In this targeted review, we summarize current knowledge on substance-use disorder (SUD)-related cognitive deficits, the link between these deficits and clinical outcomes, and the cognitive training, remediation, and pharmacological approaches that have the potential to rescue cognition. We conclude that: (i) people with SUDs have moderate deficits in memory, attention, executive functions, and decision-making (including reward expectancy, valuation, and learning); (ii) deficits in higher-order executive functions and decision-making are significant predictors of relapse; (iii) cognitive training programs targeting reward-related appetitive biases, cognitive remediation strategies targeting goal-based decision-making, and pharmacotherapies targeting memory, attention, and impulsivity have potential to rescue SUD-related cognitive deficits. We suggest avenues for future research, including developing brief, clinically oriented harmonized cognitive testing suites to improve individualized prediction of treatment outcomes; computational modeling that can achieve deep phenotyping of cognitive subtypes likely to respond to different interventions; and phenotype-targeted cognitive, pharmacological, and combined interventions. We conclude with a tentative model of neuroscience-informed precision medicine.
Original article
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Evidence supports the central role of cognition on substance-use disorder symptomology, clinical prognosis, and potential therapeutic targets

Cognitive deficits and treatment outcomes

Cognitive deficits in attention, memory, executive functions, reward/negative emotion valuation, and decision-making reflect performance differences between substance users and drug-naive controls and/or consensus from experts.2,11,13,17,18 A pertinent but different question is which of these cognitive deficits are relevant to clinical outcomes in the context of addiction treatment. Key treatment outcomes include treatment retention and adherence, reduction of drug use and abstinence, craving, and quality of life.19,20 In a systematic review of prospective studies measuring retention and abstinence-related outcomes, we showed that a test battery of general cognitive functioning indexing speed/accuracy during attention and reasoning tasks (MicroCog) was the only consistent predictor of treatment retention, and tests of uncertainty and risk-based decision-making the only consistent and robust predictor of relapse.21 The latter finding is in line with recent neuroimaging data showing that quality of the neural networks integrating the executive control system (connectivity between frontoparietal and medial frontal networks) and the reward responsiveness system (connectivity between salience, motor/sensory, and subcortical networks) is associated with cocaine abstinence following treatment and at 6-month follow-up.22

Some of the constructs identified by Delphi consensus (eg, reward expectancy and valuation) or ANA (eg, negative emotionality) have not been examined in prospective outcome studies and need more research. However, some other constructs pinpointed by these approaches (eg, habits/com pulsivity and incentive salience) have been measured with well-validated paradigms such as shifting/perseveration and attentional bias tests and, although some studies showed significant predictive validity, there was not sufficient consistency across studies.23 Tests of executive functions yielded mixed evidence although this may be due to test impurity (see section on cognitive training and rehabilitation) and significant heterogeneity in the selection of measures.

What is it about successful tests? General cognition tests predicting treatment retention may be capturing more complex aspects of the cognitive architecture. For example, speed and attention are needed to perform complex executive function tests including action selection and response inhibition tasks.23 In addition, the performance measures of these tests (precise measures of reaction time and errors) can be more sensitive to individual differences relevant to prediction, compared with the traditional outcome measures of neuropsychological tests, ie, gross measures such as the Stroop interference score or attentional lapses in the Wisconsin Card Sorting Test. In support of this view, we recently showed that the index of reaction time variability of the continuous performance test was a significant predictor of continuous treatment engagement, over and above a more specific measure of effort-reward valuation.24 Another possibility is that these tests are a proxy of IQ-related decline and thus a global measure of the impact of SUDs on fluid intelligence and related outcomes. Decision-making tests predicting drug use and relapse suggest a more straightforward story. The ability to make advantageous decisions in complex scenarios is essential to achieve long-term goals and life milestones. In the context of SUDs, greater alterations in the ability to make uncertain decisions (Iowa Gambling Task) can compromise attempts to maintain abstinence.25,26 At the same time, these tasks (especially the Iowa task) have been criticized for lack of reliability and construct validity.27 Although our personal experience is that providing appropriate task instructions and performing detailed analyses (eg, block-by-block or trial-by-trial perfor-
Several cognitive domains have clear face validity for predicting addiction treatment outcomes but may be suffering from test impurity problem. Response inhibition and action selection are integral aspects of decision-making processes, and clinicians consistently report anecdotal evidence of highly impulsive patients dropping out of treatment and restarting drug use. However, available tests such as the Stroop or the Stop Signal task have not shown consistent predictive validity. Therefore, the design of new tests that incorporate precise output metrics (to detect individual differences) and optimize both construct and predictive validity (to predict meaningful outcomes) will allow reassessment of the clinical significance of these cognitive domains. An important consideration for the design of new tests in the SUD space is the prioritization of features that can facilitate clinical usability, including brevity and automated instructions and feedback.

