Chapter 14

Utility of Computational Approaches for Precision Psychiatry: Applications to Substance Use Disorders

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Abstract

Revolutionary advances in neuroscience and genetics over the past two decades have provided unprecedented opportunities for increasing our understanding of the etiology and pathogenesis of psychiatric disorders. Despite these advances, the translation of this knowledge into clinical practice has been hindered by the significant heterogeneity within disorders and the neurobiologically imprecise categorization of patients. Traditional diagnostic categories do not capture the underlying neurobiological processes and etiological mechanisms of psychiatric disorders and cannot adequately inform prognosis and treatment. To address this gap, the National Institute on Mental Health (NIMH) has proposed an alternative research framework based on Research Domain Criteria (RDoC), which yields psychiatric classification grounded on discoveries from neuroscience and genomics. Recently, the RDoC approach has been adapted for the study of addictions with the Addictions Neuroclinical Assessment (ANA) framework (Kwako et al., Biol Psychiatry 80:179–189, 2016), which proposes that the assessment of addictions should cover multiple systems and focus on three key neurofunctional domains: *Executive Function, Incentive Salience,* and *Negative Emotionality.* Building upon the aims of the RDoC framework, a new field of "precision psychiatry" has emerged, considered to be a paradigm shift in psychiatry. Both the RDoC framework and precision psychiatry are predicated on precise measurement, which has necessitated the development of novel analytic approaches for classification and novel dimensional tools for phenotyping that can identify the unique mechanisms of psychiatric disorders at an individual level.

In this chapter, we make the case that theory-driven and data-driven computational approaches have enormous potential for increasing the precision and reliability of measurement, and the accuracy of diagnosis and prognosis in psychiatry. We review three types of computational approaches and their utility for precision psychiatry: (1) *Theory-driven approaches,* such as *computational modeling*; (2) *Data-driven approaches,* using various *machine learning* methods; and (3) *Hybrid approaches*, such as *joint modeling* and *adaptive design optimization*. We focus more narrowly on the application of these approaches to substance use disorders (SUD), where we attempt to map them on the current RDoC framework for addictions.

Key words Computational modelling, Machine learning, Precision psychiatry, Addictions

Drozdstoy Stoyanov et al. (eds.), *Computational Neuroscience*, Neuromethods, vol. 199,
https://doi.org/10.1007/978-1-0716-3230-7_14,

1 Introduction

Revolutionary advances in neuroscience and genetics over the past two decades have provided unprecedented opportunities for increasing our understanding of the etiology and pathogenesis of psychiatric disorders. Despite these advances, the translation of this knowledge into clinical practice has been hindered by the significant heterogeneity within disorders and the neurobiologically imprecise categorization of patients. It is now well known that just as multiple etiological pathways may lead to the same clinical presentation, clinically distinct diagnostic categories may also be related to the same underlying transdiagnostic mechanisms. It has become increasingly apparent that traditional diagnostic categories do not capture the underlying neurobiological processes and etiological mechanisms of psychiatric disorders and cannot adequately inform prognosis and treatment. To address the gap between etiology and nosology and to improve treatment outcomes, the National Institute on Mental Health (NIMH) has proposed an alternative research framework based on Research Domain Criteria (RDoC), which yields psychiatric classification grounded on discoveries from neuroscience and genomics as a complement to the existing classification system [2]. According to the RDoC framework, psychiatric disorders should be investigated at several interacting levels of analysis, from genes, to molecules, cells, brain circuits, cognition, behavior, and environment, which has led to a progressive transition from categorical to dimensional approaches to measurement and classification.

More recently, the RDoC approach has been adapted for the study of addictions with the Addictions Neuroclinical Assessment framework (ANA; [1]) which maps on three recurrent stages of addiction: *binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation*, each associated with different neurocircuitry and functional domains [3, 4]. The ANA proposes that the assessment of addictions should cover multiple systems and focus on three key neurofunctional domains: (1) *executive function (EF)*, associated with reduced prefrontal cortex (PFC)-mediated top-down impulse control characterizing the *preoccupation/anticipation* stage of the addiction cycle, commonly associated with craving and relapse; (2) *incentive salience (IS)*, associated with phasic reward-based dopaminergic activation in the basal ganglia and the *binge/intoxication* stage of addiction; and (3) *negative emotionality (NE)*, associated with engagement of brain stress systems and the *withdrawal/negative affect* stage of addiction, characterizing periods of abstinence. Though this framework has been applied primarily to alcohol use disorder [5], more recently it has been extended to other types of substance use disorders (SUD), including opioid use disorder, cocaine use disorder, and cannabis

