# Cognitive impairment in substance use disorders

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Cognitive impairments in substance use disorders have been extensively researched, especially since the advent of cognitive and computational neuroscience and neuroimaging methods in the last 20 years. Conceptually, altered cognitive function can be viewed as a hallmark feature of substance use disorders, with documented alterations in the well-known "executive" domains of attention, inhibition/regulation, working memory, and decision-making. Poor cognitive (sometimes referred to as "top-down") regulation of downstream motivational processes—whether appetitive (reward, incentive salience) or aversive (stress, negative affect)—is recognized as a fundamental impairment in addiction and a potentially important target for intervention. As addressed in this special issue, cognitive impairment is a transdiagnostic domain; thus, advances in the characterization and treatment of cognitive dysfunction in substance use disorders could have benefit across multiple psychiatric disorders. Toward this general goal, we summarize current findings in the abovementioned cognitive domains of substance use disorders, while suggesting a potentially useful expansion to include processes that both *precede* (precognition) and *supersede* (social cognition) what is usually thought of as strictly cognition. These additional two areas have received relatively less attention but phenomenologically and otherwise are important features of substance use disorders. The review concludes with suggestions for research and potential therapeutic targeting of both the familiar and this more comprehensive version of cognitive domains related to substance use disorders.

## Introduction

Cognitive alterations and deficits that are observed in substance use disorders[1] contribute directly and indirectly to the overall tremendous public health burden that these disorders place on society. Broadly, drug and alcohol use in human populations exists on a continuum[2,3] ranging from nonpathological to levels of substance use diagnosed as a mental health disorder in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM).[4] Here, we discuss cognitive changes that are on the spectrum where drug use already represents a disorder. This type of drug use can be defined as a "pathological pattern of behaviors related to use of the substance," characterized by a compulsive and chronically relapsing pattern of drug use, impaired control over substance use, continuation of use despite negative consequences, craving, tolerance, and withdrawal.[4,5] The

typical cognitive domains contributing to this understanding of addiction are attention, response inhibition, decision-making and working memory.

Recently a new systemic conceptual framework for neuroscience, the Research Domain Criteria (RDoC) National Institutes of Health initiative, was launched.[6] RDoC is a framework for analyzing mental processes, wherein disorders are considered in terms of disruptions along the continuum of normal to pathology across the full range and along the elemental psychological processes and behavioral functions. This approach is increasingly being used in research, where an appreciation and understanding of its utility is building. RDoC is applied transdiagnostically along the continuum of normal–pathology for the domain or construct in question, allowing one to step away from categorical diagnoses.[7]

The RDoC approach has recently been applied to substance use disorders.[8] Three addiction-relevant domains were highlighted—executive function, incentive salience, and negative emotionality.[9] These functional domains roughly correspond to classical stages in

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the addiction cycle, and they can also be viewed as concurrent contributors to addiction and relapse vulnerability (see Figure 1). These three domains, intended to cover the core elements of the addiction cycle as a disorder, can be measured across a variety of substance use disorders. In this review we will focus on the executive (cognitive) domain, providing an overview of impairments that may serve as intermediate phenotypes for (behavioral, pharmacologic, or neurostimulatory) intervention.

This overview proposes to extend the three established cognitive domains in substance use disorders to include (1) precognition, featuring processes that occur outside or before conscious cognition per se; and (2) social cognition, including metacognition/insight theory of mind (ToM). These expanded domains may be an integral part of the human addiction phenotype and could potentially hold the key to aspects of the addiction phenotype that make treatment and functional impairments in substance use disorders so challenging (Figure 1).

Several models of addiction address cognitive impairments that either predispose a person to addiction or
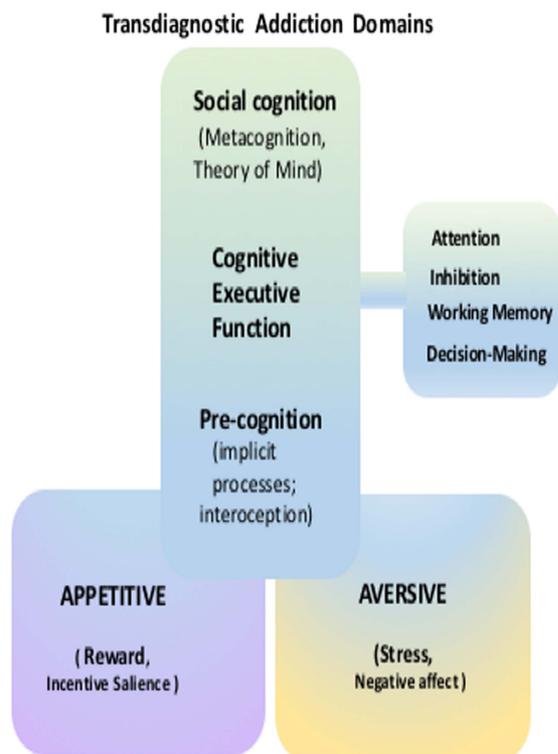


