A)], and time (trials 1–8), and the between-subjects factors group and sex revealed a significant effect of CS ($F_{3, 34} = 25.19$, $p < .001$) and time ($F_{7, 30} = 76.08$, $p < .001$). A significant interaction, CS × time was found ($F_{21, 37} = 19.34$, $p < .001$), indicating a differential responding pattern to the CS+ and CS– over time. No effect of group ($F_{1, 36} = 2.06$, *ns*) or sex ($F_{1, 34} = 1.28$, *ns*) was found. Figure 1A demonstrates the decline in shock expectancy to the CS+ along 8 trials of extinction (both groups are combined).

To test for spontaneous recovery, the rating to CS1+ (B) on the last extinction trial (Day 2) was compared with the ratings of CS1+ (B) on the first re-extinction trial on Day 3, with the between-subjects factors group and sex. ANOVA showed a significant main effect of time ($F_{1, 36} = 13.98$, $p = .001$). No interaction between time and the between-subjects factor group ($F_{1, 36} = 0.26$, *ns*) was found. Figure 1A shows the rise in shock expectancy to the CS+ in first trials of re-extinction, followed by decline during re-extinction trials. Figure 2A shows the spontaneous recovery effect of both groups.

To test the renewal effect on Day 3, expectancy ratings following first trial of CS1+ (A), CS1+ in acquisition context, were compared with CS1+ (B), CS1+ in extinction context, with the between-subjects factors group and sex. ANOVA neither revealed a significant main effect of context ($F_{1, 36} = 1.72$, *ns*) nor an interaction with group ($F_{1, 36} = 0.24$, *ns*). Figure 2B presents the expectancy ratings to CS1+ in context A and B, and shows no significant difference between acquisition and extinction context (no renewal), even though, descriptively, expectancy ratings were higher in context A.

### SCR

For acquisition, ANOVA with the within-subjects factors CS (CS+, CS–), context (context A, context B), and time (trials 1–16) and the between-subjects factors group and sex showed a significant main effect of CS ($F_{1, 31} = 34.7$, $p < .001$) and time ($F_{5.44, 168.86} = 4.57$, $p < .001$) on SCR. The factors context ($F_{1, 31} = 0.12$, *ns*), group ($F_{1, 30} = 0.3$, *ns*) and sex ($F_{1, 31} = 0.28$, *ns*) had no significant effect. Figure 1B presents the mean SCRs to all four CSs during acquisition.

For extinction, ANOVA with the within-subjects factors CS [CS1+ (B), CS2– (A), CS4– (B), CS5– (A)], and time (trials 1–8), and the between-subjects factors group and sex showed a significant main effect of time ($F_{3.53, 116.72} = 10.75$, $p < .001$) on SCR. Neither group ($F_{1, 33} = 1.86$, *ns*) nor sex ($F_{1, 33} = 0.54$, *ns*) had a significant effect. Figure 1B compares SCR in the first trials of extinction to the last trials in all four CSs. The figure shows that the former reinforced stimulus, CS1+ (B), and the new stimulus, CS5– (A), led to a higher response compared with the two "safe" stimuli, CS2– (A), CS4– (B).

To test for occurrence of spontaneous recovery, the SCR to CS1+(B) on the last extinction trial (Day 2) was compared with the response to CS1+(B) on the first trial on Day 3, with the between-subjects factors group and sex. ANOVA revealed a significant main effect of time ($F_{1, 34} = 4.83$, $p < .05$). Neither group ($F_{1, 34} = 1.13$, *ns*) nor sex ($F_{1, 34} = 0.4$, *ns*) showed a significant effect. Figures 1B and 2C demonstrate the spontaneous recovery in both groups.

To test for a renewal effect on Day 3, SCR on first trial of CS1+(A; CS1+ in acquisition context) was compared with

