Symposium

Listening to the Data: Computational Approaches to Addiction and Learning

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Computational approaches hold great promise for identifying novel treatment targets and creating translational therapeutics for substance use disorders. From circuitries underlying decision-making to computationally derived neural markers of drug-cue reactivity, this review is a summary of the approaches to data presented at our 2023 Society for Neuroscience Mini-Symposium. Here, we highlight data- and hypothesis-driven computational approaches that recently afforded advancements in addiction and learning neuroscience. First, we discuss the value of hypothesis-driven algorithmic modeling approaches, which integrate behavioral, neural, and cognitive outputs to refine hypothesis testing. Then, we review the advantages of data-driven dimensionality reduction and machine learning methods for uncovering novel predictor variables and elucidating relationships in high-dimensional data. Overall, this review highlights recent breakthroughs in cognitive mapping, model-based analysis of behavior/risky decision-making, patterns of drug taking, relapse, and neuromarker discovery, and showcases the benefits of novel modeling techniques, across both preclinical and clinical data.

Introduction

Substance use disorder (SUD) is a chronic, relapsing brain disease characterized by continued drug use despite negative consequences. To receive an SUD diagnosis (using Diagnostic and Statistical Manual of Mental Disorders, Ed 5), individuals must exhibit significant impairment or distress and meet at least 2 of 11 symptoms that fit within categories of impaired control, risky drug use, social problems, and pharmacological effects, within a 12 month period (American Psychological Association, 2013; Suzuki and Kober, 2018). The 2021 National Survey on Drug Use and Health reports that 46.3 million people in the United States (12 years or older) met criteria for an SUD in the past year, and 43.7 million were classified as needing SUD treatment (Substance Abuse and Mental Health Services Administration, 2021, 2022). However, the multidimensional nature of this disorder complicates treatment. Despite decades of research, effective treatments for substance use disorder remain elusive. Identifying effective treatments requires collaboration between clinical and preclinical research to facilitate a unified understanding of the nature of SUDs. Targets identified by clinical neurobiological research can be probed preclinically in tightly controlled experiments to identify therapeutic potential (Venniro et al., 2020). Identified treatments can then follow the translational pipeline to test efficacy in humans.

In April 2013, the National Institute of Health launched the BRAIN Initiative (Brain Research through Advancing Innovative Neurotechnologies), with the goal of revolutionizing our present understanding of the brain, and to advance treatments through prioritizing support of the development of neurotechnologies (National Institutes of Health, 2013). The need for management of the rich data afforded by these approaches has increased exponentially, a challenge requiring the use of data-driven and/or theory- or model-driven computational tools (Yip and Konova, 2023). Data-driven tools can reduce dense, complex, and high-dimensional datasets to digestible representations that uncover underlying patterns. Theory-driven tools use functional or neurocomputational hypotheses to guide the interpretation of contained data collections in a process of falsification/validation testing. The field of computational psychiatry has evolved to approach data using hybrid models that incorporate both data- and theory-driven analyses (Yip and Konova, 2023).

While computational approaches are not new to the study of psychopathology in general (Wang and Krystal, 2014) and addiction research in particular (Redish et al., 2008; Mollick and Kober, 2020; R. Smith et al., 2021; Kato et al., 2023), they have primarily been used to analyze behavioral data from human and animal studies or as tools that offer interesting theoretical frameworks, and have yet to have a significant impact on clinical practice (Hitchcock et al., 2022; Karvelis et al., 2023). Human

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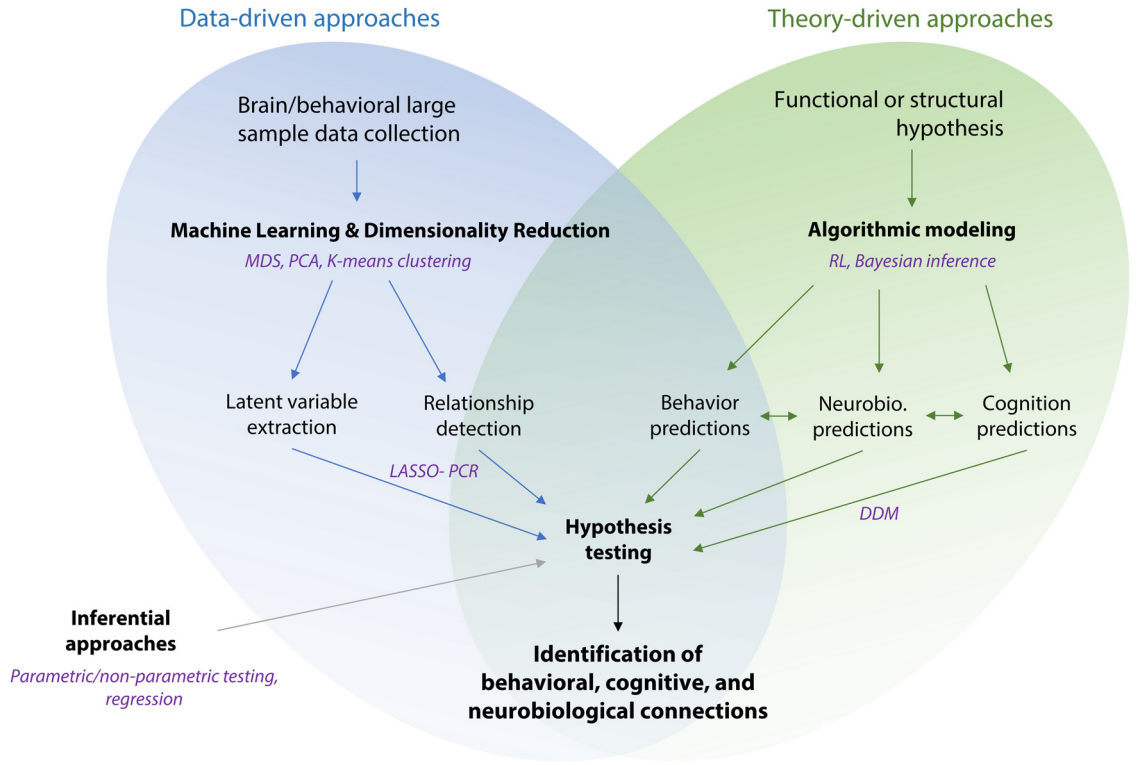

