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Multiple ambiguities in the measurement of drug craving: Comment on “Neuroimaging craving: Urge intensity matters”

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Craving is a core feature of all addictive disorders, exemplified by its inclusion in the new DSM-5 (1). Yet, investigating the neurobiology of craving is fraught with ambiguity. Craving is an inherently subjective human experience, replete with cognitive, emotional, interoceptive, metacognitive, and physiological components that are difficult, if not impossible, to fully capture in animal studies. Thus, the neurobiology of craving has been principally examined via human neuroimaging studies that have revealed that a diffuse network of brain regions are reliably engaged by drug-related cues [reviews: (2-6)].

Here, Wilson and Sayette raise the intriguing possibility that these studies could be unintentionally measuring low-level desire rather than probing the neural correlates of *clinically-relevant* craving, (7). In support, they point to neuroimaging studies of nicotine users in which craving probes often fail to elicit endorsement of even the scales’ midpoints. Furthermore, many of these studies have allowed ad- libitum smoking prior to cue exposure, promoting satiation that can minimize or obscure subjective and neural craving responses. The authors conclude that consideration of ‘urge intensity’ in imaging studies could help clarify the neurobiological basis of overpowering, clinically-relevant craving. We agree that refinement of the craving concept is vital to advancing the clinical neuroscience of drug addiction, and we raise the following additional caveats for consideration.

First, it will be important to disentangle the multifaceted construct of craving from the effects of deprivation or withdrawal. For nicotine, which is consumed in well- defined patterns that maintain relatively consistent bodily levels of nicotine, deprivation might directly correspond with craving. In contrast, for stimulants (e.g., cocaine, methamphetamine), which are often consumed in binge cycles, the link between craving and deprivation could be more tenuous. In our work, cocaine-addicted individuals reported the highest levels of cocaine ‘wanting’, a proxy of craving, when recalling a time they were already ‘under the influence’ of the drug (versus the contexts of ‘right now’ or ‘in general’)

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(8); that is, craving was highest when deprivation was ostensibly lowest. Moreover, individuals with more recent cocaine use (i.e., cocaine-positive urine screens versus cocaine-negative urine screens) rated cocaine pictures as being more affectively pleasant (9) and chose more of them for viewing (versus pleasant pictures) on tasks of simulated drug choice (10). In direct support, others have shown that priming doses of cocaine in cocaine-addicted individuals increased craving (11) and subsequent choice for cocaine over money (12).

Second, it will be important to better integrate craving measures with imaging measures. This can help to maximize applicability across multiple addictions and enable more precise investigation of the underlying craving construct. The approach of assessing differences in neural activation between addicted subgroups (e.g., stratified by craving level, recency of use, etc.) is susceptible to numerous confounds that could drive observed differences. As we suggested above, craving may overlap with withdrawal, depending on the population under study. A potentially improved strategy is to exploit, in a participant-specific manner, the variability in craving intensity *within* the experimental paradigm itself. This approach could provide more accurate tracking of their association by increasing temporal proximity between the measured craving and the neuroimaging data. For example, one could have participants indicate on a trial-by-trial basis their craving level upon exposure to a drug cue or by making a drug-related decision. This latter design, based on behavioral response (choice), could also help address obstacles of impaired insight/self-awareness (13), which in an important subgroup of addicted individuals may impede the effective assessment of online craving and subjective drug-cue reactivity (14, 15). Importantly, these types of designs would enable parametric correlation of trial-by-trial responses with the associated neural signals for each individual. One could compare how low-level desire and clinically-relevant craving may diverge in neural location and magnitude, and across groups of addicted individuals. Such parametric designs are standard in research on non-pathological food cravings (16). They are also amenable to sophisticated, more sensitive analytic approaches [e.g., multivoxel pattern analysis (17)]. They potentially could be used for interventional purposes (e.g., training individuals to reduce craving or drug-biased responding).

In sum, we agree that neurobiology of craving, despite being a long-standing focus of intense basic and clinical investigation, remains unclear. Disambiguating the neurobiological basis of drug craving could fundamentally advance our understanding of drug addiction and its treatment-resistant nature.

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