# Wiping Drug Memories

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help to clear chromosomes from the cleavage plane. Thus, Aurora B lies at the heart of at least two pathways that coordinate chromosome segregation with cytokinesis in yeast and mammalian cells.

How does Aurora B sense trailing chromatin? The NoCut pathway in budding yeast can be activated by ectopically bringing Aurora B into contact with chromatin, which suggests that spatial proximity with chromatin generates the signal to delay abscission (*8*). Another important open question is how collision of the contractile machinery with chromatin causes DNA damage. Is this simply because of physical forces exerted by the contractile machinery or other biochemical processes that are linked to cytokinesis? The mechanism uncovered here (*5*) reveals one way that cells avoid becoming a case for the insurance.


**References**

1. A. Janssen, M. van der Burg, K. Szuhai, G. J. Kops, R. H. Medema, *Science* **333**, 1895 (2011).
2. F. A. Barr, U. Gruneberg, *Cell* **131**, 847 (2007).
3. C. Norden *et al*., *Cell* **125**, 85 (2006).
4. P. Steigemann *et al*., *Cell* **136**, 473 (2009).
5. J. G. Carlton, A. Caballe, M. Agromayor, M. Kloc, J. Martin-Serrano, *Science* **336**, 220 (2012); 10.1126/science.1217180.
6. J. G. Carlton, J. Martin-Serrano, *Science* **316**, 1908 (2007).
7. J. Guizetti *et al*., *Science* **331**, 1616 (2011).
8. M. Mendoza *et al*., *Nat. Cell Biol.* **11**, 477 (2009).
9. Q. Shi, R. W. King, *Nature* **437**, 1038 (2005).
10. T. Fujiwara *et al*., *Nature* **437**, 1043 (2005).
11. N. Nakazawa, R. Mehrotra, M. Ebe, M. Yanagida, *J. Cell Sci.* **124**, 1795 (2011).
12. K. Tada, H. Susumu, T. Sakuno, Y. Watanabe, *Nature* **474**, 477 (2011).
13. F. Mora-Bermúdez, D. Gerlich, J. Ellenberg, *Nat. Cell Biol.* **7**, 822 (2007).


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NEUROSCIENCE

# Wiping Drug Memories

A nonpharmacological approach alters the memory of drug exposure in rats and has implications for treating relapse in human addicts.

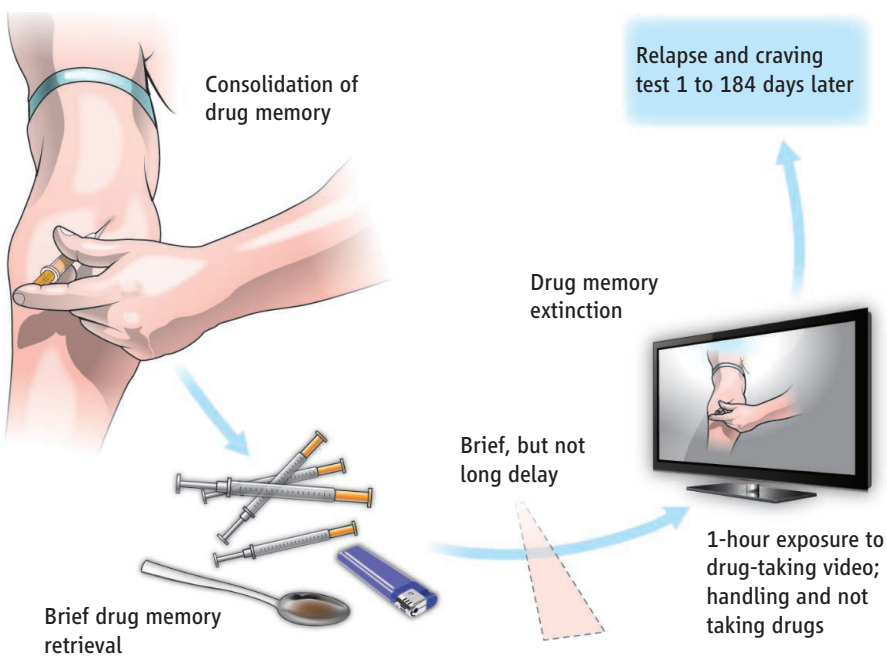
**Amy L. Milton and Barry J. Everitt**

The tendency to relapse in individuals who are trying to remain abstinent is a major, but as yet unrealized, treatment target for drug addiction. On page 241 in this issue, Xue *et al*. (*1*) suggest that the memories elicited by drug cues and contexts can be diminished, thereby reducing their impact on relapse in both animals and people addicted to drugs.