Figure 1. Schematic representation of data- and theory-driven approaches to addiction and learning neuroscience data analysis that were reviewed here (italicized in purple). MDS = multidimensional scaling, PCA = principal component analysis, LASSO-PCR = least absolute shrinkage and selection operator–principal component regression, RL = reinforcement learning, DDM = drift diffusion modeling.

subjects research requires large sample sizes because of increased variability arising from genetic and environmental heterogeneity. When demographic and genetic information is considered in statistical models, the number of independent variables necessitates more complex data analysis approaches. Animal studies have independent variables that are well controlled (e.g., age, environment, strain, sex); thus, data analysis has historically been approached using inferential statistics with few target-dependent variables of interest. However, in recent years, advancement in tools to assess neurobiology and increased emphasis on investigating sex differences, polysubstance use, and SUD comorbidities have resulted in complex datasets and a need for preclinical researchers to consider additional statistical approaches. Overall, the field of computational psychiatry is on the rise, and computational tools have the potential to elucidate the neurobiology of motivated behavior and advance effective SUD treatment development (Wang and Krystal, 2014; Adams et al., 2016; Huys et al., 2016; Yip et al., 2022; Karvelis et al., 2023).

The current review showcases the approaches featured in the 2023 Society for Neuroscience Mini-Symposium panel, "Listening to the Data: Novel Computational Approaches to Addiction and Reward Processing," and is not intended to provide a comprehensive review of the field. First, we consider the value of classic inferential statistics and their limitations. Then, we discuss the impact of algorithmic, dimensionality reduction, and machine learning approaches in the field to date, and discuss the advantages, challenges, and utility of these methods for future research (Fig. 1).

Classic inferential approaches

Classical inferential statistics have been traditionally used for hypothesis testing (e.g., χ^2, t tests, ANOVAs) and/or to analyze relationships between independent variables and one or more dependent variables (e.g., regression analyses). These methods are powerful, rigorous, and reliable when properly used, and they have advanced our understanding of the neurobiology of substance use. However, there are some limitations to their use. Many of these methods assume data normality and independence, which can be difficult to obtain in behavioral and cognitive neuroscience (Allua and Thompson, 2009). Classic inferential approaches are sensitive to outliers, and violations of normality and independence assumptions create misleading and biased results (Amon and Holden, 2021). When outlier data are removed to meet assumptions, valuable and representational data may be removed with it. Subjects of greatest interest to addiction research may lie in the extremes of resultant data (e.g., are higher drug-seekers). Additionally, classic inferential statistics are challenged when multiple hypotheses are tested at the same time, leading to increased Type 1 errors (false positives) (P. F. Smith, 2017), and corrections for multiplicity on large datasets can be problematic, leading to overly limiting or powerful comparisons (Berry, 2007). Moreover, given that most hypotheses can only be tested in terms of "X statistically different from Y," these approaches have difficulty capturing complex relationships and interactions of pathogenic components that characterize psychiatric disorders, including SUDs.

Computational approaches can address some of these challenges. They can facilitate the processing of large and diverse datasets and provide model-based hypotheses to guide data collection and analysis. They can be used to model behavioral, cognitive, and neural processes; uncover new variables; detect patterns; and integrate multiple data modalities. We suggest that there are certain contexts in which computational methods may

yield more useful and valid results, and that these approaches can supplement findings from classic methods to explore deeper meaning in extracted data. In the following sections, we will expand on a few notable examples, including the use of reinforcement learning algorithms, Bayesian inference, evidence accumulation models, multidimensional scaling, and principal component regression.

Algorithmic models

Here, we loosely use the term "algorithmic models" to describe mathematical frameworks by which complex relationships between neurobehavioral variables are formally stated in a set of rules describing the expected impact that a variable's state change has on its related variables. Such algorithmic models have been extensively used in addiction neuroscience (Redish et al., 2008; Mollick and Kober, 2020; R. Smith et al., 2021; Kato et al., 2023). These approaches allow us to disentangle and measure complex, dynamic behavioral constructs that are otherwise ambiguous and hard to quantify. Fitting behavioral (or neural) data to algorithms allows for testing of specific quantitative hypotheses about the structure of decision-making or cognitive processes and their plasticity (e.g., because of learning or neuro-modulation), mapping precise psychological constructs to experimental results. These algorithms provide generative value, informing future work and analyses, and aiding the interpretation of extant data (Tolomeo et al., 2021).