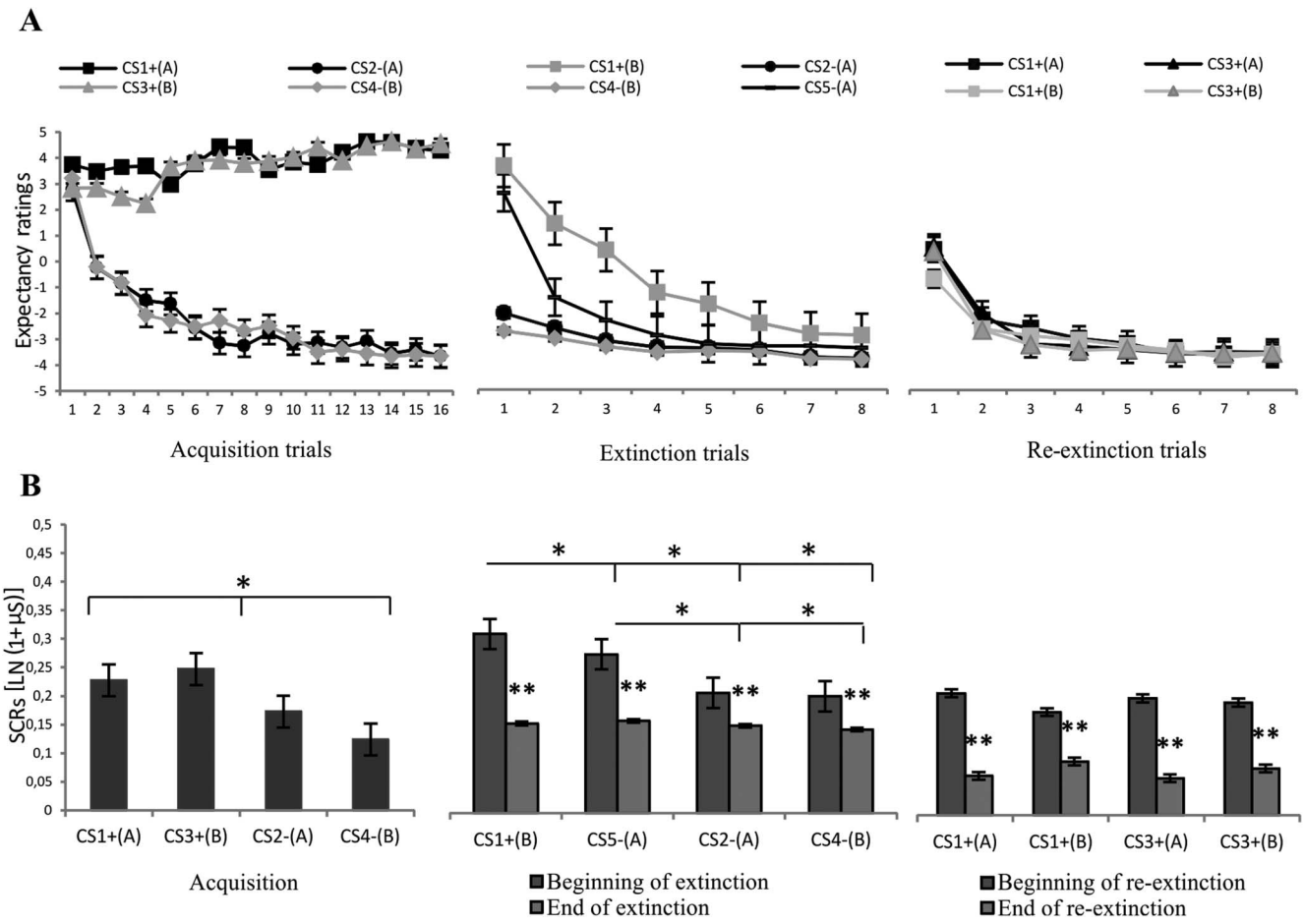


*Figure 1.* Expectancy ratings and mean skin conductance responses (SCRs) during acquisition, extinction, and re-extinction (experimental Days 1, 2, and 3, respectively) in both experimental groups (combined). *Figure 1A.* Expectancy ratings, acquisition: Expectancy ratings of CS representing shock (+) or no-shock (–) in two different contexts (A or B) during 16 trials of acquisition. Extinction: Expectancy ratings of formerly reinforced (+) or not-reinforced (–) CS in two different contexts (A or B) during eight trials of extinction. Re-extinction: Expectancy ratings of formerly reinforced (+) CS in two different contexts (A or B) during eight trials of re-extinction. No significant difference between the groups was found in acquisition, extinction or re-extinction. *Figure 1B.* SCRs, acquisition: Mean SCRs in 16 trials of acquisition to CSs representing shock (+) or no-shock (–) in two different contexts (A or B). Significant differences between CS+ and CS– were found; no effect of context. Extinction: Mean SCRs to the formerly reinforced (+) or not-reinforced (-) CS in two different contexts (A or B) in the beginning (first four trials) compared with end (last four trials) of extinction. At the beginning of extinction, the former reinforced stimulus (CS1+), presented under a different context (B), led to a significantly higher response compared with all other stimuli; a new stimulus (CS5–) led to a significantly higher response compared with CS2– and CS4–. No difference was found between CS2– and CS4–. The response to each stimulus was significantly higher at the beginning of extinction than at the end of extinction. At the end of extinction, no significant differences between the stimuli were found. Re-extinction: Mean SCRs to the formerly reinforced (+) CS in two different contexts (A or B) in the beginning (first trial) compared with the end (last trial) of re-extinction. During re-extinction, the former reinforced stimuli (CS1+, CS3+) were presented in the two contexts (A and B). No difference (no ABA renewal) was found between the stimuli. The response to each stimulus was significantly higher at the beginning of re-extinction than at the end of re-extinction. Significant differences between the groups were detected in re-extinction and are presented on *Figure 2.* $^{**}$ $p < .01$; $^{*}$ $p < .05$. Error bars represent standard error of the mean.

