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A preregistered, direct replication attempt of the retrieval-extinction effect in cued fear conditioning in rats

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ABSTRACT

In 2009, Monfils and colleagues proposed a behavioral procedure that was said to result in a permanent attenuation of a previously established fear memory, thereby precluding a possible return of fear after extinction (Monfils, Cowansage, Klann, & LeDoux, 2009). By presenting a single retrieval trial one hour before standard extinction training, they found an enduring reduction of fear. The retrieval-extinction procedure holds great clinical potential, particularly for anxiety patients, but the findings are not undisputed, and several conceptual replications have failed to reproduce the effect. These failures have largely been attributed to small procedural differences. This preregistered study is the first endeavor to exactly replicate three key experiments of the original report by Monfils et al. (2009), thereby gauging the robustness of their seminal findings.

Despite adhering to the original procedures as closely as possible, we did not find any evidence for reduced return of fear with the retrieval-extinction procedure relative to regular extinction training, as assessed through spontaneous recovery, reinstatement and renewal. Behavior of animals in the control condition (extinction only) was comparable to that in the original studies and provided an adequate baseline to reveal differences with the retrieval-extinction condition. Our null findings indicate that the effect sizes in the original paper may have been inflated and question the legitimacy of previously proposed moderators of the retrieval-extinction effect. We argue that direct experimental evaluation of purported moderators of the retrieval-extinction effect will be key to shed more light on its nature and prerequisites.

1. Introduction

Anxiety disorders and posttraumatic stress disorder are among the most prevalent psychiatric disorders (Kessler et al., 2005), and are hallmarked by substantial disability and poor quality of life (DSM-5). An effective behavioral treatment strategy for these disorders is exposure (Hofmann & Smits, 2008; Ougrin, 2011), which entails in vivo or imaginal contact with the feared object or situation. An important downside of exposure therapy is the relatively frequent relapse of fear after seemingly successful treatment (Craske & Mystkowski, 2006; Loerinc et al., 2015; Yonkers, Bruce, Dyck, & Keller, 2003). Extinction learning of conditioned fear memories in the laboratory bears some resemblance to exposure therapy (Myers & Davis, 2002; Scheveneels, Boddez, Vervliet, & Hermans, 2016; Vervliet, Craske, & Hermans, 2013). Likewise, under several circumstances, researchers observe a return of fear after successful extinction learning (Bouton, 2002, 2004). This has been interpreted as evidence that extinction does not produce an erasure of the fear memory, but rather involves new learning, resulting in an extinction memory that coexists and competes with the original fear memory. Which memory will be retrieved upon confrontation with the conditioned and subsequently extinguished stimulus depends on the circumstances. The fear memory is, for example, more likely to surface again after the passing of time (spontaneous recovery), after experiencing an aversive event (reinstatement) or outside of the extinction context (renewal). Similarly, even after successful exposure therapy, the original fear memory is not erased, thereby forming an enduring risk for relapse.

In a highly influential paper, Monfils and colleagues proposed a modified extinction procedure that was said to result in a more permanent attenuation of the fear memory, thereby precluding a possible return of fear (Monfils, Cowansage, Klann, & LeDoux, 2009). Using a cued fear conditioning procedure in rats, a tone fear memory was formed and then extinguished again one day later. Various recovery assays, including spontaneous recovery after

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one month, reinstatement, renewal, and reacquisition tests, provided evidence that the fear memory was retained through extinction. However, in a group of animals that received a single isolated tone presentation one hour before extinction training, there was a significant attenuation of the return of fear. These findings were soon confirmed in human subjects (Schiller et al., 2010) and mice (Clem & Huganir, 2010). The recovery-reducing effect of the retrieval-extinction procedure was attributed to the extinction training interfering with reconsolidation of the fear memory after retrieval. It has been argued that consolidated memories can enter a labile state upon retrieval. During this window of instability (<6 h), a fear memory storing the association between a conditioned stimulus (CS) and an aversive unconditioned stimulus (US; e.g., shock) may be impaired using certain pharmacological manipulations (Beckers & Kindt, 2017; Debiec & Ledoux, 2004; Nader, Schafe, & Le Doux, 2000) that are assumed to disrupt the reconsolidation of the fear memory into its stable form. Monfils and colleagues proposed that, whereas the administration of amnestic drugs upon memory retrieval can prevent the reconsolidation of a fear memory, extinction training applied within the reconsolidation window can induce updating of the reactivated memory trace, by incorporating non-threatening information about the CS. Their data indeed supported that the retrieval-extinction procedure resulted in a more persistent fear reduction as compared with standard extinction training.

