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Review

Beyond Cue Reactivity: Non-Drug-Related Motivationally Relevant Stimuli Are Necessary to Understand Reactivity to Drug-Related Cues

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Abstract

Neurobiological models of addiction posit that drug use can alter reward processes in two ways: (1) by increasing the motivational relevance of drugs and drug-related cues and (2) by reducing the motivational relevance of non-drug-related rewards. Here, we discuss the results from a series of neuroimaging studies in which we assessed the extent to which these hypotheses apply to nicotine dependence. In these studies, we recorded smokers' and nonsmokers' brain responses to a wide array of motivationally relevant visual stimuli that included pleasant, unpleasant, cigarette-related, and neutral images. Based on these findings, we highlight the flaws of the traditional cue reactivity paradigm and we conclude that responses to non-drug-related motivationally relevant stimuli should be used to appropriately gauge the motivational relevance of cigarette-related cues and to identify smokers attributing higher motivational relevance to drug-related cues than to non-drug-related rewards. Identifying these individuals is clinically relevant as they achieve lower rates of long-term smoking abstinence when attempting to quit. Finally, we show how this approach may be extended beyond nicotine dependence to inform theoretical and clinical research in the study of obesity.

Implications: The cue reactivity paradigm (ie, comparing responses evoked by drug-related cues to those evoked by neutral cues) cannot provide conclusive information about the motivational relevance of drug-related cues. Responses to non-drug-related motivationally relevant stimuli should be used to appropriately gauge the level of motivational relevance that substance-dependent individuals attribute to drug-related cues.

Introduction

Addiction is considered a brain disease in which genetic, environmental, and social factors interact and contribute to its onset, maintenance, and chronic relapsing nature.[1] Addictive substances target neurobiological systems that mediate reward-related behavioral responses. Neurobiological models posit that drug use can alter reward processes in two ways: (1) by abnormally increasing the motivational relevance of drugs and drug-related cues and (2) by reducing the motivational relevance of non-drug-related rewards.[1–4]

Brain imaging techniques such as event-related potentials (ERPs) and functional magnetic resonance imaging (fMRI) are ideal tools to empirically test these hypotheses because they allow researchers to evaluate brain responses to both drug-related cues and non-drug related rewards. However, addiction scientists do not typically include both pleasant and drug-related cues in the same experimental paradigm and often limit themselves to assessing brain reactivity to neutral stimuli and drug-related cues, a procedure also known as the cue reactivity paradigm.[5–7] We hypothesized that restricting the range of stimuli presented during cue reactivity paradigms prevents scientists from validly and efficiently testing within the same experimental paradigm, whether drug-dependent individuals attribute higher motivational relevance to drug-related cues than to non-drug-related motivationally relevant stimuli.

Using nicotine dependence as a model, we systematically investigated how smokers and nonsmokers process cigarette-related cues within a broader emotional context that also includes standardized pleasant and unpleasant stimuli. Below, we discuss the results from a series of studies that indicate that validly gauging the motivational relevance of drug-related cues requires assessing brain responses to non-drug-related motivationally relevant stimuli. In light of the clinical implications of our findings, we suggest that researchers who are interested in other conditions that may be characterized by altered reactivity to reward-related stimuli (eg, obesity) should utilize the enhanced cue reactivity paradigm.

The Cue Reactivity Paradigm Cannot Provide Conclusive Information About the Motivational Relevance of Drug-Related Cues

