Journal Club

Editor's Note: These short, critical reviews of recent papers in the *Journal*, written exclusively by graduate students or postdoctoral fellows, are intended to summarize the important findings of the paper and provide additional insight and commentary. For more information on the format and purpose of the Journal Club, please see http://www.jneurosci.org/misc/ifa_features.shtml.

Memory Erasure, Enhanced Extinction and Disrupted Reconsolidation

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Review of Graham and Richardson

Suppression of behaviors driven by unwanted memories can potentially be used as a treatment strategy for posttraumatic stress disorder (PTSD) and other anxiety disorders in which maladaptive behaviors may stem from the retrieval of fearful memories. Such retrieval can occur following exposure to a cue previously associated with a fearful event. Although a desirable treatment outcome would be to break the association between the cue and the fearful event, a complete unlearning is seldom observed, and therefore the fear response tends to relapse. In animal studies, associative fear memory is typically acquired in a Pavlovian fear conditioning paradigm, in which a neutral conditioned stimulus (CS), such as a tone, is paired with an aversive unconditioned stimulus (US), such as a foot-shock, resulting in a conditioned fear response to the CS. The most widely used strategy to suppress behaviors driven by fear memories is extinction training, in which repeated presentations of the CS in the absence of the US result in a reduction in the conditioned fear response. It is now widely accepted that extinction does not reflect memory erasure or unlearning, but rather a new learning process of a CS–no-event contingency, which competes with the original CS–US association in determining behavior during a retention test (Bouton, 2002). This view of extinction has been supported by the demonstration of recovery of fear responses after extinction. This recovery is seen after a single reexposure to the US in the absence of the CS (reinstatement); when the test is conducted in the context of the conditioning training, which is different from the extinction training context (renewal); or after the passage of time (spontaneous recovery). These phenomena provide evidence that the original CS–US memory trace was not erased, destroyed, or unlearned during extinction training.

Recently, Graham and Richardson (2009) showed that fibroblast growth factor-2 (FGF2), which regulates neural development, regenerative plasticity, and neurogenesis (Unsicker et al., 1991), enhances extinction and disrupts reinstatement and renewal of the conditioned response in young rats when administered before or after extinction training. In a recent article published in *The Journal of Neuroscience,* Graham and Richardson (2011) further expand this line of research, showing that FGF2 facilitates extinction of fear memories in adult rats by acting in the basolateral amygdala (BLA). More specifically, the authors show that rats with FGF2 infused into the BLA immediately after extinction training exhibit less freezing to the presentation of the CS compared with vehicle controls and to FGF2-treated rats that did not receive extinction training. The authors provide further evidence that FGF2 is a powerful extinction enhancer by showing that four times the amount of extinction training was required for control rats to exhibit levels of performance as low as those induced by postextinction FGF2 treatment. Furthermore, the authors found that FGF2 infusion into the BLA after extinction attenuated the renewal of fear response when the rats were tested in the original context. Finally, US (shock)-induced reinstatement of the conditioned fear response was abolished by FGF2 treatment. Together, these findings suggest that FGF2 activation in the BLA not only enhances extinction of fear response, but also prevents its relapse, and therefore may provide an ideal therapeutic strategy for anxiety disorders.

The results of Graham and Richardson (2011) have significant implications for the understanding of the involvement of FGF2 in extinction processes. First, these data expand on the authors' previous findings, showing that systemic administration of FGF2 enhances extinction in younger rats. Specifically, the effects of FGF2 on extinction and relapse of fear seem to be similar in young and adult rats, suggesting that the mechanisms of extinction affected by this growth factor are similar in preadolescence and adulthood. Second, this study shows that the effects of FGF2 on extinction are mediated, at least in part, by the BLA. This conclusion is consistent with the wealth of literature implicating the BLA in the formation, maintenance, and extinction of fearful memories (Phelps and LeDoux, 2005).

