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Using complex behavior to understand brain mechanisms in health and disease

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At this point in the history of the science of behavior, a focus on neuroscience-based outcomes has become dominant in neuropsychiatric fields at the preclinical and clinical levels of analysis. The notion that behavior is caused by brain function, and that changing brain function can alter behavior, has fueled this push to understand these neurobiological mechanisms. Within this conceptual framework and the funding to incentivize its adoption, the neuroscience field grew rapidly with the goal to understand the relation between the brain and behavior. As such, a reductionist perspective emerged whereby neural manipulations of increasing sophistication became required for assessing the necessity and sufficiency of a particular brain mechanism's role in behavior (Krakauer et al., 2017). Yet, despite the amazing advances in neuroscience, some, such as the former director of the National Institute of Mental Health, Dr. Thomas Insel, have noted the lack of progress in treatment outcomes for mental illness following the shift in funding from behavioral research to genetics and neuroscience research (Barry, 2022).

This opening paragraph brings us to a key point of this Special Issue titled "Using complex behavior to understand brain mechanisms in health and disease." Namely, we cannot isolate a behavior and solely understand that behavior in terms of brain structure and function without reference to environmental variables. The role of the environmental variables in determining behavior, the impact of behavior on the environment, and the interactions of behavior and the environment with the brain must *all* be considered. We believe that understanding the reciprocal relationships between the brain, the environment, and behavior will yield important insights and translationally relevant findings, but this requires a focus on understanding the motivational state of an animal and its affordances. As Killeen and Jacobs (2017) wrote, "We remain behaviorists because behavior, its antecedents and consequents, remains our primary concern." Along these lines, Niv (2021) argued that a well-designed behavioral paradigm may yield more insight into brain function than reductionist neural studies. This suggestion highlights the need for careful behavioral analysis before or along with neural analysis (Soto, 2020). We agree and hope this Special Issue amplifies this message.

Neuroscientists continue to develop new tools to dissect intricate neural structures and their functions—at times in isolation from behavior or with limited to no tests of generality. There is no doubt that these neuroscientific tools have furthered our understanding of brain function in both adaptive and maladaptive states, potentially informing the basis of neurological and psychiatric diseases. However, more work is needed to fully understand complex brain–environment–behavior interactions. Although neurobiological and pharmacological outcomes in isolation from behavior may be reproducible, it is not clear how these

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mechanisms relate to the organism and how it interacts with its environment. Thus, the relation of these outcomes to complex behavioral processes is critical in uncovering their translational relevance. Together, advances in our understanding of behavioral systems, states, and dispositions will provide more detailed information on the conditional relationships between neurobiology and behavior. This in turn may yield critical translational results relevant to health and disease.

In this Special Issue, we highlight empirical research that spans a diversity of topics including the role of organismic (e.g., brain, age, sex) and environmental variables on substance use behavior and the effects of drugs on behavior, the role of history on operant performance, the impact of dietary manipulations on physiology and behavior, and the use of operant procedures to evaluate a rat model of autism spectrum disorder. This Special Issue also includes several important reviews on the contribution of operant studies to our understanding of schizophrenia using a rat model of schizophrenia risk, a theoretical framework for understanding the role of the nervous system, the logical fallacies and misinterpretations that hinder progress in our understanding of drug use and misuse, the use of dose-addition analyses to understand polysubstance use, the contribution of cholinergic and dopaminergic signaling in behavior occurring in healthy states and substance use disorders, the specification of a method for examining impulsive choice suitable for use in behavioral neuroscience research, a review of human laboratory studies of cocaine reinforcement, a review of sex differences and neurobiological determinants of choice between drug and nondrug reinforcers, and a machine learning approach for predicting behavioral histories based on a small sample of data.