**FIGURE 1.** A visual representation of several transdiagnostic research domains of addiction. Substantial prior research has been conducted on fundamental alterations in the appetitive and aversive motivations processes. The focus of the current paper is a continuum of cognition, ranging from precognitive (implicit) processes to classical executive function (attention, inhibition, working memory, and decision-making) and social cognition (metacognition theory of mind).

result from drug exposure. For example, Goldstein and Volkow[10] proposed a model in which disrupted cortical top-down processes are a result of prefrontal cortex (PFC) dysfunction that leads to impaired response inhibition and salience attribution.[10,11] In other words, there is a decreased ability to modify behavior related to drug and drug cues (response inhibition impairment) coupled with an abnormal salience (salience attribution change) of drug and drug-related cues.[10] Other models emphasizing cognition include Monterosso and Ainslie's description of impulsive choice in humans as a hyperbolic (rather than exponential) function.[12] They argue that impulsive behaviors (e.g., the preference for smaller, more immediate rewards vs. larger, more delayed rewards) often result from a breakdown of cognitive self-control mechanisms. Bickel and Marsch[13] expanded on this model and applied it to addiction, showing that individuals with addiction discount delayed rewards to a much greater extent than healthy controls.[14] Sofuoglu and colleagues[15] proposed a dual-process model, wherein a balance between "top-down" and "bottom-up" processes compete for control of behavior. They argue that neurobiological bottom-up processes are implicit and more automatic, and when heightened, increase the risk of drug use and relapse. Executive top-down processes, impaired in individuals with addiction, are more deliberative and are responsible for modulating the downstream (more automatic) processes.

## Attention

Addiction is characterized by a strong attentional preference for drugs and drug-related cues.[16–18] Attentional biases are often implicit[19] and occur automatically.[20] Some researchers suggest that drug-related cues gain positive incentive properties through a classical conditioning process,[21,22] while other researchers posit that negative affect can increase the salience ("attention-grabbing" quality) of drug-related cues,[23] both of which facilitate drug-seeking behaviors. Whether established through positive or negative motivation, attentional bias can then drive drug seeking,[24] reflected in a shift of salience for drug-related cues and behavioral resources being directed toward the goal of drug consumption.

There are several tasks used to measure attentional bias. The Stroop interference task asks individuals to name the font color of several words; interference occurs when the content of the word is different from the font or is emotionally charged (drug words),[25] resulting in a slower reaction time. Generally, users of nicotine,[26–28] cocaine,[29,30] heroin,[30–33] cannabis,[34,35] and alcohol[36] have slower reaction times when encountering words associated with their substance use disorders. Visual attention tasks can also reveal accelerated reaction times to drug-related stimuli.[37–40] Illustrating that attention

may drive approach, other tasks have measured the attention-driven approach to drug-related cues using a "joystick" procedure. In these tasks, participants either push (avoidance) or pull (approach) a joystick in response to drug-related cues, whether explicit or implicit.[41]

Researchers have begun using these tasks to alter attentional biases (e.g., attentional bias modification training) in an attempt to decrease drug use. Results have shown that attentional bias modification can reduce bias to alcohol cues[41–44] but not cocaine cues.[45] Thus far, results are modest, with the field still actively researching the most effective way to alter attentional bias to substance-related cues—and to translate these attempted changes into clinical outcomes.[46] The underwhelming clinical results underscore the entrenched nature of attentional bias to drug-related cues and their potential importance as a treatment target.