Memories persist through the process of reconsolidation (*2*). When retrieved, a previously consolidated memory can enter a labile state in which new information can be introduced, before the memory restabilizes to persist in the brain, in its new updated form (*3*). By reexposing addicts to drug cues, a process similar to "cue-exposure therapy" (*4*), Xue *et al*. have manipulated the memory-updating process to overwrite the original memory and thereby reduce the risk of relapse in the long term. Rather than solely inducing memory extinction—the formation of a new "cue–no drug" memory that competes with the original "cue-drug" memory—the authors have used "extinction within the reconsolidation window" to reduce drug-seeking. A similar procedure for cue-fear memories has been shown to reduce fear in rats and humans (*5*, *6*).

The authors used two models of drug use in rats that allow associations to form between stimuli (cues) and contexts, and two addictive drugs, cocaine and heroin. In the acute model, rats received injections of either cocaine or heroin in a specific environment or control injections in another environment. Subsequently, their preference for the drug-paired environment, tested when the rats were drug-free, provided a measure of their drug memory. Animals were reexposed to the drug-paired environment to reactivate the cue-drug memory and after a delay of 10 min, 1 hour, or 6 hours, they were exposed continuously to the same drug environment (but given no drug) to engage memory extinction processes. Only in the 10-min and 1-hour groups was subsequent preference for the drug environment abolished, and it did not return even after "reminder" injections of the drug.

This apparent loss of drug memory was also observed in a more complex drug self-administration model, which more




**Decreasing craving and relapse.** A nonpharmacological method that weakens original cue-drug memories can decrease drug craving and relapse in abstinent heroin addicts (*1*). Heroin addicts associate drug cues and contexts with the addictive drug effect, establishing a drug memory. If a heroin addict (who has undergone detoxification) is shown images of drug-associated cues (such as drug paraphernalia) over an extended time period, this engages memory extinction processes, but this procedure does not erase the original cue-drug memory and the cravings can return. However, if the addict undergoes a brief "memory reactivation session" 10 min before extinction, this engages a memory reconsolidation process, which updates the old memory. The result is a greatly diminished "drug memory" later on, and drug cravings are reduced.

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closely approximates addictive behavior in humans. Rats were trained to self-administer either cocaine or heroin, in the presence of drug-associated cues, over an extended period during which cue-drug memories were formed (*7*, *8*). The animals then either underwent only extinction training or received a brief cue-drug memory-reactivation session 10 min before extinction training. When assessed 1 month later, only the group that had received the reminder and extinction showed a reduced tendency to resume drug-seeking behavior following exposure to either drug-associated cues or a reminder injection of cocaine or heroin. Furthermore, although extinction training occurred in a different environment to that of self-administration training, the resumption of drug seeking was reduced in the original self-administration environment. Thus, the usual context specificity of extinction (*9*) was overcome, suggesting that it may be possible to treat individuals in the clinic, with the beneficial effects of the treatment realized in the now-abstinent drug user's environment.

Remarkably, the authors successfully translated the approach of manipulating reconsolidation and extinction to a population of heroin addicts (see the figure). Three groups of patients, having undergone heroin detoxification, were briefly exposed to either a drug-relevant video or a control video followed, 10 min or 6 hours later, by 60 min of heroin cue extinction (they were exposed to imagery and drug paraphernalia, but given no drugs). Subjective craving and physiological responses (heart rate and blood pressure) were measured from 1 to 184 days later. Only the group that had the 10-min delay between the heroin video and extinction showed a marked reduction in craving and blood pressure after presentation of heroin-associated cues at every time point tested.