use disorder [6, 7]. It has been employed predominantly in the context of assessment and treatment of SUD [8], but has recently been proposed for SUD prevention [9]. A nontrivial practical limitation of the RDoC approach is that the multi-dimensional assessment that it requires entails administering lengthy assessment batteries, which may take up to 10 h of testing [1]. This is a significant rate- and cost-limiting factor, which prevents the wider implementation of the RDoC approach in clinical research and practice. Another practical limitation is that current methods for biomarker discovery such as neuroimaging and various-omics approaches are costly, invasive, and not suitable for clinical practice. Neurobehavioral assessments can overcome some of these limitations as they are noninvasive and relatively inexpensive; however, they seem to have stagnated, with many clinical neuropsychological tests developed decades ago still in use [10]. They also rely on crude summary statistics that are not particularly informative about the underlying neurocognitive processes and are minimally sensitive to individual differences, a prerequisite if a test is to have good diagnostic and predictive utility. The behavioral metrics of these tasks are most often atheoretical with respect to the underlying mechanisms and their neurocircuit signatures are poorly understood because the tasks are designed to measure broad cognitive functions (e.g., "executive functions") rather than specific neurocognitive processes. Of particular concern is the low replicability of neuropsychological and neuroimaging findings [11–13] and the surprisingly low test-retest reliability of even the most well-established neurocognitive tasks [14], where effects are reliable when measuring the behavior of groups of individuals but not when examining how an individual performs across repeated assessments [15]. This has led to a "crisis of confidence" in psychological science [13], which has made some question the existence of key psychological constructs central to addiction, such as impulsivity [16]. Critically, the "reliability paradox" [14] suggests that many fMRI-based biomarkers that use such neurocognitive tasks may also be unreliable [17–19] and that well-established approaches in cognitive psychology and neuropsychology may not directly translate to the study of individual differences in brain structure and function (but see [20, 21]). The lack of reliable, precise, and efficient neurobehavioral measures is therefore one of the most formidable challenges in measuring RDoC constructs. Clearly, novel alternate metrics are needed to measure complex behavior and neurofunctional domains.

Building upon the aims of the RDoC framework to map clinical observations on neurobiological mechanisms, a new field of "precision psychiatry" has emerged over the past few years, considered to be a paradigm shift in the field of psychiatry [22, 23]. It integrates advances in neuroscience and technology into a computational framework, with the goal to develop

personalized therapeutic approaches tailored to the specific characteristics of each individual [23]. The RDoC framework and precision psychiatry are both predicated on precise measurement, which has necessitated the development of new analytic approaches for classification and novel dimensional tools for phenotyping that can identify the unique mechanisms of psychiatric disease at an individual level. Dimensional approaches have helped identify key trans-disease processes such as delay discounting, considered key diagnostic and prognostic biomarkers of addiction [24, 25], and other types of reinforcement pathology [26]. Such approaches have helped address a critical challenge in the treatment of addiction: the significant heterogeneity within addiction to a specific drug, and the similarity of underlying processes across addictions to different drugs.

In this chapter, we make the case that theory-driven and data-driven computational approaches have enormous potential for increasing the precision and reliability of measurement, and the accuracy of diagnosis and prognosis in psychiatry. We review three types of computational approaches and their utility for precision psychiatry: (1) *theory-driven approaches,* such as *computational modeling*, which have shown utility as novel phenotyping tools that may increase the precision of neurocognitive phenotyping, refine diagnosis, and aid intervention selection; (2) *hybrid approaches*, such as *joint modeling* and *adaptive design optimization*, which increase the efficiency and reliability of neurocognitive phenotyping; and (3) *data-driven approaches* using various *machine learning* methods that are particularly useful for predictive modeling, stratification, classification, and biotyping in psychiatry. We focus more narrowly on the application of these approaches to substance use disorders (SUD), where we attempt to map them on current RDoC frameworks for addictions. We argue that increasing the precision of clinical phenotyping by integrating genetically informed personality, neurocognitive, and neuroimaging approaches within a computational framework will be critical for identifying etiological markers of different biotypes of addiction that could be targeted by modular combinations of behavioral, neurostimulatory, and pharmacological interventions, personalized to individual multivariate computational profiles.