Algorithms based on reinforcement learning have already advanced our understanding of maladaptive decision-making, which is a hallmark of SUDs (Redish, 2004). Within this framework, goal-directed decision-making requires the selection and execution of one behavior in response to stimuli, followed by appraisal of that choice, and adjustment of future decisions given past outcomes to obtain the optimal outcome. Computationally, goal-directed behavior may be best represented by model-based reinforcement learning frameworks, while compulsive behavior may be best represented by model-free frameworks (Dayan and Niv, 2008; Daw et al., 2011; Montague et al., 2012; Dolan and Dayan, 2013; Voon et al., 2017). This proposed model-based/model-free dichotomy is consistent with the theory proposed by Everitt and Robbins (2016) that the transition from voluntary, recreational (goal-directed) drug use to compulsive, habitual use underlies the maladaptive decision-making pattern that characterizes SUD.

In a recent publication, Costa et al. (2023) created a novel model-based reinforcement learning algorithm to characterize the role of the lateral orbitofrontal cortex (lOFC) in learning, in male rats. The authors inhibited the lOFC during the initial training of two outcome-specific associations, and later tested whether a cognitive map was properly formed in a reinforcer devaluation probe. Classical inferential analyses suggested that lOFC inactivation impaired model-based learning but revealed little about the underlying cognitive mechanisms. Several reinforcement learning models were then fit to individual behavioral responses, and this showed that it was unlikely that the lOFC was responsible for deploying associative representations during model-based task performance (one of the leading hypotheses in the field), or for creating cognitive maps per se (a competing interpretation). Instead, reinforcement learning algorithms revealed a circumscribed role of the lOFC in creating outcome-specific maps, essentially determining the resolution of learned associations. This detailed interpretation was only possible by comparing the fits and predictions of precise algorithmic models. Critically, lOFC dysfunction and the inability to properly form cognitive maps are thought to be a key feature of SUDs (Schoenbaum et al., 2016); and being able to dissociate subtle cognitive variables, as was done in this study, is an important step toward understanding how changes in brain function can lead to behavioral pathology.

Bayesian approaches are widely used in computational psychiatry, both in the context of modeling human and animal cognition (e.g., in estimations of precision/uncertainty in perception and decision-making) (Diaconescu et al., 2014, 2017; Ma and Jazayeri, 2014; Stephan and Mathys, 2014) and in Bayesian data analysis of computational methods (Lee, 2011; Ahn et al., 2014; Vandekerckhove et al., 2018; Lee et al., 2019). However, Bayesian inference approaches are relatively new in SUD data analysis, with distinct strengths compared with other methods (R. Smith et al., 2021; Kato et al., 2023). Frequentist (non-Bayesian) models underperform when accounting for enhanced habitual responding in drug users (Lim et al., 2019), or when reward-seeking behaviors are not cue-induced (Kato et al., 2023). Bayesian inference models, in comparison, overcome these limitations by computing an agent's states, actions, and outcomes as probability distributions (equivalent to priors and posteriors in Bayes' theorem). Priors update to posteriors based on a prediction error signal, which is hypothesized to be encoded by dopamine phasic bursts, representing the discrepancy between one's beliefs and actual observations (Friston et al., 2012). Expanding on this line of thought, Kato et al. (2023) proposed that Bayesian inference models cannot only extend the explanatory potential of reinforcement learning theories, but also incorporate behavioral addictions (i.e., gambling), which may not depend so heavily on the reward/cost function. In contrast, reinforcement learning reward prediction error-based theories heavily pivot on the reward value because they assume that decision-making alterations are caused by dopamine-related, drug-induced alterations determining the reward/cost function instigating motivated behavior.

Evidence accumulation models, such as the drift diffusion model (DDM), are another category of algorithmic models that allow for analysis of the latent cognitive processes involved in decision-making (Ratcliff, 1978; Myers et al., 2022). These models can account for choices as well as shapes and locations of reaction time data simultaneously, a feature that allows them to successfully explain complex behavioral data from decision-making tasks. Initially developed to explain simple, two-choice perceptual decisions in humans (Ratcliff, 1978), the DDM deconstructs the decision-making process into key contributing factors: the decision starting point, the information accumulation rate toward an option, thresholds that determine the required quantity of information before decision-making, and the contribution of nondecision elements (e.g., sensory and motor processing) to the total response time. Use of the DDM can reveal differences between groups in underlying cognitive processes, despite behavioral profiles looking similar when analyzed using traditional methods. DDMs have been successful in modeling decision-making across numerous domains (both perceptual and value-based), including in aging, child development, clinical populations, and animal species (Ratcliff, 1978; Myers et al., 2022). Further, correlates of the processes described by DDMs have been validated through neural and brain activity measures (e.g., electrophysiology, EEG, fMRI) (Gupta et al., 2021).

DDMs have been used to model the psychological and neurobiological processes in substance-related and addictive disorders in humans. In comparing ex-nicotine smokers and current daily smokers on a value-based decision-making task, drift diffusion modeling revealed that ex-smokers were more cautious in making value-based decisions about tobacco-related cues than current

daily smokers (Copeland et al., 2023). To investigate the effect of binge-drinking intoxication and hangover on response selection, DDM and EEG were combined, revealing that acute intoxication decreases information accumulation rates and shortens nondecision information encoding times which were related to specific changes in EEG event-related potentials (Stock et al., 2017). In gambling disorder, the use of DDM has linked reduced decision thresholds (less cautious responding) with increased risky choice and active gambling (Peters and D'Esposito, 2020; Peters et al., 2020; Bruder et al., 2021).

