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Fear attenuation collaborations to optimize translation

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Abstract

Here, we describe the efforts we dedicated to the challenge of modifying entrenched emotionally-laden memories. In recent years, through a number of collaborations and using a combination of behavioral, molecular, and computational approaches, we: 1. Developed novel approaches to fear attenuation that engage mechanisms that differ from those engaged during extinction (Monfils), 2. Examined whether our approaches can generalize to other reinforcers (Lee, Gonzales, Chaudhri, Cofresi, and Monfils), 3. Derived principled explanations for the differential outcomes of our approaches (Niv, Gershman, Song, and Monfils), 4. Developed better assessment metrics to evaluate outcome success (Shumake and Monfils)**,** 5. Identified biomarkers that can explain significant variance in our outcomes of interest (Shumake and Monfils), and 6. Developed better basic research assays and translated efforts to the clinic (Smits, Telch, Otto, Shumake, and Monfils). We briefly highlight each of these milestones, and conclude with final remarks and extracted principles.

Keywords

Fear memory; fear learning; extinction; reconsolidation; computational; translational

Thirty-one percent of the population will meet criteria for an anxiety-related disorder in their lifetime (Harvard Medical School, 2017). For many, the toll is personal—post-traumatic stress disorder (PTSD), obsessive-compulsive disorder (OCD), generalized anxiety disorder (GAD), Health illness anxiety disorder (HAD), specific phobia, panic disorder (PD), and agoraphobia directly impact relationships, work, and the ability to enjoy a fulfilling, meaningful life (Kamphuis and Telch, 2000; Sloan and Telch, 2002; Vos et al., 2017; Wolitzky et al., 2009). For the first author on this article (Monfils), the initial interest and foray into this field was through the lens of memory. As compared to clinical colleagues, Monfils didn't initially set out to understand anxiety-related disorders to help those affected by them. She was drawn to the field by the interesting complexity of the form of memory that appears to underlie fear-based memories. While memories, broadly speaking, generally

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fall into distinct camps of explicit vs. implicit, emotional memories possess intertwined elements of both. As she delved further into understanding these memories, and as she aimed to develop tools that could prove helpful in undoing them, she discovered possible avenues that could translate into intervention strategies that may help patients. In the years that followed, together with a number of collaborators from various complimentary backgrounds, she set out to continue understanding memories, but with an eye tuned to translation. Monfils would likely never have pursued this work if it weren't for the inspiring colleagues she met along the way. In essence, the story of this work is grounded in showcasing how collaborative efforts are more than the sum of their parts, and how close colleagues shape one-another's thinking and as a result, research pursuits.

Here, we describe the efforts we dedicated to the challenge of modifying entrenched emotionally-laden memories. In recent years, through a number of collaborations and using a combination of behavioral, molecular, and computational approaches, we: 1. Developed novel approaches to fear attenuation that engage mechanisms that differ from those engaged during extinction (Monfils), 2. Examined whether our approaches can generalize to other reinforcers (Lee, Gonzales, Chaudhri, Cofresi, and Monfils), 3. Derived principled explanations for the differential outcomes of our approaches (Niv, Gershman, Song, Jones, and Monfils), 4. Developed better assessment metrics to evaluate outcome success (Shumake and Monfils), 5. Identified biomarkers that can explain significant variance in our outcomes of interest (Shumake and Monfils), and 6. Developed better basic research assays and translated efforts to the clinic (Smits, Telch, Otto, Shumake, and Monfils). We briefly highlight each of these milestones, and conclude with final remarks and extracted principles.

1. Novel approaches to fear attenuation that engage mechanisms that differ from those engaged during extinction

For years, the gold-standard approach to tackle trauma and other anxiety-related disorders has been exposure therapy. Exposure therapy involves repeated confrontation to feared cues and the prevention of fear-guided avoidance or escape maneuvers. Depending on the presenting problem and related case formulation, feared cues are internal (e.g., bodily sensations, thoughts, images, memories, emotions) or/and external (e.g., people, animals, situations) and thus exposure practice can be delivered in various modalities (e.g., in vivo, imaginal, virtual reality, interoceptive; Smits, Jacquart, et al. 2022; Smits, Powers, and Otto 2019; Telch et al., 2014). In the lab, fear learning is often examined using a conditioning paradigm where a conditional stimulus (CS) is paired with some aversive outcome (e.g., a mild electric shock) until an association between them is formed (which could require as few as one pairing). Exposure therapy shares mechanisms with extinction learning, an approach and phenomenon in which the repeated presentation of a conditioned stimulus (CS) without an aversive outcome leads to new inhibitory learning, and the formation of a new safe association to the CS. This new memory trace does not modify the original fear memory but rather creates a second, competing memory, which leaves individuals susceptible to the return of fear (Bouton, 1988; Craske & Mystkowski, 2007; Myers & Davis, 2002). When retrieved, memories are thought to be rendered temporarily labile before restabilizing in a process known as reconsolidation (Misanin et al., 1968; Sara, 2000).

Applying pharmacological agents that interfere with reconsolidation mechanisms during an opportunistic window can persistently modify memories (Bustos et al., 2006; Dębiec & Ledoux, 2004; Nader et al., 2000). Reconsolidation-based approaches have generated much interest as potential treatments for the maladaptive fear memories that underlie anxiety-related disorders; however, most available amnesic agents are harmful to humans and those that are not, such as the beta-adrenergic antagonist propranolol, have had limited success (e.g., Bos et al., 2014; Schroyens et al., 2017).