## Response Inhibition

Loss of control over drug use is a key feature of addiction.[4] Inhibitory control refers generally to the ability to suppress or counter responses—whether these responses are behaviors, thoughts, or motivational states. In addiction, impairments in inhibitory control may account for the fundamental difficulty in resisting the motivational "pull" of drugs, thus increasing the vulnerability to relapse.[47,48] Poor inhibitory control may also account for several behavioral patterns that are common in substance use disorders, including increased impulsivity,[49–51] increased sensation seeking,[52] increased risk-taking for rewards,[53,54] and poor decision-making (e.g., choosing small immediate rewards over delayed, larger rewards),[55] discussed in more detail later. Neuropsychological and neuroimaging studies have localized inhibitory control circuitry in the PFC[56]; these circuits normally function in a top-down way to govern downstream motivational systems for drugs and natural rewards.[47,57,58] This ability to inhibit impulses toward reward, to delay gratification, shows significant variability across individuals, and these differences can be detected very early in development,[59] well before any drug exposure. Importantly, however, chronic exposure to some drug classes (especially stimulants) can actually erode the "braking ability" of the brain.[60–62]

The most common tasks for probing inhibitory control feature instructed attempts to inhibit a simple prepotent motor response. The "go/no-go" task presents a stream of "go" stimuli (often simple letters or shapes) that require a rapid button press, while infrequent "no-go" stimuli require "withholding" the button press.[63] Accidentally pressing the button to a no-go target indicates a failure to inhibit. "Stop-signal" tasks require the inhibition of a motor response that is already underway,[64,65] with reaction time (to stop) as the primary measure. Though

these motor tasks are simpler than real-world situations requiring inhibition (e.g., resisting drug use), poor performance in these tasks is generally well correlated with higher-order failures of inhibition, such as drug relapse.[66] In an attempt to capture real-world inhibition struggles, some tasks have used valenced stimuli as signals, requiring inhibition of approach to "positive" stimuli,[67,68] and responding in a valenced go/no-go task was actually better correlated with clinical symptom severity (impulsivity in attention-deficit hyperactivity disorder)[68] than responding in standard non-valenced go/no-go tasks.

Laboratory models that require participants to attempt inhibition of craving to drug video cues[69] provide a close parallel to the real-world challenges faced by patients in recovery. These paradigms reveal that patients with a better outcome prognosis demonstrate good communication (functional connection) between cortical inhibitory regions (i.e., the dorsal anterior cingulate) and downstream motivational circuitry (e.g., the amygdala), whereas patients with a poor outcome prognosis lack this critical connection. In general, the neuroimaging literature has identified poorer recruitment (hypoactivity) of top-down inhibitory regions in drug users versus controls during simple laboratory tasks of inhibition; this is especially marked in stimulant users.[47,48,56,58,70–72] Intriguingly, cocaine patients who achieve extended abstinence actually demonstrate a *heightened ability* to recruit cognitive control regions.[73] This could suggest either that recovery of inhibitory ability improves with (cocaine) abstinence and/or that individuals with strong inhibitory ability are more likely to achieve extended abstinence.[74] Longitudinal studies will be needed to address these possibilities.

Studies attempting to improve inhibitory function either with medications that target frontal circuitry[64,65] or by direct neural stimulation (Transcranial Magnetic Stimulation or transcranial direct current stimulation) of inhibitory circuitry[75,76] are still in the early stages. However, they offer continued encouragement that inhibition is a clinically meaningful intermediate phenotype for targeted interventions.

## Working Memory

Baddeley defined working memory as a system for the temporary maintenance and manipulation of information, necessary for the performance of such complex cognitive activities as comprehension, learning, and reasoning.[77] It is thought to include three subsystems: a phonological loop, concerned with verbal and acoustic information; a visuospatial sketchpad, concerned with visual information; and the central executive, a capacity-limited control system that allocates finite resources and actively manipulates them.[78,79]

Tasks that measure working memory (n-back, visuospatial, digit and word recall, verbal memory, etc.), have revealed cognitive deficits in individuals with a substance use disorder.[10,80–85] Working memory impairments could be associated with chronic toxic effects of drug use,[84] and lower executive cognitive ability has been found to increase susceptibility to problematic drug use.[86] As such, working memory represents a therapeutic target in substance use disorders that could be potentially linked with functional outcomes. Retraining working memory may help to bolster the central executive subsystem of working memory, which may help other cognitive functioning.[79] Thus, addiction researchers have begun to target working memory with the goal of improving cognitive control. For example, Bickel and colleagues used a program (e.g., verbal memory, recall of numbers and words) to train the working memory of individuals with stimulant use disorders.[82] Those authors were able to show improvements of delay-discounting, but not working memory. Houben and colleagues used working memory training on individuals with alcohol use disorders and found both reduced alcohol use and improved working memory.[87]

Another rationale for targeting working memory relates to dopaminergic mechanisms, known to be central to addiction.[88] Working memory capacity is dependent on dopaminergic mechanisms,[89] and it has been shown that working memory training affects dopamine systems.[90,91] When behavioral interventions are not fully effective, having pharmacological approaches could act as a facilitation tool. For example, there is accumulated evidence that working memory impairments might be compensated with psychoactive drugs,[92–94] optimizing dopaminergic function in individuals with addiction. In turn, this may aid them in achieving long-sought functional restoration and support the goals of drug use reduction and abstinence.

