



Drug Addiction and the Hippocampus

Joshua D. Berke, *et al.*
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Drug Addiction and the Hippocampus

Vorel *et al.* (1) reported that stimulation of the hippocampus at theta frequency caused reinstatement of drug-taking behavior, in rats that had learned to lever-press for cocaine and subsequently had had this behavior extinguished by substituting saline for cocaine. They suggested that the hippocampal stimulation may cause a “read-out of an encoded association between the context of the cocaine experience” and the cocaine. In an accompanying news article (2), the lead author was quoted as claiming to have “anatomically located the relapse circuits in the brain.”

Although the Vorel *et al.* study is useful, we suggest that an alternative interpretation could be more likely. We question whether simultaneous activation of massive excitatory pathways in the hippocampus is likely to have produced “read-out” of a pattern of neural activity that represents a specific learned association. Further, the hippocampus would be expected to repeatedly enter theta rhythm spontaneously while the animal is in the testing chamber (3). If the key context is present, why would the association not be utilized even without the stimulation?

It has long been established that the hippocampus has an important role in inhibiting previously acquired and now irrelevant responses, among other functions in organizing memories (4, 5). Interfering with hippocampal function can increase behaviors that are not hippocampus-dependent (6). Thus, rather than provoking read-out of a specific learned association, the hippocampal stimulation may have reinstated drug-taking behavior by disrupting the hippocampus’s role in inhibiting the newly irrelevant lever-pressing behavior. In this interpretation, the key hippocampal contribution would be to provide the “memory” of the extinction of the lever-pressing, not the original lever-pressing behavior itself. Although the authors performed stimulation at a different frequency (2 Hz) as a control, this less physiologically relevant frequency may simply have caused less disruption to normal hippocampal function. An important additional control might be pharmacologic inactivation of the hippocampus, which, in our view, would be equally likely to block the hippocampal contribution.

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Response: Berke and Eichenbaum interpret our finding (1) as inactivation of the inhibitory role of the hippocampus in behavior. The proposed inhibitory role is largely based on lesion studies (2). However, electrical stimulation of the hippocampus has similar effects to chemical activation with the excitatory amino acid *N*-methyl-D-aspartate (NMDA). Both electrical (3, 4) and NMDA (5, 6) stimulation induce long-lasting dopamine (DA) release in the nucleus accumbens (NAC). In contrast, pharmacological inactivation of the hippocampus blocks DA release in the NAC during novelty exposure (7). Both electrical (4) and NMDA (5, 6) stimulation enhance locomotor behavior. Electrical stimulation therefore seems to represent activation, not inactivation, of hippocampal function. It remains to be seen whether NMDA stimulation of the hippocampus induces cocaine-seeking behavior.

Another question raised in the comment is whether activation of massive pathways in the hippocampus could produce the read-out of a learned association. However, theta activity during approach behavior is widespread and synchronized throughout large domains of the hippocampus (8). Moreover, large hippocampal areas are involved in the retrieval of specific associations (9).

Berke and Eichenbaum suggest that the hippocampus will repeatedly enter theta rhythm spontaneously while the rat is in the testing chamber. Theta rhythms occur just prior to and during voluntary movements (10) and approach behavior (8, 11). During extinction, lever pressing and goal-directed behavior progressively diminish. Correspondingly, theta activity disappears under extinction conditions (8, 12).

The authors of the comment also wonder

why the association is not utilized even without the stimulation although the key context is present. During cocaine self-administration, excitatory associations are formed between the operant chamber and cocaine. During extinction, inhibitory associations are formed, and responding becomes suppressed. Thus, two associations are formed between the context and cocaine. After extinction the inhibitory, not the excitatory, association is utilized (13).

Finally, Berke and Eichenbaum propose a pharmacological inactivation experiment that seems useful to test their hypothesis (2) that normal hippocampal function inhibits lever-pressing behavior and that the hippocampus provides the “memory” of extinction. Moreover, the experiment seems feasible, because muscimol has been used to pharmacologically inactivate the hippocampus in a conditioned-fear experiment (14). However, inactivation did not disinhibit conditioned fear responding (14), as an inhibition hypothesis of hippocampal function (2) would predict. Rather, responding was suppressed, and the “memory” of extinction was generalized to different contexts (14).

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