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What does it take to demonstrate memory erasure? Theoretical comment on Norrholm et al (2008)

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Abstract

An issue of increasing interest in Pavlovian conditioning is to identify ways to facilitate the development and persistence of extinction. Both behavioral and molecular lines of evidence demonstrate that learning during extinction can be enhanced. Similar evidence has been offered to support the idea that extinction causes the original association to be unlearned, or erased. Differentiating between extinction and erasure accounts is extremely difficult and requires many assumptions about the fundamental nature of how memory storage maps into memory expression. In this issue of *Behavioral Neuroscience*, Norrholm, et al (2008) describe a study of extinction with humans that has the potential to serve as a translational bridge between rodent work and clinical applications. They find less recovery of a conditioned fear response when extinction occurs 10-min compared to 72-hr after conditioning; however, the recovery of subjects' expectancies of the fearful stimulus is independent of when extinction occurred. These findings and others discussed here demonstrate some of the challenges in making inferences about memory erasure during extinction.

Keywords

Extinction; consolidation; reconsolidation; memory storage; memory erasure

Behavioral and pharmacological approaches to strengthen the long-term consequences of a learning experience often focus on ways of enhancing memory formation. This approach has been successful at strengthening new memories that form as a result of an initial learning experience (e.g., McGaugh, 2004). It also has been successful at strengthening processes involved in extinction, resulting in the rapid and persistent loss of a previously established conditioned response (e.g., Walker, Ressler, Lu, & Davis, 2002). Extinction has been a particularly interesting process to strengthen because behavioral enhancements in extinction may occur by facilitating the development of some new learning process during extinction, or by impairing some process associated with the neural representation of the original memory (see Lattal, Radulovic, & Lukowiak, 2006; Myers & Davis, 2007). Several recent studies have characterized some of the behavioral and molecular conditions that may favor memory erasure (or unlearning) as a mechanism for extinction. These findings are provocative, but there are many reasons to be cautious about interpreting any extinction effect as being caused by memory erasure.

Although extinction is commonly described as a learning process that involves new memory formation, theories of extinction have indeed sometimes appealed to erasure mechanisms to explain aspects of extinction (e.g., Estes 1950; reviewed in Delamater, 2004; Rescorla, 2004). This idea that extinction may sometimes erase the original memory is explored in the

experiments reported by Norrholm, Vervliet, Jovanovic, Boshoven, Myers, Davis, & Rothbaum (2008). Their approach is particularly noteworthy because they take a commonly used behavioral paradigm with rodents and extend it to humans. This enables them to ask questions about similar mechanisms between humans and rodents, and, more important for studies of extinction, this preparation allows Norrholm et al (2008) to examine how the behavioral response corresponds to subjects' self-reported knowledge of the stimulus contingencies (revealed through an expectancy measure). Although the expectancy measure is not without complications, it gives the subjects two possible ways to answer the question, "Do you remember the initial contingencies?" Norrholm et al (2008) show that the answer to this question may be "no" when conditioned responses are examined, but it may be "yes" when expectancy measures are used.

The designs of Norrholm et al's extinction experiments are based on a key assumption that underlies many neurobiological accounts of memory, which is that a behavioral experience instigates a cascade of cellular and molecular events that consolidate an experience into a relatively stable, permanent memory (reviewed in McGaugh, 2000). This consolidation process can be impaired or enhanced by any number of pharmacological and behavioral interventions, provided those interventions occur in close proximity to the learning experience. One of these interventions may potentially include an extinction trial – if extinction occurs soon after acquisition (immediate extinction), the extinction memory may override or compete with the initial memory for consolidation, resulting in a permanently weakened initial memory (e.g., Myers, Ressler, & Davis, 2006). Norrholm et al (2008) demonstrate that although immediate extinction may weaken spontaneous recovery of a conditioned fear response, it does not prevent recovery of expectancy ratings. This difference emphasizes the importance of asking questions about extinction and memory erasure in multiple ways.

Because a number of recent studies have suggested that extinction may involve unlearning mechanisms, it is important to give careful thought to the kind of evidence needed to demonstrate memory erasure. This needs to be considered in the context of extinction, as well as in the context of reconsolidation, where pharmacological interventions after a brief extinction trial may permanently erase (or enhance, depending on the intervention) the original memory. All of the studies that demonstrate memory erasure make compelling cases based on behavioral and molecular results, but they are faced with the same inherent challenge. That is, what are the behavioral and molecular mechanisms underlying memory formation and storage? Until we have a full understanding of the external and internal circumstances that cause memory formation, we will be hard pressed to conclude that any manipulation has retroactively eliminated that memory.

