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Computational Theories of Alcohol Use Disorder: Mapping Learning and Choice Mechanisms on Symptoms

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Abstract
Alcohol use disorder (AUD) is characterized by a combination of symptoms including excessive craving, loss of control, and progressive neglect of alternative pleasures. A mechanistic understanding of what drives these symptoms is needed to improve diagnostic stratification and to develop new treatment and prevention strategies for AUD. To date, there is no consensus regarding a unifying mechanistic framework that accounts for the different symptoms of AUD. Reinforcement learning (RL) and economic choice theories may be key to elucidating the underlying processes of symptom development and maintenance in AUD. These algorithms may account for the different behavioral and physiological phenomena and are suited to dissect mechanisms linked to different symptoms of AUD. We here review different RL and economic choice models and how they map onto three symptoms of AUD: (1) cue-induced craving, (2) neglect of alternative rewards, and (3) consumption despite adverse consequences. For each symptom and theory, we describe findings from animal and human studies. In humans, we focus on empirical studies that investigated RL models in the context of treatment outcome in AUD. The review indicates important gaps to be addressed in the future by highlighting the challenges in transferring findings from RL and economic choice studies to clinical application. We also critically evaluate the potential and pitfalls of a symptom-oriented approach and highlight the importance of elucidating the role of learning and decision-making processes across diagnostic boundaries.

Introduction

Substance use disorders (SUDs) are widespread conditions with severe economic, social, and health consequences. Among a variety of SUDs, alcohol use disorder

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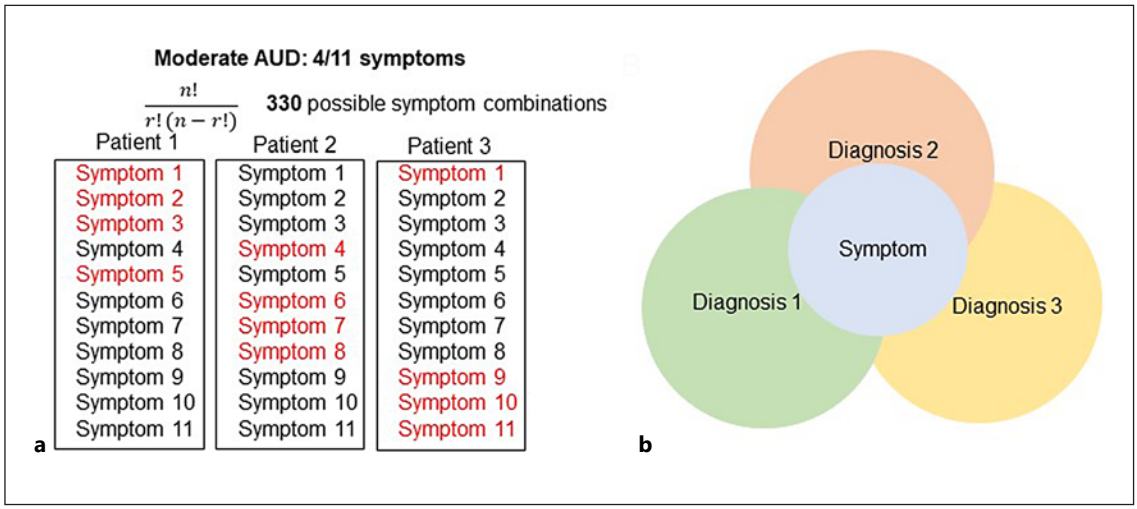

Fig. 1. a Examples for symptom heterogeneity within AUD diagnosis. Diagnosis of moderate AUD can result from a random combination of symptoms, so that patients with the same diagnosis can have only marginal or no symptom overlap at all. **b** Some symptoms are seen across psychiatric disorders, and the elucidation of the mechanism that are at the core of this symptom might provide critical neurobiological insights.

(AUD) in combination with tobacco use is the leading cause of morbidity and mortality worldwide [1–3] and has the most severe and harmful societal and individual consequences [4, 5]. Symptoms of AUD include alcohol consumption despite other intentions or negative consequences, neglect of pleasures and activities that are not linked to alcohol intake, and strong cravings for alcohol. Current diagnostical approaches for AUD are categorical, as a subset of symptoms has to be met for diagnosis. The DSM-5 criteria for AUD have adapted a polythetic approach that aims to transfer the dichotomic classification into a more dimensional classification that allows inferring pathological severity. Accordingly, AUD diagnoses can now be distinguished into three different severity measures depending on a count out of 11 possible symptoms resulting in mild (2–3 symptoms), moderate (4–5 symptoms), and severe AUD (more than 6 symptoms). ICD-11 will retain the categories of harmful use and dependence [6]. Although these diagnostic approaches are widely used to guide clinical practice, it has been questioned whether they are helpful in elucidating the neurobiological and psychological mechanisms underlying AUD [7]. However, a detailed understanding of the neurocognitive mechanisms that underlie specific symptoms of AUD is needed. For instance, insights about the neural and psychological processes that lead to the symptom of craving could inform future studies that aim to advance treatment options for patients that are particularly affected by this symptom. In this review, we aim to adopt a mechanism-based approach to symptoms of AUD. We describe contemporary computational models of learning and decision-making as one potential tool to provide a mechanistic understanding of AUD. We link computational models to separate symptoms of AUD and describe a potential translational bridge between animal findings and clinical studies in patient cohorts. Lastly, we highlight the need to transfer scientific findings from computational modeling studies to clinical care and evaluate the potential and pitfalls of a symptom-oriented approach.

Heterogeneity within Diagnoses

Patients with an AUD diagnosis differ widely. Categorical diagnosis systems make the implicit assumptions of additivity of symptom combinations [8, 9], and this approach results in a wide heterogeneity within the diagnosis. For instance, a moderate AUD diagnosis, according to the DSM-5, may include a random combination of four out of eleven symptoms. However, due to the high number of possible combinations, this can result in only minimal symptom overlap between subjects with the same diagnosis (see Fig. 1). This symptom heterogeneity in AUD might partly explain low treatment responses but may be a rich source of variability for risk stratification when aiming for more personalized care [10]. Studies that use additive symptom profiles might thus neglect information that could be obtained from diverse symptom dimensions. It has been argued that different symptom di-

mensions may more precisely map on neurocognitive processes [11, 12].