2 Theory-Driven Approaches: Computational Modeling and Computational Phenotyping

The human brain has long been considered the archetype of computation [27], as its key function is to compute by storing and summarizing information and using that information to make predictions about the future [28, 29]. The past 10 years have witnessed the emergence of the discipline of computational psychiatry [30],

which seeks to characterize mental dysfunction in terms of aberrant computations [31]. Theory-driven computational approaches such as computational modeling have been proposed to provide a new paradigm for understanding psychopathology [28], which can help address the "explanatory gap" and lack of suitable levels of description that link findings at the molecular level to clinical entities, such as addictions and other psychiatric disorders [31, 32].

In the field of substance use disorders, computational modeling has been applied primarily to the study of decision-making, as impulsive and maladaptive decision-making is considered one of the core neurocognitive deficits of individuals with SUD and other addictive disorders [33, 34]. Indeed, many of the diagnostic criteria for SUD could be considered directly or indirectly related to abnormalities in decision-making (e.g., persistent drug use despite negative consequences, consuming larger amounts and for longer period of time than intended, persistent desire, and sense of compulsion to take the substance). In real life, individuals with SUD show profound impairments in judgment and decision-making, characterized by a tendency to choose immediate rewards, at the expense of often devastating negative consequences in the future. Such real-life impairments are typically measured with neurocognitive tasks that mimic major life contingencies in a realistic manner, such as gambling and discounting tasks that involve different reward and punishment contingencies [34, 35]. Abnormally steep delay discounting rates, indicating preference for immediate but smaller rewards, have been reliably associated with both quantity-frequency of use and with severity of SUD [35], including alcohol [36], nicotine [37], heroin [38–40], and cocaine use disorders [38, 41]. The neural systems probed by delay discounting paradigms are also well-known; therefore, delay discounting is a promising candidate for the RDoC approach [42, 43].

It is important to study decision-making with different decision tasks, to obtain converging evidence about the cognitive and affective mechanisms underlying decision-making deficits [44]. Of the various decision tasks used in the literature, the Iowa Gambling Task (IGT) [33, 45] is one of the oldest, originally developed in the early 1990s as an attempt to capture the prominent difficulties in day-to-day functioning displayed by patients with lesions of the ventromedial prefrontal cortex (vmPFC), who otherwise showed no demonstrable deficits on standard intellectual and neuropsychological tasks. It was designed to simulate real-life decision-making, defined as the ability to select the most advantageous course of action from a set of possible alternative behaviors, where decision makers learn by trial and error to choose among four decks of cards that produce both wins and losses. Impaired performance on the task is taken as an indicator of insensitivity to future consequences or "myopia for the future" [45]. The task has become one of the most widely used decision tasks in the addiction literature and is

one of the earliest for which computational cognitive models were developed. The first cognitive model for the IGT was the Expectancy Valence Learning (EVL) model, developed by Busemeyer and Stout [46]. Since then, a number of additional models have been developed to better capture the behavioral patterns of the task, such as the Prospect Valence Learning (PVL) model [47], the Value-Plus-Perseverance (VPP) model [48], and most recently the Outcome-Representation Learning (ORL) model [49]. Though individuals with SUD are consistently impaired on the task [33, 50–58], it has been difficult to discern differences in decision-making between people with different types of SUD or with different comorbid disorders based solely on the standard performance indices, because even though the task has high sensitivity to decision-making impairments in individuals with SUD, it has proven equally sensitive to capturing decision-making impairments in patients with other externalizing disorders such as antisocial personality disorder, psychopathy, and ADHD [57, 59–61].

Though gambling and discounting tasks are ecologically valid and capture important aspects of real-life functioning, they are designed to be complex and involve numerous motivational, learning, and choice processes [44, 46]. Similar to the heterogeneity of substance use and other psychiatric disorders, there is an inherent heterogeneity in the computational processes involved in such tasks, reflecting different mechanisms underlying decision-making, such as sensitivity to reward, sensitivity to loss, risk aversion, risk tolerance, ambiguity tolerance, and exploration/exploitation, among others. Consequently, impaired performance on the tasks may have many different causes [44]. Similar to how the current diagnostic classification system does not capture the numerous etiological mechanisms underlying psychiatric disorders, traditional neurobehavioral performance indices on these tasks do not capture the different underlying causes of impaired performance. Computational modeling of such cognitively complex tasks have proven much more informative in this regard, as they deconstruct neurobehavioral performance into underlying latent processes, and use the parameter estimates of these processes to understand the specific mechanisms underlying the neurocognitive deficits manifested by different clinical populations [46, 50, 62].