Computationally, the outcomes of the tests should be suitable for computational modeling that can tease apart clinically significant subtypes to inform precision medicine approaches. These features (usability and suitability for modeling) will also contribute to the next frontier and most ambitious challenge in this context—the harmonization of a cognitive test battery for addiction (akin to the MATRICS battery for schizophrenia). Based on current knowledge, we propose that this battery incorporate indices of IQ, speed/accuracy-based attention and reasoning, decision-making, and novel m easures of action selection/response inhibition and reward learning. Desired features include customized computerization, automated instructions and feedback reports, brevity (or potential to become more efficient through psychometric modeling) and suitability to conduct cognitive neuroscience-informed models for computational modeling on output variables.

**Computational modeling**

An outstanding limitation of current methods of cognitive assessment, especially complex attention, executive function and decision-making tasks frequently used in the context of SUDs, is the so-called test impurity. Complex cognitive tests simultaneously tap into several different cognitive abilities. Some of these abilities are prerequisite skills needed to engage complex skills. And some others are complex, higher-order cognitive skills, just not the ones that the test primarily intends to measure. For example, participants performing a decision-making task need to recruit basic attention and remember the stimuli and instructions. When making decisions, some individuals may use working memory strategies to “hold online” options with better reward values, whereas others may employ response inhibition skills to withhold responses driven by past immediate outcomes. This phenomenon partly explains why some constructs with high face validity, such as response inhibition, have not consistently predicted clinical outcomes of SUD treatment.

One way to address test impurity while simultaneously increasing m easure precision is by using cognitive modeling, or computational modeling of cognitive processes. Computational models enable researchers to deconstruct a cognitive task or activity on a limited number of subprocesses (parameters) and their predicted interactions, and to build models to precisely measure individual variation in each of those parameters (parameter estimates). Early applications of cognitive modeling to decision-making tasks in SUDs showed that the performance of substance users in the Iowa Gambling Task could be decomposed into several different subprocesses, including sensitivity to reward and punishment, m ent, immediate versus distal decision-making, and chance consistency. Using this modeling, they could establish that the decision-making deficits of cocaine users were mostly driven by hypersensitivity to reward and lack of choice consistency, whereas the deficits of cannabis users were mostly driven by recency effects. Other simpler forms of cognitive modeling, such as drift-diffusion modeling and hyperbolic curve modeling, have been successfully applied to examine value-based and perceptual decision-making tasks (reviews in refs 36, 37). More recently, modeling-free modeling, which estimates the extent to which decision-making performance is driven by habitual versus...
goal-oriented responses, is gaining traction in the cognitive neuroscience literature and has been successfully applied to m easure the decision-m aking deficits of m ethamphetamines users. In addition to individual-based decision-making, novel computational models have started to deconstruct and estimate individual variation in complex social decision-making, incorporating complex abstract parameters such as guilt. Altogether, growing evidence suggests that computational modeling could assist the design of novel cognitive tasks and test batteries that achieve more precise and predictive measures of latent cognitive processes.

Cognitive training and rehabilitation

There are two main approaches to restore cognitive deficits: (i) computerized cognitive training; (ii) cognitive rehabilitation. Computerized cognitive training uses software to retrain specific cognitive processes through repeated exercises aimed to build cognitive capacity. Cognitive rehabilitation or remediation focuses on meta-cognitive training and strategy learning, instructing participants to apply cognitive resources in a goal-driven and strategic way. Unlike cognitive training, it is typically guided by therapists and focuses on real-life activities (instead of task-based exercises). A key assumption within addiction neuroscience is the existence of an im balance between the bottom-up cognitive systems that are sensitized to the reward value of drug-related stimuli and the top-down executive and decision-making systems that fail to guide response selection according to long-term goals. From a cognitive architectural and functional standpoint, it seems m ore feasible to retrain automatic bottom-up processes through cognitive training and repeated exercise. On the other hand, top-down goal-driven behavior requires greater complexity and entropy to adapt cognitive strategies to the current context and future goals, and thus is more suitable to be trained through cognitive rehabilitation approaches. In support of this notion, the two most successful cognitive remediation approaches for addiction use these principles. Cognitive bias modification (CBM) uses software-based cognitive exercises to retrain automatic attentional/approach biases towards drug stimuli. By training participants to avoid drug-related images and approach alternative reinforcers, CBM decreases the motivational appeal of drug stimuli. An interesting emerging approach is to combine different neuroscience-informed interventions that synergistically tap into bottom-up versus top-down cognitive processes. Within this context, there are three potential approaches: (i) combining cognitive training with existing evidence-based interventions; (ii) combining cognitive training and exercise (regulates drug cues related salience and proneness to neuroplasticity); and (iii) combining two different cognitive trainings.