Although an increasing amount is known about the cellular and molecular mechanisms underlying reconsolidation (*10*, *11*) and extinction (*12*)—e.g., both depend upon activation of *N*-methyl-D-aspartate (NMDA) receptors and intracellular signaling pathways—little is known about the nature of the interaction between reconsolidation and extinction that would explain why the extinction observed in this procedure is so profound and escapes its usual context specificity (*9*). Xue *et al.* point to a possible involvement of the atypical protein kinase C isoform PKMζ, a scaffold protein that maintains α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors in potentiated synapses (*13*) and so may reflect the structural changes in neurons that support a stabilized memory (*14*). Extinction training increased PKMζ expression in the infralimbic cortex, which has long been implicated in the extinction of drug memories (*12*), and this increase was further enhanced by a memory reminder session before extinction training, perhaps strengthening extinction. Likewise, extinction reduced the expression of PKMζ in the basolateral amygdala, an area critical for the reconsolidation of cue-drug memories (*11*), and this was further reduced by a memory reminder session before extinction training, perhaps suggesting impaired reconsolidation. How these changes occur, how they relate to each other, and whether they are causal in the apparent, subsequent amnesia remain to be investigated.

Perhaps the most remarkable aspect of these findings is that the effects of a purely behavioral manipulation in rats that in no sense were "addicted" translate so readily to patients who have been addicted to heroin for more than 9 years. This is especially so considering that even in the animal model with longer, 10-day drug self-administration histories, drug-taking behavior itself was explicitly extinguished, although no analogous process occurs either in the real-world environment of those addicted to drugs, or in the clinical study, in which there was only passive exposure to drug memory–eliciting stimuli. With these conundrums in mind and the obscure molecular mechanism, the findings nevertheless encourage the view that targeting maladaptive memories that play an important role in the persistence of addictive behavior may provide a new avenue for treatment interventions (*15*).


**References**

1. Y.-X. Xue *et al.*, *Science* **336**, 241 (2012).
2. K. Nader, *Trends Neurosci.* **26**, 65 (2003).
3. J. L. C. Lee, *Trends Neurosci.* **32**, 413 (2009).
4. C. A. Conklin, S. T. Tiffany, *Addiction* **97**, 155 (2002).
5. M. H. Monfils, K. K. Cowansage, E. Klann, J. E. LeDoux, *Science* **324**, 951 (2009).
6. D. Schiller *et al.*, *Nature* **463**, 49 (2010).
7. A. L. Milton, B. J. Everitt, *Eur. J. Neurosci.* **31**, 2308 (2010).
8. M. M. Torregrossa, P. R. Corlett, J. R. Taylor, *Neurobiol. Learn. Mem.* **96**, 609 (2011).
9. M. E. Bouton, *Biol. Psychiatry* **52**, 976 (2002).
10. J. L. C. Lee, B. J. Everitt, K. L. Thomas, *Science* **304**, 839 (2004).
11. A. L. Milton, J. L. C. Lee, V. J. Butler, R. Gardner, B. J. Everitt, *J. Neurosci.* **28**, 8230 (2008).
12. K. M. Myers, W. A. Carlezon Jr. M. Davis, *Neuropsychopharmacology* **36**, 274 (2011).
13. Y. Yao *et al.*, *J. Neurosci.* **28**, 7820 (2008).
14. R. Shema, T. C. Sacktor, Y. Dudai, *Science* **317**, 951 (2007).
15. A. L. Milton, B. J. Everitt, *Neurosci. Biobehav. Rev.* **36**, 1119 (2012).


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PSYCHOLOGY

# Monkey See, Monkey Read

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Baboons can distinguish between written words and nonwords.

Reading great literature provides a humanistic approach to understanding one's nature and place in history. Likewise, the scientific study of the biological bases of reading may provide insights into the origins of human cognition. On page 245 of this issue, Grainger *et al*. (*1*) show that these biological mechanisms may be rooted much deeper in human evolutionary history than previously supposed (see the first figure).

Biological approaches to cognition propose that specialized neural modules evolved to solve specific problems encountered in the physical or social environment, such as identifying and remembering the faces of the members of one's group. However, reading and writing appeared too recently and spread too rapidly within and between populations to have required genetic changes to support it. In a striking example, the writing system for Cherokee, a previously unwritten language, was invented in the early 19th century, and was widely learned and used in Cherokee society within one generation (*2*). Clearly, reading is supported by neural mechanisms that are much older than the behavior itself and that presumably evolved before the human diaspora from Africa.

Ultimately, reading depends on language. But at what stage in the process of translating written symbols into meaning is language necessary? Some insight is provided by the observation that animals can learn to discriminate letters from one another; pigeons even seem to do so in a manner resembling

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