Is the loss of behavior evidence for memory erasure?

Norrholm, et al. (2008) exploit the long-studied phenomenon of spontaneous recovery to assess the persistence of extinction. Spontaneous recovery is perhaps the best known of those paradigms that are thought to reveal the presence of the original memory after extinction. Other paradigms also have been used, including contextual renewal, reinstatement, rapid reconditioning, and Pavlovian-to-instrumental transfer. At a very broad level, these paradigms all demonstrate that at least some aspect of the original memory is preserved during extinction. Recent studies that show memory erasure have used some of these paradigms as tools to try to distinguish between enhanced extinction and impaired reconsolidation accounts of performance. The rationale behind this approach is that if the eliminated behavior does not return (for example, with the passage of time or with a change in context), then the effect likely does not reflect an effect on extinction because extinguished responses should show recovery and renewal.

The problem with this way of thinking is that any manipulation that enhances extinction learning would presumably decrease the likelihood that the behavior would return with time, changes in context, or reminder treatments. Indeed, this has long been shown to be true; Pavlov (1927) demonstrated that less spontaneous recovery occurs with more extinction. More recently, Denniston, Chang, and Miller (2003) found that increasing the number of extinction trials weakens contextual renewal. These effects can be explained by assuming, as Pavlov did, that some inhibitory process continues to strengthen even after changes are no longer evident in behavior (e.g., “silent extinction beyond zero,” Pavlov, 1927).

These post-extinction recovery effects are well documented, but a close examination of the data reveals that spontaneous recovery and renewal are often incomplete (see Delamater, 2004; Rescorla, 2004). The absence of complete recovery or renewal could mean that part of the memory was erased. Or it may mean that the experimental variables were not sensitive enough to reveal complete recovery (e.g., the retention interval was too short) or renewal (e.g., the extinction context did not have enough unique contextual features). Demonstrating that behavior fails to show spontaneous recovery, renewal, or reinstatement after extinction is therefore not necessarily helpful in determining whether a pharmacological or behavioral manipulation erased the original memory or enhanced the extinction memory.

Clearly, the absence of recovery and related phenomena should not by themselves be taken as evidence for memory erasure. It is important to also recognize that the converse also is true: the presence of spontaneous recovery does not necessarily mean that the original memory was fully preserved during extinction. For example, stimulus sampling theory, which was developed over 50 years ago by Estes and colleagues and remains influential in modern neurobiological accounts of memory (e.g., Fanselow, 1999; Riccio, Millin, & Bogart, 2006; Rudy, Huff, & Matus-Amat, 2004), can account for extinction and spontaneous recovery while taking an erasure perspective. Extinction may sever the association between some components of the CS and the US. When the CS is presented soon after extinction, the organism is likely to re-sample those same CS components that now have no association with the US, resulting in weak responding. But with time, it becomes more likely that other components still associated with the US will be sampled, resulting in spontaneous recovery (see Rescorla, 2004). Thus, just as the absence of spontaneous recovery does not mean that the memory was erased, the presence of spontaneous recovery does not necessarily mean that it was fully preserved.

What experimental comparisons are necessary to make inferences about extinction?

Behavioral experiments on extinction have characterized a number of techniques to examine the persistence of extinction across time, contexts, and re-exposures to the initial contingencies. Although there is general agreement that these techniques capture something of the persistence of extinction, a close examination of the literature reveals that there is not uniform agreement on what constitutes appropriate experimental comparisons to establish effects on extinction. At some level, this is not a problem, because the more that a particular effect persists across different measures, the more convincing it becomes. Difficulties arise when the conclusion that one draws from the experiment changes as a function of the experimental comparisons that are made.