One of the most common experimental paradigms used to investigate the motivational relevance of drug-related cues is the cue reactivity paradigm. In this paradigm, scientists compare brain responses evoked by drug-related cues (eg, images of drug paraphernalia or people engaging in drug use) to those evoked by neutral stimuli (eg, household objects).[7,8] The rationale for hypothesizing that smokers would react more to cigarette-related cues than to neutral stimuli arises from preclinical results obtained using Pavlovian conditioning procedures. When a neutral stimulus (the conditioned stimulus) predicts drug delivery (the unconditioned stimulus), it becomes attractive and desirable, and its presence is sufficient to motivate compulsive drug seeking behaviors in animals.[9] According to the incentive sensitization theory, the most important psychological aspect characterizing drug dependence is the development of abnormally high sensitivity to the motivational properties of the drug and drug-associated stimuli.[10] Pathological behaviors evoked by stimuli with high levels of incentive salience (eg, cue-induced reinstatement of previously extinguished drug pursuit behaviors) are a consequence of the aberrant responses that these stimuli evoke in the brain's motivational circuits.[11] Although the term incentive salience refers to a very specific line of neurobehavioral findings in the preclinical literature and the extent to which sensitization occurs in humans is still debated,[10] substance-dependent individuals, including smokers, report engaging in behaviors strikingly similar to those shown by animals in the presence of drug-related cues. For example, smokers often report that the presence of cigarette-related cues can trigger intense cravings and precipitate relapse during a quit attempt.[12,13] Brain imaging studies have shown that drug-related cues activate brain regions associated with attentional control and reward processes to a greater extent than neutral cues.[8,14–19] These results are often used to support the notion that drug-related cues hijack the brain's motivational systems and that exaggerated reactivity to drug-related cues could be considered the neural substrate of drug craving.

However, merely observing a difference between drug-related and neutral stimuli, the only two categories typically included in the cue reactivity paradigm, is not sufficient to conclude that brain responses to drug-related cues are aberrant or exaggerated. To reach this conclusion, a more appropriate control condition is necessary: The inclusion of non-drug-related stimuli capable of engaging brain motivational systems is essential. Observing higher reactivity to drug-related cues than to non-drug-related motivationally relevant stimuli in brain areas involved in motivational processes would provide stronger empirical support for the hypothesis that drug-related cues hijack human brain motivational systems and promote drug seeking over alternative behaviors. Furthermore, measuring reactivity to both drug-related and non-drug-related motivationally relevant stimuli in the same experiment would also offer scientists the opportunity to assess the extent to which substance-dependent individuals show blunted reactivity to non-drug related pleasant stimuli; a key feature hypothesized in neurobiological models of addiction typically assessed via self-report.[20,21]

The Picture Viewing Paradigm and Affective Neuroscience

For decades, affective neuroscientists have investigated brain responses to motivationally relevant and neutral stimuli using the picture viewing paradigm. In fact, the International Affective Picture System (IAPS)[22] was developed to provide a standardized set of stimuli to researchers studying affective reactivity.[23] A large body of studies using ERPs and fMRI shows that emotional images reliably engage the human brain's motivational systems.[24]

ERPs directly measure brain activity in response to specific events, are composed of distinct components that evolve rapidly over time (ie, over few hundreds of milliseconds), and are associated with specific mental processes.[25] The presentation of emotional images modulates the amplitude of several ERP components.[26] Among them, the late positive potential (LPP) is considered the most replicable and reliable index of motivational relevance.[24,27] The LPP is a sustained ERP component that peaks between 400 and 700 ms after stimulus onset over central and parietal electrode sites. Both pleasant and unpleasant images increase the LPP amplitude as a function of their affective intensity.[28–32]

fMRI measures hemodynamic responses associated with neuronal activity evoked by specific stimuli.[33] Several fMRI studies have shown that emotional images prompt larger blood-oxygen level dependent (BOLD) responses in a network of brain regions that includes the extended visual system (inferior temporal cortex, posterior parietal cortex, and extrastriate occipital cortex), the limbic system, the amygdala, the medial prefrontal cortex, and the inferior frontal cortex.[34] This pattern of activation is attributable to emotional images capturing attention and engaging the brain's motivational systems.[24,35,36] Since the amplitude of the LPP covaries with the BOLD activation observed in the visual areas,[37,38] both ERPs and fMRI allow the assessment of the motivational relevance of affective images. However, fMRI offers the opportunity to monitor activation of brain regions specifically sensitive to rewards and reward-related stimuli (eg, striatum, subgenual anterior cingulate cortex, ventromedial prefrontal cortex).[34,39] Furthermore, studies that assessed brain responses to primary (eg, juice delivery, erotic picture presentation) and secondary rewards (eg, monetary gains) show that, regardless of the good at stake, overlapping areas are active.[19,39]

Do Smokers Have Larger Brain Responses to Cigarette-Related Cues Than to Other Emotional Stimuli?