A little over a decade ago, Monfils et al. (2009) developed an approach to update fear memories behaviorally by combining principles of extinction and reconsolidation. Specifically, delivering extinction trials during the reconsolidation window resulted in a persistent attenuation of fear memories (Monfils et al., 2009). This safe, relatively simple, and noninvasive paradigm, termed retrieval-extinction (or post-retrieval extinction), was shortly thereafter also found to be successful at preventing the return of fear in healthy fear conditioned humans, through a collaboration with Liz Phelps and Daniela Schiller (Schiller et al., 2010).

The only procedural difference between extinction and retrieval-extinction is that the latter features a longer gap between the first and second CS presentations. So, are they mechanistically different? A number of studies have compared the mechanisms engaged in extinction vs. retrieval-extinction, and found that they possess different neural signatures (See Figure 1). We previously examined zinc-finger protein 268 (Zif268), a marker of reconsolidation, and phosphorylated ribosomal protein S6 (rpS6P), a protein associated with GluR1 activation (Tedesco et al., 2014) in brain regions known to be involved in reconsolidation and extinction, and found that retrieval-extinction increased Zif268 and rpS6P in the prefrontal cortex (prelimbic and infralimbic) and lateral nucleus of the amygdala (LA) but not hippocampal CA1. Retrieval alone led to the same increases in Zif268 but to a lesser extent, but neither retrieval alone nor extinction alone increased rpS6P. Our findings suggested that rather than being akin to standard extinction or reconsolidation, retrieval-extinction engaged mechanisms proper to both. In another study in rats, we analyzed *Arc* cellular compartment analysis of temporal activity using fluorescence *in situ* hybridization (catFISH) on brains from rats that had undergone either retrieval-extinction or extinction in order to compare the patterns of neural activation at the start and end of the two paradigms (Lee et al., 2016). We found that while the two groups showed similar cytoplasmic *Arc* expression in the prelimbic cortex, infralimbic cortex, and LA, higher nuclear and double nuclear-cytoplasmic expression were observed in the extinction group. Since *Arc* translocates from the nucleus to the cytoplasm approximately 25 minutes after neural activation, our results indicate that retrieval-extinction and extinction initially show similar patterns of activation, but diverge as their respective underlying mechanisms progress. Effectively, we correctly predicted that extinction and retrieval-extinction would lead to comparable circuit activation at the beginning of training, which generally corresponds to memory retrieval. For the first time, we were also able to determine which cells, of those that were active near the end of our training paradigms, were also active at the beginning and which were *de novo* recruited. Our findings showed differential engagement of amygdala and mPFC subregions during extinction vs. retrieval + extinction,

and thus further highlighted their specific dynamic contributions at the moment where their mechanistic contributions are thought to diverge.

Another study used catFISH of the *Homer1a* and *cFos* genes and showed that mice that received retrieval-extinction training displayed activity in the same cells in the basolateral amygdala, infralimbic cortex, and dentate gyrus than those that were originally active during fear acquisition (Khalaf et al., 2018; Khalaf and Gräff, 2019), consistent with memory updating. Our original study (Monfils et al., 2009) also identified mechanistic differences in GluR1 receptor phosphorylation between a retrieval that was followed by an extinction trial either 3 min (for extinction) or one hour (for retrieval-extinction) later, suggesting that even early in our paradigm, there was the onset of differing brain activity. Other groups have also noted mechanistic differences between extinction and retrieval-extinction in rodents (e.g., Clem and Huganir, 2010; Rao-Ruiz et al., 2011). In humans, neural activity can be inferred by analysis of the blood-oxygen-level-dependent (BOLD) signal acquired through magnetic resonance imaging (MRI). A number of groups have shown differential activation between extinction and retrieval-extinction in humans (Agren et al., 2012; Schiller et al., 2013; Björkstrand et al., 2015), but others have not (Klucken et al., 2016). Taken together, the findings showcase that extinction and retrieval-extinction engage different and enduring mechanisms early in their respective processes. That our retrieval-extinction paradigm could attenuate fear memories, and seemed to engage distinct mechanisms was promising, but we thought it would be important to examine whether it might generalize to other reinforcers. Fortuitously, one of Monfils' colleagues at UT Austin (Joanne Lee) is an expert in appetitive memory, and was interested in testing the prediction.

2. Is this approach broadly applicable to other reinforcers? (Lee, Gonzales, Chaudhri, Cofresi)

Examining whether the retrieval-extinction paradigm might serve to attenuate appetitive memories afforded an interesting opportunity—that of testing whether orienting phenotype might be a predictor of behavioral outcome. When presented with a light cue followed by food, some rats simply approach the foodcup (Nonorienters), while others will first orient to the light in addition to displaying the food-cup approach behavior (Orienters)—phenotypes that are very similar to goal- and sign-trackers (Flagel et al., 2007). Evidence suggests that cue-directed orienting may reflect enhanced attentional and/or emotional processing of the cue, and could mean that there are inherently divergent forms of cue-information processing in Orienters and Nonorienters. In our study, we tested how orienting phenotype might affect appetitive memory updating with either appetitive extinction memory or a new fear memory (Olshavsky, Song, et al., 2013). We found that both extinction and new fear learning given within the reconsolidation window were effective at persistently updating the initial appetitive memory in the Orienters, but not the Nonorienters. Interestingly, the orienting phenotype effect seemed to be specific to appetitive memories; there was no differential effect of orienting on fear memory updating (Olshavsky, Jones, et al., 2013). We later tested whether retrieval-extinction could update Pavlovian alcohol memories, in a series of collaborations that are detailed here (Monfils et al., 2022). Briefly, we found our retrieval-extinction paradigm to be effective in attenuating alcohol seeking (Cofresi et

