





RESEARCH HIGHLIGHT



Addressing the when, what, and why of opioid craving and drug-related valuation

Justin C. Strickland¹   and Cecilia L. Bergeria¹

© The Author(s), under exclusive licence to American College of Neuropsychopharmacology 2021

Neuropsychopharmacology (2022) 47:1429–1430; <https://doi.org/10.1038/s41386-021-01261-6>

In this issue of *Neuropsychopharmacology*, Biernacki et al [1], describe an extension of their recent research on the neuroeconomics of food craving [2] designed to study the relationship between opioid craving and opioid-specific valuation. Patients receiving methadone treatment for opioid use disorder completed a willingness-to-pay task with personalized stimuli varying on a subjective dimension of drug relatedness, but generally matched on ratings of desirability. Prediction of trial bids showed increases in valuation for more opioid-related items under momentary conditions in which a participant experienced greater opioid craving. This elegant work helps to address the *when, what, and why* of opioid craving while posing important directions for this line of work.

Collection of trial intensive willingness-to-pay data at two time points designed to vary in craving state – one shortly following methadone administration and one 24 h following dosing—allowed Biernacki et al [1], to separate the between and within-person processes underlying the relationship between opioid craving and valuation. Specifically, analyses indicated that interactions between drug relatedness and craving were observed at both between- and within-person levels meaning that (a) participants with greater overall opioid craving showed greater overall valuation for stimuli that were more drug related and (b) in moments when participants reported opioid craving that was greater than usual, the association between drug relatedness and valuation was also more positive.


Isolating these *when* of opioid craving tests important hypotheses related to the Simpson's paradox that could otherwise limit implementation and translation of these findings to a clinical context. The Simpson's paradox is a common ecological fallacy in which population-level correlates are in an opposite direction of momentary correlates for a given variable. A simple example of the Simpson's paradox is present in the association between physical activity and heart attack risk – people who exercise are less likely to have a heart attack than those that do not (a population-level association), but for any given person, having a heart attack is more likely when they are exercising compared to when they are not (a momentary association). Failing to distinguish these two pathways can lead to failed or even harmful interventions; for instance, if the momentary data that show greater risk when exercising were used to design a population-based prevention method, it would dangerously recommend reducing exercise to prevent heart attacks. In the present work, Biernacki et al [1], effectively show that not only do people who

experience higher opioid craving, on average, report this more positive likeness-dependent valuation, but that this relationship is seen in the same direction and of a similar or greater strength at a moment-to-moment level. Interventions that target both mechanisms, such as through more general regulatory techniques and through more contextually specific just-in-time approaches, are thus worth exploring to reduce relapse propensity through this craving-to-valuation pathway.

Craving in the study by Biernacki et al [1], was measured by asking participants their “desire for” indexed as how much they wanted heroin or methadone periodically within blocks of the task. This *what* of craving considers a specific aspect of the construct, highlighting ongoing discussions and gaps regarding the measurement of craving in addiction research. Informal conversations about craving often assume an “I know it when I see it” form. Scientific discourse poses a similar fuzziness in the variety of validated measures for opioid craving and lack of consensus about the construct's nature and structure [3]. That a precise definition was applied here is a key strength, but also introduces novel questions about whether the value-dependent mechanisms identified extend to other common conceptualizations of craving that include not only “desire” but expectation of positive and negative reinforcement, changes in cognitive control, and pain-specific factors (among others). The expression of craving is also posited to vary across treatment course (e.g., craving soon after abstinence versus craving during protracted recovery) and between people (e.g., some patients never report “craving” a drug or only for specific reasons). Tests of the neurobehavioral mechanisms proposed under these alternative operationalizations and contexts could help to clarify the shared and unique aspects of this historically heterogenous construct.

The *why* of craving is also addressed in the authors' study by testing a multiplicative gains process previously identified in research on the relationship between food craving and food-related valuation [2]. Support for a consistent quantity-dependent mechanism was observed at both between and within-subject levels. That is, as the number of items available became larger, the association between craving (opioids here and food previously) and outcome-relatedness for predicting valuation grew stronger.

The multiplicative mechanism shared by food and opioid craving combined with the context-dependency described earlier raises a significant conceptual point about the nature of addictive behaviors and common models of addiction. Namely, the authors' findings collectively suggest that craving for both drug and

¹Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, 5510 Nathan Shock Drive, Baltimore, MD 21224, USA. email: jstric14@jhmi.edu

Received: 18 December 2021 Accepted: 21 December 2021

Published online: 9 January 2022

non-drug commodities operates along an outcome-selective mechanism valuation process that is sensitive to changes in person state (e.g., craving level) and context (e.g., the relatedness and amount of an outcome). Rather than a bias to value drug-related items indiscriminately, the present data indicate that behaviors like drug use that are often outwardly considered irrational may be explainable at a mechanistic level of value computation that is normative and based on measurably and modifiable state and context factors (at least for some of the people, some of the time [4]). This idea stands in contrast to popular dogmas about addiction that suggest substance use leads to gross, global, and unambiguous impairments in decision-making processes. Instead, the authors' findings highlight a growing appreciation of nuance in models of addiction, choice, and decision-making and important interactions that occur between person and place in this regard [see recent discussion of these ideas in ref. [5].

The work described by Biernacki et al [1]. is likely to be influential and stimulate novel research programs across diverse areas of addiction science. Studies like this will ultimately help to bridge the translational gap between basic science evaluating core neurobehavioral mechanisms underlying choice and decision-making and clinical science developing and implementing more effective and individualized interventions for substance use disorders.

REFERENCES

1. Biernacki K, Lopez-Guzman S, Messinger J, Banavar NV, Rotrosen J, Glimcher PW, et al. A neuroeconomic signature of opioid craving: how fluctuations in craving bias drug-related and nondrug-related value. *Neuropsychopharmacology*. 2021. <https://doi.org/10.1038/s41386-021-01248-3>.
2. Konova AB, Louie K, Glimcher PW. The computational form of craving is a selective multiplication of economic value. *Proc Natl Acad Sci USA*. 2018;115:4122–27.
3. Kleykamp BA, De Santis M, Dworkin RH, Huhn AS, Kampman KM, Montoya ID, et al. Craving and opioid use disorder: a scoping review. *Drug Alcohol Depend*. 2019; 205:107639.
4. Epstein DH. Let's agree to agree: a comment on Hogarth (2020), with a plea for not-so-competing theories of addiction. *Neuropsychopharmacology*. 2020;45:715–6.
5. Pickard H. Is addiction a brain disease? A plea for agnosticism and heterogeneity. *Psychopharmacology*. 2021. <https://doi.org/10.1007/s00213-021-06013-4>.

ACKNOWLEDGEMENTS

Support for JCS was provided by NIDA R03DA054098. Support for CLB was provided by NIDA R21DA054952.

AUTHOR CONTRIBUTIONS

All authors contributed equally to the writing of this work.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Justin C. Strickland.

Reprints and permission information is available at <http://www.nature.com/reprints>

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.