Moreover, patients with a specific AUD severity level (mild, moderate, severe) according to the DSM-5 may not always suffer to a comparable extent. By simply adding up symptoms to infer pathological severity, the polythetic approach of the DSM-5 makes the implicit assumption of equal symptom importance [8]. However, some combinations could imply less pathology than other configurations [13]. Thus, using the severity index of AUD according to DSM-5 to study the underlying processes of AUD does not address heterogeneity within diagnosis and heterogeneity in the underlying biological and cognitive mechanisms.

Comorbidity between Diagnoses

Comorbidity in AUD and other mental health disorders is the rule rather than the exception [14]. According to epidemiological surveys, the prevalence of major depressive disorder in AUD is estimated at up to 22% [15]. Moreover, a DSM-5 AUD diagnosis increases the odds of other SUDs by a factor of 3.3 [1]. Although the pathways of these comorbidities remain only partly elucidated [16], it suggests that in many cases, AUD shares neurocognitive substrates with other diagnoses. Moreover, some symptoms in AUD might be linked to other symptoms in other diagnostical categories, and this phenotypic overlap may reflect important etiological overlap [17]. When strictly focusing on diagnostic boundaries, these important links could be neglected.

Similar Symptoms across Diagnoses

Some AUD symptoms seen in other psychiatric conditions are, thus, not confined to the AUD diagnosis. For instance, craving is a hallmark feature across SUDs, gambling disorders, and some eating disorders [18, 19]. Importantly, disorders that share such symptoms have commonly been linked to altered measures that operationalize certain psychological constructs such as impulsivity [20]. A dimensional approach in psychiatric research, therefore, focuses on the identification of neurobiological mechanisms that are associated with clinically relevant symptoms that cut across the boundaries of traditional categorical classification [21, 22]. For instance, steeper delay discounting – i.e., a relative preference of immediate over long-term rewards – is one facet of impulsivity and has been reported in AUD [23], gambling disorder [24], and ADHD [25]. Likewise, reduced goal-directed control – that is, decision-making that is detached from anticipated internal goals – has been associated with a range of putatively "compulsive" disorders, such as AUD [26], gambling disorder [27], and obsessive-compulsive disorder (OCD) [28].

However, constructs such as impulsivity and, likewise, compulsivity [20, 28], appear multifaceted and pose significant measurement challenges to identify their unique contributions including the role of automatic or even "compulsive" drug intake [9, 29]. On the same note, one recent study has shown that reduced goal-directed decision-making is associated with self-reports of compulsivity across patients with OCD and anxiety disorder, while there is no difference regarding the type of clinical diagnosis of OCD [30]. This latter study, though not in the context of AUD, illustrates that a focus on categorical diagnoses may promote neglect of heterogeneity within and similarities across diagnostic categories.

Value-Based Learning and Decision-Making in AUD

Patients suffering from AUD consume alcohol despite severe negative (long-term) consequences and the intention to remain abstinent. Moreover, pleasures from alternative activities are often hardly rewarding to them [7]. This set of symptoms has led to the assumption that AUD is associated with alterations in value-based decision-making [23]. Per definition, value-based decision-making describes how subjective values are formed and mapped to single choices [31, 32]. Broadly, there are two different theoretical and paradigmatic approaches to study such processes across species that is reinforcement learning (RL) and economical choices. RL is used both in computational neuroscience and in machine learning and describes how values associated with different stimuli or actions are updated with respect to positive and negative outcomes expected in the future [33]. Thus, RL tasks are designed to capture how feedback impacts learning and decision-making [33, 34]. Economical choices, on the other side, are inspired by the field of behavioral economics and describe theoretical models on how utility (experimentally disentangled from learning) impacts choices [35].

The Potential of Computational Models to Investigate Symptoms in AUD

RL and economic choice models both rely on the assumption that behavior aims to maximize rewards and that this process can be modeled algorithmically based on a latent set of parameters. This approach enables researchers to directly test whether a specific behavior is best described by certain latent meaningful parameters [36]. As AUD has long been associated with aberrant

learning and decision-making, computational models are one promising tool to mechanistically describe these alterations. Importantly, all RL and economic choice models depend on a theory about the precise utility of the underlying parameters. Thus, one advantage of computational models is that they motivate researchers to conceptually analyze, specify, and formalize theoretical hypotheses regarding decision-making [37].

Some computational models (particularly those from RL) further bear the advantage that they have been found to capture several aspects of neural activity [38–41]. Therefore, such models have been suggested to lay a fertile ground for cross-species translation. For instance, in animals, computational modeling of single-cell recordings during associative learning can help to identify the biophysiological processes that mediate these learning processes [42]. The very same algorithms can also be used to model functional magnetic resonance imaging data [43] or electroencephalographic recordings [44] during human associative learning. Another example is the back-translation of the two-step decision-making task from humans [45] to animals [46], which confirmed findings of the relation between dopamine signaling and model-based decision-making found initially in humans [47] and in rats [46]. Thus, by using the same, or at least very similar, tasks and modeling techniques across species, one can infer whether similar biophysiological processes are involved in a specific cognitive process and also benefit from the different methodological opportunities in some animals as compared to humans. However, while such research indicates clear advances for neuroscience, the promises toward clinical application remain challenging, and to date, there are comparably few investigations that directly address such cross-species translation with computational modeling techniques in a clinically relevant context. One fruitful paradigm that enables us to study a clinically relevant process implicated in SUDs is the 5-choice serial reaction time task (5-CSRTT). Premature responding in this task is increased after chronic alcohol intake in animals [48] and humans [49]. Moreover, altered response behavior in this task has been suggested to serve as a behavioral endophenotype that predisposes to SUD [50, 51]. Thus, tasks that test a clinically meaningful process in animals and humans can help to shed light on the determinants and consequences of certain psychopathologies.