CS1+(B; CS1+ in extinction context) with the between-subjects factors group and sex. ANOVA showed an interaction of group and sex ($F_{1, 34} = 4.63$, $p < .05$). A significant difference between CS1+ in the acquisition and extinction contexts (renewal effect) was found only in females from the reactivation + extinction group ($F_{1, 9} = 5.5$, $p < .05$). No effect was detected in males from either the reactivation + extinction ($F_{1, 8} = .008$, ns) or extinction only group ($F_{1, 8} = 0.02$, *ns*), or in females from the extinction-

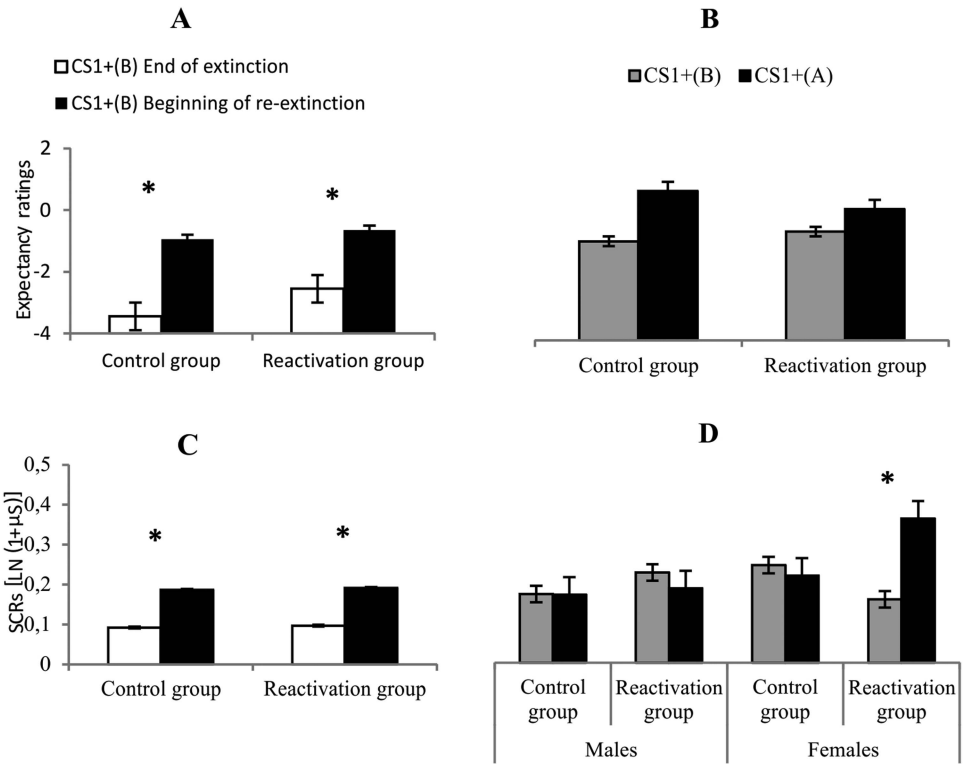


*Figure 2. Figure 2A, 2C*. Spontaneous recovery tests. *Figure 2A.* Expectancy ratings for the last CS1+ presentation on extinction (Day 2) compared with the first CS1+ presentation on re-extinction (Day 3; context B on both days). Spontaneous recovery was found in both groups, but no difference between the groups emerged. *Figure 2C*. SCR for the last CS1+ presentation on extinction (Day 2) compared with the first CS1+ presentation on re-extinction (Day 3; context B on both days). Spontaneous recovery was found in both groups, but no difference between the groups emerged. *Figures 2B, 2D*. Renewal tests. *Figure 2B*. Expectancy rating to CS1+ during re-extinction (Day 3) in the first trial in extinction context (B) compared with the first trial in acquisition context (A). No significant renewal effect was found in both groups, no difference between the groups was detected. *Figure 2D*. SCR to CS1+ during re-extinction (Day 3) in the first trial in extinction context (B) compared with the first trial in acquisition context (A). A renewal effect was found only in women from the reactivation group. $^{*}$ $p < .05$. Error bars represent standard errors of the mean.