Findings in the addiction literature consistently reveal that computational model parameter estimates of different psychological processes involved in decision-making are more sensitive to dissociating substance-specific and disorder-specific neurocognitive profiles than standard neurobehavioral performance indices across a variety of decision tasks [49, 50, 62–67]. For example, computational model parameters of the IGT robustly discriminate between opiate and stimulant-dependent individuals even in protracted abstinence [49, 50]. Despite no group differences on the tradi-

tional performance index on the task (net score), computational modeling has uncovered notable differences in the underlying processes driving the decision-making performance of different types of substance users: reduced sensitivity to loss in opiate users [49, 50] vs increased sensitivity to reward [50] and preference for switching selections (exploration) in stimulant users [49].

Unlike the IGT, which measures decision-making under uncertainty and ambiguity and involves learning by trial and error, the Cambridge Gambling Task (CGT) is a probabilistic task measuring decision-making and risk-taking outside of a learning context, where no uncertainty is involved [68]. Though not as extensively studied in the addiction field as the IGT, findings are consistent and reveal decision-making impairments in different types of substance users [60, 66, 68–71]. Romeu et al. [66] recently developed the first computational model for the task, which, similar to findings with the IGT, revealed differences in decision-making between healthy controls and individuals with different types of SUD ("pure" heroin, "pure" amphetamine, polysubstance) that were not observable with traditional metrics. All three types of substance users were characterized by lower sensitivity to loss and higher delay aversion than controls, though mono-substance dependent (i.e., "pure") heroin and amphetamine users were more sensitive to loss than polysubstance users. In addition, pure amphetamine users showed lower probability distortion than pure heroin users and controls, reflecting greater willingness to make less optimal choices. These findings were recently replicated by Todesco et al. [72] who revealed lower sensitivity to loss and lower probability distortion in polysubstance users relative to controls. Computational modeling of another decision task, the Balloon Analogue Risk Task (BART; [73]) measuring risky decision-making, revealed similarly reduced loss aversion and increased risk preference in heroin users [65]. The application of computational models may therefore elucidate the unique effects of various features of addictive disorders, such as the influence of specific drug classes or comorbid psychopathology. This may help identify neurocomputational biotypes of individuals with SUD, characterized by unique and computationally distinct decision-making deficits and accompanying neural circuit abnormalities. Such parameters of gain- and loss-related sensitivity show significant potential as novel "computational signatures" for different types of SUD and other forms of psychopathology, which could help refine neurocognitive addiction phenotypes, identify computational biomarkers, and develop more rigorous models of addiction.

Computational phenotypes have already led to many new insights into the neurobehavioral mechanisms underlying substance use and addictive disorders, but their clinical utility has only recently started to be considered [30]. To date, theory-driven

computational approaches have demonstrated clinical utility primarily via back translation from "clinic-to-computation," by demonstrating how specific disorders map onto specific computational processes [74]. In contrast, forward translation, from computation to clinic, is still rare [74] and is the next frontier in computational research. Clinically, theory-driven computational phenotypes hold promise for improving treatment success by providing novel actionable targets for prevention and intervention and increasing the precision and efficacy of treatment interventions for addictive disorders [8]. For example, delay discounting has been successfully targeted by novel interventions such as episodic future thinking, which have resulted in reductions not only in delay discounting but also in substance use [75–77]. The utility of computational modeling to precision psychiatry has recently been shown in a treatment context, where computational methods were able to capture treatment-sensitive aspects of decision-making, such as changes in loss sensitivity that were not accessible via traditional methods [72]. Further, dynamic changes in specific computational parameters of decision-making over time, such as daily fluctuations in ambiguity tolerance and risk preference, have been shown to predict imminent relapse in abstinent opioid-dependent individuals [63]. This suggests that computational parameters may have prognostic and diagnostic utility to inform not only with whom to intervene, but also when to intervene. Such computational signatures and within-person fluctuations in computational parameters could provide a dynamic characterization of different addiction trajectories and transitions between different stages of addiction [78].

