Cortical Regulation of the Ability to Resist Temptation for Punishment-Paired Alcohol

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Compulsion-like motivation for intoxicants, where intake persists in the face of known negative consequences, is a major contributor to human addiction (1,2), and there is considerable interest in understanding the molecular and brain circuit mechanisms that drive this pathological behavior. While there are different conceptualizations of compulsion [as discussed by Lüscher *et al.* (1) and Hopf (2)], one widely used animal model is the willingness to respond for an intoxicant even when paired with an acute negative event such as footshock. There is some question about whether resistance to acute punishment correctly models human compulsion, especially since negative consequences for humans with addiction often occur in the future rather than at the same time as procuring/consuming an intoxicant. However, it is also likely that people who are seeking treatment will experience possible negative outcomes much more acutely—for example, where the thought of losing one's job or family comes to mind at the same time one looks at the whiskey bottle and struggles with the decision to drink or to not drink. In addition, studies of punishment-resistant responding for alcohol in rodents (3,4) and human heavy drinkers (5) implicate a similar insula, medial prefrontal cortex (mPFC), and nucleus accumbens (NAc) circuit, suggesting that a common brain system can mediate compulsion-like responding across species. These regions are central to the salience network and are involved in responding to high-importance events (including overcoming a challenge to get a desired reward), and an increasing body of literature suggests that brain regions linked to regulating the salience network are important mediators of compulsion-like addictive drives (6).

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In addition to a willingness to respond despite adversity, it is equally important to understand the mechanisms that allow negative consequences to suppress addictive drives. Indeed, these likely contribute to self-control mechanisms, and one goal of human therapy is to strengthen such processes to help people with addiction to maintain abstinence. In this regard, work from Halladay *et al.* (7) in this issue of *Biological Psychiatry* provides important new insights on how specific prefrontal cortical connections are able to reduce responding for alcohol when punishing shocks are possible. After days of lever pressing for alcohol, mice had one session where every other press of the alcohol-paired lever delivered a shock, which greatly decreased responding. In a probe trial the following day, no shocks were delivered but animals continued to avoid pressing the alcohol lever. Of particular interest, Halladay *et al.* (7) identified events where a mouse stretched its body toward the alcohol-paired lever but then retracted its body, suggesting that the mouse initiated but then aborted a possible alcohol response. This abort response may correspond with "exerting self-control in the face of temptation," and thus the authors first examined neuronal activity in the ventral and dorsal parts of the mPFC (ventromedial PFC [vmPFC] and dorsomedial PFC [dmPFC], respectively) to uncover how these regions may contribute to suppressing responses for alcohol in order to avoid shock.

Importantly, a population of vmPFC neurons shows strong encoding before and during abort events, during both the shock-paired session and the subsequent probe trial. Another separate population of vmPFC neurons fires for alcohol lever presses, which disappears during the session with actual punishments. Thus, different populations of vmPFC neurons fire in association with reward-directed action or with preventing action. This agrees overall with previous work implicating the vmPFC for reward value and also showing that the vmPFC has different ensembles of neurons that act for and against reward-seeking action [see references in Halladay *et al.* (7)]. Thus, the vmPFC is an interesting area in its encoding of reward value across different reward domains, which is associated with reward-directed action. At the same time, some vmPFC neurons encode behavioral suppression. This could reflect the positive (or "reward") value of avoiding a negative outcome, and while this use of reward may extend

beyond what is typically considered reward, it may be ethologically more relevant when considering how positive and negative anticipated outcomes impact chosen action. It is also interesting that the vmPFC encodes abort responses and that vmPFC lever press firing disappears during the shock-pairing session. Thus, both changes in vmPFC activity (gain of abort-related firing, loss of lever press firing) are consistent with an overall goal of not responding in order to avoid the negative shock.