al., 2017). Other groups have also found retrieval-extinction to be effective in preventing relapse in cocaine and heroin cravings (Sartor and Aston-Jones, 2014; Xue et al., 2012). That the retrieval-extinction effect generalized beyond fear memory modification was encouraging, as it strengthened the possibility that memory updating was a ubiquitous adaptive feature of brain processing. Around the time that we were carrying out our initial appetitive experiments, Monfils and Yael Niv were discussing a potential collaboration in which the Niv lab might employ computational modeling to explain some of the behavioral phenomena Monfils and colleagues had observed.

3. Principled explanations for differential outcomes (Niv, Gershman, Song)

Prior to meeting Yael Niv, the idea of "explanation" behind phenomena was generally akin to "biological underpinnings" for Monfils. Through collaborations with Niv's lab (Sam Gershman, early on, and Mingyu Song, later), Monfils developed an appreciation for the explanatory power of principled explanations—that is theoretical reasoning that can be readily tested with computational models. Collaborating with Gershman, Niv, and Song gave us a different framework from which to understand our data, and generate predictions. A number of interesting findings came out of those collaborations (Gershman et al., 2013; Gershman et al., 2017; Song et al., 2022), and shaped how we think about memory updating, from thereon. In a nutshell, Gershman and Niv proposed that extinction training might lead to the inference of a new state or context in an individual's brain (which they termed, following terminology from machine learning algorithms, a new latent cause), one that is different from the latent cause that was in effect during the original training. This idea raised an interesting question: under what conditions might new latent causes, or new memories be formed? According to their theory, when experienced events have little similarity to past events, a new latent cause is inferred and stored in memory, and the new events are associated with this new latent cause. To test this prediction, Gershman (who visited the Monfils lab and ran experiments in collaboration with her graduate student at the time, Carolyn Jones) tested whether fear memories would be better updated if experience in extinction training closely resembled fear learning. In other words, Gershman tested whether maximizing the similarity between extinction and acquisition, while still (gradually) extinguishing the relationship between the CS and the aversive outcome, would modify the extinction memory and therefore prevent the return of fear. To explicitly make extinction training more similar to fear learning, we used a gradual extinction protocol, in which the early extinction trials co-terminate with a shock (as they would during fear learning), and then progressively phased out the shocks. Our control groups consisted of standard extinction, and reverse gradual extinction (where the tone-shock trials were initially rare, and became more frequent as the extinction session progressed; in all cases the last 9 trials were without shock to achieve attenuation of fear during the extinction session itself).). We found that gradually reducing the frequency of aversive stimuli, rather than eliminating them abruptly, prevented the return of fear (Gershman et al., 2013). These findings, and their proposed underlying computationally-derived reasoning (Song et al., 2022), gave us new insight into how retrieval-extinction might function (Gershman et al., 2017); that is, we grew persuaded that the initial retrieval (which is similar to what animals, including humans might experience during fear acquisition) likely opened the initial latent cause, and rendered it

susceptible to updating. This updating then took place during the ensuing extinction session. The fact that an interoceptive threat remains ongoing during the period that followed the isolated retrieval trial likely created a state of constant updating, and fostered similarity between the initial trial and the extinction session that followed. Intuitively, one might reasonably ask why a non-reinforced CS would be perceived as similar to that experienced during fear learning. We would contend that despite the CS not being explicitly reinforced, for a fear memory, the retrieval leads to physiological responding that itself can act as a reinforcer (increased skin conductance response, increased blood pressure, irregular heart rate). During a standard extinction session, this physiological response is relatively short-lived, because it is followed quite rapidly by another CS that is not explicitly reinforced, and then another, and so forth, such that the brain rapidly makes the determination that the CS under the present circumstances is not the same as the CS under fear acquisition conditions. During a retrieval-extinction session the waiting period between the first CS and those that follow is much longer, the physiological hyperarousal can thus linger for a while, and as such, the first CS resembles the acquisition conditions more closely (that is, the individual expects a negative outcome, and the increased physiological arousal appears to match that expectation). We suspect that the brain perceives a retrieval-extinction session in a very similar way to an acquisition session, and once more conditioned stimuli are presented, they simply serve to update the initial fear memory (Gershman et al., 2017). Of course, if true, for the updating to occur would depend on how an individual's brain might perceive the initial retrieval trial: either as vastly discrepant from the fear acquisition (which would lead to a new latent cause, and thus not prevent the return of fear), or one that is similar enough to the fear acquisition that it may warrant updating the initial latent cause (thus preventing the return of fear). We later found that another way to foster similarity is to manipulate how predictable the CS occurrences may be during extinction. By simply making the CS presentations variable, we were able to improve extinction outcomes (Auchter et al., 2017). The propensity to update memories may also be a product of an individual's tolerance for uncertainty and ambiguity, and inclination to modify core beliefs (Pisupati et al., 2023).