## Decision-Making Systems

Seemingly poor decision-making is a prominent feature of addiction, reflected in the continued use of drugs and alcohol in the face of negative consequences.[4] This type of behavior may seem counterintuitive, but there are several theories that address why/how these "poor" choices continue to be made. Verdejo-García and Bechara's "somatic markers" theory[95] states that individuals with addiction have reduced awareness of learned emotional warning signals from the body (interoception) that translates into risky decision-making and "myopia" for the future, similar to individuals with ventromedial PFC lesions. Similarly, Bickel and Marsch focus on cognitive impairment that leads to a discounting of larger, delayed rewards for a preferred smaller, more immediate reward.[13] These poor decisions are thought to

arise from an imbalance of top-down and bottom-up processing. Top-down processing involves deliberative decisions, which are flexible and sensitive to devaluation, but are slow and cognitively intensive.[96] On the other hand, more automatic actions, such as habit-based and classically conditioned behaviors are fast but inflexible and insensitive to devaluation.[96] Initially, decisions to use drugs and alcohol are more deliberate, but with continued use, these actions will transition into more automatic behaviors, eventually becoming compulsive.[97] Contributing to this transition to more automatic decision-making is (learned) incentive salience, the tendency of drug-related cues to take on motivating properties.[22]

Several tasks are used to measure aspects of decision-making systems. For example, delay-discounting tasks allow for the assessment of how well someone is able to delay immediate gratification for a higher-value reward later.[13] Individuals with addiction tend to discount larger, delayed rewards more than healthy controls, and these higher rates of discounting larger, future rewards have been shown to be associated with disadvantageous behaviors,[13] including drug use. Other tasks, such as the Iowa gambling task measure real-time decision-making, and people with addiction generally perform worse than controls; a subgroup of addicted individuals may lack the implicit interoceptive guidance toward a more advantageous strategy.[98]

Researchers have adapted several methods in an attempt to restore the balance of top-down and bottom-up processing. For example, working memory training (as discussed earlier) seems to bolster the central executive subsystem, reducing discounting,[82] improving working memory,[87] and decreasing substance use.[87] Recently, meditation has shown promise as a way to potentially improve executive control[99] and to improve awareness of internal states (and the ability to label them), thus countering alexithymia[100] and potentially improving interoception. Contingency management approaches may boost deliberative decision-making and help reduce automated drug-choice behaviors by making concrete non-drug rewards immediately available[101] and contingent on a reduction in drug use. Contingency management approaches have good impact while the procedures are in place,[102–104] with the transition to the broader real-world setting as the clinical challenge. Preclinical research has demonstrated that automatic behaviors are malleable (e.g., inactivating parts of the brain that underlie habit-based behaviors [e.g., dorsolateral striatum] reduces automatic actions and increases cognitive regulation by other brain areas [e.g., hippocampus]).[105] In humans, devaluation of drug-related stimuli can reduce drug use behaviors,[106] also pointing to the potential modification of decision-making with behavioral strategies. However, given the reflexive

nature of automated decision processes—not just in addiction pathology, but in everyday decision-making— the clinical impact of behavioral strategies is often modest and has encouraged the testing of additional approaches. Direct neurostimulation of cortical areas via transcranial magnetic stimulation offers a promising approach, as it has been shown to reduce craving [107,108] and delay discounting.[109] Pharmacologic approaches to improve decision-making with "cognitive enhancers" also offer preliminary evidence that is promising. For example, modafinil (dopamine drug with potential abuse liability) improved delay discounting,[110] and atomoxetine (non-dopamine drug without abuse liability) improved impaired executive function.[111] Even though a clinical trial of atomoxetine in cocaine addiction was disappointing,[112] there is an ongoing need for medications that can either reduce the implicit, automated processes in decision-making, bolster the deliberative processes, or both.