Perhaps the most common way to measure extinction is to examine the change in behavior from the beginning to the end of extinction. Decreases in responding are taken as evidence for extinction, and greater decreases in one group compared to another are taken as evidence for enhanced extinction. The difficulty in making the inference is that the expression of behavior changes with time, independent of extinction (e.g., Kamin, 1957; Kumar, 1970). Without direct

comparisons to groups that received similar treatments in the absence of extinction, it is impossible to know whether a decrease (or increase) in responding during extinction reflects changes in learning or changes in the expression of behavior as a function of time since conditioning. For example, if a drug injected during extinction causes an increase in responding, the temptation is to conclude that the drug enhanced the memory. But such an interpretation assumes that the direction of behavior relative to its starting point reflects the direction of associative change. Without a control group that does not receive extinction, it is difficult to know how to interpret differences that emerge during extinction. Indeed, close inspection of some recent demonstrations of pharmacological enhancements in reconsolidation over multiple extinction trials reveal that these enhancements appear to be eliminated when comparisons are made to control groups that did not receive extinction (e.g., Tronson, Wiseman, Olausson, & Taylor, 2006).

Like analyses of extinction, experiments on spontaneous recovery often involve a comparison of the same subject's performance during tests soon and long after extinction. Such tests necessarily have confounding variables, such as the age of the animal at the time of test, the amount of time that has passed since conditioning, and, in the case of repeated testing, the additional learning that may occur during the first test, which is often an additional extinction session. It is important to factor in all of these possibilities when designing experimental comparisons. The ideal situation, of course, is when any of several possible testing configurations reveals the same finding, such as when the amount of time since conditioning is matched in animals receiving tests soon and long after extinction (e.g., Rescorla, 2005; cf. Anagnostaras, Maren, & Fanselow, 1999).

Norrholm et al (2008) were extremely thorough in examining extinction and recovery effects by including between- and within-subjects comparisons at different points during and after extinction. Their approach is also noteworthy because they consider how differences in baseline (pre-CS) responding may influence responding during the CS. By emphasizing that there are multiple experimental and statistical comparisons that can be used to assess extinction and by examining different response measures (startle and expectancy), Norrholm et al (2008) provide a very thorough and necessarily complex picture of the role of timing in extinction.

Is the reversal of a molecular process evidence for memory erasure?

The absence of behavior can be attributed to many processes besides memory erasure, but perhaps a more persuasive case for memory erasure could be made at the molecular level. Several recent studies have asked whether, under certain circumstances, extinction may reverse the cellular and molecular processes that are initiated by a learning experience (e.g., Kim, et al., 2007; Mao, Hsiao, & Gean, 2006). If it could be shown that the molecular signals that operate during memory consolidation are in fact reversed, this could be taken as evidence that the memory has stopped forming and therefore is erased. Memory consolidation and storage involve the action of many receptor systems, protein kinases, and transcription factors, but the ways in which these signals interact to form long-term memories remains unclear (see Radulovic & Tronson, 2008). In many studies, manipulations that impair memory also impair synaptic plasticity, as revealed through effects on long-term potentiation (LTP) and long-term depression (e.g., Massey & Bashir, 2007).

Recent studies have found that under some circumstances, extinction causes depotentiation, reversing the potentiated neuronal firing observed during LTP. During depotentiation many of the molecular mechanisms underlying LTP are reversed (e.g., AMPA receptors are internalized; protein kinases such as Akt, MAPK, CaMKII are dephosphorylated; see Zhou & Poo, 2004). Mao et al. (2006) showed that learning induced expression of certain AMPA

receptor subtypes (GluR1) within the amygdala was abolished by extinction 1 hr but not 24 hr after auditory fear acquisition. This finding is consistent with extinction soon (1 hr) but not long (24 hr) after acquisition depotentiating the molecular substrates for LTP. In contrast, Kim et al. (2007) found that extinction 24 hr after the acquisition of fear conditioning decreased AMPA receptor expression in amygdala synaptosomes. Although these different findings may be attributed to procedural differences (e.g., extinction strength, molecular preparation) it is still difficult to say when or if extinction reverses certain molecular markers of LTP. Even if we knew with certainty when this occurs, we are still faced with the challenge of demonstrating that this specific process leads to memory erasure.

The question ultimately is a behavioral one: what are the long-term behavioral consequences of decreased AMPA receptor expression in the amygdala and are there ways to think about this other than memory erasure? Synaptic plasticity *in vivo* is controlled through a variety of cellular (e.g., GABA, dopamine, K channels, transporters) and molecular mechanisms (e.g., histone acetylation, actin rearrangement; for review see Kim and Linden, 2007). Although many of these cellular and molecular mechanisms are involved in memory consolidation, we still know very little about how these processes translate into long-term storage of memories (e.g., Kim & Jang, 2006; Shors & Matzel, 1997). Thus, changes among receptors or signaling molecules in one brain region may not be sufficient evidence for the existence (or nonexistence) of a memory. Further, seemingly opposing processes at the molecular level (e.g., phosphorylation and dephosphorylation, protein synthesis and proteolysis) are likely all involved in initial memory formation and extinction. Molecular studies are therefore faced with the same challenges that face behavioral studies: the answer about the existence of a memory may be greatly tied to theoretical assumptions about memory storage and to how questions are experimentally addressed.