only group ($F_{1,\ 8} = 0.6$, *ns*). Figure 2D depicts the response to CS1+ (A) and CS1+ (B) and shows that the renewal effect was found only in females from the reactivation + extinction group. In addition, percent of SCR recovery for CS1+ (A) was compared with CS1+ (B) with the between-subjects factors group and sex. ANOVA showed a marginally significant interaction of group and sex ($F_{1,\ 34} = 2.89$, $p = .098$). A marginally significant difference between CS1+ (A) and CS1+ (B) recovery (renewal effect) was found in females from the reactivation + extinction group ($F_{1,\ 9} = 4.04$, $p = .075$; data not shown). No effect was detected in males from either the reactivation + extinction ($F_{1,\ 9} = .001$, ns) or extinction only group ($F_{1,8} = 0.07$, *ns*), or in females from the extinction only group ($F_{1,\ 8} = 0.01$, *ns*).

## Discussion

The present study has attempted to use postretrieval-extinction learning to prevent the return of contextually controlled cued fear in humans. The study used a 3-day reconsolidation design, adopted from Schiller et al. (2010) while using fear-relevant stimuli (Kindt, Soeter, & Vervliet, 2009) in contextual settings (Ungör & Lachnit, 2006). In contradiction to the hypothesis, the results showed spontaneous fear recovery in both groups. In addition, no robust renewal effects could be observed in either group. Unexpectedly, a renewal effect was seen in females from the reactivation + extinction group. Several methodological differences between this study and studies in which a reconsolidation effect was found (Agren et al., 2012; Clem & Huganir, 2010; Monfils, Cowansage, Klann, & LeDoux, 2009; Rao-Ruiz et al., 2011; Schiller et al., 2010) could explain these results.

### Fear Acquisition for Fear-Relevant or Fear-Irrelevant Stimuli

The objects of clinical fears are usually fear-relevant. To make conditioning more robust and ecologically valid, we used aversive animal pictures as CSs. The results revealed no significant differences between groups in spontaneous fear recovery, that is, the return of fear could not be blocked. These findings stand in contrast to Schiller et al.'s (2010) results, and may be explained by

the choice of biologically fear-relevant stimuli, as opposed to fear-irrelevant stimuli (i.e., differently colored shapes used in Schiller et al., 2010). Fear-relevant stimuli may have led to a stronger fear memory, which was not as vulnerable as the neutral shapes. Similarly, Soeter and Kindt (2011) and Golkar et al. (2012) could not replicate Schiller et al.'s (2010) findings while using fear-relevant stimuli.

## Context Salience

When extinction learning is performed in a context other than the original acquisition context, it is quite common for a fear response to return (Bouton & King, 1983). Monfils et al. (2009) have successfully prevented the renewal of fear by using postretrieval-extinction learning in rodents. Chan et al. (2010), however, could not find consistent effects of postretrieval extinction on the return of fear. In our study, the ABA renewal effect was examined by comparing the response to stimulus CS1+ on Day 3 in acquisition and extinction context (Ungör & Lachnit, 2008). Assuming postretrieval extinction could prevent the return of fear, one would have expected to see a renewal effect in the extinction-only group but not in the reactivation + extinction group. However, no robust renewal effects were seen in expectancy ratings of both groups. In fact, a renewal effect was seen only in SCR of females from the reactivation + extinction group.