Interestingly, the extinction training given to rats just before FGF2 infusion

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into the BLA was short (6 CS presentations), and yielded weak extinction, i.e., the fearful response was reduced, but not completely extinguished even at the last extinction trial. This short CS-alone extinction training raises the possibility of an alternative explanation for the observed results, namely, that the reduced performance of the FGF2 group resulted from disruption of reconsolidation of the original CS–US memory. It has been established that in animals trained in fear conditioning, an amnestic treatment given immediately after a short extinction-like presentation of the CS alone results in reduced conditioned fear response in a subsequent retention test, whereas in the absence of the amnestic treatment, the fear response is either unaffected or enhanced (for review, see Nader and Hardt, 2009). These observations led to the establishment of the reconsolidation theory, which postulates that a short CS-alone trial leads to memory retrieval (reactivation) that initiates a temporary destabilization and labile state of the memory, during which the memory, i.e., the original CS–US association, can be modified, strengthened or attenuated/erased, before reconsolidating and becoming stable again (Dudai, 2006; Nader and Hardt, 2009). In terms of psychological processes, disruption of reconsolidation is thought to weaken the original association between the CS and the US, i.e., the subject forgets that the CS ever predicted the US (Dudai, 2006; Nader and Hardt, 2009). In contrast, extinction is considered to reflect the learning of a new contingency (Bouton, 2002), namely, that the CS ceased to predict the US. As a consequence, relapse occurs after extinction, but not after disruption of reconsolidation, as the original memory trace is still present after the former but not after the latter (Duvarci and Nader, 2004).

The main parameters shown to determine whether the presentation of the CS alone will result in extinction or in a memory reactivation–reconsolidation process are the duration of the session and the number of trials. More specifically, following a short CS-alone session, memory reconsolidation processes are dominant, whereas extended, repeated sessions lead to extinction processes (Lee et al., 2006). The CS-alone training parameters used by Graham and Richardson (2011) can be considered either as short extinction training or as a long memory reactivation session that triggers reconsolidation. As a consequence, the effects of FGF2 can be described as enhancement of extinction or as disruption of reconsolidation, since the behavioral outcomes of both are the same, i.e., poorer performance.

Graham and Richardson (2011) clearly favored the interpretation of enhancement of extinction, because the extinction training session used in this study was longer than the brief reactivation session used in typical reconsolidation studies. Nevertheless, the authors did not exclude the possibility that the decreased fear response of FGF2-treated animals could be attributable to a disruption of reconsolidation. Moreover, the authors suggested that the enhanced extinction itself might involve unlearning or erasure components. This suggestion raises the possibility that with borderline parameters such as those used in this study, extinction and reconsolidation processes might coexist, and therefore FGF2 treatment might have led to reduced conditioned fear response via two different mechanisms: (1) enhancement of the formation of a new CS–no-event association that competes with the original CS–US memory trace (enhancement of extinction) and (2) attenuation, or erasure of the original CS–US memory trace (disruption of reconsolidation). Interestingly, the findings in this study support this dual-process possibility, as they provide evidence for the existence of both processes: on one hand, FGF2-treated rats exhibit an effect of renewal, a phenomenon found after extinction, but not after disruption of reconsolidation (Duvarci and Nader, 2004). On the other hand, US-induced reinstatement, which is typically demonstrated after extinction but not after memory erasure (Bouton, 2002), was not demonstrated in FGF2-treated rats.

Further investigation is necessary to adequately determine whether FGF2 enhances extinction, disrupts reconsolidation, or both. One way to address this question would be to include at least two sets of more determinative parameters known to lead to extinction and memory reactivation/reconsolidation. Perhaps a more elegant way to dissociate the effects of FGF2 on these two processes would be to reactivate the memory without using extinction-like trials. For example, a memory can be reactivated using a reinforced session (CS–US presentation) rather than a CS-alone session (Duvarci and Nader, 2004). In this case, if post-reactivation FGF2 administration still induces amnestic effects, it should most likely be attributed to disruption of reconsolidation. However, if the performance after such manipulation is intact, then the amnestic effects shown after postextinction treatment cannot be attributed to disruption of reconsolidation, and should therefore be attributed to potentiation of extinction. More generally, using such control experiments in the field will allow a more solid interpretation and better understanding of the supposedly different pharmacological, structural, and molecular mechanisms underlying extinction and reconsolidation.

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