2.1 Joint Modeling

Novel computational modeling approaches such as "joint modeling" aim to link behavior across different tasks and measurement modalities [64, 79]. In many cases, multiple neurocognitive tasks and cognitive models purport to describe similar processes, but it is difficult to evaluate whether they measure the same latent processes or traits. To address this question, recent studies have modeled behavior across decision tasks by connecting cognitive model parameters from different tasks to common latent constructs, such as impulsivity. For example, a recent joint modeling study of the CGT and the Monetary Choice Questionnaire (MCQ) of delay discounting [64] revealed that the tasks appear to index separate neurocognitive dimensions of impulsivity, with the MCQ indexing choice impulsivity [80], whereas the CGT tapped on action impulsivity [81]. Further, the temporal discounting parameter on the delay-discounting task (MCQ) was more closely related to trait measures of externalizing psychopathology and aggression, whereas temporal discounting on the CGT was related to neurobehavioral response inhibition failures [64]. A key feature of the joint

modeling approach is that it allows linking neurobehavioral data directly to neural activity [79, 82–84]; therefore, joint modeling holds promise for linking behaviors not only across different tasks, but also across different domains of functioning (e.g., neurocognitive, neurocircuitry) [79]. Computational models have also been used to guide model-based neuroimaging approaches and by providing a framework to study neural mechanisms of various cognitive processes, show distinct advantages, and offer insights into *how* a particular process is implemented in the brain as opposed to merely identifying *where* the process is located [85, 86]. In general, joint models exhibit greater predictive validity than neural or behavioral data alone, allowing more precise and mechanistically informative characterization of neurocognitive profiles and neural function associated with different types of SUD and psychiatric disorders [79].

Within the framework of the three stages of addiction [3], computational modeling parameters that parse different neurocognitive functions such as decision-making, could increase understanding of the role of different decision-making processes at different stages of the addiction cycle and mapping these processes to the ANA domains. For instance, *increased sensitivity to reward* may most closely characterize the *binge/intoxication* stage of addiction and the *incentive salience* ANA domain, driven by positive reinforcement mechanisms involving preferentially the dopaminergic and opioid systems. In contrast, *reduced sensitivity to loss (or reduced loss aversion)* may better characterize the *withdrawal/negative affect stage* of addiction and the *negative emotionality* ANA domain, driven by negative reinforcement mechanisms that preferentially engage the extended amygdala and its projections. The *executive function* ANA domain and the *preoccupation/anticipation stage* of addiction may be characterized by an imbalance between model-based and model-free decision-making systems [87] and a conflict between Pavlovian and instrumental systems [88]. Using computational approaches to characterize and map the ANA domains promises to identify novel actionable targets for prevention and treatment of SUD that may supplement existing programs and inform the development of new programs [8, 89–91]. The application of computational models may also elucidate the specific effects of various features of addictive disorders, such as the influence of specific drug classes or comorbid externalizing and internalizing psychopathology, thereby leading to identification of subtypes of individuals with SUD, characterized by specific types of cognitive and affective deficits. This could further increase the validity of the tasks as sensitive and specific measures of distinct "computational signatures," which could be targeted by interventions tailored to the specific type of neurocomputational risk profile.

3 Hybrid Approaches/Adaptive Design Optimization

While computational tools have increased the knowledge extracted from neurocognitive tasks, there are surprisingly few high-quality assays for monitoring and characterizing neurocognitive domains. One of the major problems in identifying reliable biomarkers of addiction and other psychiatric disorders is the low reproducibility of neurocognitive findings and the surprisingly low test-retest reliability of well-established and widely used neuropsychological tasks. Computational modeling holds promise for addressing the "Reliability Paradox," or the failure of robust cognitive paradigms to produce reliable individual differences [14]. For example, a recent study that compared traditional neurobehavioral indices from working memory, priming, associative interference, and impulsivity tasks against computational models of these tasks revealed that computational model parameters show substantially better test-retest reliability than the standard behavioral indices, increasing reliability by as much as 0.8 on a −1 to 1 scale [15]. Advances in Bayesian statistics and machine learning offer algorithm-based ways to generate optimal and efficient experimental designs so as to minimize uninformative and wasted experimental trials [92]. Bayesian computational approaches can improve not only the reliability but also the efficiency of neurocognitive assessment and help develop RDoC measures that provide more rapid and precise behavioral markers of different types of SUDs. One such approach is *adaptive design optimization (ADO)* [93], which aims to find the most informative design for estimating model parameters on the fly during an experiment. ADO is a "smart" search machine learning algorithm, whose search is guided by one or more computational models, depending on the objectives of the research. When comparing competing models (e.g., of decision-making), it searches for the stimulus that is most likely to discriminate the models. When its goal is to estimate model parameters, it presents the stimulus that is expected to generate the most informative response for parameter estimation. The model(s), combined with participants' responses, are updated at each trial to optimize stimulus selection with the goal of achieving efficiency, precision, and reliability. This approach has a promising track record for improving the efficiency and precision of psychiatric assessment [94–96]. ADO is a model-based machine-learning approach to optimization in the sense that it requires a quantitative model that predicts experimental outcomes based on the model's parameters and design variables. ADO has been successfully applied for identifying best-fitting models in gambling tasks [97] and delay discounting tasks [98], as well as to optimally assess visual acuity [96] in