In this study, different frames, with distinct colors, names, and textures surrounding the aversive animal pictures, were used as different contexts. Ungör & Lachnit (2006) and Hamacher-Dang, Ungör, & Wolf (2013) were able to show significant renewal effects when they used different restaurant frames as contexts in a nonaversive predictive learning task. It is suggested that in the fear conditioning paradigm, while using fear-relevant stimuli, these context changes might not be taken into account (Hamm, Vaitl, & Lang, 1989). The robust renewal effect in SCRs seen only in females from the reactivation + extinction group, could have resulted from the female participants' response to the reminder cue used for reactivation. The exposure to the formerly reinforced CS1+ (albeit unreinforced and without the zoo frame of the acquisition context) may have enhanced the fear toward the stimulus in its acquisition context, perhaps generalizing it to the acquisition context (A) itself, creating contextual fear (Baas, 2013). Sex differences in the prevalence of anxiety disorders (Kessler et al., 2005) and emotional learning (Cahill, Gorski, & Le, 2003; Merz et al., 2012) may depend on sex hormones and the female's menstrual cycle (Milad, Igoe, Lebron-Milad, & Novales, 2009; Milad et al., 2010; Zeidan et al., 2011), and can explain why contextual fear was found in females only. As the reduction of endogenous sex hormones by hormonal contraceptives can alter emotional learning in females (Graham & Milad, 2013; Merz et al., 2012), it is suggested, that their use by all female participants in the current study altered the emotional learning, leading to contextual fear following the reactivation procedure. As amygdala activation (Tabbert et al., 2011) or SCRs (Knight, Nguyen, & Bandettini, 2003) following fear conditioning can be seen under some circumstances in the absence of awareness, this may explain why the effect was seen only in autonomic arousal, measured by SCRs, and not in the cognitive measure of expectancy ratings. To examine this further, future research should use the fear potentiated startle, estimating the ongoing affective state, as additional measure of fear (Kindt & Soeter, 2013).

## Reactivation of Contextual Fear

Schiller et al. (2010) used a cued fear paradigm in humans. Without context manipulation, the pre-extinction reactivation consisted of a single unreinforced presentation of the CS, which led to a reduction in the return of fear. Monfils et al. (2009) reactivated the formerly reinforced CS in the to-be-extinction context, and found reduced renewal. In the present study, the reactivated stimulus was presented without any zoo frame (neither acquisition nor the to-be extinction context). If the reactivation context is of importance, then lack of extinction context may explain why reactivation had no beneficial effect. However, Chan et al. (2010) examined the effects of reactivation in acquisition or extinction contexts on the return of fear in both contexts and had inconsistent results. A beneficial effect of memory reactivation was found only when reactivation occurred in the acquisition context and testing was performed in the extinction context. In other words, extinction was enhanced but renewal was not affected. When reactivation occurred in the to-be-extinction context, fear was enhanced. These contradicting effects, that may be a result of procedural differences between Chan et al. (2010) and Monfils et al. (2009), further demonstrate the sensitivity of postreactivation extinction learning to subtle methodological alternations.

## Conclusion

To conclude, the present study failed to find a beneficial effect of postretrieval-extinction learning on spontaneous recovery and renewal of contextually controlled cued conditioning to fear-relevant stimuli in humans. Spontaneous return of fear was found across groups, while the renewal effect was rather weak. The choice of stimuli, context salience or reactivation context may explain the lack of reconsolidation effect. Similar to other studies (Golkar, Bellander, Olsson, & Öhman, 2012; Kindt & Soeter, 2013), the failure to show a reconsolidation effect suggest that the effects of postretrieval-extinction learning are rather sensitive to methodological changes (Auber, Tedesco, Jones, Monfils, & Chiamulera, 2013). Due to its boundary conditions, reconsolidation may thus be difficult to effectively translate to clinical settings.

## References

Agren, T., Engman, J., Frick, A., Björkstrand, J., Larsson, E., Furmark, M., & Fredrikson, M. (2012). Disruption of reconsolidation erases a fear memory trace in the human amygdala. *Science, 337,* 1550–1552. doi: 10.1126/science.1223006

Alberini, C. M. (2005). Mechanisms of memory stabilization: Are consolidation and reconsolidation similar or distinct processes? *Trends in Neurosciences, 28,* 51–56. doi:10.1016/j.tins.2004.11.001

Alberini, C. M. (2008). The role of protein synthesis during the labile phases of memory: Revisiting the skepticism. *Neurobiology of Learning and Memory, 89,* 234–246. doi:10.1016/j.nlm.2007.08.007

Auber, A., Tedesco, V., Jones, C., Monfils, M., & Chiamulera, C. (2013). Post-retrieval extinction as reconsolidation interference? Methodological issues or boundary conditions? *Psychopharmacology, 226,* 631–647. doi:10.1007/s00213-013-3004-1

Baas, J. M. (2013). Individual differences in predicting aversive events and modulating contextual anxiety in a context and cue conditioning paradigm. *Biological Psychology, 92,* 17–25. doi:10.1016/j.biopsycho.2012.02.001

Bouton, M. E. (2002). Context, ambiguity, and unlearning: Sources of relapse after behavioral extinction. *Biological Psychiatry, 52,* 976–986. doi:10.1016/S0006-3223(02)01546-9