Further, as noted by others [52], computational models in themselves are no panacea, as they do not necessarily rely on strong theoretical claims about the studied pathology, and their components do not necessarily link well with the underlying psychological processes. As with every model, it is important to specify (1) the purpose of the computational model and (2) the mapping between the computational model and the "real world," that is, (i) the associated neurobiology and (ii) the psychiatric disorder or a specific symptom [53]. Importantly, if these principles are disregarded, the application of computational modeling can be useless or even misleading. Although some researchers have argued that computational modeling as a tool to study decision-making might be relevant for the larger agenda to transfer basic scientific findings to clinical applicability [36, 54–56], there is, to date, only limited evidence for this promise in SUD research [9]. However, the "computational psychiatry" discipline is still comparably new and there are several roadmaps published and further developed of how clinical translation could be realized [54, 57]. A recent study in opioid dependence has indicated a high potential for transfer to clinical assessment [58]. In this study, a computational parameter indicating risky decision-making directly preceded opioid relapse. As the decision-making task is easily applicable and has low costs, future studies could now transfer this finding into clinical intervention and assign stratified care (e.g., more frequent or a different kind of therapy) to patients who show risky decision-making and test whether this helps to prevent relapse specifically in these individuals in a clinical intervention design. In the next section, we describe established algorithmic models of SUDs. While most of these computational models have also been covered in recent reviews [52], we here expand RL models with economic choice models and further link these models to distinct addictive phenomena (symptoms). While we feel that this mapping of models to symptoms is useful to elucidate the mechanisms that underlie distinct phenomena in SUDs, others [52] have argued that effective models of addiction should describe a range of symptoms and the progression and stages of addiction to be of practical clinical use.

Main Part: Computational Models and Symptoms of Alcohol Use Disorder

Symptom: Cue-Induced Craving

Craving, defined as a strong desire for a particular substance or behavior, is a psychological phenomenon at the core of AUD and has long been recognized as an important target for treatment. One hallmark feature of craving is that it is often elicited by cues previously paired with the rewarding effects of a certain substance [59]. Thus,

when exposed to the sights, smells, or places previously associated with highly potent reinforcers, such as alcohol, individuals suffering from AUD have difficulties resisting the temptation to seek them out [60]. Theoretically, cue-induced craving, therefore, reflects a conditioned response to reward-associated stimuli and is therefore considered a consequence of Pavlovian conditioning [61]. One prominent neurobiological theory suggests that cue-induced craving reflects the attribution of incentive salience to reward-predictive cues as a consequence of incremental neuroadaptations [62, 63]. Accordingly, excessive intake of alcohol or other drugs of abuse renders mesocorticolimbic systems hypersensitive, so that these systems cause pathological "wanting." There is wide consensus about the important role of the dopaminergic system in these neuroadaptations. Evidence for this comes from single-cell recordings demonstrating that all drugs of abuse, including alcohol, lead to the phasic release of dopamine in the midbrain [64, 65]. Interestingly, the temporal dynamics of such phasic dopamine release in the midbrain play a major role in associative learning [66]. In his seminal work, Schultz and colleagues demonstrated that stimulus-reward learning shifts phasic firing of midbrain dopamine neurons from an unconditioned (e.g., food) to a conditioned reinforcer (e.g., light stimulus) [66]. Thus, while alcohol acts as an unconditioned reinforcer, environmental cues associated with alcohol become conditioned reinforcers over the course of the development of AUD. Consequently, cue-induced craving might reflect a conditioned response that is being accompanied by a shift in midbrain dopaminergic firing patterns [67, 68].

Findings in Animals and Humans

Interestingly, recent animal work has shown that only individuals who show a strong behavioral response to a conditioned stimulus (so-called "sign-trackers") show a shift in dopaminergic transmission [69, 70] from the unconditioned to the conditioned reinforcer. An experiment that is commonly used to identify sign-tracking individuals is a Pavlovian-conditioning procedure, where a cue predicts the delivery of food at a different location. Whereas sign-tracking individuals tend to approach the cue location and show motivated behavior such as increased licking, other individuals do not develop this cue-reactive behavior and instead focus on the location of food delivery itself (so-called goal-trackers). It is assumed that only in sign-tracking individuals does the conditioned stimulus itself become attractive because it is attributed with incentive salience, whereas this is not the case for goal-trackers. Sign-tracking behavior was shown to be linked to increased levels of impulsivity, as measured by delay discounting [71, 72]. In line with the assumption that incentive salience attribution and the associated dopaminergic firing patterns are important features of addiction, sign-trackers show stronger addictive behaviors after drug exposure [70, 73]. More precisely, sign-tracking individuals exhibit increased cocaine-induced psychomotor sensitization, suggesting that these individuals are particularly susceptible to cocaine-induced plasticity that contributes to the development of SUDs [73].

In humans, evidence for the role of incentive salience attribution in the development and maintenance of AUD comes from de novo associative learning and cue-reactivity studies. The former typically investigates how alcohol infusion or consumption alters responding to a preceding environmental cue. By using this procedure, it was shown that alcohol alters the incentive properties of such cues, as indicated by orienting and neural responses [74, 75]. This study design is usually used in high-risk or social drinking populations. Cue-reactivity studies, on the other hand, are typically performed in AUD patients and do not assess associative learning per se but are thought to reflect conditioned responses to alcohol cues. Several studies have shown that individuals suffering from AUD show increased physiological [76] and neural responses in mesocorticolimbic structures to alcohol compared to neutral cues [68, 77, 78]. These findings have been helpful in elucidating the neural systems underlying cue-induced craving in AUD and have further initiated pharmacological intervention studies to reduce cue-induced craving [79–83]. However, so far, these studies have not allowed elucidating the cognitive mechanisms that underlie cue-induced craving.

Computational Theory

The most prominent computational model that captures incentive salience attribution as a core mechanism of cue-induced craving is Rescorla-Wagner learning as well as more generally Temporal Difference Reinforcement Learning (TDRL). These algorithms conceptually formalize associative learning as they quantify how reward-predictive cues iteratively and slowly gain value through repeated pairing with a reward. The signal that drives this update is the reward prediction error (RPE), which is indicative of the difference between expectations and observations. Essentially, if the achieved reward was better than expected, the RPE is positive, which leads to an increase in the value attributed to the reward-predic-

tive cue. If the RPE is zero, the value function correctly predicts the reward, and the value function is no longer updated. Rodent studies have shown that the firing rate of neurons in the midbrain mimics the RPE term in the TDRL algorithm [84, 85]. Human fMRI studies using this RL framework have highlighted the role of the ventral striatum in mediating associative learning [86, 87]. In line with animal findings [70], a recent study showed that RPE signals in the striatum during associative learning are directly linked with the individual propensity to attribute incentive salience to a reward-predicting cue. In this study, Schad, Rapp [43] characterized healthy individuals as sign-trackers through gaze biases during an associative learning procedure and demonstrated increased RPE signatures in the nucleus accumbens in sign-tracking individuals.