A positive answer to this question, rather than simply observing higher reactivity to cigarette-related than to neutral stimuli, would provide stronger support for the hypothesis that cigarette-related cues are motivationally relevant. Hence, we recruited smokers and nonsmokers in a series of studies and analyzed their brain responses to a wide array of cigarette-related, neutral, pleasant, and unpleasant images. The results from this enhanced cue reactivity paradigm, while somewhat surprising, were consistent across several studies in which we used both ERPs and fMRI. ERPs showed that while cigarette-related cues prompted larger LPPs in current smokers than nonsmokers, pleasant and unpleasant images also had the same effect.[40,41] Although the results supported the idea that for smokers, cigarette-related cues are motivationally relevant stimuli that capture attentional resources,[42,43] the effects were not unique to cigarette-related cues. These findings highlight a key issue associated with the classic cue reactivity paradigm: if we had included only cigarette-related and neutral stimuli, it would not have been possible to determine whether differences between these two conditions were due to smokers' higher reactivity to emotional stimuli in general, or to higher reactivity to cigarette-related cues in particular.

A second issue became evident upon more fine-grained analysis of the LPP amplitude evoked by different sub-categories of emotional stimuli.[44] This analysis was possible because we included pleasant and unpleasant picture categories with different levels of motivational relevance (ie, erotica and romantic; mutilations and sad). As expected, both smokers and nonsmokers reacted with progressively higher LPPs to images with higher motivational relevance (ie, LPP to neutral < sad and romantic < mutilations and erotica). However, both smokers and nonsmokers showed LPPs of similar amplitude to cigarette-related images and mildly-arousing pleasant and unpleasant stimuli. Although nonsmokers might have reacted to cigarette-related cues because they found them unpleasant,[40,45] this finding seems at odds with the idea that cigarette-related cues hold high motivational relevance for smokers (if that were the case, one would expect the magnitude of the LPP to cigarette cues to approach or exceed that of highly-arousing pleasant and unpleasant stimuli). The results from an fMRI study, where we collected whole brain BOLD responses to the same categories of pictures, replicated and extended these results. In line with the hypothesis that emotional and cigarette-related images capture attentional resources in smokers, both categories of stimuli activated regions in the extended visual system, but cigarette-related images prompted responses that more closely resembled those evoked by low-arousal pleasant and unpleasant stimuli rather than highly arousing stimuli.[46] In fact, when we specifically analyzed activation within the amygdala region, known to be sensitive to the motivational relevance of visual stimuli irrespective of their hedonic value,[47] we observed that BOLD signal increased as a function of motivational relevance for non-cigarette-related images, but not for cigarette-related cues. When we analyzed activation within regions specifically sensitive to hedonic value (ie, dorsal striatum, anterior cingulate cortex), we confirmed the appetitive nature of cigarette-related cues for smokers,[45,48,49] but also noticed the relative weakness of the activation that these stimuli evoke relative to other highly arousing, pleasant stimuli.

In summary, results from our studies indicate that, contrary to prevailing assumptions, the "average" brain responses evoked by cigarette-related cues in smokers are not abnormally high or aberrant. In fact, cigarette-related images evoke brain responses that are similar to those evoked by (pleasant) stimuli with low motivational relevance. Although it has been suggested that smoking abstinence might increase brain reactivity to cigarette-related cues,[8,18] evidence for this effect in the standard cue reactivity paradigm is relatively weak: A meta-analysis that included studies investigating ERP responses to drug-related cues[15] failed to detect significant differences between abstinent and non-abstinent individuals, and another one that focused specifically on studies using fMRI to investigate reactivity to cigarette-related cues[14] found higher reactivity to cigarette-related cues in nicotine deprived smokers only in two relatively small areas located in the occipital cortex and the superior frontal gyrus. When we recorded ERPs to emotional stimuli (including cigarettes) before and after 24 hours of nicotine abstinence,[41,50,51] we did not observe significant differences between the abstinent and non-abstinent conditions.