Bouton, M. E., & King, D. (1983). Contextual control of the extinction of conditioned fear: Tests for the associative value of the context. *Journal of Experimental Psychology: Animal Behavior Processes, 9,* 248–265. doi:10.1037/0097-7403.9.3.248

Brunet, A., Orr, S. P., Tremblay, J., Robertson, K., Nader, K., & Pitman, R. K. (2008). Effect of post-retrieval propranolol on psychophysiologic responding during subsequent script-driven traumatic imagery in post-traumatic stress disorder. *Journal of Psychiatric Research, 42,* 503–506. doi:10.1016/j.jpsychires.2007.05.006

Cahill, L., Gorski, L., & Le, K. (2003). Enhanced human memory consolidation with post-learning stress: Interaction with the degree of arousal at encoding. *Learning & Memory, 10,* 270–274. doi:10.1101/lm.62403

Cahill, L., Prins, B., Webe, M., & McGaugh, J. (1994). Beta-adrenergic activation and memory for emotional events. *Nature, 371,* 702–704. doi:10.1038/371702a0

Cai, W. H., Blundell, J., Han, J., Greene, R., & Powell, C. (2006). Postreactivation glucocorticoids impair recall of established fear memory. *The Journal of Neuroscience, 26,* 9560–9566. doi:10.1523/JNEUROSCI.2397-06.2006

Chan, W. Y., Leung, H., Westbrook, R., & McNally, G. (2010). Effects of recent exposure to a conditioned stimulus on extinction of Pavlovian fear conditioning. *Learning & Memory, 17,* 512–521. doi:10.1101/lm.1912510

Clem, R. L., & Huganir, R. L. (2010). Calcium-permeable AMPA receptor dynamics mediate fear memory erasure. *Science, 330,* 1108–1112. doi:10.1126/science.1195298

Craske, M. (1999). *Anxiety disorders: Psychological approaches to theory and treatment*. Boulder, CO: Westview Press.

Delgado, M. R., Olsson, A., & Phelps, E. (2006). Extending animal models of fear conditioning to humans. *Biological Psychology, 73,* 39–48. doi:10.1016/j.biopsycho.2006.01.006

Dudai, Y. (2004). The neurobiology of consolidations, or, how stable is the engram? *Annual Review of Psychology, 55,* 51–86. doi:10.1146/annurev.psych.55.090902.142050

Duvarci, S., & Nader, K. (2004). Characterization of fear memory reconsolidation. *The Journal of Neuroscience, 24,* 9269–9275. doi:10.1523/JNEUROSCI.2971-04.2004

Forcato, C., Burgos, V., Argibay, P., Molina, V., Pedreira, M., & Maldonado, H. (2007). Reconsolidation of declerative memory in humans. *Learning & Memory, 14,* 295–303. doi:10.1101/lm.486107

Golkar, A., Bellander, M., Olsson, A., & Öhman, A. (2012). Are fear memories erasable? Reconsolidation of learned fear with fear-relevant and fear-irrelevant stimuli. *Frontiers in Behavioral Neuroscience, 6,* 80–89. doi:10.3389/fnbeh.2012.00080

Graham, B. M., & Milad, M. R. (2013). Blockade of estrogen by hormonal contraceptives impairs fear extinction in female rats and women. *Biological Psychiatry, 73,* 371–378. doi:10.1016/j.biopsych.2012.09.018

Grillon, C. (2002). Startle reactivity and anxiety disorders: Aversive conditioning, context and neurobiology. *Biological Psychiatry, 52,* 958–975. doi:10.1016/S0006-3223(02)01665-7

Hamacher-Dang, T., Ungör, M., & Wolf, O. T. (2013). Stress impairs retrieval of extinguished and unextinguished associations in a predictive learning task. *Neurobiology of Learning and Memory, 104,* 1–8. doi:10.1016/j.nlm.2013.04.007

Hamm, A., Vaitl, D., & Lang, P. (1989). Fear conditioning, meaning and belongingness: A selective association analysis. *Journal of Abnormal Psychology, 98,* 395–406. doi:10.1037/0021-843X.98.4.395

Hupbach, A., Gomez, L., Hardt, O., & Nadel, R. (2007). Reconsolidation of episodic memories: A subtle reminder triggers integration of new information. *Learning & Memory, 14,* 47–53. doi:10.1101/lm.365707

Kessler, R., Berglund, P., Demler, O., Jin, R., Merikangas, K., & Walters, E. (2005). Lifetime prevalence and age-of-onset distributions of *DSM–IV* disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry, 62,* 593–602. doi:10.1001/archpsyc.62.6.593