Departing from the RL of associative learning, one recent study has used an economic choice framework to infer the computational mechanisms of craving [88]. This study was not within the field of AUD but instead investigated food cravings in healthy individuals. Subjects had to indicate how much money they were willing to spend on different quantities of food items. They performed this task twice and experienced a multisensory exposure of a palatable food cue between these two tasks. Across subjects, the exposure of the palatable food cue changed the willingness to pay for the same food item. Using model comparison, it was shown that the exposure of the food cue led to a multiplicative linear reweighing of the internal value representation. Although this recent study focuses on food craving, it stresses the potential of economic choice tasks to infer the cognitive mechanisms of the craving state and could potentially inspire clinical trials for pathological craving.

A recent account additionally stressed how craving in addiction might be triggered, particularly by early positive memories of alcohol and drug intake [89]. According to this theoretical account, such vivid episodic memories (anecdotally referred to as *first high* or *drug fantasy*) are inflated and computationally outweigh the real drug value, thus contributing to persistent consumption and/or relapse.

Symptom: Neglect of Alternative Rewards

Giving up important social and occupational activities because of alcohol use is an important symptom of AUD. Thus, AUD is associated with increased choices of alcohol over healthy alternatives [7, 90]. While cue-induced craving is considered mainly as a result of associative Pavlovian learning (see above), the symptom of alcohol choices over healthy alternatives is considered a consequence of instrumental learning. One central component of instrumental learning is Thorndike's *law of effect*, according to which actions followed by reward are more likely to be repeated than actions followed by punishment. Alcohol and other drugs of abuse are powerful to shape actions because of their initially reinforcing properties attributed to the associated activation in the dopaminergic midbrain system–particularly the nucleus accumbens [91]. However, although this mechanism can explain why AUD individuals choose alcohol, it does not fully explain why AUD subjects neglect healthy alternatives. One potential neurobiological account for this symptom is the "hijacking of the reward system" [92]. For instance, reduced availability of D2-receptors, putatively reflecting a down-regulation, was reported in AUD patients [93–96]. This might reduce experienced pleasure from non-alcohol reward and further lead to the perpetuation of alcohol intake as a means to temporarily compensate for this deficit because alcohol- and drug-associated release in DA is considerably higher than non-drug reinforcers [92, 97].

Findings in Animals and Humans

In animals, evidence for choices of alcohol instead of alternative rewards as a hallmark addiction feature comes from experiments that assess choices to drugs and alternative highly potent reinforcers such as sugar [98, 99]. In a study by Augier, Barbier [90], rats were first trained to self-administer alcohol and were then offered a mutually exclusive choice between alcohol and saccharin. Results indicated that most rats quickly started to choose more saccharin than alcohol. However, a minority of rats continued to choose alcohol despite access to the saccharin alternative. As the relative proportion of "alcohol-preferring rats" aligned well with human addiction rates [90], this experimental procedure laid a plausible ground to investigate the molecular mechanism underlying alcohol choices at the expense of alternative rewards as a hallmark feature of AUD.

In humans, studies that investigate alcohol over alternative rewards most commonly use economic demand tasks, in which participants report their hypothetical consumption of alcohol and alternative rewards across a range of prices [100]. These paradigms allow us to infer the relative value of alcohol as compared to other rewards. A recent systematic review including 41 studies across clinical and nonclinical samples [101] demonstrated a robust association between AUD symptom severity and an increased relative value ascribed to alcohol compared to alternative rewards. One further paradigmatic

approach to examine relative choice preference between alcohol and alternative rewards are concurrent choice paradigms, in which individuals choose to watch alcohol-related or alternative reward-related scenarios [100]. By using such a design, it was shown that the extent to which AUD patients chose alcohol over alternative pictures was significantly associated with symptom severity and alcohol use frequency before treatment [102]. These studies provide a fruitful ground for future studies on the factors that may modify increased alcohol choices at the expense of alternative rewards. However, although these studies indeed demonstrate an association between AUD and a relative shift in the valuation system toward alcohol rewards, it remains unclear whether this shift indeed reflects a reduced valuation toward alternative rewards or just an increased valuation of the drug. In a clinical perspective, social rewards are powerful reinforcers that can outweigh the value of drugs in SUD and therefore have protective effects. In rats, the delivery of social rewards decreases heroin and methamphetamine self-administration and the incubation of craving [103–105]. For humans, this knowledge is incorporated into the community reinforcement approach, which harnesses operant principles by using social contacts such as support groups [106]. Thus, it remains unclear to what extent the valuation of alternative rewards in SUDs is indeed diminished or whether drugs are just overvalued.