Preclinical behavioral tasks commonly incorporate two-choice decision-making components, which yield data that are ideal for DDM analysis; however, DDMs are underutilized in animal studies. DDM parameters represent common cognitive processes (not necessarily task- or species-dependent) that are comparable between paradigms. By using all choice data and the full shape of the reaction time distributions for these choices, rather than traditional metrics such as the mean and SD in classical inferential approaches, DDMs allow for the uncovering of underlying decision-making processes that drive behavior. DDMs can also be incorporated in reinforcement learning models as the decision rule for action selection in place of softmax (Fontanesi et al., 2019), which allows for concurrent investigation of reward learning and decision-making. Increased application of DDMs to rodent behavioral datasets may provide novel insight into the underlying cognitive processes and neural substrates that contribute to maladaptive decision-making in addictions as well as improve interpretability and relevance of findings from animal models of addiction to humans (Hales et al., 2023).

An implementation of the DDM that uses hierarchical Bayesian methods to estimate model parameters, the hierarchical Bayesian estimation of the drift diffusion model (HDDM) (Wiecki et al., 2013), can simultaneously estimate individual values and group distributions while providing more precise parameter estimates. The HDDM can be used to investigate how trial-by-trial measurements, such as outcomes from fMRI, influence decision-making processes. In preclinical settings, HDDM has the potential to better model latent cognitive variables at play during multiple-choice paradigms where an animal must decide whether to seek a drug or a nondrug reward (food, social interaction, etc.) (Ahmed et al., 2013). HDDM can readily detect dependencies of latent parameters on different brain measures (Wiecki et al., 2013), such as Ca^{2+} influx dynamics, neuronal firing, or neurotransmitter release, offering an unparalleled opportunity to reveal novel abnormal cognitive processes underlying excessive drug reinforcement and subsequent displacement of alternative rewards. As models evolve in sophistication and require inclusion of numerous parameters, integration with other types of methodologies, such as dimensionality reduction (discussed below), can be useful to help identify the key features explaining behavior.

Dimensionality reduction approaches and machine learning

The neurobiology of SUD is inherently complex. SUDs are commonly comorbid with other psychiatric disorders (Udo and Grilo, 2019; National Institute on Drug Abuse, 2020). Additional consideration of genetic factors, environmental influences, polysubstance use, sex differences, and individual variability yields intricate datasets that are challenging to interpret. Dimensionality reduction methods are valuable tools to reduce complexity while retaining essential information. Two notable approaches to analyze this type of data, principal component analysis (PCA) and MDS, are unsupervised machine learning algorithms that reduce data dimensionality and noise, prevent overfitting, and increase interpretability. As with reinforcement learning algorithms, the use of dimensionality reduction is not new and has been previously applied in addiction research (Konu et al., 2001; Kramer et al., 2010; Maremmani et al., 2017; Hoffmeister et al., 2019; Tan et al., 2020; Dunn et al., 2023). While similar in goal, the methods and approaches differ. MDS focuses on the correlational relationships between variables and maps them onto two-dimensional space for visualization, while PCA transforms such relationships into new variables, called principal components, that capture the covariance in data (Hout et al., 2013; Jolliffe and Cadima, 2016). The resulting principal components can represent a hidden variable, not directly measurable in the experimental design, but patent in the set of interrelationships found between the observations obtained. In this way, these methods are valuable for exploratory and confirmatory data analysis, pattern recognition, and to elucidate relationships that were not yet apparent from the use of classical approaches in addiction research.

Principal components identified by PCA can be applied as new independent variables in classical inferential analyses, such as linear regression. Linear regression is sensitive to multicollinearity, departures from normality, and overfitting of multidimensional data. Principal component regression (PCR) is a two-step process by which new independent variables are first uncovered by PCA, and then fit as regressors in a subsequent model. By first reducing dimensionality through PCA, this approach alleviates issues of multicollinearity and overfitting. Further, it transforms the data into experimental outcomes predicted by underlying constructs or processes, revealing relationships not directly observed through experimental outcome measurements.

In a few notable examples from recent years, PCA has aided in the characterization of precipitated withdrawal symptoms following opioid antagonist or partial agonist administration (Dunn et al., 2023) and helped identify common personality traits among drug users for comorbidity theory development (Maremmani et al., 2017). This method helped classify features of alcohol craving unique to those with alcohol use disorder (Kramer et al., 2010), discerned factors predictive of alcohol use disorder development (Hoffmeister et al., 2019), and identified genetic-behavioral endophenotypes underlying vulnerability to excessive drug-seeking (Flagel et al., 2016; Slosky et al., 2022). PCA has also advanced our understanding of addiction neurobiology in revealing the protective effect of luteolin (a flavonoid) reducing meth-induced neurotoxicity is because of intricate changes in striatal PI3K/AKT intracellular cascades in male rats (Tan et al., 2020).

