Commentary

Patterns of Neural Responses, Pavlovian-to-Instrumental Transfer, and Prediction of Relapse

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The ability to predict susceptibility to drug relapse for people with substance use disorders is a kind of holy grail that is often hoped for but difficult to achieve. In this issue of *Biological Psychiatry*, Sekutowicz *et al.* (1) creatively combine multivoxel pattern analysis of brain imaging patterns with exposure to a behavioral conditioning procedure (Pavlovian-to-instrumental transfer [PIT]) to achieve such an aim. Moreover, these methods were able to make a prediction on future patterns of drinking in young adults without dependence.

A widely accepted tenet in the field of psychopharmacology is that cues associated with drug use can instigate drug relapse (2). Such ideas reflect the influence that concepts and methods derived from the field of the experimental analysis of behavior have had on modern theory and research into substance use and abuse. Conceptualized in this way, drug seeking is an instrumental (or operant) behavior that is reinforced by drug delivery and consumption (i.e., the consummatory or "taking" phase). Thus, patterns of drug seeking and taking can be considered analogous to a rat pressing a lever for food reinforcement in an operant chamber. Likewise, stimuli that signal drug delivery or predict drug availability can act as Pavlovian conditioned stimuli, analogous to the tuning fork in Pavlov's classic experiments. Though instrumental and Pavlovian conditioning have different characteristics, they often occur together in the same environmental context and clearly interact with each other. One manifestation of this interaction is that Pavlovian-conditioned stimuli previously associated with a reinforcer can act to instigate and invigorate instrumental responding, a phenomenon known as PIT (3). Basic behavioral neuroscience research with animals has characterized the involvement of a series of interconnected brain circuits, including mesolimbic dopamine, the nucleus accumbens, and dorsal the striatum, as well as the basolateral and central amygdala, in PIT (4–9). In addition to these studies highlighting the role of subcortical circuits in PIT, some studies also have identified a role for the infralimbic prefrontal cortex (10).

Sekutowicz *et al.* (1) attempted to determine if neural responses during exposure to PIT conditions in humans could provide a predictive biomarker for future drinking behavior. They studied a group of detoxified alcohol-dependent patients as participants and used functional magnetic resonance imaging (fMRI) and multivoxel pattern analysis to predict future relapse based on brain activation patterns induced by PIT exposure. Multivoxel analysis was used because it provides more complete information about the patterns of brain activity, and based on previous research it was hypothesized that this analysis would be relatively sensitive in detecting individual differences. It was hypothesized that this imaging analysis of

PIT-induced activation patterns would successfully discriminate between future behavior in terms of relapse versus abstinence.

The particular PIT procedure used could be classified as a form of general, rather than specific, PIT. Specific PIT is said to occur when a conditioned stimulus is paired with the same reinforcer as that used for reinforcing the instrumental response, while general PIT procedures involve pairing the conditioned stimulus with a different reinforcer. The behavioral procedures are explained in detail in Sekutowicz *et al.*'s (1) Supplement. Briefly, participants were separately trained on an instrumental task that involved button pressing to collect shells that were ultimately transferable for a monetary reward. The primary stimulus conditions used for assessment of PIT consisted of alcohol-associated stimuli, in which the Pavlovian cues consisted of pictures of alcoholic and nonalcoholic beverages. There was no specific Pavlovian training for this, because all participants had a history of alcohol use disorder and therefore had already experienced considerable exposure to alcohol-related cues. In fact, this presumption is what makes this PIT condition fit the description of general PIT, because it is assumed that the original unconditioned stimulus predicted by the alcohol-related cues was alcohol itself, while monetary reward was used in the actual PIT experiment. The particular cues used for the alcohol PIT condition were beverage-related stimuli (either pictures of a favorite alcoholic drink or pictures of water as a control). The effects of presentation of the alcohol- versus water-related cues on instrumental behavior (i.e., PIT sessions) were assessed during fMRI imaging sessions. Moreover, the effects of the beverage-related PIT stimuli were compared with those obtained using a monetary-based PIT (i.e., using monetary Pavlovian conditioning of a compound fractal tone stimulus).

The primary goal of this study was to determine if neural PIT responses would be able to predict future relapse in alcohol-dependent patients who underwent detoxification. The results supported the hypothesis that fMRI neural responses gathered during the PIT session could accurately predict future relapse, reliably discriminating between patients that relapsed in the future and those who did not. The prediction of relapse was almost completely based on neural activation patterns observed in the medial prefrontal cortex during alcohol-related PIT. The medial prefrontal cortex is a region that is known to be involved in cognitive control, executive function, behavioral inhibition, impulsivity, and other behavioral functions related to substance abuse. Other brain areas that were regions of interest, including the nucleus accumbens, which has been implicated in aspects of PIT and various drug use phenomena,

were not significantly related to future relapse as identified by these procedures. In order to provide control subjects for the alcohol-related PIT condition, Sekutowicz *et al.* (1) attempted to see if the monetary PIT condition that was done in a parallel experiment could also predict future relapse. In fact, this condition was not a significant predictor of future relapse, and as described in their Supplement, other factors, including demographic, clinical, and neurocognitive variables, did not reliably distinguish between people who relapsed and people who did not. There appears to be some degree of specificity in the ability of this particular alcohol-related PIT condition to instigate prefrontal cortex neural responses that are predictive of future relapse.

Perhaps most interestingly, an additional aspect of this study determined if PIT-related neural activation patterns could serve as a biomarker for future drinking behavior in people who were not diagnosed with alcohol dependence. Therefore, the imaging classifier that was identified as predicting relapse in patients with alcohol use disorder also was used to predict future drinking behavior a separate group of young social drinkers. These participants were young male social drinkers, and in this case these individuals did not meet the diagnostic criteria for alcohol dependence. For this study, it was hypothesized that if PIT activation patterns could be a useful biomarker for prediction of future drinking in people diagnosed with alcohol use disorder, then the same classifier might be able to make predictions about future drinking in nondependent individuals. Importantly, it was observed that young social drinkers who were classified as future abstainers showed a greater reduction in alcohol consumption during a 12-month follow-up than those who were classified as individuals with a potential for future relapse.

Sekutowicz *et al.*'s (1) conclusions have several important implications for researchers and clinicians in the field of substance abuse. First, they provide results that are consistent with the known involvement of the prefrontal cortex in substance abuse disorders, including factors related to relapse (2,10). Second, they provide important support for the idea that responsiveness to drug-related cues is a critical factor in relapse. Finally, and most importantly, they offer evidence indicating that fMRI responses obtained during PIT involving alcohol-related cues could provide a prognostic biomarker for future drinking behavior, specifically including the likelihood of relapse. This information could be useful for predicting risk for relapse in patients undergoing treatment and could also predict susceptibility to excessive alcohol consumption in people who are not currently dependent on alcohol. Such a biomarker, if validated by future studies, could prove to be an invaluable tool that would greatly enhance relapse prevention in clinical treatment.

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