Computational Theory

One computational algorithm that models increased drug or alcohol choices at the expense of choices that lead to alternative rewards has been introduced by Redish [107]. This model has originally been developed to simulate increased cocaine intake at the expense of natural rewards in cocaine-dependent individuals, but we here adapt it to AUD. Similar to the above-mentioned RL model of incentive salience attribution [84, 85], this model uses a TDRL algorithm with an RPE signal, hypothetically carried by dopamine. Based on the assumption that alcohol leads to a non-habituating surge of dopamine, over-selection of alcohol choices is modeled by adding a non-compensable alcohol-induced dopamine release to the TDRL model. Formally, this includes an additional parameter in the RPE which produces an always positive RPE independent of the change in the value function. This way, the learned value of alcohol becomes inflated over time and overshadows the values of alternative reinforcers, resulting in an over-selection of actions that lead to alcohol use in AUD. Simulation of behavior using this algorithm overlaps with findings in rodents and humans, as the respective agent becomes less sensitive to the rising quantity of alternative rewards after excessive alcohol intake [107]. Although Redish's model has been described as a significant advance in the dopamine theory of SUD, it has also been subject to criticism [108]. In this model, inflated drug values can in principle go to infinity, which is both psychologically and biologically implausible. More importantly, the model by Redish was challenged by blocking experiments. In such experiments, individuals acquire a response associated with stimulus A to receive a reward. Then, simultaneous presentations of A and a stimulus B are paired with the reward. Usually, no learning occurs (blocking) for B, as A already fully predicts the reward, so there is no prediction error to support new learning. The model by Redish proposes that alcohol and drugs of abuse always produce a positive prediction error. Therefore, no blocking should occur and subjects should learn to associate B with the reward. However, the experiment by Panlilio, Thorndike [109] demonstrated that this was not the case, and blocking occurred, thus challenging the model by Redish. Another argument potentially limiting the Redish model is the possibility that alcohol over alternative choices may also result from the devaluation of alternative rewards. Indeed, Ahmed [108] noted that the Redish model only affects the value of alcohol choices as a consequence of chronic alcohol intake, leaving the value of choices leading to alternative rewards completely unaffected. This may be an important missing link for a more complete picture of alcohol over non-alcohol choices.

Beyond these RL theories, recent theoretical approaches have highlighted the utility of drift-diffusion models (DDM), a class of choice models, to formalize increased alcohol choices at the expense of natural reward choices as a consequence of chronic alcohol intake [110]. DDMs operate on the assumption that when faced with a particular choice set, internal evidence for each choice accumulates over time until the evidence for one choice crosses a response or decision boundary [100]. In the context of AUD, lower response thresholds/decision boundaries for alcohol versus alternative rewards indicate a shift in the valuation system toward alcohol. An experimental procedure that would point to this includes value-based decision-making tasks, where subjects choose between alcohol rewards and non-alcohol rewards, respectively. DDMs can be used to infer specific underlying parameters like the rate of evidence accumulation and response threshold for each category. Although this account does not allow a direct comparison between alcohol and alternative reward choices, it bears the potential to examine

alcohol hypervaluation and *alternative reward hypovaluation* as a hallmark feature of AUD. This would indicate that AUD patients indeed attribute more value to alcohol-associated stimuli but attribute decreased value to alternative reward-predictive stimuli. More precisely, AUD patients as compared to control subjects should have a higher rate of evidence accumulation and a lower response threshold for alcohol rewards, whereas the opposite (lower rate of evidence accumulation and a higher response threshold) is expected for alternative rewards [110, 111]. Interestingly, a recent study showed that depressed patients compared to healthy controls displayed a lower rate of evidence accumulation for general rewards (as represented by reward points) [112]. In this study, reward valuation was compared with cost valuation, which was found to be intact in depressive individuals. However, given the high comorbidity of AUD and depression [15], this result indicates that reduced evidence accumulation for non-alcohol-related rewards might act as a transdiagnostic mechanism.

Symptom: Consumption despite Negative Consequences

One hallmark feature of AUD is the consumption of alcohol despite severe long-term negative physical, social, and financial consequences [113]. Here, we focus on theories of behavioral control over instrumental learning [114, 115] to understand choices with long-term negative consequences. According to these theories, consumption despite negative consequences may reflect an endpoint of transitions in behavioral control over alcohol intake: from initial alcohol intake, where alcohol is voluntarily consumed because of its reinforcing effects, through loss of control over this behavior, until alcohol consumption ultimately becomes "compulsive," which renders alcohol choices insensitive to the long-term detrimental consequences of chronic alcohol intake [116, 117]. In psychological terminology, these phases during addiction development come along with a transition from goal-directed to habitual behavior [118]. Goal-directed actions are executed because of an anticipated goal. Per definition, these actions are sensitive to sudden changes in action-outcome contingencies. Habit formation, on the other side, leads to actions that are automatically triggered by environmental stimuli. Habitual actions are comparably fast and efficient but also rigid. Goal-directed and habitual behaviors can be distinguished and have been associated with partially distinct as well as partially overlapping brain areas and neurotransmitter systems [45–47, 119, 120]. Humans and animals can switch between both behavioral modes; however, extensive stimulus-response learning leads to a dominance of habitual at the expense of goal-directed behavior, at least in rodents [121, 122].

It is suggested that chronic alcohol intake leads to an imbalance between goal-directed and habitual behaviors, which manifests as increased expression of previously acquired stimulus-response associations at the expense of the impact of long-term negative consequences. This imbalance could result from either increased habitual or decreased goal-directed behavior. The shift from goal-directed to habitual behavior in addiction is suggested to be accompanied by transitions from prefrontal cortical to striatal control as well as a progression from ventral to more dorsal parts of the striatum [116, 123, 124].

Findings in Animals and Humans

Studies have used different sets of experimental procedures to investigate habitual or even compulsive behavior in SUDs, and we will henceforth introduce the most prominent experiments in the literature. In line with the habit definition as a stimulus-induced response that is decoupled from the expected value of the outcome, studies testing habits typically rely on learning paradigms that assess the effect of outcome devaluation on behavior. In this experimental procedure, animals first learn to associate a cue (e.g., light) with a response (e.g., lever press) to receive a rewarding outcome (e.g., food). The outcome is then devalued (e.g., by feeding to satiety). The next stage, in which the animal is confronted with the cue, again allows us to infer whether an individual's response is goal-directed or habitual. Only if the response is goal-directed does the animal stop responding when confronted with the cue. However, when the response is habitual, the animal continues responding. By using this experimental procedure, Dickinson and Balleine [125] demonstrated that behavior reinforced by alcohol was more resistant to devaluation than behavior that had been reinforced by food. Likewise, after chronic alcohol consumption, rats became insensitive to the devaluation of alcohol [126–129]. Rats that have been repeatedly exposed to alcohol were also insensitive to sucrose devaluation [130], suggesting that alcohol can also accelerate habit formation for non-alcohol rewards.