Since its discovery, there has been an explosion of research on the use of retrieval-extinction in fear memories in humans and other animals (see supplementary figure in Monfils & Holmes, 2018), some of which have found a long-term reduction in conditioned responding, and some who have not (see Kredlow et al., 2016, and see Tables 1 and 2 for a comprehensive list). We should embrace the non-replications. Many people have followed up on the retrieval-extinction work, and each additional study provides useful data that help us understand the phenomena we are studying. Sometimes, non-replications are evidence that a phenomenon didn't exist in the first place. Sometimes, they provide information about possible boundary conditions surrounding phenomena. Often, they showcase that while a phenomenon is real, its attributed effect size was likely not reflective of the true effect size. The latter can readily be explained as a statistical power issue—something that is not unique to retrieval-extinction. For many years, sample sizes in behavioral neuroscience have been smaller than they should have been (Burton et al., 2009). While we remain confident that the retrieval+extinction effect is real, we believe it is likely that not every individual might respond to the approach. This realization regarding the non-replications prompted Monfils to think of two additional angles to pursue: 1. Developing better assessment metrics to

evaluate outcome success; 2. identifying biomarkers that can explain significant variance in our outcomes of interest.

4. Better assessment metrics to evaluate outcome success (Shumake and Monfils)

After a few years in the field, and continued interactions with clinical researchers, Monfils began to notice that the metrics of success between the clinic and the basic non-human animal research didn't align. Rodent research predominantly relied on mean data—that is, researchers reported group means, and tested whether an experimental group, *on average*, significantly differed from a control group. Much of the clinical research instead reports not only on group means, but on *success rate*, that is, the proportion of individuals that respond to a given treatment. This makes sense. An individual does not care whether something works better on average. We like to know: how many individuals are responders? But also: what is the likelihood that this will work for me?

One of the perks of working with rodents is that they are more homogeneous. In a sense, it's also a drawback—one may reasonably ask: do they really mirror the human condition? In delving deeper into the data, it is clear that rats, too, have noticeable individual differences, and that explaining such differences may help us develop better treatment approaches, as well as promote better translational value. Shumake and Monfils set out to develop data-driven criteria for defining a standard benchmark that would indicate "remission" from conditioned fear in rodents (Shumake et al., 2018). We performed logistic regression analyses on a relatively large (by rat standards) dataset (n ~ 200) to better describe our subjects' responding, and their respective individual responses. In the same study, we also employed agglomerative hierarchical cluster analysis to identify homogeneous subgroups of rats according to their respective patterns of fear acquisition, extinction, and reinstatement. Our findings enabled us to derive a practical benchmark to assess remission in rats, such that we can now report data in a fashion similar to that used in clinical research—success rates. Furthermore our cluster analysis unveiled 7 distinct homogeneous subgroups of rats: Subgroup 1: Mild initial fear with successful extinction and long-term fear reduction (20%); Subgroup 2: Severe initial fear with moderately successful extinction followed by return of fear (20%); Subgroup 3: Mild initial fear with largely successful extinction followed by return of fear (15%); Subgroup 4: Severe initial fear with largely successful extinction and long- term fear reduction (13%); Subgroup 5: Severe, persistent fear (13%); Subgroup 6: Fear incubation (12%); Subgroup 7: A more extreme version of Subgroup 2 (8%) (See Figure 2). What these findings highlight, is that 1. Rats are not completely unlike humans in their individual responding, 2. Owing to the subclusters present in datasets, small sample sizes are likely to yield distortions in data outcomes, since they are statistically unlikely to be representative of the population. Our group (Smits, Monfils, Telch, Shumake and Otto) is currently running a 2-site clinical trial, and we plan to perform cluster analyses to examine how individuals in our transdiagnostic sample differentially respond to treatment. When we completed the rat cluster analyses, we pondered whether some of the rats that were assigned to one treatment group might have responded differently had they been in another. This thought led us on the path of trying to identify biomarkers of extinction non-responding.

5. Identifying biomarkers that can explain significant variance in our outcomes of interest (Shumake, Telch, Otto, Smits, Monfils)

