www.nature.com/npp

American College of Neuropsychopharmacology

RESEARCH HIGHLIGHT

Compulsion and substance use disorder: potential importance of boundary conditions

Cassandra D. Gipson [1]✉ and Joshua S. Beckmann [2]

Neuropsychopharmacology (2023) 48:432–433; https://doi.org/10.1038/s41386-022-01462-7

For the past several decades, preclinical modeling of substance use disorders (SUDs) has shifted away from tolerance and withdrawal, toward the creation of models thought to reflect translationally relevant aspects of the clinical condition. A telescoped focus has been placed on creating non-human models in attempt to recapitulate the behavioral aspects of human SUD, including escalation of drug use, taking drug despite negative consequences, drug seeking when the drug is unavailable or the response is associated with adverse consequences as a model of "compulsivity", among others [1]. These models have resulted in a plethora of information regarding the neurobiology of various animal subgroups, defined by observed behavior within specific experimental contexts.

In this issue of *Neuropsychopharmacology*, Pascoli and colleagues used footshock during cocaine self-administration to identify two phenotypes of mice: shock-resistant or those that continue to self-administer cocaine in the presence of footshock (termed "perseverers") and shock-sensitive or those that do not (termed "renouncers") [2]. The authors used a fixed ratio schedule of cocaine reinforcement coupled intermittently with a single shock intensity (0.2 mA) to define the behavioral groups. The authors then used ex vivo electrophysiological methodologies to measure synaptic plasticity in orbitofrontal cortex (OFC) to dorsal striatum (DS) synapses (DS_{OFC}). The primary findings indicate that mice grouped as perseverers show higher ratios of AMPA-to-NMDA receptor currents in both dopamine D1 receptor (D1R)-expressing spiny projection neurons (SPNs) and D2R SPNs after a punishment session, whereas only synapses of D1R SPNs were strengthened following acquisition, when no punishment was given. In renouncers, D1R SPNs did not show strengthening following cocaine self-administration. The conclusions drawn from these findings is that potentiation of the D1R-expressing DS_{OFC} synapses gives insight into what neurobiological changes accompany compulsion-like behavior.

The paper of Pascoli et al. [2] has several notable strengths, including the use of cutting-edge techniques that allow for cell-type and circuit specificity relevant to behavior. Specifically, the use of transgenic mice and adeno-associated viruses that allow for specific optogenetic manipulation of the DS_{OFC} circuit yields refined information regarding the role of specific pathways involved in cocaine-related behaviors. Further, the use of patch clamp electrophysiology allows for characterization of the strength of DS_{OFC} synapses under varied conditions. There is also a focus on cell-type specificity via characterization of cells that contain D1R or D2Rs. This is important because the field has demonstrated numerous dichotomies in the function of these different cell types on neurobiology and behavior. Finally, there is a clear focus on individual differences relevant to cocaine self-administration, which may uncover important information regarding individual differences in neurobiology. These positive aspects of the paper potentially shed light on the role of D1R versus D2R SPNs in cocaine-related behaviors.

However, there appears to be a tendency in the current paper and the field at large to approach behavioral procedures as pure, turnkey metrics for a specific construct of interest (e.g., compulsion), used as a method to prompt some hypothetical process or function, onto which neural function is then mapped. While the above approach is not without some merit, it is inclined to gloss over detail. Behavioral procedures are often reflective of complex contexts, involving multiple contingencies, various schedules of consequences (some controlled by the experimenter and some not), complex stimulus arrangements, etc. Considering the above, we suggest that any associated behavioral or neural organization observed is likely a product of the context defined by the procedures used to measure such organization. Further, differences in organization might be due to differential control via several contextual elements, rather than solely reflective of differences in the specific hypothetical construct attributed to the procedure.

Failure of a specific consequence to serve as a punisher as conceived, expected, or designed by the experimenter, does not necessarily reflect a maladaptive underlying neural mechanic coupled to compulsion. Within the context of the present experiment, other alternative interpretations are, at least, possible, including (but not limited to) shock-induced changes in cocaine valuation, relative cocaine-shock valuation, differential sensitivity to shock, response competition, etc. However, rather than dissociate compulsion and its hypothesized mechanisms from alternatives, replication of compulsion within the same procedural contexts is often coupled with additional or more specific neural measurement and offered as additional evidence that compulsion is the likely culprit.

Despite the large amount of drug-related data generated within specific contexts from rodent models ostensibly reflective of compulsivity, there is little clinical evidence to support habitual responding for drugs of abuse in humans, beyond the

[1]Department of Pharmacology and Nutritional Sciences, University of Kentucky, Lexington, KY, USA. [2]Department of Psychology, University of Kentucky, Lexington, KY, USA. ✉email: cdgips2@uky.edu

Received: 7 September 2022 Accepted: 12 September 2022
Published online: 29 September 2022

commonplace interpretation of formal drug-taking patterns as compulsive. Yet, form and function are not necessarily the same. Recent clinical studies show either null or weak effects regarding reductions in goal-directed behavior in drug users as compared to control participants [3]. Additionally, recent work suggests that SUD might be better described as a behavior mediated by differential valuation processes, rather than compulsivity [4]. Furthermore, there is evidence that the majority of those diagnosed with SUD "mature out" [5], and contingency management treatments for SUD are effective. Importantly, these are phenomena that, at least, appear inconsistent with the construct of compulsivity as defined in the field. Thus, most experimental evidence for compulsivity and SUD comes from animal studies using specific procedural conditions, which may not lead to intended goals of translational unveiling of SUD neurobiology.

The growing discrepancy between clinical and the preclinical results above suggests the theory of drug-induced compulsivity as the sole cause of SUD is likely overly simplistic and may come down to the procedural contexts in which behavior and accompanying neural signaling are measured. Similar to Pascoli et al. (in press) [2], most non-human studies have drawn conclusions regarding compulsivity from procedures that have very specific contexts. For example, a large majority of studies do not assess the sensitivity of drug responding to alternative consequences or vary experimental parameters like shock intensity on a continuum. As such, future preclinical work might be directed toward identifying the boundary conditions within which "compulsive" drug-related responding is observed, working to differentiate compulsive from competing interpretations within those conditions, and determining whether or not such conditions are reflective of those associated with SUD.

REFERENCES

1. Deroche-Gamonet V, Belin D, Piazza PV. Evidence for addiction-like behavior in the rat. Science. 2004;305:1014–7.
2. Pascoli V, Hiver A, Li Y, Harada M, Esmaeili V, Lüscher C. Cell-type specific synaptic plasticity in dorsal striatum is associated with punishment-resistance compulsive-like cocaine self-administration in mice. Neuropsychopharmacology. 2022. https://doi.org/10.1038/s41386-022-01429-8.
3. Nebe S, Kroemer NB, Schad DJ, Bernhardt N, Sebold M, Muller DK, et al. No association of goal-directed and habitual control with alcohol consumption in young adults. Addict Biol. 2018;23:379–93.
4. Hogarth L. Addiction is driven by excessive goal-directed drug choice under negative affect: translational critique of habit and compulsion theory. Neuropsychopharmacology. 2020;45:720–35.
5. Heyman GM. How individuals make choices explains addiction's distinctive, non-eliminable features. Behav Brain Res. 2021;15:397.

AUTHOR CONTRIBUTIONS

CDG wrote the initial draft of the commentary, and JSB contributed additional text. Both CDG and JSB edited the manuscript and approved the final version.

FUNDING

Authors are supported by DA046526 and DA049130 (to CGR), and DA045023 and DA047368 (to JSB).

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Cassandra D. Gipson.