A second prominent test for habit formation is contingency degradation. This experimental procedure tests the sensitivity to changes in action-outcome relationships. The most prominent method to degrade action-outcome contingencies involves making actions and inactions equally predictive of reinforcer delivery. The logic behind the task is similar to that of the devaluation paradigm:

Only if an animal's behavior is goal-directed should it alter its responses to the degraded action-outcome contingencies. A recent study demonstrated that animals that show increased responses toward reward-predictive cues are less likely to alter their behavior when response-alcohol associations are degraded or when alcohol responses are devalued [131]. This study indicates that these animals are particularly prone to the development of alcohol-associated habits. A similar study showed that animals that are more resistant to outcome devaluation and less prone to contingency degradation are also more likely to show alcohol seeking and drinking that is resistant to punishment [132]. Thus, animals that preferentially show habitual behavior are also more prone to ("compulsive") alcohol seeking and consumption in spite of immediate punishment. However, it has been criticized that the devaluation procedures that has been established in animals fails to address long-term aversive consequences of drug intake; instead, it only assess drug intake in spite of immediate punishment, which does not capture human addictive behavior [9]. Moreover, although there is accumulating evidence for the habit hypothesis in SUD in animals, evidence for a shift toward habits in AUD is inconsistent. The translation of the alcohol devaluation design to the human field typically includes a concurrent choice token economy procedure, through which baseline alcohol choice is assessed. In the second stage, the alcohol is devalued using satiety, taste adulteration, or health warnings. Finally, alcohol choice is measured again using the concurrent choice token economy procedure. By using this design, it was shown that acute alcohol intake impairs devaluation sensitivity, indicating a shift toward habitual responding [133]. However, in social drinkers, alcohol devaluation reduced alcohol choice and consumption, thus demonstrating devaluation sensitivity [134]. In humans, several studies have also used devaluation procedures of non-alcohol-related rewards to investigate whether AUD is associated with a special propensity to develop general habit-like responses. In a study by Sjoerds, de Wit [135], AUD patients putatively showed an overreliance on non-alcohol-related stimulus-response habit learning. This aligns well with behavioral deficits in goal-directed behavior in other SUDs, such as nicotine [136] and cocaine dependence [137]. Likewise, it matches with a recent report demonstrating increased habitual tendencies in a contingency degradation task and a measure of self-report in human cocaine dependence [138]. However, Hogarth [29] noted that group differences in some of these studies were very likely to be attributed to task disengagement and impaired explicit contingency knowledge (potentially reflecting unspecific deficits in general learning capacities) in the AUD/SUD group and thus concluded that, to date, there is comparably little evidence for the habit hypothesis of human addiction. In line with this assumption, a recent study found no impairments in goal-directed behavior in AUD patients [139].

Another way to infer whether AUD is characterized by insensitivity to negative consequences is through cost-discounting tasks, in which individuals have to indicate how much alcohol they would consume with rising quantities of prices. In these paradigms, the price at which alcohol consumption drops to zero is considered the impact of costs on the decision process. The habit theory predicts that AUD should be associated with a reduced impact of costs on the decision process; therefore, AUD patients should be willing to accept higher costs until alcohol consumption hypothetically drops to zero. To date, there is only scarce evidence in humans for this hypothesis. Indeed, AUD was shown to be unrelated to cost sensitivity of alcohol [140, 141]. These negative findings have led to a more general critique of the hypothesis of habitual drug consumption in AUD. For example, Hogarth has argued that AUD and other SUDs are characterized by increased goal-directed action selection under negative affect [29]. He suggested that negative and aversive affective states, such as withdrawal/stress or negative mood, powerfully increase the expected alcohol value and thereby lead to goal-directed alcohol selection, which momentarily outweighs the expected value of abstinence. This momentary state-dependent increase in goal-directed alcohol intake still resonates with the long-term negative consequences of chronic intake but rather emphasizes the necessity to study dynamic and state-dependent shifts in control over alcohol intake.

Taken together, the findings regarding the habit theory in human AUD are, to date, inconsistent. Pickard [142] argues that ongoing alcohol intake despite negative consequences might not serve as a distinct and independent phenomenon of AUD but instead represents a consequence of increased alcohol valuation. Alcohol in AUD can lead to relief from pain, fatigue, stress, boredom, and negative emotions and could thus be a means to many valuable ends that outweigh the negative consequences. Accordingly, Pickard [142] suggests that individuals suffering from AUD do not drink because they neglect the negative consequences (e.g., out of compulsion) but continue drinking because alcohol has tremendous value to them. However, she argues that science and society tend to stick to the habit/compulsion model of addiction de-

spite evidence to the contrary, because eliminating this prominent view might have negative clinical and political consequences. She suggests that the neglect of a model that characterizes addiction as a neurobiological disease of compulsion might facilitate the return of a model that considers addiction as a disorder of choice. However, the latter model can promote negative and ubiquitous moral condemnations for drug users, e.g., the assumption that drug users choose freely to use drugs because they embrace a life of hedonism, when in fact, they may be biased toward drug use to cope with traumatization and other severe negative life events [9]. Therefore, Pickard suggests that clinical and policy interventions should fight such moralism directly instead of cleaving to the concept of habits and compulsion.

Computational Theory

Several different computational routes have been introduced to model habitual drug intake [143], each one with its strength and limitations. Here, we will focus on a model that suggests an imbalance between habitual versus goal-directed behavior. According to this framework, habitual versus goal-directed behavior in AUD and other SUDs can be modeled as model-free and model-based RL algorithms, respectively [144, 145]. While these algorithms have been differently applied to Pavlovian and instrumental learning, within this context we consider only the instrumental learning form. Model-free (MF) algorithms retrospectively assign values to actions and are therefore based on the direct experience of action-outcome associations. These algorithms are computationally efficient but also rigid, as changes in action-outcome contingencies will only slowly update the value of the action. One example of an MF algorithm is TDRL, according to which action values are updated based on RPEs. Model-based (MB) algorithms, on the contrary, do not rely on the direct experience of action-outcome associations. Instead, they rely on the understanding of the structure of the "world" according to which the consequences of actions are predicted. These algorithms are computationally expensive but also flexible.