There is significant variability in extinction/exposure responding, and from a translational perspective, identifying whether an individual might be a good candidate for this type of approach prior to administering treatment could improve outcomes, and minimize effort and cost. Inspired by work from the Telch lab, who had shown that individuals prone to anxiety disorders displayed heightened emotional reactivity to CO2 challenge (Telch et al.,2010; 2011, 2012), we set out to examine whether CO2 reactivity may serve as a practical means to determine whether an individual may be a good candidate for exposure therapy. A number of studies had been published suggesting that, in principle, using CO2 reactivity as a biomarker of extinction non-response may have merit: Sharko et al (2017) had found that differences in orexin activity in the hypothalamus accounted for individual differences in extinction, Johnson et al (2011; 2015) had previously reported that CO2 exposure activates orexin neurons, Sears and colleagues (2013) had shown that orexin from the lateral hypothalamus modulates amygdala-dependent fear learning, and Flores et al (2014) had found that orexin receptor antagonism facilitated extinction, and increased the recruitment of lateral amygdala neurons that project to the infralimbic cortex during extinction learning (Flores et al., 2017). Taken together, this body of work supported our hypothesis that individual differences in orexin activation in the lateral hypothalamus could account for individual differences in extinction, and that CO2 reactivity may serve as a non-invasive proxy-readout of active orexin. This latter point matters, because there currently isn't a non-invasive way to directly quantify active orexin in the lateral hypothalamus. We tested, in rats, the prediction that CO2 reactivity would explain significant variance in orexin activity in the lateral hypothalamus, and in turn, that orexin activity would predict extinction long-term memory. Using a combination of statistical approaches, we found that CO2 reactivity was significantly predictive of orexin in the lateral hypothalamus, as well as extinction long-term memory in a sample (n~ 60) of fear-conditioned rats (Monfils et al., 2019). More recently, in collaboration with the Lee lab, we extended the findings to show that CO2 reactivity also predicted extinction of an appetitive memory (Raskin et al., 2023). We are now running a 2-site clinical trial to determine whether our initial promising findings in rats will translate to a transdiagnostic population in the clinic (Smits, Monfils, et al., 2022). The true test will be to determine whether our approach can scale to the level of identifying the best treatment on an individual basis.

6. Developing better basic research assays and translating efforts to the clinic (Smits, Telch, Otto, Shumake, and Monfils).

Translation work grew front and center early in our research efforts, in great part thanks to Monfils being hired at UT Austin where she immediately started to regularly meet and discuss science with Mike (Telch) (and shortly thereafter Jasper [Smits], and eventually Michael [Otto]).

A number of studies have sought to extend the retrieval-extinction paradigm to update maladaptive fear memories. Two studies incorporated a reactivation cue of either a neutral

or phobic stimulus ten minutes before exposure therapy in virtual reality in patients with specific phobia (Maples-Keller et al., 2017; Shiban et al., 2015), and found that patients in both the reactivated and the non-reactivated groups responded equally well to therapy and maintained their treatment gains. There were no differences in clinical measures at any of the measured time points. One potential factor may be that individuals may be recalling forth memories in anticipation of treatment when in the waiting room. Doing so would render standard exposure similar to retrieval-exposure. It should also be noted that exposure therapy is generally quite effective at treating phobias (Carpenter et al., 2018). As such, one interpretation may be that the retrieval-extinction was *as effective* as standard exposure in these studies. In two other studies, our group tested the efficacy of a ten-second reactivation 25-30 minutes prior to *in vivo* exposure therapy for phobia of snakes or spiders (Lancaster et al., 2020; Telch et al., 2017). In both studies, we found a benefit of reactivation before exposure. We observed a reduction in self-reported fear at follow-up relative to groups in which reactivation was presented *after* exposure (Telch et al., 2017), and found a 21% reduction in the exposure dosage needed to achieve the same symptom reduction as deepened exposure or exposure alone (Lancaster et al., 2020).

In another study, Kredlow and Otto (2015) examined whether retrieval-extinction might be effective in updating traumatic memories in an analog sample of individuals that were exposed to the Boston Marathon bombing. Participants first retrieved their negative autobiographical memories of the day's events, then they underwent interference with a story of either positive, neutral or negative valence. Those that experienced interference with a negative story recalled significantly fewer details than those in the no story group when tested one week later. Using a different experimental twist, Kessler et al (2018) tested whether reactivated traumatic memories could be disrupted with a game of Tetris. A sample of PTSD inpatients reactivated an intrusive memory by briefly writing a trauma script, and then they received memory interference with the game Tetris. The reactivation treatment resulted in a decrease in the frequency of intrusions by 64%, significantly more than the reduction of 11% for the group that did not receive memory reactivation. Vermes et al (2020) tested whether a 5-minute reactivation one hour prior to imaginal exposure might improve outcomes in group of individuals with trauma, and found that while those that received reactivation did not report any improvement relative to those that didn't on subjective measures of symptom severity, they did show a reduction in galvanic skin responding.

Another study incorporated elements of retrieval-extinction into a novel treatment protocol for PTSD (Gray et al., 2019). The treatment involved reactivating the traumatic memory by retelling it just until physiological responses were observed, and then incorporating cognitive distancing and restructuring techniques into the trauma script. Of those who completed the three two-hour long sessions, 67% achieved remission, and their symptoms reduced significantly more than those on the wait list. In addition, there was no return of fear after treatment, with post-treatment symptom severity scores remaining stable two and six weeks later. Taken together, these studies show that behavioral updating following memory reactivation remains a promising treatment approach—while not universally the best approach for all, it may prove to be the ideal one for some.