## Precognition

Processes that are rapid and implicit and that even occur outside conscious awareness are important precursors and contributors to each of the classic executive cognitive domains reviewed here (attention, inhibition, working memory, and decision-making). In Figure 1, processes in the precognitive realm are shaded in blue, and can originate from appetitive or aversive motivational states. Though some of these may eventually be reflected in an explicit (shaded in green) cognition or decision, for example, "I will plan to buy drugs when I get paid tomorrow," others may shape drug-related feelings and behavior while remaining completely outside awareness.

In the domain of attention, the response to drug cues is fast, involuntary, and implicit – the product of powerful prior associative learning. The individual struggling with a substance use disorder does not need to consciously, deliberately focus attention on a drug-related cue for it to have a motivating effect.[19,116] Indeed, the riveted attention to a drug-related cue may occur even when successful task performance instead depends on a flexible shift of attention *away* from drug images.[16,20] Precognitive processes also play a role in inhibition tasks. As previously detailed, these tasks typically instruct deliberate, explicit, conscious attempts to inhibit a "prepotent" (whether motor- or drug-related) response. However, the prepotency of the responses to be inhibited depends on their "near-automatic" nature. For example, motor prepotency results from a rapid series of button presses to a "go" signal, and a prepotent approach to drug stimuli is the near-automatic result of much prior learning. In the domain of working memory, an individual's ability to maintain and update

information, to allocate cognitive resources, generally happens implicitly, from moment to moment, without a conscious focus. Experimental tasks that probe working memory may instruct the participant to intentionally recall an item earlier in a string (e.g., the n-back test), but in real life, this kind of memory occurs in an ongoing precognitive way, without explicit awareness and without prompting. The realm of decision-making especially highlights the "competition" between fast, implicit, precognitive responses (e.g., the approach response to immediate reward and discounting of delayed future rewards) versus slower, deliberative responses (e.g., taking the future into account, including any future negative consequences of the approach to the drug reward). The human challenge of balancing fast, implicit, precognitive decision processes against slow, deliberative processes has been recognized across history and is the foundation for several "dual-process" models[113] of decision-making.

Given the broad contribution of precognitive processes, what are the implications for addiction treatment? As conventional cognitive behavioral treatments are directed to faulty explicit cognitions, these interventions may not affect implicit processes. That the high rates of relapse that are common for substance use disorders have remained relatively unchanged across the decades may reflect (at least in part) a difficulty in addressing the precognitive domain. As noted earlier, from the few available studies, behavioral attempts to change the attentional bias to drug cues have met with only modest success,[41] and studies using working memory training are still in the early stages.[82,87] Encouragingly, pharmacologic interventions might be well suited to the precognitive domain. As an example, a recent study demonstrated that the noradrenaline uptake inhibitor atomoxetine was able to reduce attentional bias to cocaine cues[114] (though a clinical trial did not demonstrate benefit[112]), and the opioid antagonist naltrexone was shown to improve the recruitment of modulatory circuitry (lateral orbitofrontal cortex) in a "now–later" decision-making task.[115] The GABA$_B$ agonist baclofen, known to reduce dopamine release,[116] was shown to blunt the mesolimbic activation triggered by 33 msec cocaine cues presented outside conscious awareness.[117] The ability of brief "unseen" drug cues to trigger motivational circuitry[118,119] offers a paradigm for screening the ability of candidate medications to impact precognition, complementing conventional self-reports of conscious motivational ("craving") states.

A construct with a special relationship to the precognition domain is interoception, the organism's sense of its own internal state(s).[120–122] Broadly, interoception is based on bodily sensations reflecting a change in internal state (e.g., hunger, thirst, temperature) or autonomic visceral responses (e.g., heart

palpitations, sweating, gut motility) arising in response to powerful external stimuli (e.g., pain, threat, sexual opportunity, even the anticipated reward from drugs of abuse). Importantly, these varied bodily sensations can also become attached, through learning, to previously neutral cues, enabling the cues to guide the organism *away* from danger, or *toward* reward.[121,123,124]