neurotypical individuals. All of these studies demonstrate that ADO substantially reduced the number of trials required to do model comparisons or parameter estimation. This indicates that ADO may significantly increase task efficiency, reduce the length and burden of administration of current RDoC assessment batteries, and facilitate their wider implementation in clinical practice.

ADO has also been shown to dramatically increase the test-retest reliability of common tasks compared to non-ADO methods. For example, a recent ADO study [99] revealed 0.95 and higher test-retest reliability of the discounting rate within only 10–20 trials (under 1–2 min of testing), which captured approximately 10% more variance in test-retest reliability, was 3–5 times more precise, and 3–8 times more efficient than the staircase method. Of note, ADO shows excellent reliability in different populations, including college students, patients with SUDs, and online Amazon MTurk workers [99]. Critically, ADO task parameters demonstrate linkages with real-world substance use outcomes akin to computational parameters from longer and more burdensome tasks. For example, preliminary findings suggest that model parameters from ADO-based tasks could predict future cigarette use, which further suggests that ADO is a promising approach for assessing and predicting addictive and other psychiatric conditions [100].

4 Data-Driven Approaches/Machine Learning

The scientific community is always looking for well-powered and unbiased methods for identifying features of interest. Combining neurocomputational signatures with clinical, behavioral, neuroimaging, genetic, and other types of data in large multivariate datasets promises to increase the interpretability of neurocognitive phenotyping and increase the precision of prediction and classification in psychiatry [101]. Rapid improvements in computational resources and the quality of big data nowadays allows combining multiple sources of data in large datasets and freely sharing the data and tools with the scientific community. This has led to rapid development of data-driven computational methods using various machine learning (ML) approaches that have increased our understanding of the multi-dimensional features and associated neural substrates and genetic underpinnings of different forms of psychopathology. Machine-learning has found steadily increasing applications in the addiction literature. Supervised ML methods have been used to predict adolescent alcohol use [102] and misuse [103], distinguish between smokers and non-smokers [104–106], between people with and without cocaine use disorder [107, 108] or cannabis use disorder [109–111], and between people with different types of

SUD [107, 112–116]. These ML studies have identified multivariate neurobiological, neurocognitive, psychiatric, and personality profiles that differentiate addictions to different classes of drugs. Some studies have identified common features for multiple SUD, emphasizing the trans-diagnostic utility of certain neurocognitive and personality characteristics that may increase vulnerability to addiction in general, regardless of drug class. For example, higher delay discounting [113] and impulsive/antisocial features of psychopathy [112] have emerged as significant trans-diagnosing markers classifying alcohol-, opiate-, and stimulant use disorders. In addition, delay discounting has been identified as the most prominent predictor of successful smoking cessation [117], underscoring its significant role in the recovery stage of the addiction cycle. On the other hand, substance-specific markers classifying addictions to different classes of drugs have also been identified. For example, Ahn and Vassileva [112] identified unique multivariate personality, psychiatric, and neurocognitive features that classified opiate and stimulant addictions with a high degree of accuracy. Amphetamine users were (uniquely) characterized by higher sensation-seeking, hostility, response deliberation time, and delay discounting. Heroin users were uniquely characterized by attention deficits, impaired decision-making, lower risk-taking, callous/unemotional features of psychopathy, impulsivity under negative emotional states ("negative urgency"), depression, anxiety, and aggression. Out of 54 features, the impulsive/antisocial factor of the Hare Psychopathy Checklist (PCL:SV) was the strongest and only common classification marker of both heroin and amphetamine dependence [112]. Others have used connectome-based modeling to identify substance-specific neural networks involved in abstinence from opiates and cocaine [115], and brain morphology to differentially predict alcohol, tobacco, and cannabis use initiation in adolescents [114], highlighting the importance of studying both common and unique markers of different types of SUD.