The two-step task has been designed to particularly assess the relative contribution of these two behavioral modes in humans and rodents [46, 146]. Actions in this task can either be guided by past experience (MF) or prospectively planned according to an internal model of the task structure (MB). In humans, several studies have used this task to test whether the balance between MF and MB behavior is shifted in AUD. In the first study, we showed that AUD was associated with a shift away from model-based behavior [26]. However, between-group effects in this study did not survive when controlling for cognitive capacities. Two other studies with larger sample sizes found no group differences regarding the balance between both behavioral modes between AUD patients and healthy controls [28, 147]. Sebold, Nebe [147] also found no association between MF/MB behavior per se and the prospective treatment outcome in AUD. However, alcohol expectancies interacted with MB behavior to predict relapse, i.e., persons who displayed high alcohol expectancies plus decreased MB behavior had a worse treatment outcome. Moreover, reduced MB neural correlates in the medial prefrontal cortex were indicative of prospective relapse. Similarly, the study by Voon, Derbyshire [28] found increased MB behavior with protracted abstinence in AUD patients, although MB behavior was not directly impaired in AUD. This latter study suggests that intact MB behavior might be of relevance for AUD recovery. However, none of the above-mentioned studies in AUD patients demonstrated an association between AUD severity and decreased MB behavior, suggesting that goal-directedness does not continuously decrease when AUD symptoms become more prevalent or severe. This lack of association speaks against the hypothesis that an AUD diagnosis per se is associated with alterations in the balance between model-free and model-based behavior.

Some studies have also used the same task to investigate the association between MB behavior and subclinical alcohol intake. The findings of these studies are again mixed. One study found no association between MB/MF behavior and self-reports of alcohol intake in young individuals without a diagnosis of AUD [148], which is in accordance with a recent report from Patzelt, Kool [149], albeit the latter study was based on a modified task [150]. Contrary to these studies, Donamayor, Strelchuk [151] found that severe binge-drinking in healthy individuals was negatively associated with MB behavior, which is in line with findings from a large online study including more than 1,400 individuals that found a negative association between Alcohol Use Disorder Identification Test (AUDIT) scores and MB behavior [11]. With respect to a role in the longitudinal development of alcohol use, a recent study [152] observed that low MB behavior at study inclusion relates to a steeper increase in alcohol intake over the follow-up period of 3 years. While these are inconsistent results that warrant replication, we suggest that conflicting results regarding the link between MB behavior and AUD may largely be due to symptom heterogeneity within AUD samples. Future studies should fur-

ther delineate this assumption by systematically investigating whether the specific symptom of ongoing alcohol intake despite adverse consequences is related to reductions in MB behavior or should compare MB behavior in matched AUD patients who either fulfill or do not fulfill this symptom.

Whereas the two-step task enables us to test the balance of model-free and model-based decision-making, another simpler class of paradigms only tests flexibility to changing action-outcome contingencies (akin to the second stage of the two-step task). One example is a probabilistic reversal learning task, where individuals have to learn action-outcome contingencies (e.g., stimulus A is more frequently rewarded and stimulus B is more frequently punished) until the action-outcome contingencies are reversed (now stimulus B is frequently rewarded and stimulus A is frequently punished). Many of these tasks employ anti-correlated reward probabilities, which enable the use of counterfactual reasoning (e.g., if A was not good anymore, B should now be good). Thus, in these tasks, a drop in the value of one option implies an increase in the other's value, and pure model-free RL is not sensitive to this simple task structure [153–155]. Interestingly, reversal learning was used across species [156, 157] and in many human patient studies [158–160], indicating that reward-based cognitive flexibility as an important transdiagnostic construct not only relevant to SUD. With regard to AUD, chronic ethanol exposure has been shown to result in preservative responding after reversals in animals [161]. Likewise, even moderate doses of ethanol impaired reversal learning over 2 weeks [162]. In humans, increased preservative behavior after reversals has been reported in college students who binge drink [163] and in patients with AUD [164, 165] and other SUDs [160, 166]. While these studies relied on pure behavioral analyses, some studies have also added computational modeling to their analytic repertoire. These studies commonly use RL models that rely on iteratively updating using RPE signals. The comparison of RPE-related neural signals between AUD and HCs allows the inference of the neurobiologically embedded mechanism underlying inflexible choice behavior in AUD. By using such an approach, three studies demonstrated no impairments in the expression of striatal RPEs per se [153, 167, 168]. However, abnormal functional connectivity between the striatum and dorsolateral prefrontal cortex predicted the magnitude of craving in AUD patients [167]. Similarly, the representation of RPEs in the ventral striatum was found to be similar to healthy controls; however, it correlated inversely with craving in AUD patients. Moreover, RPEs were associated with dopamine synthesis capacity in healthy controls but not in AUD patients, pointing to altered dopamine function in AUD [168]. Beyond using these simple model-free RL models, two recent studies in AUD fitted complementary RL models that directly model the inference about the anticorrelated structure of the reward contingencies in the reversal learning task (e.g., if one stimulus leads to reward, the alternative stimulus must lead to punishment). In one study, such a "double-update" model better explained the behavioral data of AUD patients and healthy controls than more simplified models that did not infer alternative choices [169]. Another study revealed that while healthy controls' behavior in a reversal-learning task was best explained by a double-update model that inferred about alternative choices, AUD patients' behavior was best explained by a model that did not incorporate these alternative choice options [153]. Differences in model parameterization of choice sensitivity effects may explain differences in model selection results in these two latter studies. Interestingly, in both studies [153, 169], the behavioral deficits in the AUD group were particularly evident after punishments and have therefore been interpreted as a potential mechanism underlying ongoing intake despite negative consequences in AUD. How this insensitivity to reverse behavior in accordance to punishment arises from RL is a clinically highly important question. The study by Reiter, Deserno [153] suggests reduced updating about alternative actions following punishment. However, increased effects of repeated experience early during learning might be an alternative RL account of perseveration [170]. Dissociation of such effects clearly requires further experimental task development.