With these links both to danger and to reward, it is understandable that interoception has been featured in human addiction models. Bechara and colleagues[98] hypothesized that impaired interoception (aka "somatic markers") for *negative* stimuli (e.g., the negative consequences of drug choice) could contribute to relapse. On the other hand, heightened interoception for the positive (appetitive) arousal triggered by drug reminder cues can also be a relapse vulnerability,[57,118,125] fueling the "incentive salience" of these cues. Whether for aversive or appetitive states, the anterior insula has been strongly implicated in interoceptive processing and emotional awareness.[119] Supporting the clinical significance of the insula in interoception, an attenuated response in the insula during decision-making predicted relapse in methamphetamine users.[126,127] Intriguingly, cigarette smokers who sustained injury to the insula—presumably impacting both appetitive and aversive interoceptions—lost the motivation to smoke (they "simply forgot to crave a cigarette").[128,129] As in these examples, interoceptions often have their origins in the precognitive domain and can influence addiction-relevant decision-making, even when—perhaps especially when—the individual has limited self-awareness. Indeed, some therapeutic approaches in substance use (and other disorders) are geared to improving the individuals' conscious, explicit awareness of their internal states as a step toward greater cognitive control. Novel treatments targeting the insula with real-time neuro-feedback[130–132] or direct brain stimulation[133] underscore the promise of interoceptive processes as a meaningful therapeutic target in substance use disorders.

## Social Cognition

### Metacognition

We humans have the ability to look inside ourselves, which allows us to understand the relationship between ourselves and others, to monitor our own thought processes, and to control thoughts, all of these activities are related to metacognition. However, impairments of metacognition can have negative consequences on decision-making, such as being overconfident about a poor decision or lacking confidence in a better decision.[134,135]

The scope of metacognitive impairment in substance use disorders has not been well researched, despite it being a striking and critical feature of the addiction phenotype. For example, many researchers report a dissociation between self-report and behavior, low treatment compliance, frequent relapse, impaired psychosocial functioning, and a lack of perception that treatment is actually needed. In 2015, more than 21 million individuals (12 or older) were classified as needing treatment for a substance use disorder. Just more than 10% actually received treatment for a disorder; however, among the rest (~19 million), only about 5% perceived the need for treatment.[136] Goldstein and colleagues have reported that this impairment is reflective of an existing dysfunction in the neural circuitry.[137] Neurologically, it is thought that mechanisms of metacognition reside in frontal structures, such as the rostral anterior cingulate cortex,[138,139] and that dysfunction of ventrolateral PFC may be an important contributor to the insight impairment.[140]

Metacognitive deficits can be thought of as impairments of insight, shown to be a common feature in addiction.[141,142] In the substance use disorder literature, lack of insight has sometimes been conflated with "denial." However, the two are distinct. Denial implies a refusal or contradiction of something of which the person is aware, while lack of insight involves a lack of awareness of something present in the individual. Some researchers in mental health disorders separate clinical insight, which is a construct composed of awareness of illness, recognizing the need for treatment, and relabeling symptoms, and impaired general insight, which is connected with poorer treatment outcome, an inability to perceive the severity of illness, poor psychosocial functioning, higher relapse, and low self-esteem.[143] If individuals with substance use disorders are not able to assess the level of severity of their impairments, or in some cases are not even aware that they have a disorder, this may help explain the lack of perceived need for treatment. It is worth noting that even after recognizing the need for help and seeking treatment, patients may still struggle and relapse. Thus self-awareness is important but maybe not sufficient for recovery.

It has also been noted that addiction involves deficits of self-awareness and behavioral control similar to what is seen in other neuropsychiatric disorders (e.g., mood, psychotic, and neurological disorders).[137,144,145] Research has suggested that this insight deficit is reflected in one of the key attributes of substance use disorder defined in the DSM classification: drugs are used despite negative consequences. Self-awareness deficits and metacognitive impairments persist even in remitted drug users, revealed, for example, by remitted users' poor association between self-reported confidence in performance and *actual* performance on a visuo-perceptual accuracy task.[146]

We are aware of at least two methods to address the insight deficit and bolster metacognitive abilities. One is

metacognitive therapy (MCT), which was first developed to address impairments of cognition that occur in several stress-related disorders such as depression, anxiety, PTSD, and obsessive-compulsive disorder.[147–152] Metacognitive therapy has been described a hybrid of cognitive-behavioral therapy and psychoeducation[153,154] and has been shown to be efficacious in reducing schizophrenia-related anxiety and depression symptoms.[155,156] Another method is metacognitive strategy instruction, which was found to be helpful for those with below-average decision-making performance but not for those with average or above-average decision-making performance.[136] Recent metacognitive models have been directed toward addiction,[148,157] but formal clinical trials in substance use disorders using MCT or metacognitive strategy instruction are not yet available.