7. Closing remarks

Over the past ~ 15 years, we developed a new approach to target emotional memories, generalized our approach and biomarker findings from fear to appetitive learning, identified a potential principled explanation for our findings, developed a benchmark to better evaluate outcomes in rats, identified a potential biomarker of extinction non-response and translated some of our early successes in rats to the clinic. This work could not have been possible without the collaborative efforts of colleagues with not only complementary expertise, but a desire to venture out of their respective silos to test novel ideas. In truth, the collaborations were not inherently intuitive, initially. For many years, researchers focusing on human vs. non-human subjects rarely directly worked together directly (with some notable exceptions). An appeal of working with rats as a biological model to derive principles that can generalize to humans is their apparent simplicity—despite their individual differences, they are more homogeneous as a population than humans. Still, doing so often leads to a conundrum: are rats *too* simple to enable us to understand the complexity of humans? In truth, it is our opinion that we still haven't yet done rats justice when it comes to appreciating their complexity. Indeed, while measuring freezing to estimate fear memory is appealing as a straightforward outcome, it doesn't tell the whole story. For example, in rodents, there are other behaviors beyond freezing which are affected by fear conditioning. One such behavior is conditioned suppression, wherein a conditioned behavior such as reward seeking is suppressed by the presentation of a fear CS. While retrieval-extinction was found to be superior to extinction alone in preventing the reinstatement of conditioned freezing, there was no difference in conditioned suppression of reward seeking (Shumake & Monfils, 2015). This indicates that retrieval-extinction may be able to reduce conditioned fear but not to the extent necessary to resume pleasurable activities in the presence of the CS. It is relevant to note here that some dissociation between extinction outcomes is also documented in the human literature. A number of studies have shown no or low associations between physiologic (skin conductance levels) and expectancy (declarative ratings) of threat in de novo conditioning paradigms in humans (e.g., Constantinou et al., 2021; Lubin et al., 2023). Moreover, changes in the valence of conditioned stimuli (the evaluative "likingess" of these stimuli) tend to lag behind changes in fear extinction (Hermans et al., 2002) and predict return of fear (Dirikx et al., 2004). These findings from tightly controlled, laboratory studies are reflected in clinical studies where there has been difficulty finding a measure of extinction that reliably predicts outcome in exposure-based treatment trials (Benito et al. in submission), with some studies showing the importance of attending to cue valance in addition to fears of the cue (Dour et al., 2016). Accordingly, there is a potential for non-human animal studies to provide greater clarity on the scope or depth of extinction responses, including the perspectives afforded by different types of new learning (e.g., indices of expectancy vs. evaluative learning) needed for a fuller resolution of conditioned fear responding.

In recent years, as we've continued translational efforts, the Monfils lab has also begun to develop studies to better understand the behavioral repertoire of the rat, including its complexity in response to evolving social dynamics within groups of rats. Certainly, humans are social animals, and our social network dynamics play a critical role in our mental

health. The same is true of rats, and understanding them in that light should further improve translation efforts. Consistent with this idea, Kredlow's meta-analysis of retrieval-extinction revealed differences in outcomes based on the rats' housing conditions (group- vs. singly-housed; Kredlow et al., 2016).

Data are data, but how we collect and analyze them is shaped by our theoretical approach, which is itself a product of who we are as scientists—that is, humans with our own unique experience, influenced by the context within which we think and design scientific studies. In other words, the studies we design are very much influenced by the company we keep.

Science, by design, is iterative and self-correcting. A theory that proves "true" is likely one that has not been revisited enough. Despite successes and discoveries in the last decade or so, the scope of tackling traumatic memories remains immense, and the impact on those afflicted significant. So, the work continues.

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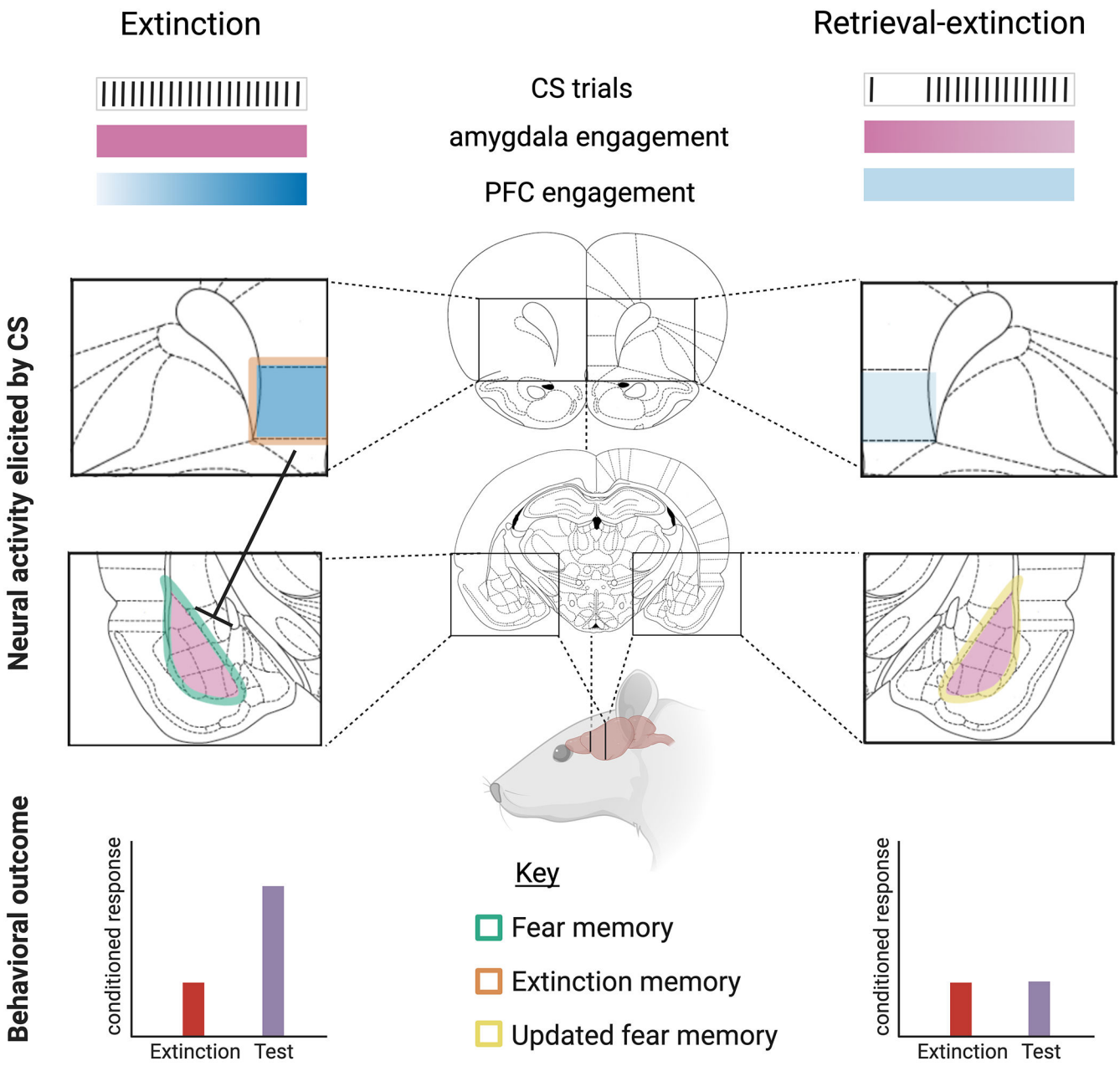

