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Viewpoint

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Sensation within the Skin

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ABSTRACT: This Viewpoint emphasizes interoceptive discriminative stimulus modulation of voluntary operant behavior (a la B. F. Skinner), rather than elicitation of Pavlovian conditioned reflexes. In doing so, I will restate how the operant drug discrimination paradigm may not only elucidate smoking and other addictive behaviors but also anxiety (Troisi, J. R., II. (2003) Spontaneous recovery during, but not following, extinction of the discriminative stimulus effects of nicotine in rats: Reinstatement of stimulus control. *Psychol. Rec.* 53, 579−592).

KEYWORDS: *interoception, nicotine, drug discrimination, cue exposure therapy, reinforcer devaluation, motivating operations*

In their mini-review, *Interoception and Learning: Import to Understanding and Treating Diseases and Psychopathologies*, Drs. Rick Bevins and Joyce Besheer[2] (B&B) note that interoceptive Pavlovian conditional stimuli (CSs) play important roles in tobacco abuse (smoking) and anxiety (e.g., panic disorder). B&B briefly summarize Pavlov's work on conditioned reflexology in noting interoceptive involvement mediated by the insular cortexes. Attention is then called again to the work of Pavlov and Bykov who first investigated interoceptive CSs. To be sure, drug effects (e.g., nicotine) function as Pavlovian USs in promoting interoceptive changes in the nervous system. Certainly, conditioned "fear" to exteroceptive CSs established with aversive USs (e.g., foot shock for rats) has been a staple assay for studying classical conditioning. B&B focused first on data from Dr. Bevins' lab that demonstrated Pavlovian CS effects of nicotine in rats. They then summarized studies showing how a brief duration exposure to CO_2 can methodologically function as a CS for a longer duration CO_2-unconditional stimulus (US) in eliciting anxiety. While the latter of these examples is compelling, the former deserves more attention for its clinically translational importance.

SMOKING

Smoking behavior, at least in part, is maintained by its consequences, that is, nicotine; it is voluntary behavior and, hence, operant in nature. B&B's eventual focus concerns how nicotine can function as an interoceptive Pavlovian CS in rats in discriminated "goal-tracking" procedures that utilize liquid sucrose as a US. Remarkable and quite informative neurochemical drug substitution tests have been conducted over the years by Dr. Bevins' lab showing central specificity of the nicotine CS at the $\alpha_4\beta_2$ nAChR receptor, as extensively shown in studies with the two-lever operant drug discrimination method. In a 2003 investigation, this author[1] noted that the interoceptive discriminative stimulus (S^D) effects of nicotine might provide an effective paradigm for simulating how other interoceptive stimuli might gain control in modulating voluntary operant behavior maintained by drug reward. That investigation proposed that the interoceptive nicotine stimulus (or alcohol stimulus) might evoke responsiveness to operant discriminative stimuli, and the behaviors they occasion, in smoking and alcohol consumption. The clinical literature on cue-exposure therapy (a Pavlovian-based behavioral extinction approach used for drug abuse treatment, which has failed[3]) was also acknowledged because that investigation was the first to demonstrate extinction of responding under the interoceptive S^D effects of nicotine.

B&B provided a hypothetical vignette of an individual (i.e., Jill) who smokes a cigarette following a 5 day withdrawal period. Jill sees a cigarette pack, pulls out a cigarette, requests a light, places the cigarette on her lips, ignites the cigarette, and deeply inhales. The interoceptive "subjective" effect of the nicotine abates Jill's "mental fog" that has been present for 1 week. B&B then immediately juxtaposed the external stimuli in Jill's smoking repertoire with Pavlov's CS buzzer. A more recent review paper[3] provided similar, and extensive, hypothetical human examples with regard to interoceptive modulation of drug-seeking and taking behavior (e.g., alcohol, crack cocaine, and heroin). There, it was emphasized that drug-seeking and drug-taking represent extended chains of topographically different operant behaviors linked by exteroceptive S^Ds and conditioned reinforcers (not Pavlovian CSs) and eventuate in either the positive reinforcing ("pleasurable" interoceptive effect) or negative reinforcing (elimination of an aversive interoceptive state) effects of the drug. These extended behavioral chains *can* be evoked by other antecedent interoceptive states (e.g., anxiety, fear, or other drug states) that *can* function as interoceptive S^Ds or motivating stimuli and hence modulate responsiveness to exteroceptive S^Ds within the chain.[1,3,4] Dissecting the functional roles of interoceptive Pavlovian and operant stimuli is paramount for interpreting drug-related behavior (i.e., smoking in this instance).[3] B&B's vignette of Jill exemplifies how exteroceptive operant S^D's occasion sequences of behaviors maintained by drug-reward. Jill's nicotine withdrawal represents an aversive interoceptive "subjective" state that temporarily *increases the value* of nicotine (a motivating operation) for the reduction of the nicotine withdrawal. Therefore, it seems that nicotine temporarily

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functions as a *valued* operant negative reinforcer in B&B's vignette—not as an interoceptive Pavlovian CS.