Clearly, these findings have exciting implications regarding the possibility of fear memory modification and hold great clinical potential. However, the fear recovery-reducing effect of the retrieval-extinction procedure is not undisputed and many have questioned whether merely changing the spacing of initial extinction training should result in such a marked loss of the fear memory. Alternative accounts for the superior fear reduction observed after retrieval-extinction relative to regular extinction (e.g., increased variability or spacing of the extinction trials (Rowe & Craske, 1998; Urcelay, Wheeler, & Miller, 2009)) suggest that it may reflect enhanced extinction learning, resulting in a stronger or more retrievable extinction memory, rather than the persistent modification of the initial fear memory (Baker, McNally, & Richardson, 2013; Ponnusamy et al., 2016). The distinction between the reconsolidation-based explanation of Monfils and colleagues and alternative accounts is not trivial, given that the former implies a permanent disruption of the original fear memory, in which case there could never be a return of fear, under any circumstances.

Although Monfils and colleagues have been able to replicate the effect multiple times, independent conceptual replications have met with varying success (see Table 1). To the best of our knowledge, a significant reduction of the return of cued fear in adult rats has not yet been reported outside of the Monfils lab. Already in 2010, an Australian group published a series of experiments that closely followed the original procedures, but failed to replicate the fear recovery-reducing effect, and even found fear augmentation in some cases (Chan, Leung, Westbrook, & McNally, 2010). Note that these authors did deviate from the original procedure on some aspects (e.g., a different rat strain was used, animals were handled for three days before the start of experiments, animals were housed in groups of eight, and no experiment assessing the long-term effect on spontaneous recovery was included). In a recent meta-analysis, Kredlow, Unger, and Otto (2016) calculated an estimate of the effect size of the retrieval-extinction procedure.

Table 1
Previous publications (n = 22) using the retrieval-extinction procedure in rodent fear conditioning studies.

Publication	Fear reduction?	Subjects	Conditioned stimulus	Included in Kredlow et al. (2016)?
Flavell, Barber, and Lee (2011)	Yes	Rats	Context	Yes
Liu et al. (2014)	Yes	Rats	Context	No
Piñeyro, Ferrer Monti, Alfei, Bueno, and Urcelay (2013)	Yes	Rats	Context	No
Rao-Ruiz et al. (2011)	Yes	Mice	Context	Yes
Costanzi, Cannas, Saraulli, Rossi-Arnaud, and Cestari (2011)	No[b]	Mice	Context	No
Gräff et al. (2014)	No[b]	Mice	Context	No
Stafford, Maughan, Ilioi, and Lattal (2013)	No	Mice	Context	No
Auchter et al. (2017)[a]	Yes	Rats	Cue	No
Baker et al. (2013)	Yes[c]	Rats (p34-37)	Cue	Yes[d]
Clem and Huganir (2010)	Yes[e]	Mice	Cue	Yes
Jones and Monfils (2016)[a]	Yes[b]	Rats (p45)	Cue	No
Jones, Ringuet, and Monfils (2013)[a]	Yes	Rats	Cue	Yes
Monfils et al. (2009)[a]	Yes	Rats	Cue	Yes
Olshavsky, Jones, Lee, and Monfils (2013)[a]	Yes	Rats	Cue	Yes
Pattwell et al. (2016)	Yes	Mice	Cue	No
Chan et al. (2010)	No	Rats	Cue	Yes
Chan (2014, chap. 5)	No	Rats	Cue	Yes
Flavell et al. (2011)	No	Rats	Cue	Yes
Gräff et al. (2014)	No[b,f]	Mice	Cue	No
Ishii et al. (2012)	No	Mice	Cue	Yes
Ishii et al. (2015)	No	Mice	Cue	No
Ishii et al. (2015)	No	Mice (p28-32)	Cue	No
MacPherson et al. (2013)	No	Mice	Cue	No
Pattwell et al. (2016)	No	Mice (p30)	Cue	No
Ponnusamy et al. (2016)	No[c,g]	Rats	Cue	No
Xu et al. (2013)	No[f]	Mice	Cue	No

An overview of all published (until March 2017) retrieval-extinction studies and whether they reported significantly superior reduction of fear recovery relative to regular extinction. Adult animals were used for all studies, unless indicated otherwise. For studies that used animals in (late) adolescence, the age (postnatal day, p) at the time of extinction is indicated.

[a] Study by Monfils and co-workers.
[b] Remote fear memories (≥20-day interval between acquisition and retrieval).
[c] Significant reduction of fear recovery was found in a reversed control group (Ext-Ret).
[d] No significant reduction of fear recovery in the re-analysis by Kredlow, Unger, and Otto (2016).
[e] No reduction of fear recovery was found for less recent fear memories (7-day interval between acquisition and retrieval).
[f] Duration of the CS was longer during retrieval and extinction than during acquisition.
[g] A trend (p = 0.073) toward a reduction of spontaneous recovery was observed.