Figure 1.

Initial CS presentations during extinction and retrieval-extinction both activate the prefrontal cortex (PFC) and amygdala; however, as the procedures progress, their patterns of neural activation diverge. Extinction continues to engage the PFC while retrieval-extinction does not. While both paradigms continue to activate the amygdala, retrieval-extinction activates the same cells that were originally active during fear acquisition. Upon test, extinction relies upon the PFC to suppress the fear memory in the amygdala, resulting in a return of conditioned response. Retrieval-extinction is thought to update the original fear memory in the amygdala, preventing the return of fear (Clem and Huganir 2010; Monfils et al., 2009; Monfils and Holmes 2018). Created with BioRender.com.

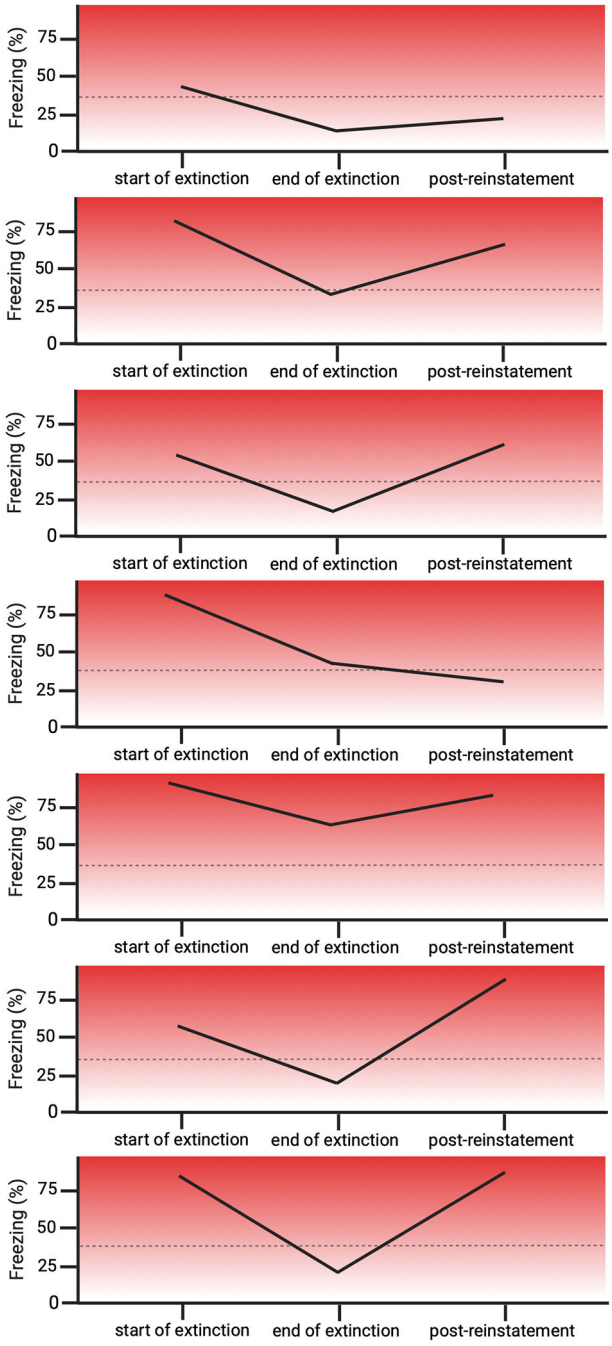

Figure 2.