A few large multidisciplinary collaborations have produced large phenotypically rich datasets that have served as key drivers and accelerators of data-driven computational research. The IMAGEN consortium [118] is a multidisciplinary European collaboration in imaging genomics aiming to detect longitudinal associations between genotype and brain structure and function and disentangle gene–environment interactions. The Human Connectome Project [119, 120] is another large imaging genetics study that uses multimodal imaging technology to understand the network of human brain functions and map its neuroanatomical connectivity patterns. The Enhancing Neuroimaging Genetics through Meta-Analysis (ENIGMA) consortium [121] brings together researchers in imaging genomics, neurology, and psychiatry, and involves 30 working

groups spanning 185 institutions in 35 countries worldwide to understand brain structure and function in different psychiatric and neurological disorders. The Adolescent Brain Cognitive Development^{SM} (ABCD) Study [122–125] is the largest ($N = 11{,}875$) longitudinal study of brain development in the United States, examining risk and resilience factors associated with substance use and other psychiatric and physical outcomes from middle childhood to early adulthood. These research initiatives have been supplemented by government-sponsored big genomics projects such as the UK Biobank in the United Kingdom with over 500,000 participants [126] and All of Us in the United States created by President Obama's Precision Medicine Initiative [127], which aims to recruit over 1 million Americans. These large citizen-science projects have shed light on numerous psychological facets of cognitive, social, emotional, and physical development and have generated vast amounts of high-dimensional data that requires increasingly sophisticated methods for processing and analysis.

Unsupervised ML methods such as clustering have proven to be especially useful for data-driven disease subtyping and identification of biotypes. Biotypes are subtypes of a broader syndrome or disorder defined by distinct aggregations of behavioral, mood, and genetic markers with specific dysfunctions in the functional and structural connectivity of large-scale neural circuits that govern mood, behavior control, and self-reflective functions [128, 129]. Biotypes are increasingly proposed as an alternative to clinical phenomenology in the classification of disease because their organizing features center on neurobiological mechanisms rather than differentiations based on broad symptomatology. Though applied to other psychiatric disorders, such as anxiety, depression [23, 129, 130], schizophrenia, and bipolar disorder [128, 131–133], the biotype approach is still relatively unexplored in the study of addictions. Few studies to date have applied this approach to SUD and other addictive disorders, which is a significant gap in the literature. Zhu et al. [134] used connectivity features from resting state fMRI to identify three biotypes of alcohol misuse—mild, comorbid, and moderate—which demonstrated significant differences in alcohol use frequency and connectivity involving the frontal, parietal, subcortical, and default mode networks. To understand comorbidities between addictions and the transition/replacement of one addiction form with another, Zarate et al. [135] conducted a network analysis of 10 forms of addictive behaviors (alcohol, drugs, tobacco, sex, online gambling, Internet use, Internet gaming, social media use, shopping, and exercise). Findings suggest that most forms of addictive behaviors are uniquely different and that there are clusters of addiction symptoms (e.g., drug and alcohol misuse, gambling) that have particularly strong influ-

ence on the entire network of addictive behaviors. Developing a taxonomy of neurocomputational addiction biotypes based on the ANA framework that maps onto neural circuits involved in addictions may facilitate the translation of empirical data into clinical practice by informing the development of novel, innovative treatment alternatives that are individually tailored to specific subgroups of individuals who share common addiction vulnerabilities. The biotype approach has used neuroimaging, genetic, physiological, clinical, cognitive, environmental, and other sources of data for classification and prediction. This approach could benefit substantially from the inclusion of theoretically derived "computational signatures" of decision-making and other cognitive and affective functions implicated in addiction into the machine learning models along with other relevant sources of data to identify neurocomputational biotypes, which, in turn, could be targeted by modular interventions tailored to individual neurocomputational risk profiles.

5 Summary and Conclusion

Computational approaches have vast potential for optimizing precision psychiatry at a few different levels (Fig. 1). Theory-based approaches such as computational modeling and joint modeling could be integrated into multimodal assessments of RDoC constructs of mechanistic significance for addictions and other psychiatric disorders. Novel interventions could be developed that target the computational signatures (e.g., reward sensitivity, loss aversion, ambiguity tolerance, etc.) identified by theory-based approaches. Hybrid computational approaches like ADO could help develop "smart" assessment batteries, comprised of efficient, reliable, and precise neurocognitive tasks with superior psychometric properties. These batteries could be easily adapted to web-based platforms and mobile apps, as well as in longitudinal designs using ecological momentary assessment to track daily within-subject variability. Data-driven computational approaches could help develop novel mechanistic taxonomies and identify neurocomputational biotypes of specific psychiatric disorders, which could help guide the choice of intervention(s). Translating these computational approaches to clinical practice can be facilitated by open-source and user-friendly software packages, such as *hBayesDM* (hierarchical Bayesian modeling of decision-making tasks) [136] that offers computational models of an array of decision tasks, *easyML* (easy Machine Learning) [137] for machine learning approaches, and *ADOpy* [138] for adaptive design optimization.