The general claim from Dr. Bevins' lab has been that investigation of the interoceptive Pavlovian CS effects of nicotine may be important for understanding nicotine abuse and its treatment. However, to date, no studies have shown that a brief or small dose of nicotine can function as a CS for a subsequently administered larger dose of nicotine US (but see ref 1). If the interoceptive nicotine CS regulates behavior related to the nicotine operant reinforcer or Pavlovian US, a study addressing this hypothesis is warranted. In fact, nicotine S^Ds modulate operant responses far greater than nicotine CSs (as cited in ref 3). Nevertheless, B&B have noted extensively that the interoceptive Pavlovian nicotine CS might be important for evoking voluntary responses to exteroceptive stimuli that are related to smoking and drinking—as previously noted by the present author.[1] They summarized a study from Dr. Bevins' lab in which the CS effects of nicotine for a liquid sucrose US was undermined by devaluation of the sucrose with LiCl (an emetic). Interestingly, in a prior study by the present author,[4] nicotine functioned as an operant S^D that occasioned nose poking for food reward in food restricted rats. Rats were then satiated by providing unlimited food in their home cages. Responsiveness decreased substantially (i.e., reinforcer devaluation) and extinction of nose poking rates decreased to zero-levels. When the rats were food restricted again (reinforcer revaluation), responsiveness to the counterbalanced nicotine S^D increased dramatically and discriminative control re-emerged, thus showing a relapse-like behavior to nicotine. That study noted how overlapping interoceptive stimuli likely interacted with the nicotine S^D (e.g., satiety mechanisms, hormonal changes, stomach distention), and posited that "hunger" and satiety likely entered into a conditional interoceptive stimulus relationship with the presence and absence of the nicotine S^D. These findings are in parallel to drug replacement therapy. For example, methadone or nicotine replacement (e.g., varenicline) only temporarily devalues the reinforcing effects of opiates and tobacco. A similar investigation was carried out in my lab with a heterogeneous chain that was modulated by the nicotine S^D and an exteroceptive light S^D that linked two different responses. When one chain was extinguished with saline, the opposing chain of behavior recovered when nicotine was readministered. These studies support previous claims[1] that the operant drug discrimination procedure with nicotine may be clinically translational for showing how interoceptive states modulate responding for drug reward.

ANXIETY AND PANIC

Anxiety increases tobacco smoking and alcohol consumption.[3] The drug pentylenetetrazole (PTZ) acts to inhibit GABAergic activation; it is an anxiogenic drug that produces interoceptive operant S^D effects in rats that are blocked by benzodiazepine anxiolytics. Nicotine and alcohol withdrawal produce anxiety, which further contributes to their use/abuse. Operant drug discrimination methodology with rats has revealed several stimulus effects of anxiety promoted by nicotine (or alcohol) withdrawal (e.g., see ref 5). For example, when rats are chronically exposed to nicotine, and then challenged with the nAChR antagonist mecamylamine, withdrawal is precipitated and can function as an interoceptive S^D. Under such conditions, responding has been shown to generalize to PTZ, and the effects are blocked by diazepam. Similar results have also been shown with acute withdrawal from high doses of ethanol. At the level of the receptor, it seems that we have only begun to sort out the interoceptive discriminative stimulus effects of fear and anxiety as also promoted by drug withdrawal.

CONCLUSION

Drugs act on neuroreceptors, thereby producing a host of interoceptive stimulus effects that result in (or are the result of) classical and operant conditioning. Dissecting their stimulus functions, and their interaction, in the regulation of voluntary and involuntary behavior will undoubtedly foster better clinical treatment outcomes for drug abuse (e.g., smoking) and other mental pathologies, such as anxiety, that often co-occur with drug abuse. B&B have also attempted to advance this view.

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Notes

The authors declare no competing financial interest.

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