What Is the Role of Individual Differences in Modulating Smokers' Brain Responses to Reward-Related Cues?

At first glance, observing that smokers do not show particularly intense responses to cigarette-related cues seems unexpected and in conflict with the critical role that neurobiological models and clinical observations attribute to cues in triggering compulsive drug seeking. However, the data presented above, like those usually presented in the literature, are average responses. When we average across the whole sample, we would observe higher brain responses to cigarette-related cues than to pleasant stimuli only if most smokers find cigarette-related cues more motivationally relevant than pleasant stimuli. Assuming that most smokers find cigarette-related stimuli to be among the most motivationally relevant stimuli is likely incorrect. In fact, even the authors of the incentive sensitization theory, the model that places the greatest emphasis on drug-related cues as the crucial motivational spur to take drugs for addicts, emphasize that there are large individual differences in the propensity to attribute incentive salience to drug-related cues.[52]

Evidence of the key role played by individual differences in modulating reward-related behaviors comes from the phenomenon called sign-tracking.[53,54] In classical conditioning paradigms, when a discrete cue predicts subsequent food delivery, animals develop two distinctive behaviors: Sign-tracking (the tendency to approach and interact with the conditioned stimulus, ie, the "sign" that predicts food delivery), or goal-tracking (the tendency to approach the location where the food reward is delivered, ie, the "goal"). Robinson and colleagues proposed that sign-tracking develops in animals that attribute excessive incentive salience to reward-related cues. For sign-trackers, discrete reward-related cues acquire the properties of the reward itself, in that the cues capture attention, become attractive, become "wanted," and can generate a conditioned motivational state.[55] Animal models showed that sign-tracking is mediated by dopaminergic projections from the midbrain to the striatum, medial prefrontal cortex, and anterior cingulate cortex.[54,56–58] Importantly, animals that sign-track to discrete food-related cues also sign-track to drug-related cues and are particularly vulnerable to developing cue-induced compulsive drug seeking behaviors that have striking similarities with human cue-induced drug consumption.[59,60]

These preclinical findings suggest that the enhanced cue reactivity paradigm would permit studying the human neurobehavioral correlates of sign-tracking, as this paradigm includes both stimuli that acquired relevance by being repeatedly paired with drug delivery

(ie, the cigarette-related cues) and primary rewards (images that, in general, people find intrinsically rewarding, eg, erotic images[61]). To the extent that sign-trackers find reward-related cues more motivationally relevant than primary rewards, smokers characterized by this trait should have larger LPPs to cigarette-related cues than primary rewards. Goal-trackers should show the opposite brain reactivity pattern. Furthermore, given sign-trackers' higher vulnerability to cue-induced drug seeking behavior observed in preclinical studies,[62] smokers classified as sign-trackers should also be at higher risk of relapse during a quit attempt, when the presence of cigarette-related cues plays a major role.[63]