Kindt, M., & Soeter, M. (2013). Reconsolidation in a human fear conditioning study: A test of extinction as updating mechanism. *Biological Psychology, 92,* 43–50. doi:10.1016/j.biopsycho.2011.09.016

Kindt, M., Soeter, M., & Vervliet, B. (2009). Beyond extinction: Erasing human fear responses and preventing the return of fear. *Nature Neuroscience, 12,* 256–258. doi:10.1038/nn.2271

Knight, D. C., Nguyen, H. T., & Bandettini, P. A. (2003). Expression of conditional fear with and without awareness. *Proceedings of the National Academy of Sciences of the United States of America, 100,* 15280–15283. doi:10.1073/pnas.2535780100

Lang, P., Bradley, M., & Cuthbert, B. (2005). *International affective picture system (IAPS): Affective ratings of pictures and instruction manual* (Technical Report No. A-6). Gainesville, FL: University of Florida.

Lee, J., Everitt, B., & Thomas, K. (2004). Independent cellular processes for hippocampal memory consolidation and reconsolidation. *Science, 304,* 839–843. doi:10.1126/science.1095760

Lewis, D. (1979). Psychobiology of active and inactive memory. *Psychological Bulletin, 86,* 1054–1083. doi:10.1037/0033-2909.86.5.1054

Merz, C., Tabbert, K., Schweckendiek, J., Klucken, T., Vaitl, D., Stark, R., & Wolf, O. T. (2012). Neuronal correlates of extinction learning are modulated by sex hormones. *Social Cognitive and Affective Neuroscience, 7,* 819–830. doi:10.1093/scan/nsr063

Milad, M., Igoe, S., Lebron-Milad, K., & Novales, J. (2009). Estrous cycle phase and gonadal hormones influence conditioned fear extinction. *Neuroscience, 164,* 887–895. doi:10.1016/j.neuroscience.2009.09.011

Milad, M. R., Orr, S. P., Pitman, R. K., & Rauch, S. L. (2005). Context modulation of memory for fear extinction in humans. *Psychophysiology, 42,* 456–464. doi:10.1111/j.1469-8986.2005.00302.x

Milad, M. R., Zeidan, M. A., Contero, A., Pitman, R. K., Klibanski, A., Rauch, S. L., & Goldstein, J. M. (2010). The influence of gonadal hormones on conditioned fear extinction in healthy humans. *Neuroscience, 168,* 652–658. doi:10.1016/j.neuroscience.2010.04.030

Monfils, M., Cowansage, K., Klann, E., & LeDoux, J. (2009). Extinction-reconsolidation boundaries: Key to persistent attenuation of fear memories. *Science, 324,* 951–955. doi:10.1126/science.1167975

Myers, K., & Davis, M. (2007). Mechanisms of fear extinction. *Molecular Psychiatry, 12,* pp.120–150. doi:10.1038/sj.mp.4001939

Nader, K., Schafe, G., & LeDoux, J. (2000). Fear memories requires protein synthesis in the amygdala for reconsolidation after retrieval. *Nature, 406,* 722–726. doi:10.1038/35021052

Norrholm, S., Javanovic, T., Vervliet, B., Myers, K., Davis, M., Rothbaum, B., & Duncan, E. (2006). Conditioned fear extinction and reinstatement in a human fear potentiated startle paradigm. *Learning & Memory, 13,* 681–686. doi:10.1101/lm.393906

Oyarzún, J., Lopez-Barroso, D., Fuentemilla, L., Curcurell, D., Pedraza, C., Rodriguez-Fornells, A., & de Diego-Balaguer, R. (2012). Updating fearful memories with extinction training during reconsolidation: A human study using auditory aversive stimuli. *PloS ONE, 7,* e38849. doi:10.1371/journal.pone.0038849

Pedreira, M. (2004). Mismatch between what is expected and what actually occurs triggers memory reconsolidation or Extinction. *Learning & Memory, 11,* 579–585. doi:10.1101/lm.76904

Rao-Ruiz, P., Rotaru, D. C., van der Loo, R. J., Mansvelder, H. D., Stiedl, O., Smit, A. B., & Spijker, S. (2011). Retrieval-specific endocytosis of

GluA2-AMPARs underlies adaptive reconsolidation of contextual fear. *Nature Neuroscience, 14,* 1302–1308. doi:10.1038/nn.2907

Rescorla, R. (1988). Pavlovian conditioning. It's not what you think it is. *American Psychologist, 43,* 151–160. doi:10.1037/0003-066X.43.3.151