From the initial kickoff meeting conceptualizing objectives to the last emails finalizing the edits to this Introduction, we have enjoyed the journey and its end—this Special Issue. As you can see from the list of topics just described, the response was tremendous from the scientific community investigating complex behavior and potential pharmacological and neural mechanisms. We thank the authors for generously sharing their perspectives, data, insights, and potential avenues for future inquiry. As a reader of this Special Issue, we hope you gain as much as we did from the following contributions (in order of appearance):

Sosa and Alcalá describe feedback control theory, which postulates how a bidirectional interaction between an organism and its environment results in behavior across its lifetime. In this review article and commentary, the argument is made that a feedback control approach synchronizes better to neurobiology than canonical behavior analysis, and a paradigm shift is considered.

Plessas, Espinosa-Ramos, Parry, Cowie, and Landon utilized machine learning to detect patterns in reinforcement behavior across a range of reinforcers. They used artificial spiking neural networks on previously published pigeon datasets to detect patterns in choices. These networks can identify patterns in behavior and predict histories in groups. Computational approaches like this one can determine the types of factors that influence behavior across large groups of animals and potentially identify interventions that effectively influence future behaviors—something that could be applied to a wide range of disease states.

Because of the widespread use of progressive ratio schedules for studies of effort-based motivation and drug reinforcement, **Johnson, Christensen, Kelly, and Calipari** investigated how operant training on fixed versus variable schedules ultimately affects progressive ratio performance. They report that there was a robust training effect on progressive ratio performance, regardless of which ratio schedule was used for pretraining. Further, response rates during training were correlated with progressive ratio extinction performance.

Ren, Carratala-Ros, Ecevitoglu, Rotolo, Edelstein, Presby, Stevenson, Chrobak, and Salamone report on the effects of tetrabenazine, a vesicular monoamine transporter inhibitor, on responding under a fixed ratio schedule of reinforcement using high-carbohydrate food pellets as reinforcers in the presence of freely available chow. Tetrabenazine, at a dose that preferentially depletes dopamine, decreased lever pressing while increasing chow intake. A detailed behavioral analysis revealed how behavior was affected to produce this shift. Ren et al. conclude that such detailed analyses will be useful for insights into the clinical effects of tetrabenazine and other vesicular monoamine transporter inhibitors in humans.

Torres, Khan, Fernandez-Kim, Spann, Albarado, Wagner, Morrison, and Soto used a single-case experimental design approach combined with a multilevel linear analysis to evaluate the effects of dietary protein restriction on body weights, food consumption, and preference for protein solution in C57BL/6J mice and Fgf21 knockout mice that do not express the liver-derived hormone FGF21. The effects of dietary protein restriction in C57BL/6J mice—decreased rate of weight gain, increased food consumption, and increased preference for protein solution—reverse when dietary protein levels are restored to normal and those effects are absent in Fgf21 knockout mice. Torres and colleagues argue that the reversibility of dietary protein effects allows for the application of single-case experimental designs to the study of the brain signaling pathways that mediate the effects of dietary protein restriction and establish that such effects can be demonstrated at the level of individual mice.

Concurrent chain procedures are often used to study choice, preference, and reinforcement. The **Hughes, Langford, Van Heukelom, Blejewski, and Pitts** article describes how concurrent chain procedures can be modified to study reinforcement factors involved in impulsive choice. Their findings indicate that this approach offers insight into possible methods for studying the complex neurobiological mechanisms regulating behavior in individual organisms.

Strickland, Stoops, Banks, and Gipson, in a theoretical commentary, apply three logical fallacies including circular explanation, affirming the consequent, and reification to commonly utilized behavioral models in the addiction neuroscience field. The authors describe how these logical issues may lead the field to conclude that causes of behavior relevant to drug use have been found when they actually have not. Alternative strategies are suggested for refocusing research with behavioral models in the hope that the translational links between animal models and clinical studies can be strengthened.

Nunes, Kebede, Bagdas, and Addy review the literature on dopaminergic and cholinergic modulation of motivated behaviors with a focus on work using effort-choice tasks. They suggest that these tasks permit assessment of motivational changes of behavior. Further, the authors highlight the importance of cholinergic transmission and its dysregulation in substance use/misuse and well as mood disorders.