### Theory of mind

Within the social cognition domain of addiction, there exists a relatively understudied cognitive construct called theory of mind (ToM). ToM is described as the cognitive capacity to have an implicit assumption about the behavior and intentions of others, as driven by their desires, attitudes, and beliefs.[158–160] The capacity for social insight in humans is dependent upon this process. ToM mainly consists of two subtypes: "cognitive" ToM for attribution of beliefs and intentions and "affective" ToM for attribution of emotions.[161] Studies of ToM and its impairment in mental disorders traditionally were investigated in developmental psychology in children[162,163] but then were applied to disorders such as autism, schizophrenia, and personality and neurological disorders, in which impairments in social cognition are very central to their phenotypical presentation.[159,164–168] In psychotic spectrum disorder and schizophrenia, for example, social cognition impairment has been strongly linked with functional outcome.[169–171] In addition, evidence has accumulated that ToM mediates the pathway from neurocognition to functional outcome in young adults with recent onsets of mood, anxiety, and personality disorders,[172] and in people with bipolar disorders, ToM deficits could be viewed as a core deficit feature, which is independent from other symptoms and patient characteristics.[173] For substance use disorders, recent meta-analysis of social cognition in alcohol use disorder showed a significant deficit in emotion recognition and cognitive ToM.[174] ToM impairments were also found in individuals with cocaine use disorders[175] but not recreational cocaine[176] or cannabis users.[177,178] More sensitive neurophysiological measures of brain activity (e.g., fMRI), may be able to further identify differences in the ToM neural network activation of individuals using substances recreationally and those with clinically diagnosable substance use disorders.

In regard to assessment tasks, the "Reading the Mind in the Eyes" task has been used to examine affective ToM.[179] The "Theory of Mind Stories" task has been used to examine second-order understanding of false beliefs,[180] and there are other tasks in development (e.g., using a virtual reality paradigm[181]). Interventions that have shown to bring positive change in affective ToM are possible, including psychodynamic art therapy, which was previously shown to reduce symptoms in patients with schizophrenia.[182]

Social cognition impairments are present transdiagnostically across neuropsychiatric disorders, including substance use disorders. However, more research in social cognition deficits for substance use disorders is needed to potentially add treatment options that may translate into long-sought functional gains.

## Conclusion

This review presents an overview of cognitive impairments in drug and alcohol use disorders. Cognitive impairments are addressed as a continuum, with one end representing the more precognitive processes and the other end extending to higher levels, such as social cognition; in between are the familiar cognitive executive domains (Figure 1). In this review of the cognitive executive domain, we found that most of the research has been focused on characterizing patients versus controls and documenting differences in each of these domains (e.g., attention, response inhibition, working memory, decision-making systems). For each of these domains, there is also an emerging body of evidence for its status as an intermediate phenotype and potential target for intervention. However, the translation from intermediate phenotype to clinical outcome is still in the early stages. Novel treatments (e.g., neurostimulation, pharmacologic "rebalancing") offer promise for the next phase of translational research, inclusive of cognitive deficits in substance use disorders. We described a "cognitive continuum," for which the extremes (precognition, social cognition) have been less studied. We suggest the unique features of these domains (e.g., impaired interoception, metacognitive deficits, impaired insight into illness) offer viable therapeutic targets that may both require and stimulate entirely new interventions.

It is important to recognize that, in cross-sectional research, it is difficult to determine whether drug use was predated, predisposed, exacerbated, or caused entirely by cognitive impairments. New longitudinal studies in developmental cohorts[183] before drug exposure will help to determine the relative contribution of individual variables (e.g., genetics, epigenetics, adversity) versus drug variables (e.g., type of drug, dose, exposure, frequency) to the observed impairments. This information is critical both for selecting therapeutic

targets and for shaping therapeutic expectations (e.g., restoring function vs. remedial biological supports).

Finally, worth noting, the phenotypical features stemming from both the familiar and extended cognitive domains are not confined to addiction but are both dimensional and transdiagnostic and relevant for other neuropsychiatric disorders and conditions (a focus of RDoC). Thus, therapeutic discoveries in the addiction arena might be expected to have direct relevance for other major psychiatric disorders sharing the dimensions of these cognitive impairments.[184] Research in these domains will also be helpful in empirically determining the unique contributions of intermediate phenotypes versus an overall psychopathology (e.g., factor "p"[185]) in guiding treatments and predicting clinical outcomes.

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