Can a whole brain analysis help solve the problem of memory erasure?

Systems analyses reveal the difficulty with isolating the molecular underpinnings of memory storage because memories migrate from one structure to another (Kim and Fanselow, 1992), may be stored in a sensory modality specific manner (Shema et al., 2007), and are likely distributed among different structures (e.g., Gold, 2004). The question for a molecular approach to extinction thus becomes not only when do we look for memory erasure, but also where do we look? This is difficult to answer because activation of a memory stored in one brain region may be inhibited by another brain region during extinction. Using a tool such as functional magnetic resonance imaging (fMRI) during acquisition and extinction permits analysis of a memory's functional signature during extinction. In this regard, a systems level analysis may provide insight into erasure and inhibition during extinction.

There is evidence from studies with people and rodents that the prefrontal cortex (PFC) is involved in extinction and memory suppression. Anderson and Green (2001) found that subjects who were asked to actively suppress memories showed greatly attenuated recall when tested, even when offered monetary incentive for correct responses. The degree of memory suppression correlated with higher fMRI activity in the dorsolateral prefrontal cortex and less activity in the hippocampus (Anderson et al., 2004). Although instruction-based memory suppression may differ from extinction, both processes rely on the PFC to modulate brain regions associated with memory formation, retrieval, and expression (e.g., amygdala and hippocampus; e.g., Milad, et al., 2007; Phelps, Delgado, Nearing, & LeDoux, 2004). The PFC sends inhibitory signals to those regions (e.g., Das, et al 2005; Hariri et al 2003), although these outputs are not always inhibitory in nature (see Quirk & Beer, 2006). A study that determined how differential activation of one region or another is affected by immediate and delayed extinction would be helpful in the context of memory erasure. Monitoring the entire brain with a functional imaging assay may give insight into the presence of a memory at a systems level.

Even so, what if no discernable trace of the memory (inhibitory or otherwise) can be found at the systems level? As with molecular studies, until we know how memory storage maps onto neural activation, this approach by itself is unlikely to provide deeper insight into the conditions that produce memory erasure compared to the other approaches.

Conclusion

Studies like Norrholm et al (2008) that examine basic learning processes in humans are an important bridge between the rodent laboratory and the clinic. Demonstrations that effects on behavior may not correspond to effects on expectancies, such as those reported by Norrholm et al (2008), also suggest that one should be cautious in drawing general conclusions from studies with single measures of performance. This is especially true given that effects of a given manipulation on extinction in rodents may depend critically on many factors, such as the organisms' history with a drug (e.g., Parnas, Weber, & Richardson, 2005), with extinction itself (Kim & Richardson, 2008; Langon & Richardson, 2008), and with the testing conditions (e.g., Lattal, 2007). Extinction effects also depend on unknown factors that control individual differences in rate of extinction (e.g., Norrholm, et al., 2006, 2008; Weber, Hart, & Richardson, 2007).

All of these questions about extinction and memory erasure are unlikely to be resolved without interaction among behavioral, molecular, and systems level approaches. It is clear that many factors must be considered when examining extinction and memory erasure and that the answer to any particular question will depend on experimental comparisons and choice of molecular and systems-level targets. But even within the level of behavioral analysis, the results reported by Norrholm, et al (2008) emphasize the importance of examining multiple measures of learning and performance during extinction and spontaneous recovery testing. If Norrholm, et al (2008) examined only one measure (conditioned responding or expectancy reports), their conclusions would have been very different. By assessing learning and memory in different ways, they ultimately paint a complicated but interesting picture of the conditions that promote extinction and weaken spontaneous recovery (cf., Delamater & Holland, 2008, for a related approach with rodents). Carefully designed and thoughtfully analyzed parametric approaches to the behavioral study of extinction like the ones used by Norrholm, et al. (2008) will ultimately help clarify the conditions under which extinction may be long-lasting, even if it will ultimately prove impossible to demonstrate that a memory has been erased.

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