Adapted from Shumake et al., 2018 showing phenotypic extinction subgroups identified by cluster analysis of 215 subjects. Each panel indicates a subgroup with similar freezing trajectories, ordered from largest group (top) to smallest group (bottom). Black lines depict the median freezing behavior for each subgroup across three phases of training (24 hr after acquisition, end of extinction, and 24 hr after reinstatement). The horizontal dashed line indicates data-driven criteria for fear remission (37.5%). Subgroup 1: Mild initial fear with successful extinction and long-term fear reduction (20% of sample). Subgroup 2:

Severe initial fear with moderately successful extinction followed by return of fear (20% of sample). Subgroup 3: Mild initial fear with largely successful extinction followed by return of fear (15% of sample). Subgroup 4: Severe initial fear with largely successful extinction and long-term fear reduction (13% of sample). Subgroup 5: Severe, persistent fear (13% of sample). Subgroup 6: Fear incubation (12% of sample). Subgroup 7: A more extreme version of Subgroup 2 (8% of sample).

Table 1.

Retrieval-extinction effects on return of fear

Author, year	Species	Ret+Ext better?
Agren, Engman, et al., 2012	Human	
Björkstrand et al., 2015	Human	
Björkstrand et al., 2016	Human	
Björkstrand et al., 2017	Human	
Chalkia et al., 2020	Human	
Chen, Li, Zhang, et al., 2021	Human	
Fernandez-Rey et al., 2018	Human	
Fricchione et al., 2016	Human	
Golkar et al., 2012	Human	
Johnson & Casey, 2015	Human	
Kindt & Soeter, 2013	Human	
Klucken et al., 2016	Human	
Kredlow et al., 2018	Human	
Lancaster et al., 2020	Human	
Oyarzún et al., 2012	Human	
Schiller et al., 2010	Human	
Soeter & Kindt, 2011	Human	
Steinfurth et al., 2014	Human	
Telch et al., 2017	Human	
Thompson & Lipp, 2017	Human	
Vermes et al., 2020	Human	
Warren et al., 2014	Human	
Zimmermann & Bach, 2020	Human	
Clem & Huganir, 2010	Mouse	
Costanzi et al., 2011	Mouse	
Ishii et al., 2012	Mouse	
Ishii et al., 2015	Mouse	
Piñeyro et al., 2014	Mouse	
Rao-Ruiz et al., 2011	Mouse	
Stafford et al., 2013	Mouse	
An et al., 2018	Rat	
Auchter, Cormack, et al., 2017	Rat	
Chan et al., 2010	Rat	
Flavell et al., 2011	Rat	
Goode et al., 2017	Rat	
Lee et al., 2016	Rat	
Luyten & Beckers, 2017	Rat	

Author, year	Species	Ret+Ext better?
Monti et al., 2017	Rat	
Olshavsky et al., 2013	Rat	
Ponnusamy et al., 2016	Rat	
Shumake & Monfils, 2015	Rat	
Tedesco et al., 2014	Rat	
Jones et al., 2013	Rat	
Jones et al., 2016	Rat	

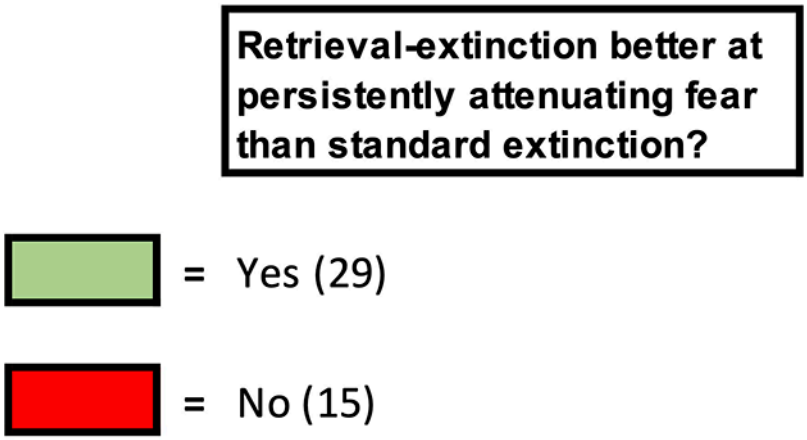

Table 2.

Retrieval-extinction effects on reward seeking behavior

Author, year	Species	Substance	Procedure	Ret+Ext better?
Bamabe et al., 2023	Human	cigarette		
Das et al., 2018 *	Human	alcohol		
Gera et al., 2019 *	Human	money		
Germeroth et al., 2017	Human	cigarette		
Zhao et al., 2022	Human	internet gambling		
Chang et al., 2022	Mouse	cocaine	CPP	
Lv et al., 2022	Mouse	morphine	CPP	
Chen et al., 2019	Rat	methamphetamine	self-admin	
Cofresi et al., 2017	Rat	alcohol		
Flavell et al., 2011	Rat	food		
Ma et al., 2012	Rat	morphine	CPP	
Millan et al., 2013	Rat	alcohol	self-admin	
Luo et al., 2015	Rat	cocaine	self-admin	
Olshavsky, Song et al., 2013 **	Rat	food		
Sator & Aston-Jones, 2014	Rat	cocaine	CPP	
Struil et al., 2019	Rat	cocaine, nicotine	self-admin	
Xue et al., 2012	Rat, Human	heroin, cocaine, morphine	CPP, self-admin	
Yuan et al., 2019	Rat	heroin	self-admin	

*Counterconditinoing aftter retrieval

**Counterconditinoing or extinction aftter retrieval