Discussion

In this review, we have summarized experimental and computational approaches to learning and decision-making to better understand and explain the symptoms of AUD. We focused on how RL and economic choice models may account for cue-induced craving, neglect of non-alcohol rewards, and consumption despite negative consequences. Over the past decades (Heinz et al., 2017), this has led to an increased understanding of the altered cognitive processes that underlie AUD. However, there remains a gap between the evidence of disrupted learning and choice in AUD and their clinical implications. In this regard, a mechanism-based approach to symptoms might be beneficial as compared to diagnosis-centered ap-

proaches, as it directly allows us to account for symptom heterogeneity within the AUD cohort and further helps to infer relevant pathological processes across diagnostic boundaries. Computational models of learning and decision-making play a key role within this approach, as they specify and test theoretical assumptions and assess how well they align with specific symptoms of AUD. As pointed out, the larger agenda of theory-informed RL and choice models faces the key challenge to transfer basic science findings into clinical practice [36, 57]. One idea of how these models may guide clinical practice is that changes in certain computational parameters could help to objectify and potentially also predict treatment effectiveness of psychotherapy [171, 172]. This would allow a more stratified therapy approach, putatively even in a process-specific manner. A second idea of how computational theory-informed RL and choice models may guide clinical practice in the future is that certain decision parameters could help inform clinicians about whether an individual should continue or discontinue a certain pharmacological treatment. For instance, a decision parameter indicating effort allocation was shown to be associated with relapse risk after antidepressant discontinuation in patients suffering from major depression [173]. This study in the field of depression indicates that computational markers could indeed be useful for tailoring pharmacological treatments to patients' needs. An approach focusing on key dimensions of symptoms and their neurobiological correlates might be helpful for this promise [174, 175]. A recent study confirmed that psychiatric medication is commonly prescribed in line with symptoms rather than DSM diagnoses [176]. The understanding of the neural mechanisms and cognitive dimensions that lie at the core of these symptoms might potentially foster the development of new pharmacological treatments.

Limitations

Beyond the above-mentioned benefits, a mechanisms-oriented approach to symptoms of AUD has its limitations. First of all, despite significant criticism of the epistemic problems of diagnoses in psychiatry, diagnoses have been constructed *because* symptoms co-occur in specific patterns and are thus rendered clinically plausible and relevant [9]. For instance, in the study by Augier, Barbier [90], individuals who chose alcohol over alternative rewards were also those that continued to self-administer after shock punishments, suggesting that the symptom of choosing alcohol over alternative rewards might be functionally (and potentially neurobiologically) linked to the symptom of alcohol intake despite negative consequences. By neglecting the co-occurrence or temporal development of specific symptom configurations (as within a diagnostic category), mechanism-oriented research might fail to appreciate an important piece of information about the underlying biology of psychiatric conditions. Thus, we here do not propose that a mechanism-oriented approach to symptoms of AUD should fully replace a diagnosis-centered approach. Instead, we suggest that these different approaches could inform and complement each other.

One necessary further step is to align a mechanism-centered approach to symptoms in AUD with the dynamics of the addiction cycle. One important phenotype of addictive disorders is their chronic and cyclic nature, as affected individuals often face recurrent episodes of relapse between phases of abstinence. Relapse prevention remains the overarching aim of most intervention strategies, and therefore, the investigation of the underlying mechanism of the addiction cycle is a key aim. While the above-described symptoms are assumed to be grounded in either Pavlovian (cue-induced craving) or instrumental learning (choosing alcohol over alternative rewards, choosing alcohol despite negative consequences), the temporal interaction between these learning forms may serve as a mechanistic model for relapse. More precisely, Pavlovian-to-Instrumental transfer (PIT) quantifies the extent to which reward-associated Pavlovian cues invigorate a previously learned instrumental response. This cue-induced invigoration has been considered a core phenomenon underlying relapse in animal models and human studies [see Garbusow et al., this issue and [64, 130, 177, 178]. In humans, several studies have demonstrated that AUD patients, particularly those with poor treatment outcomes, show increased non-alcohol-related PIT effects [179–182]. Interestingly, on a neural level, these PIT effects are associated with increased neural activity in the ventral striatum [180], thus suggesting a potential neurobiological correlate. Furthermore, a genetic polymorphism of the opioid system, which has also been associated with treatment response to naltrexone [183], is related to the behavioral expression of the PIT effect [184]. These studies further suggest that the biological and cognitive mechanisms that are related to the addiction cycle might serve as a potential target for pharmacological treatment stratification of AUD.

Another important methodological limitation that needs to be considered is that the test-retest reliability of the discussed learning and choice tasks, but also cognitive-behavioral tasks including fMRI experiments more broadly, is low [185, 186]. This is a substantial problem for the inevitable acquisition of longitudinal data to target

clinically meaningful questions such as heterogeneity in treatment response. This is because poor reliability of behavior-symptom or brain-behavior variables puts an upper bound on the maximum effect sizes detectable. This could be a contributor to the abundant notion of small effect sizes in psychiatric neuroscience [187]. Further, low reliability also could substantially limit the enthusiasm regarding potential smartphone-based data collections including the collection of rich longitudinal behavioral and even physiological data [188–190]. However, recent studies indicate that the problem of poor reliability may be overcome by pooling data of variables from multiple sources or by using methods that fully capture the data of all participants from all conditions and all sessions in a trial-by-trial manner in descriptive and computational models [155, 191]. Using the latter techniques, tasks with comparably short durations can still reach reliability levels sufficiently high for use in a clinical context.

Conclusion

Taken together, we provide a comprehensive account of the state of the computational mechanism of choice and learning to understand symptoms of AUD. Despite the necessity for ongoing methodological improvements, we suggest that the future may particularly benefit from incorporating computational approaches to model symptoms of AUD.

Statement of Ethics

A preprint version of this article (preprint of the most recent date modified, version 2) is available on psyarxiv: Sebold, M., Kiebel, S. J., Smolka, M. N., Heinz, A., & Deserno, L. (2021, August 30). Computational theories of AUD: Mapping learning and choice mechanisms on symptoms. https://doi.org/10.31234/osf.io/az2x8 [Preprint]. Last edited: February 22, 2022.

Conflict of Interest Statement

All the authors (Miriam Sebold, Michael N. Smolka, Stefan J. Kiebel, Andreas Heinz, and Lorenz Deserno) have no conflicts of interest to declare.

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Author Contributions

Miriam Sebold initiated the concept and overall idea of the manuscript. Miriam Sebold and Lorenz Deserno drafted the manuscript. Michael N. Smolka, Stefan J. Kiebel, and Andreas Heinz gave critical input to revise the manuscript.

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