Recently, Luján et al. (2023) used PCR to elucidate valuable information from NAc fiber photometry readouts during cocaine self-administration in mice. Cocaine-evoked dopamine transients were recorded from male and female mice during every drug interaction throughout self-administration, extinction, and cue-induced reinstatement. Both classical inferential analysis (Pearson's correlations) and PCR identified a significant relationship between cue-evoked dopamine transients and reinstatement. However, only PCR detected a relationship between drug-evoked dopamine transients, characterized by increases in dopamine fluorescence following intravenous drug delivery, and relapse incidence, because of the high dimensionality of the resultant data. Individual dopamine measurements were first reduced by PCA to three low-dimensional representations of drug-evoked dopamine reactivity, accounting for 75% of all dopaminergic variance. Then, the principal components were applied as regressors to predict cue-induced

reinstatement of cocaine-seeking. PCR revealed that the low-dimensional representations of drug-evoked dopaminergic reactivity accurately predicted reinstatement, accounting for 73% of the observed variance (increased to 82% when considering sex). In this case, a computational approach was better fit for the complex data output than classical approaches. In the same study, variations in accumbal dopamine release were examined between male and female mice. A conventional inferential approach (averaged fluorescence amplitude Student's *t* tests) identified numerous sex differences, seemingly incongruent with the comparable levels of relapse behavior in both sexes. By revisiting the low-dimensional representation of dopamine responses from PCA, a shared pattern of dopamine release was found, reconciling the neural and behavioral findings. This highlights the potential utility of PCA in revealing hidden patterns and associations within the data, which may not be immediately apparent using traditional inferential analyses alone.

Challenges to data analysis are presented when a dataset contains a large number of predictors relative to a dependent outcome with limited data points, or a low sample size. The least absolute shrinkage and selection operator–principal component regression (LASSO-PCR) algorithm was developed to overcome this challenge. LASSO-PCR is a multistep machine learning approach similar to the PCR method mentioned above. First, PCA reduces dimensionality by identifying principal components. The principal components are then fit as regressors to a linear regression model with a LASSO algorithm, which refines the prediction, aiding in variable selection (Tibshirani, 1996). Using this method, Koban et al. (2023) found that whole-brain activity evoked by visual cues of drugs in adults with SUDs and their matched controls can predict self-reported craving ($p < 0.0002$) as well as discriminate between drug users and nonusers with a high degree of cross-validated accuracy (82%). After performing dimensionality reduction of brain-wide fMRI using data and identifying brain networks characterized by high covariation of voxels (PCR), the LASSO algorithm implemented a refinement to the prediction (in this case, reported feelings of craving) by penalizing the contribution of less relevant principal components. The analysis arising from LASSO-PCR permitted the determination of a Neurobiological Craving Signature, encompassing cue-evoked brain activity patterns from the ventromedial PFC, ventral striatum, supplementary motor area, and anterior midcingulate cortex, as a reliable predictor of self-reported drug craving and classifier of drug use status (Koban et al., 2023). This work indicates the potential for the identification of objective diagnostic, prognostic, and predictive neural markers of drug craving and relapse in humans (Food & Drug Administration-National Institutes of Health Biomarker Working Group, 2016). To the best of our knowledge, we are unaware of other applications of this method in SUD research.

Compared with PCR approaches, MDS is less widely used in addiction neuroscience. As mentioned above, MDS permits the visualization of interrelationships of multiple variables of interest in two-dimensional space. Commonly, an additional unsupervised machine learning algorithm, *K*-means clustering, is used to segment these visualized data into groups based on similarity, with "*K*" representing the number of desired clusters. MDS used with *K*-means clustering has revealed previously unseen relationships between pain sensitivity and opioid reward in rodents (Brice-Tutt et al., 2023).

Additionally, MDS has been used to uncover complex relationships between sex, alcohol and oxycodone co-use, and neural activation in rats (Wilkinson et al., 2023). In this model, male and female rats self-administered oxycodone for 3 h followed by 6 h access to two-bottle choice alcohol/water. Economic demand for oxycodone was assessed, followed by reestablishment of baseline consumption of one (oxycodone or alcohol) or both (oxycodone+alcohol) drugs, extinction, and cue-induced reinstatement testing. Brains were processed and analyzed for mesolimbic c-fos mRNA expression immediately following reinstatement. Classic inferential statistics (ANOVA) revealed no differences in oxycodone demand parameters or c-fos expression between oxycodone-only and alcohol+oxycodone-consuming male rats. However, MDS with *K*-clustering revealed dissimilarities in recruited brain regions during cued reinstatement of oxycodone-seeking: c-fos in the BLA, NAc core, and shell, related to reinstatement in oxycodone-only males, while c-fos in the dorsal striatum and prelimbic cortex related to reinstatement in male rats exposed to alcohol+oxycodone polysubstance use (Wilkinson et al., 2023). These findings highlight the utility of such approaches: while there may be no identifiable differences between groups (statistically equivalent in dependent variable measures), the complex interaction of independent variables (drug intake and frequency, brain regions recruited, etc.) may be different between sexes and drug groups.

While many are exposed to substances, there is a wide variation of responses, with only a subset that develop an SUD. Attempting to model this variability in preclinical models, dimensionality reduction and clustering approaches are gaining traction to identify vulnerable subpopulations of animals that model this heterogeneity in clinical populations. Recently, Jadhav et al. (2022) used a combined machine learning-assisted clustering approach based on *K*-median (for cocaine) and *K*-means (for alcohol) in combination with an artificial neural networks approach that allowed for reliable classification of vulnerability and resilience to addiction-like behavior in rodents across cohorts. In a separate approach, Allen et al. (2021) combined data- and theory-driven approaches in use of a Bayesian degree-corrected stochastic block model (DCSBM) to identify resilient, intermediate, and susceptible subpopulations to opioid vulnerability.