Rescorla, R. (2004). Spontaneous recovery. *Learning & Memory, 11,* 501–509. doi:10.1101/lm.77504

Rescorla, R., & Heth, C. (1975). Reinstatement of fear to an extinguished conditioned stimulus. *Journal of Experimental Psychology: Animal Behavior Processes, 1,* 88–96. doi:10.1037/0097-7403.1.1.88

Roozendaal, B. (2002). Stress and memory: Opposing effects of glucocorticoids on memory consolidation and memory retrieval. *Neurobiology of Learning and Memory, 78,* 578–595. doi:10.1006/nlme.2002.4080

Schiller, D., Monfils, M., Raio, C., Johnson, D., Ledoux, J., & Phelps, E. (2010). Preventing the return of fear in humans using reconsolidation update mechanisms. *Nature, 463,* 49–53. doi:10.1038/nature08637

Schwabe, L., Nader, K., Wolf, O. T., Beaudry, T., & Pruessner, J. (2012). Neural signature of reconsolidation impairments by propranolol in humans. *Biological Psychiatry, 71,* 380–386. doi:10.1016/j.biopsych.2011.10.028

Schwabe, L., & Wolf, O. T. (2009). New episodic learning interferes with the reconsolidation of autobiographical memories. *PLoS ONE, 4,* e7519. doi:10.1371/journal.pone.0007519

Sevenster, D., Beckers, T., & Kindt, M. (2012). Retrieval per se is not sufficient to trigger reconsolidation of human fear memory. *Neurobiology of Learning and Memory, 97,* 338–345. doi:10.1016/j.nlm.2012.01.009

Soeter, M., & Kindt, M. (2010). Dissociating response systems: Erasing fear from memory. *Neurobiology of Learning and Memory, 94,* 30–41. doi:10.1016/j.nlm.2010.03.004

Soeter, M., & Kindt, M. (2011). Disrupting reconsolidation: Pharmacological and bahavioral manipulations. *Learning & Memory, 18,* 357–366. doi:10.1101/lm.2148511

Strange, B., & Dolan, R. (2004). Beta-adrenergic modulation of emotional memory-evoked human amaygdala and hippocampus responses. *Proceedings of the National Academy of Sciences of the United States of America, 101,* 11454–11458. doi:10.1073/pnas.0404282101

Strange, B., Kroes, M., Fan, J., & Dolan, R. (2010). Emotion causes targeted forgetting of established memories. *Frontiers in Behavioral Neuroscience, 4,* doi:10.3389/fnbeh.2010.00175

Tabbert, K., Merz, C. J., Klucken, T., Schweckendiek, J., Vaitl, D., Wolf, O. T., & Stark, R. (2011). Influence of contingency awareness on neural, electrodermal and evaluative responses during fear conditioning. *Social Cognitive and Affective Neuroscience, 6,* 495–506. doi:10.1093/scan/nsq070

Taubenfeld, S. M., Milekic, M., Monti, B., & Alberini, C. (2001). The consolidation of new but not reactivated memories requires hippocampal C/EBPb. *Nature Neuroscience, 4,* pp. 813–818. doi:10.1038/90520

Ungör, M., & Lachnit, H. (2006). Contextual control in discrimination reversal learning. *Journal of Experimental Psychology: Animal Behavior Processes, 32,* 441–453. doi:10.1037/0097-7403.32.4.441

Ungör, M., & Lachnit, H. (2008). Dissociations among ABA, ABC, and AAB recovery effects. *Learning and Motivation, 39,* pp. 181–195. doi:10.1016/j.lmot.2007.08.001

Walker, M., Brakefield, T., Hobson, J., & Stickgold, R. (2003). Dissociable stages of human memory consolidation and reconsolidation. *Nature, 425,* 616–620. doi:10.1038/nature01930

Wichert, S., Wolf, O. T., & Schwabe, L. (2011). Reactivation, interference, and reconsolidation: Are recent and remote memories likewise susceptible? *Behavioral Neuroscience, 125,* 699–704. doi:10.1037/a0025235

Zeidan, M. A., Igoe, S. A., Linnman, C., Vitalo, A., Levine, J. B., Klibanski, A., . . . Milad, M. R. (2011). Estradiol modulates medial prefrontal cortex and amygdala activity during fear extinction in women and female rats. *Biological Psychiatry, 70,* 920–927. doi:10.1016/j.biopsych.2011.05.016

Received November 11, 2013
Revision received February 28, 2014
Accepted March 18, 2014 ■