To test this hypothesis, we first classified smokers based on individual differences in the amplitude of the LPPs evoked by cigarette-related, pleasant, neutral, and unpleasant stimuli when they were smoking at their regular rate, and then examined whether these baseline differences predicted abstinence outcomes during a subsequent smoking cessation attempt.[64] We classified smokers using *k*-means clustering, an algorithm that groups individuals by minimizing within-groups variability and maximizing between-groups variability.[65] The algorithm is unsupervised, taking as constraints only the number of clusters and the variables used for deriving the solution. The groups extracted using this technique could have differed with respect to any brain reactivity pattern. Nonetheless, the solution (ie, two clusters) that best fit the data was consistent with the sign-tracking versus goal-tracking dichotomy. Similar to the sign-trackers noted above, one group was characterized by larger LPP responses to cigarette-related cues than to pleasant stimuli. Similar to the goal-trackers, the other group was characterized by the opposite brain reactivity pattern: larger LPP responses to pleasant stimuli than to cigarette-related cues. Unlike pleasant and cigarette-related cues, neutral and unpleasant stimuli evoked similar responses in both groups. As we mentioned above, the amplitude of the LPP is an index of motivational relevance, not hedonic impact. Hence, these results are consistent with the suggestion that the underlying psychological factor driving these differences is the motivational relevance that individuals attribute to cigarette-related cues and pleasant stimuli. Consistent with preclinical findings, these clusters demonstrated prognostic value among participants enrolled in a smoking cessation trial. Smokers classified as sign-trackers at baseline, when they were still smoking at their regular rate, had significantly lower chances of achieving long-term (6 months) smoking abstinence during a smoking cessation intervention that started immediately after the EEG session.[64] In a subsequent fMRI study[66] we replicated and extended these findings. First, applying *k*-means cluster analysis on the BOLD responses from the extended visual system yielded two groups with the same brain reactivity patterns observed when we used the LPPs to classify individuals. This is an important result because, as mentioned above, the extended visual system is the likely LPP neural source. The behavioral results were also consistent with those observed in our previous study: smokers with larger BOLD responses to cigarette-related cues than pleasant stimuli had significantly lower abstinence rates at the 6 months follow-up. Finally, due to the better spatial resolution of fMRI, we identified several brain regions outside of the visual system showing differential activation for cigarette-related and pleasant images as a function of group membership. The brain structures identified by this analysis (eg, medial prefrontal cortex and dorsal striatum) included those previously associated with the expression of sign-tracking behavior in animal models.[54,56–58]

These results support the idea that, like sign-trackers, smokers characterized by higher reactivity to cigarette-related cues than pleasant stimuli are at increased risk of cue-induced relapse. Preclinical models also suggest that sign-tracking behavior is not a consequence of drug use, but that it pre-exists it, and may increase vulnerability to a range of maladaptive behaviors associated to abnormal reward-cue processing.[53]

What is the Role of Individual Differences in Modulating Brain Responses to Reward-Related Cues Beyond Nicotine Addiction?

The biological similarities between drug addiction and obesity led to the hypothesis that obese individuals may have problems regulating their food intake because they attribute excessive motivational relevance to food-related cues.[67–69] To test this hypothesis, researchers in the obesity field adapted the cue reactivity paradigm to record brain responses to food cues and neutral images.[70] Like in the addiction field, however, very few studies have assessed also reactivity to emotional stimuli. Similar to what we found with smokers, when we analyzed the LPP responses to food-related cues and non-food-related emotional stimuli in obese (BMI ≥ 30) and lean (BMI < 25) nonsmokers, we did not observe significant differences between groups.[71] On average, both obese and lean individuals processed food-related stimuli as stimuli with low motivational relevance. However, when we clustered individuals based on their brain reactivity patterns, the two profiles that emerged clearly fit the sign-tracking versus goal-tracking dichotomy. Nearly one-third (32%) of the sample showed blunted brain responses to pleasant stimuli and high responses to food-related stimuli, while the rest of the sample showed the opposite pattern. Furthermore, in line with the hypothesis that sign-tracking might be a risk factor associated with excessive eating, the sign-tracking group included a significantly higher proportion of obese individuals than the goal-tracking group.