In summary, unsupervised machine learning algorithms directed at pattern recognition and component analysis are important tools for uncovering patterns related to substance use in animals and humans. Specifically, incorporating such approaches alongside, or in combination with, classic inferential statistics enables the identification of relationships not easily observed with traditional methods alone.

In conclusion, in the field of addiction neuroscience, computational approaches are not yet widely adopted, potentially limiting a comprehensive understanding of the neurobiology underlying SUDs and hindering the identification of effective treatments. Here, we highlighted several computational approaches to data analysis that offer distinct advantages, and that will be featured at our 2023 SFN Mini-Symposium. We reviewed the contexts in which computational approaches yield more valid and translationally relevant results than classic inferential approaches, such as when data dimensionality or multicollinearity is high (MDS and PCA), when datasets have a large number of predictors with a limited number of dependent measures or low sample sizes (LASSO-PCR), and when cognitive mapping, learning, and decision-making processes are involved (reinforcement learning, Bayesian inference, and DDM). These methods have revolutionized our conception of addiction through use of objective, highly predictive neural diagnostic markers (Koban et al., 2023). They

have identified drug addiction endophenotypes, valuable for the future of precision treatments based on individual differences in animals (Fiore et al., 2018), and promoted theory development on brain regions associated with the transition from voluntary to compulsive drug use (Lucantonio et al., 2014). It is our hope that the present review will encourage the use of computational methods alongside existing approaches to deepen our understanding of extant data, drive hypothesis and framework development, and enable valuable predictions toward advancing addiction neuroscience. By leveraging the power and utility of computational approaches to reward and addiction neuroscience data, the field can move closer toward novel target identification and treatment development.

References

Adams RA, Huys QJ, Roiser JP (2016) Computational psychiatry: towards a mathematically informed understanding of mental illness. J Neurol Neurosurg Psychiatry 87:53–63.

Ahmed SH, Lenoir M, Guillem K (2013) Neurobiology of addiction versus drug use driven by lack of choice. Curr Opin Neurobiol 23:581–587.

Ahn WY, Vasilev G, Lee SH, Busemeyer JR, Kruschke JK, Bechara A, Vassileva J (2014) Decision-making in stimulant and opiate addicts in protracted abstinence: evidence from computational modeling with pure users. Front Psychol 5:849.

Allen C, Kuhn BN, Cannella N, Crow AD, Roberts AT, Lunerti V, Ubaldi M, Hardiman G, Solberg Woods LC, Ciccocioppo R, Kalivas PW, Chung D (2021) Network-based discovery of opioid use vulnerability in rats using the Bayesian stochastic block model. Front Psychiatry 12:745468.

Allua S, Thompson CB (2009) Inferential statistics. Air Med J 28:168–171.

American Psychological Association (2013) Diagnostic and statistical manual of mental disorders, Ed 5 (DSM-5). Washington, DC: American Psychological Association.

Amon MJ, Holden JG (2021) The mismatch of intrinsic fluctuations and the static assumptions of linear statistics. Rev Philos Psychol 12:149–173.

Berry DA (2007) The difficult and ubiquitous problems of multiplicities. Pharm Stat 6:155–160.

Brice-Tutt AC, Montgomery DS, Kramer CM, Novotny PM, Malphurs WL, Sharma A, Caudle RM, Bruijnzeel AW, Setlow B, Neubert JK, Murphy NP (2023) An ethogram analysis of cutaneous thermal pain sensitivity and oxycodone reward-related behaviors in rats. Sci Rep 13:10482.

Bruder LR, Scharer L, Peters J (2021) Reliability assessment of temporal discounting measures in virtual reality environments. Sci Rep 11:7015.

Copeland A, Stafford T, Field M (2023) Recovery from nicotine addiction: a diffusion model decomposition of value-based decision-making in current smokers and ex-smokers. nicotine. Nicotine Tob Res 25:1269–1276.

Costa KM, Scholz R, Lloyd K, Moreno-Castilla P, Gardner MP, Dayan P, Schoenbaum G (2023) The role of the lateral orbitofrontal cortex in creating cognitive maps. Nat Neurosci 26:107–115.

Daw ND, Gershman SJ, Seymour B, Dayan P, Dolan RJ (2011) Model-based influences on humans' choices and striatal prediction errors. Neuron 69:1204–1215.

Dayan P, Niv Y (2008) Reinforcement learning: the good, the bad and the ugly. Curr Opin Neurobiol 18:185–196.

Diaconescu AO, Mathys C, Weber LA, Daunizeau J, Kasper L, Lomakina EI, Fehr E, Stephan KE (2014) Inferring on the intentions of others by hierarchical Bayesian learning. PLoS Comput Biol 10:e1003810.

Diaconescu AO, Mathys C, Weber LA, Kasper L, Mauer J, Stephan KE (2017) Hierarchical prediction errors in midbrain and septum during social learning. Soc Cogn Affect Neurosci 12:618–634.

Dolan RJ, Dayan P (2013) Goals and habits in the brain. Neuron 80:312–325.

Dunn KE, Bird HE, Bergeria CL, Ware OD, Strain EC, Huhn AS (2023) Operational definition of precipitated opioid withdrawal. Front Psychiatry 14:1141980.

Everitt BJ, Robbins TW (2016) Drug addiction: updating actions to habits to compulsions ten years on. Annu Rev Psychol 67:23–50.

Fiore VG, Ognibene D, Adinoff B, Gu X (2018) A multilevel computational characterization of endophenotypes in addiction. eNeuro 5: ENEURO.0151-18.2018.