Regnier, Lile, Rush, and Stoops provide a review of the human clinical laboratory research on the reinforcing effects of cocaine. Along with a thorough discussion of how dopaminergic and nondopaminergic drugs impact measures of cocaine reinforcement, the authors provide suggestions for future research aimed at improving our understanding so as to improve approaches to understanding cocaine reinforcement and its associated misuse.

Doyle, Gannon, Mesmin, and Collins survey preclinical studies focused on identifying determinants of polydrug abuse. The authors advocate for the use of sophisticated statistical techniques (i.e., dose-addition analysis) to distinguish between additivity and synergy when two or more drugs are combined. As such, dose-addition analysis can be applied to a variety of drug use-related endpoints to better understand the behavioral pharmacology of polysubstance use.

Nall, Chalhoub, and Kalivas present a within-subject model of self-administration, drug versus food choice, extinction, and cued reinstatement of cocaine- and food-seeking in rats. They assess biological sex and include proof of concept data on how this model could be used with neural recording techniques. This study highlights the importance of using complex reinforcement paradigms to understand the competing factors that influence behavior in animal models of substance use disorder.

In a comprehensive empirical report, **Gutierrez, Creehan, de Guglielmo, Roberts, and Taffe** detail a cost-effective approach for studying ethanol and its behavioral effects in crayfish (*Procambarus clarkii*). They evaluated alterations in locomotor behavior in an open field arena as well as approach–avoidance behavior in a light–dark box. This research establishes the feasibility for using this model system to study the behavioral and pharmacological effects of ethanol.

In an empirical study, **Grant and colleagues** examined the role of the putamen, a region within the sensory-motor corticostriatal network involved in automatic, habitual actions, in the highly automated behavior of schedule-induced polydipsia (SIP). In rhesus monkeys, SIP for ethanol or water was established before inhibiting the putamen using a chemogenetic approach. Putamen inhibition induced

reversible and reliable increases in adjunctive drinking of ethanol and water.

Banks, Hutsell, and Negus had rhesus monkeys trained on a drug-versus-food choice operant task where cocaine and heroin elicited robust drug choice. Discriminative cues associated with drug self-administration were extinguished through extinction training; however, this failed to decrease drug choice. Together, this set of studies do not support the effectiveness of extinguishing drug-associated discriminative stimuli as a nonpharmacological treatment strategy for reducing drug choice in primates.

In an empirical study by **O'Brien, Vemireddy, Mohammed, and Barker**, the link between stress susceptibility and opioid use was examined. Specifically, a battery of behavioral tests was employed to determine how a history of stress impacts fentanyl-seeking behavior, and to identify individual differences in opioid use susceptibility.

Espinoza, Giner, Liano, Mendez, and O'Dell report a laboratory study on passive delivery of nicotine vapors to adolescent and adult female and male rats. They describe notable sex and age differences. Specifically, female rats approached the source of the nicotine vapor more than male rats and this effect was more profound in adolescence. Implications for these differences are considered.

Drug stimulus effects can be altered by learning history in ways that influence drug reinforcement. In an empirical study, **Barrett and Bevins** found that appetitive conditioning of the stimulus effects of nicotine increased later total nicotine intake relative to control rats which received equal—but temporally noncontiguous—conditioning. This study introduces a new methodology that allows for the direct investigation of the interaction between a drug's interoceptive stimulus effects and its reinforcing effects, and how learning shapes that interaction.

Dean and Ward detail results from a systematic series of studies on the rodent maternal immune activation (MIA) model of schizophrenia risk. They highlight the importance of operant procedures, within which procedural variables can be manipulated precisely, to the dissection of the behavioral and neurophysiological phenotype of the rodent MIA model including abnormal time perception, cognition, learning, motivation, and discrimination of internal states. They conclude that broader use of these procedures will provide insights into psychiatric disorders.

Using a valproate rat model of autism spectrum disorder, **Galizio and Odum** tested behavioral variability using a reinforced-behavioral-variability operant task. In this empirical study, valproate-exposed and control rats behaved similarly when variability was required in the task, but behavior was slightly more variable in the valproate-exposed group as compared to control when variability was not required.

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