Biological Psychiatry

Commentary

Evidence That Compulsive Reward Seeking Has Been Hiding in the Central Dorsal Striatum

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Actions are considered compulsive when individuals feel a strong desire to perform them repeatedly, often persevering despite negative consequences. An individual who experiences compulsions in the form of substance use disorder, for example, will typically continue to seek the desired substance despite adverse health, financial, and social consequences. Preclinical research has become increasingly sophisticated in its quest to mimic this process, with recent changes to it including a push to incorporate animals of both sexes, as well as steps taken to address the artificial conditions of experiments that encourage compulsive-like drug seeking in all animals as in reality only a fraction of individuals experience compulsions. Adopting such practices in animal research is important, as it permits the accurate probing of the underlying neural mechanisms of compulsive-like actions in a manner that is not viable in human studies.

Such an approach is exemplified in the current issue of *Biological Psychiatry* by Harada *et al.* (1), who report a series of elegant experiments conducted in both male and female mice in which they isolated the role of the lateral orbitofrontal cortex (lOFC) and central dorsal striatum (cDS) circuitry in compulsive-like behavior. In contrast to their previous experiments (2), Harada *et al.* (1) used a seeking-taking task, in which responding on a seeking lever gave access to a taking lever that procured rewarding brain stimulation. On a subset of trials, reaching a sufficient number of seeking presses probabilistically led to a footshock punishment instead of the taking lever. The authors found that just as not all humans exposed to rewarding substances will go on to seek them compulsively, approximately 40% of mice ceased to press the seeking lever once they were punished. The authors labeled this group "renouncers." In contrast, the remaining 60% continued their seeking behavior despite potential punishment and were labeled "perseverers" (Figure 1A). To investigate the corticostriatal circuitry underlying these individual differences, Harada *et al.* (1) first demonstrated that the cDS, medial DS, and lateral DS (lDS) receive largely independent projections from different regions of the cortex. These anatomical patterns were reflected in the functional relationships observed using optogenetic activation of each pathway, but only the lOFC-cDS pathway showed a significant increase in synaptic strength (i.e., AMPA/NMDA ratio) in perseverers compared with renouncers and naïve mice.

Having isolated the lOFC-cDS circuit, Harada *et al.* (1) then examined real-time activity during punished sessions using fiber photometry in the cDS. Prior to punishment exposure, heightened cDS activity was observed in all mice when the seeking lever retracted, presumably because this provides a critical cue that the seeking period is over and a reward is imminent. Intriguingly, this response was enhanced to a greater extent in mice that would later be clustered as perseverers, suggesting that either 1) compulsion is already present in perseverer mice or 2) enhanced cDS activity could be an early indicator of the propensity for future compulsive behavior. Moreover, only perseverers continued to show this response during seeking lever retraction once punishment was introduced, with renouncers showing a significant reduction in cDS activity compared with their prepunishment responses (Figure 1B). Although it is not clear whether perseverers and renouncers differed in their response to punishment itself, likely because renouncers received very few punishments, the neural activity of each group did not differ in any other phase of the task.

Given their earlier electrophysiological findings implicating the lOFC-cDS pathway, Harada *et al.* (1) next used chemogenetics to inhibit the lOFC while conducting photometry recordings in the cDS of perseverer mice. They found that lOFC inhibition decreased compulsive-like behavior, which consequentially reduced cDS activity in a manner that was correlated with the reduction in completed trials. Finally, they optogenetically inhibited the cDS during seeking lever retraction in perseverer mice in the final punishment sessions. This transiently reduced seeking presses, with mice returning to compulsive-like pressing when inhibition ceased, suggesting that the cDS may act in a highly dynamic manner when risking punishment to seek rewards. Importantly, optogenetic inhibition of the cDS did not influence performance when applied during baseline sessions, again suggesting a critical role for this pathway in compulsive-like reward seeking rather than a general role in reward seeking.

Overall, this study heralds several contributions to the published literature, with one of the most important being its demonstration of the unique specificity of the lOFC/cDS regions in compulsive-like action relative to other corticostriatal pathways. Previous studies have highlighted the role of the DS, and particularly the lDS, in the transition to habitual and then compulsive drug seeking (3). Here, however, Harada *et al.* (1) show that the difference between perseverers and renouncers was not in the lDS but instead in the cDS—a relatively understudied component compared with the vast published literature on the medial DS and lDS. New tools that allow pathway-specific manipulations are likely to continue to split the striatum into nonconventional subdivisions based on cortical inputs, and this will lead to a more complex but also a more precise understanding of corticostriatal functions.

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https://doi.org/10.1016/j.biopsych.2021.10.003
Biological Psychiatry December 15, 2021; 90:800–802 www.sobp.org/journal
ISSN: 0006-3223