While firing patterns are of great interest, the authors next examined the causal importance of the vmPFC for controlling shock-related suppression of alcohol responding. They use a closed-loop optogenetics system, where vmPFC cell activity is inhibited (by activating ArchT [archaerhodopsin T]) only when mice are near the alcohol lever. While control, green fluorescent protein–expressing mice still show reduced alcohol lever presses in the postpunishment probe trial, optogenetic vmPFC inhibition with ArchT restores lever pressing for alcohol even when shock is expected. Thus, vmPFC activity seems necessary for the expression of shock-related response suppression. In contrast to the vmPFC, dmPFC firing patterns were less related to abort and lever pressing, and optogenetic inhibition of the dmPFC did not alter avoidance of punished responding, suggesting that self-control in the face of shock involves the vmPFC but not the dmPFC, although the authors do note the possibility that a smaller population of dmPFC cells may encode reward avoidance (6).

The central question is the connection between vmPFC firing and specific behaviors. Indeed, there is some complexity in the authors' findings. Inhibiting the vmPFC restored lever pressing for alcohol but did not alter the number of abort responses or time spent near the alcohol lever. Thus, the observed abort-related vmPFC firing seems to not mediate the actual abort response or the drive to approach the alcohol-paired lever. Instead, their findings suggest that another brain region mediates aborts and lever approach, while vmPFC abort-related firing serves to suppress the final reward-paired action—the lever pressing for alcohol. Interestingly, control studies show that the vmPFC had no impact on behavior when animals were never subjected to punishment, suggesting that the vmPFC is specifically important for regulating behavior under conflict (discussed in more detail below).

Another wrinkle is that some vmPFC neurons fire for lever press responses, and yet inhibiting the vmPFC increases lever pressing in the shock-suppression context. This may be an important reminder that neuronal activity can change for a specific behavioral event but that there is likely to be redundant neuronal firing. The brain may not be able to prevent widespread, redundant firing, even though only particular brain areas are necessary for behavioral expression. Another possibility is that firing occurs in a given brain area as information about what is happening, in case the individual finds himself or herself in a particular context where that firing information is needed to decide on the course of action (as opposed to a context where the information is not necessary to decide on the course of action) (8). However, one other caveat is that global inhibition of a brain area may introduce its own complexities, especially if there are proaction and antiaction neurons in an area and both are inhibited, resulting in no net change in behavior [discussed in Hopf (2)].

In this regard, the authors next examined the importance of specific vmPFC projections for withholding alcohol responding after punishment. Optogenetic inhibition of vmPFC inputs to the shell region of the NAc (NAcS) (partially) restores lever pressing for alcohol without changing the number of aborts or time near the alcohol lever, which is similar to the effects of vmPFC inhibition. However, inhibiting vmPFC connections with the amygdala did not alter suppression of alcohol responding. Furthermore, probe testing primarily induced *fos* expression in NAcS D_1 receptor– but not D_2 receptor–expressing cells, and brain slice electrophysiology shows a change in glutamate receptor function in D_1 cells but not D_2 cells in the NAcS. Thus, the ability to suppress responding to avoid punishment involves specific vmPFC projections to the NAcS and may involve synaptic plasticity in this projection.

Together, the authors present interesting and important findings that help define and constrain the contribution of the vmPFC and particular projections to withholding responses in the face of punishment. Interestingly, in addition to mediating responses suppression in (7), the vmPFC also encodes and mediates expression of habit action despite reward devaluation (9,10). As mentioned above, the vmPFC may be part of the final mechanism for actions of greatest subjective value in a given context. Thus, it

would useful to directly compare, side by side, vmPFC encoding and contribution to punishment-sensitive and punishment-resistant behavior, which could directly test the hypothesis that the vmPFC mediates subjective importance as the context changes. It is also interesting that Halladay *et al.* (7) found that vmPFC inhibition has no effect in the absence of conflict. This may suggest that behaviors requiring the vmPFC involve some level of conflict or ambivalence, which may be clear in some cases (e.g., extinction of learned reward seeking) but less clear in other cases. Indeed, one central question we struggle with is whether the intake of alcohol or other intoxicants involves some level of ambivalence, even when consumption is not explicitly paired with negative consequences, while intake of a natural reward like sucrose may lack this basic ambivalence. More generally, this study underscores the importance of the vmPFC for encoding and regulating critical aspects of reward-directed action.

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