Flagel SB, Chaudhury S, Waselus M, Kelly R, Sewani S, Clinton SM, Thompson RC, Watson SJ, Akil H (2016) Genetic background and epigenetic modifications in the core of the nucleus accumbens predict addiction-like behavior in a rat model. Proc Natl Acad Sci USA 113: E2861–E2870.

Fontanesi L, Gluth S, Spektor MS, Rieskamp J (2019) A reinforcement learning diffusion decision model for value-based decisions. Psychon Bull Rev 26:1099–1121.

Food & Drug Administration-National Institutes of Health Biomarker Working Group (2016) BEST (Biomarkers, EndpointS, and other Tools) Resource. Bethesda, MD.

Friston KJ, Shiner T, FitzGerald T, Galea JM, Adams R, Brown H, Dolan RJ, Moran R, Stephan KE, Bestmann S (2012) Dopamine, affordance and active inference. PLoS Comput Biol 8:e1002327.

Gupta A, Bansal R, Alashwal H, Kacar AS, Balci F, Moustafa AA (2021) Neural substrates of the drift-diffusion model in brain disorders. Front Comput Neurosci 15:678232.

Hales CA, Clark L, Winstanley CA (2023) Computational approaches to modeling gambling behaviour: opportunities for understanding disordered gambling. Neurosci Biobehav Rev 147:105083.

Hitchcock PF, Fried EI, Frank MJ (2022) Computational psychiatry needs time and context. Annu Rev Psychol 73:243–270.

Hoffmeister JR, Cohoon AJ, Sorocco KH, Acheson A, Lovallo WR (2019) Addiction resistance to alcohol: what about heavy drinkers who avoid alcohol problems? Drug Alcohol Depend 204:107552.

Hout MC, Papesh MH, Goldinger SD (2013) Multidimensional scaling. Wiley Interdiscip Rev Cogn Sci 4:93–103.

Huys QJ, Maia TV, Frank MJ (2016) Computational psychiatry as a bridge from neuroscience to clinical applications. Nat Neurosci 19:404–413.

Jadhav KS, Boury Jamot B, Deroche-Gamonet V, Belin D, Boutrel B (2022) Towards a machine-learning assisted diagnosis of psychiatric disorders and their operationalization in preclinical research: evidence from studies on addiction-like behaviour in individual rats. Eur J Neurosci 56:6069–6083.

Jolliffe IT, Cadima J (2016) Principal component analysis: a review and recent developments. Philos Trans A Math Phys Eng Sci 374:20150202.

Karvelis P, Paulus MP, Diaconescu AO (2023) Individual differences in computational psychiatry: a review of current challenges. Neurosci Biobehav Rev 148:105137.

Kato A, Shimomura K, Ognibene D, Parvaz MA, Berner LA, Morita K, Fiore VG (2023) Computational models of behavioral addictions: state of the art and future directions. Addict Behav 140:107595.

Koban L, Wager TD, Kober H (2023) A neuromarker for drug and food craving distinguishes drug users from non-users. Nat Neurosci 26:316–325.

Konu O, Kane JK, Barrett T, Vawter MP, Chang R, Ma JZ, Donovan DM, Sharp B, Becker KG, Li MD (2001) Region-specific transcriptional response to chronic nicotine in rat brain. Brain Res 909:194–203.

Kramer JR, Chan G, Hesselbrock VM, Kuperman S, Bucholz KK, Edenberg HJ, Schuckit MA, Nurnberger JI, Foroud T, Dick DM, Bierut LJ, Porjesz B (2010) A principal components analysis of the abbreviated Desires for Alcohol Questionnaire (DAQ). J Stud Alcohol Drugs 71:150–155.

Lee MD (2011) How cognitive modeling can benefit from hierarchical Bayesian models. J Math Psychol 55:1–7.

Lee MD, Gluck KA, Walsh MM (2019) Understanding the complexity of simple decisions: modeling multiple behaviors and switching strategies. Decision 6:335–368.

Lim TV, Cardinal RN, Savulich G, Jones PS, Moustafa AA, Robbins TW, Ersche KD (2019) Impairments in reinforcement learning do not explain enhanced habit formation in cocaine use disorder. Psychopharmacology (Berl) 236:2359–2371.

Lucantonio F, Caprioli D, Schoenbaum G (2014) Transition from 'model-based' to 'model-free' behavioral control in addiction: involvement of the orbitofrontal cortex and dorsolateral striatum. Neuropharmacology 76:407–415.

Luján MÁ, Oliver BL, Young-Morrison R, Engi SA, Zhang LY, Wenzel JM, Li Y, Zlebnik NE, Cheer JF (2023) A multivariate regressor of patterned dopamine release predicts relapse to cocaine. Cell Rep 42:112553.

Ma WJ, Jazayeri M (2014) Neural coding of uncertainty and probability. Annu Rev Neurosci 37:205–220.

Maremmani AG, Pani PP, Rovai L, Bacciardi S, Maremmani I (2017) Toward the identification of a specific psychopathology of substance use disorders. Front Psychiatry 8:68.

Mollick JA, Kober H (2020) Computational models of drug use and addiction: a review. J Abnorm Psychol 129:544–555.