Biological Psychiatry

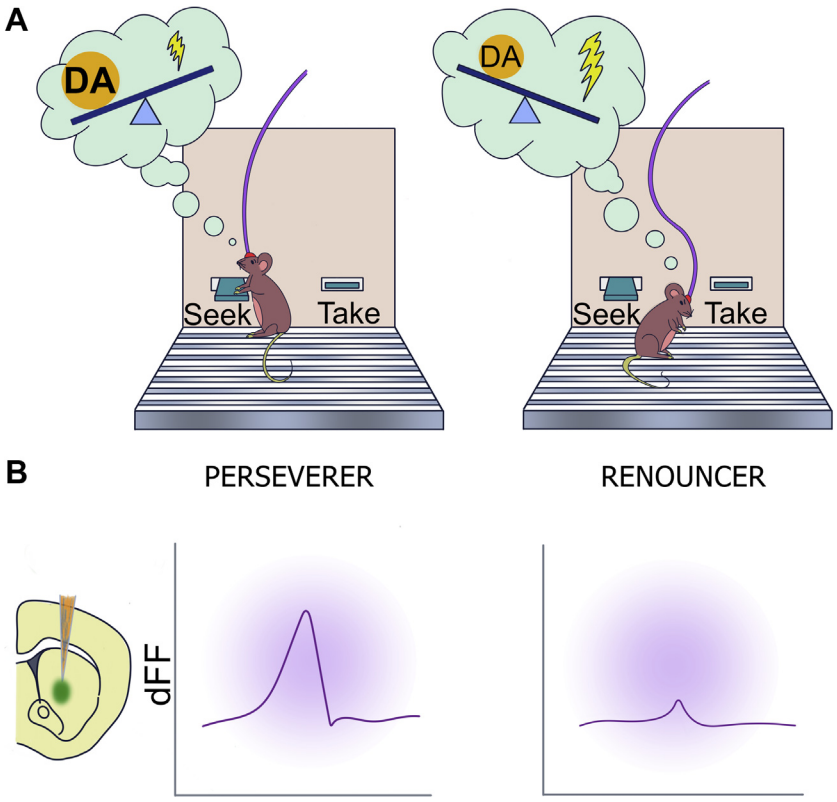

Figure 1. **(A)** Perseverers (left) continue to press the seeking lever once a footshock punishment is introduced, whereas renouncers (right) cease to press this lever. Mice are represented as weighing the potential outcomes of pressing the seeking lever, rewarding stimulation of dopamine (DA) neurons versus a footshock punisher. **(B)** A representation of central dorsal striatal activity in perseverer mice (left), where activity continues to increase in response to retraction of the seeking lever, and in renouncer mice (right) where activity reduces once punishment is introduced. dFF, normalized fluorescent responses.

Another important aspect of the results reported by Harada *et al.* (1) is their confirmation of earlier findings that the lOFC-cDS circuit is key to compulsive-like behavior. Despite the fact that, as mentioned above, this pathway has been somewhat overlooked compared with other corticostriatal pathways, it has been identified in at least 2 previous studies of compulsive-like action: one by the same authors (2), and another by Burguiere *et al.* (4). The findings of this latter investigation are particularly notable, as they showed that optogenetic stimulation abolished rather than facilitated compulsive grooming in *Sapap3*-mutant mice (i.e., mice lacking SAPAP3). This apparent contrast to both current (1) and previous (2) findings is no doubt due to the numerous methodological differences between each study, and it will be important for future research to disentangle these. Nevertheless, it is notable that both hyper- and hypoactivity of regions homologous to the OFC and DS has been observed in humans with compulsive disorders, suggesting that either or both could be related to compulsivity.

One recent neuroimaging study that specifically investigated the homologous lOFC-caudate pathway in humans suggested that its functional connectivity is indeed enhanced in people with substance use disorder relative to matched individuals that did not have this disorder (5). This provides some translational validation to the findings of Harada *et al.* (1). If we were to assume that other aspects of Harada *et al.*'s (1) are similarly translatable, then they could further imply that this pathway is particularly relevant to compulsive seeking rather than taking behavior or reward processing. That is, the seeking–taking task separates the delivery of punishment and reward to the seeking and taking lever presses respectively, and only one outcome is delivered on a given trial. This arrangement avoids the conflict that would occur if a single action could lead to reward or punishment, or if they occurred in close temporal proximity, which could lead to reevaluation of the reward's value (e.g., counterconditioning). Using this task allowed Harada *et al.* (1) to effectively isolate the roles of lOFC and cDS to seeking behavior, which could imply that this pathway mediates aspects of craving and/or preoccupation with sourcing access to drugs (i.e., seeking), which are cardinal features of compulsive substance use that are separable from the immediately rewarding effects of drug taking (3). Having now isolated these effects to the seeking phase, it will be useful for future studies to determine if perseverer and renouncer mice also differ in their general suppression of responding under punishment, or with a reduction in reward probability alone, given that these may be components of reduced seeking [see Pelloux *et al.* (6)].

In summary, the findings by Harada *et al.* (1) represent an important step forward for the field in our understanding of the role of the lOFC-cDS pathway in compulsive reward seeking, with regard to the specificity of both the pathway and the behavior. However, they also lead to new questions for future research. For instance, it is clear from multiple neuroimaging studies in humans that there are many other brain structures and pathways involved in compulsive reward seeking, and it will be of interest to determine how they might interact with the lOFC-cDS pathway to produce compulsion. One example can

be derived from the neuroimaging study by Oh *et al.* (5), which highlighted the importance of the interaction between this pathway and the habenula, a brain region notable for its role in aversive prediction error. Because of the difficulty in inferring causality from human neuroimaging studies, it would be interesting to follow this up in an animal study to determine whether the habenula is indeed interacting with this circuit to produce compulsive-like actions. Finally, because compulsivity is a complex, umbrella phenomenon that captures many heterogeneous forms of compulsive action, from persistent drug seeking and taking to excessive washing, checking, and hoarding, it would be useful to know whether activity in the lOFC-cDS pathway is also causally related to other forms of compulsivity or compulsion-like behaviors in animals.

Acknowledgments and Disclosures

This work was supported by National Health and Medical Research Council of Australia Early Career Fellowship Grant No. 1122221 (to KMT) and Australian Research Council Discovery Project Grant No. 200102445 (to LAB).

The authors report no biomedical financial interests or potential conflicts of interest.

Article Information

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Received Oct 5, 2021; accepted Oct 6, 2021.

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