To directly test the hypothesis that sign-trackers (ie, individuals characterized by larger LPPs to food-related cues than to pleasant stimuli) are at higher risk of overeating in the presence of food-related cues, we developed an experimental apparatus that allowed us to record ERPs to images and manipulate food availability on a trial-by-trial basis.[72] Using this apparatus, we recorded from 49 participants the ERPs evoked by emotional (pleasant and unpleasant), neutral, and food-related images that preceded the delivery of an M&M's candy.[73] Participants were free to eat or discard the candies that were delivered during the study. Following the same procedures of our previous studies, we computed the amplitude of the LPP evoked by each stimulus category and we used *k*-means cluster analysis to classify participants based on their brain reactivity profiles. In line with our previous studies, one group (sign-trackers) showed higher LPPs to food-related than pleasant stimuli while the other group (goal-trackers) had the opposite brain reactivity profile. Importantly, during the experiment sign-trackers ate more than twice as many candies as goal trackers (21 vs. 8) and this difference was statistically significant. These results directly support the hypothesis that individuals showing larger emotional responses (as measured by the LPP) to discrete reward-related stimuli (ie, food-related, cigarette-related cues) than rewards (ie, erotic images) are more prone to cue-induced compulsive behaviors.

Conclusions and Future Directions

In summary, these results show that even if recording brain responses to non-drug-related motivationally relevant stimuli is a relatively small methodological departure from the standard cue reactivity paradigm, it is a necessary step to validly and accurately assess the motivational relevance of drug-related cues. This paradigm has been sporadically used by researchers in the past,[45,74–79] but unlike the cue reactivity paradigm, it never became the standard to investigate the motivational relevance of drug-related cues. Indeed, among the more than 100 fMRI studies included in a recent meta-analysis of drug cue reactivity, we found only five instances in which researchers included also some sort of emotional control stimuli.[19]

We think that including emotional stimuli in the cue reactivity paradigm also represents a significant improvement towards the goal of developing a valid measure of the motivational relevance individuals attribute to rewards and reward-related cues. Although the enhanced cue reactivity paradigm alone will not fully allow researchers to identify individuals at higher risk of relapse during treatment or choose the best intervention for them, using a valid measure is a necessary preliminary step to draw accurate conclusions about the relationship between the presence of reward-related cues, the brain responses that these cues evoke, and the compulsive maladaptive behaviors that they might trigger. For example, we think that the low correlation between laboratory and real world measures of cue reactivity[80] might be due in part to the restricted range of stimuli that participants face during the standard laboratory cue reactivity paradigms relative to the wide range that they encounter in their daily life. Preclinical studies showed that the representation of value in the brain's valuation system adapts to the range of values available at any given time.[81] In a similar way, brain responses to cigarette-related cues during the standard cue reactivity paradigm might be altered by the small range of stimuli that are presented during the session. Including emotional stimuli might better approximate the real world situations in which participants encounter cigarette-related cues.

Finally, we acknowledge that further research will be necessary to support the hypothesis that the neurophysiological profiles that we identified using a passive picture viewing task are associated with sign-tracking behavior. One possible approach will be to test the extent to which smokers classified as sign-trackers using the procedure described here also show stronger biases towards behaviors associated with reward-related cues using Pavlovian-to-instrumental transfer paradigms.[82,83] Furthermore, complementing behavioral outcomes in Pavlovian-to-instrumental transfer paradigms with brain imaging will also allow researchers to better characterize the neurobiological underpinnings of sign-tracking behavior in humans.

To conclude, we recommend the systematic use of the enhanced cue reactivity paradigm to all researchers interested in investigating the neurobiological underpinnings of cue-induced maladaptive behaviors and diseases associated with altered reward processes. Taking into account reactivity to non-drug-related motivationally relevant stimuli when investigating reactivity to drug-related stimuli will lead to more refined theoretical models, and will open new opportunities for clinical interventions to effectively treat drug dependence and other maladaptive behaviors such as overeating.[5,84]

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Declaration of Interests

Drs. Cinciripini and Karam-Hage acknowledge potential conflict of interest appearance, as they have received medication Chantix from the manufacturer Pfizer to conduct two NIH-funded studies, and participated in two multisite Pfizer funded studies on Chantix. All the other authors declare no conflict of interest.

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