Montague PR, Dolan RJ, Friston KJ, Dayan P (2012) Computational psychiatry. Trends Cogn Sci 16:72–80.
Myers CE, Interian A, Moustafa AA (2022) A practical introduction to using the drift diffusion model of decision-making in cognitive psychology, neuroscience, and health sciences. Front Psychol 13:1039172.
National Institute on Drug Abuse (2020) Common Comorbidities with Substance Use Disorders Research Report. National Institutes on Drug Abuse.
National Institutes of Health (2013) Home | BRAIN Initiative. Available at https://braininitiative.nih.gov/.
Peters J, D'Esposito M (2020) The drift diffusion model as the choice rule in inter-temporal and risky choice: a case study in medial orbitofrontal cortex lesion patients and controls. PLoS Comput Biol 16:e1007615.
Peters J, Vega T, Weinstein D, Mitchell J, Kayser A (2020) Dopamine and risky decision-making in gambling disorder. eNeuro 7:ENEURO.0461-19.2020.
Ratcliff R (1978) A theory of memory retrieval. Psychol Rev 85:59–108.
Redish AD (2004) Addiction as a computational process gone awry. Science 306:1944–1947.
Redish AD, Jensen S, Johnson A (2008) A unified framework for addiction: vulnerabilities in the decision process. Behav Brain Sci 31:415–437; discussion 437.
Substance Abuse and Mental Health Services Administration (2021) SAMHSA Announces National Survey on Drug Use and Health (NSDUH): Results Detailing Mental Illness and Substance Use Levels in 2021. Available at https://www.hhs.gov/.
Substance Abuse and Mental Health Services Administration (2022) Key Substance Use and Mental Health Indicators in the United States: Results from the 2021 National Survey on Drug Use and Health (HHS Publication No. PEP22-07-01-005, NSDUH Series H-57). Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration.
Schoenbaum G, Chang CY, Lucantonio F, Takahashi YK (2016) Thinking outside the box: orbitofrontal cortex, imagination, and how we can treat addiction. Neuropsychopharmacology 41:2966–2976.
Slosky LM, Pires A, Bai Y, Clark NB, Hauser ER, Gross JD, Porkka F, Zhou Y, Chen X, Pogorelov VM, Toth K, Wetsel WC, Barak LS, Caron MG (2022) Establishment of multi-stage intravenous self-administration paradigms in mice. Sci Rep 12:21422.
Smith PF (2017) A guerilla guide to common problems in 'neurostatistics': essential statistical topics in neuroscience. J Undergrad Neurosci Educ 16:R1–R12.
Smith R, Taylor S, Bilek E (2021) Computational mechanisms of addiction: recent evidence and its relevance to addiction medicine. Curr Addict Rep 8:509–519.
Stephan KE, Mathys C (2014) Computational approaches to psychiatry. Curr Opin Neurobiol 25:85–92.
Stock AK, Hoffmann S, Beste C (2017) Effects of binge drinking and hangover on response selection sub-processes: a study using EEG and drift diffusion modeling. Addict Biol 22:1355–1365.
Suzuki S, Kober H (2018) Substance-related and addictive disorders. In: American Psychological Association handbook of psychopathology: psychopathology: understanding, assessing, and treating adult mental disorders (Butcher JN, Hooley JM, eds), pp 481–506. American Psychological Association.
Tan XH, Zhang KK, Xu JT, Qu D, Chen LJ, Li JH, Wang Q, Wang HJ, Xie XL (2020) Luteolin alleviates methamphetamine-induced neurotoxicity by suppressing PI3K/Akt pathway-modulated apoptosis and autophagy in rats. Food Chem Toxicol 137:111179.
Tibshirani R (1996) Regression shrinkage and selection via the lasso. J R Stat Soc B 58:267–288.
Tolomeo S, Yaple ZA, Yu R (2021) Neural representation of prediction error signals in substance users. Addict Biol 26:e12976.
Udo T, Grilo CM (2019) Psychiatric and medical correlates of DSM-5 eating disorders in a nationally representative sample of adults in the United States. Int J Eat Disord 52:42–50.
Vandekerckhove J, Rouder JN, Kruschke JK (2018) Editorial: Bayesian methods for advancing psychological science. Psychon Bull Rev 25:1–4.
Venniro M, Banks ML, Heilig M, Epstein DH, Shaham Y (2020) Improving translation of animal models of addiction and relapse by reverse translation. Nat Rev Neurosci 21:625–643.
Voon V, Reiter A, Sebold M, Groman S (2017) Model-based control in dimensional psychiatry. Biol Psychiatry 82:391–400.
Wang XJ, Krystal JH (2014) Computational psychiatry. Neuron 84:638–654.
Wiecki TV, Sofer I, Frank MJ (2013) HDDM: hierarchical Bayesian estimation of the Drift-Diffusion Model in Python. Front Neuroinform 7:14.
Wilkinson CS, Blount HL, Davis S, Rojas G, Wu L, Murphy NP, Schwendt M, Knackstedt LA (2023) Voluntary alcohol intake alters the motivation to seek intravenous oxycodone and neuronal activation during the reinstatement of oxycodone and sucrose seeking. BioRxiv. 549769. https://doi.org/10.1101/2023.07.20.549769.
Yip SW, Konova AB (2023) Emerging topics in computational psychiatric research: clarity through complexity? Biol Psychiatry 93:652–654.
Yip SW, Barch DM, Chase HW, Flagel S, Huys QJ, Konova AB, Montague R, Paulus M (2022) From computation to clinic. Biol Psychiatry Glob Open Sci 3:319–328.