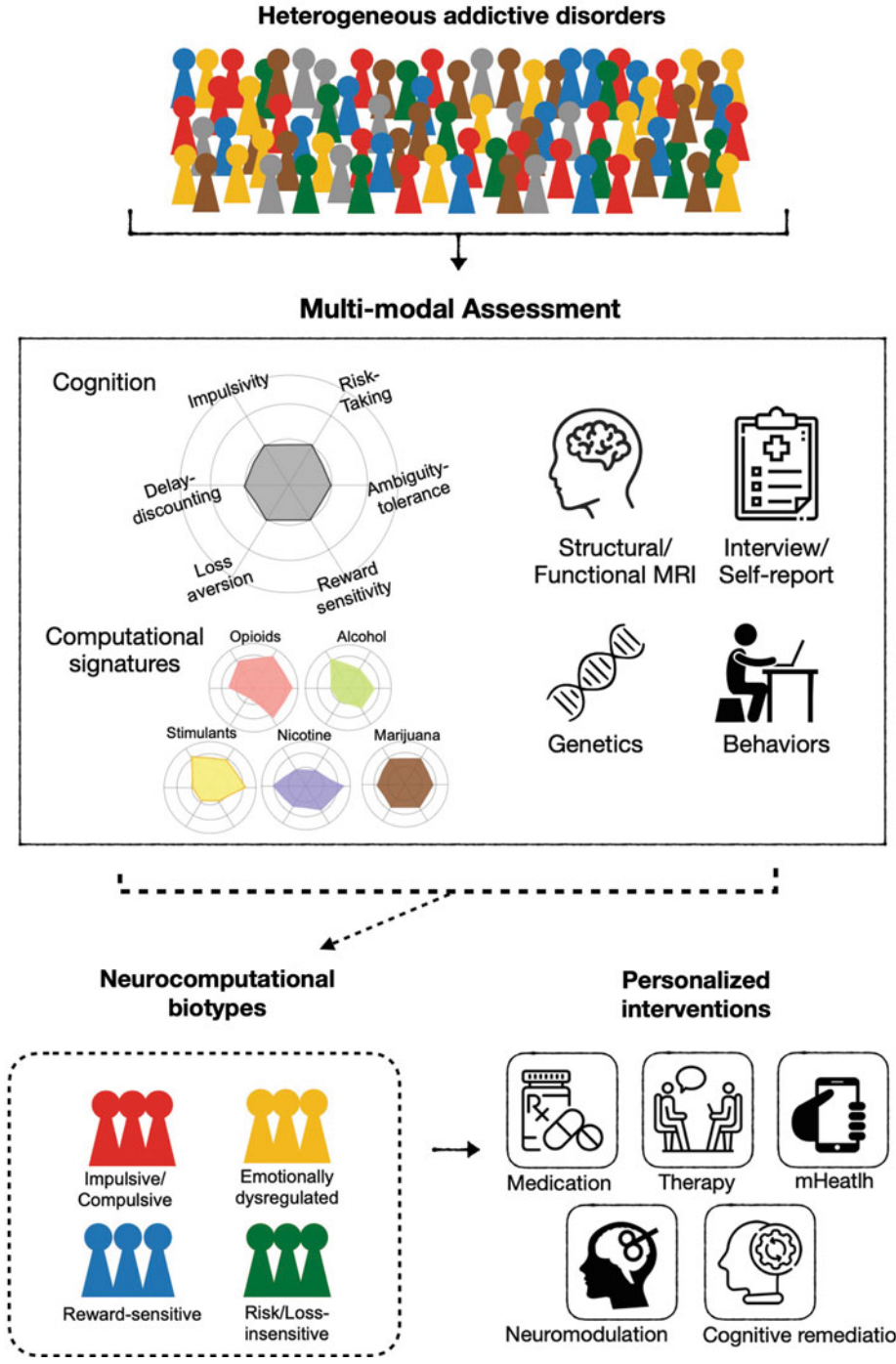

Fig. 1 A theoretical example of potential applications of theory-driven, data-driven, and hybrid computational approaches for assessment and treatment of substance use disorders

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