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From a cognitive architectural and functional standpoint, it seems more feasible to retrain automatic bottom-up processes through cognitive training and repeated exercise. On the other hand, top-down goal-driven behavior requires greater complexity and entropy to adapt cognitive strategies to the current context and future goals, and thus is more suitable to be trained through cognitive rehabilitation approaches. In support of this notion, the two most successful cognitive remediation approaches for addiction use these principles. Cognitive bias modification (CBM) uses software-based cognitive exercises to retrain automatic attentional/approach biases towards drug stimuli. By training participants to avoid drug-related images and approach alternative reinforcers, CBM decreases the motivational appeal of drug stimuli. An interesting emerging approach is to combine different neuroscience-informed interventions that synergistically tap into bottom-up versus top-down cognitive processes. Within this context, there are three potential approaches: (i) combining cognitive training with existing evidence-based interventions; (ii) combining cognitive training and exercise (regulates drug cues related salience and proneness to neuroplasticity); and (iii) combining two different cognitive trainings.
Initial evidence suggests that combining computerized cognitive training of general cognition and working memory with contingency management (CM) improves the beneficial effects of training on top-down cognitive skills.52,60 The next step is to explore the potential of this combination to improve clinical outcomes such as the reduction of drug use and abstinence. A promising approach in this context would be combining contingency management (CM) with Goal Management Training (GMT). CM would facilitate the goal of maintaining abstinence in the short-term (i.e., exchanging negative drug tests with financial incentives), while progressive training with GMT would enable participants to apply goal-based decision-making strategies in the long-term. The second approach leverages evidence showing that short- and mid-term regimens of aerobic exercise can significantly reduce drug cue-related salience,61 and increase the availability of dopamine D2-type receptors in the striatum, linked to reward valuation and impulsivity.62 Thus, combining aerobic exercise and training of top-down impulsive control via exam ple inhibitory control training may have synergistic benefits on cognitive control and craving. The third approach consisting of combining bottom-up and top-down cognitive training sounds intuitively. However, its application is not without challenges. For example, we applied a combination of cognitive bias modification and working memory training among people with alcohol-use disorders, and found that the combination training did not improve cognitive or clinical outcomes.52,60 We reasoned that one of the factors explaining the lack of success might be the risk of overwhelming cognitive abilities and generating frustration. Therefore, this approach should carefully consider the timing and the intensity of the “combination-training” for exam ple, by alternating different trainings on different days and ensuring that difficulty is progressive, or by integrating both trainings in a single package.

In addition to combination therapies, additional efforts have been made to develop modified “traditional” behavioral psychosocial treatments adapted to computerize the cognitive deficits of people with SUDs. Aharonovich et al.64 have integrated computerized strategies for cognitive deficits used in brain injury patients in a Modified Cognitive Behavioral Therapy (M-CBT). They presented the therapeutic CBT activities in a less cognitively demanding way to improve learning, memory, and executive functions (e.g., reduced session length and increased weekly frequency, short-term plied corn nunciation, concrete and visual presentation of content of sessions, workbooks with visual illustrations and to-do lists, use of mnemonic and external memory aids, repetition until mastery occurs). M-CBT was not superior to CBT in terms of treatment retention or drug use reduction, although participants enrolled in M-CBT reported a greater treat ment satisfaction, and those who completed at least 9 weeks of treatment showed a trend towards a greater reduction of cocaine use.

Finally, an important aspect to address in future studies of cognitive training and rehabilitation is what aspects of these interventions may work better for different patient subtypes. Research on moderators of cognitive training and rehabilitation effects is particularly useful in this context. For exam ple, in the context of treatment for alcohol use, Houben et al.65 found that participants with strong impulsivity to drink alcohol benefitted the most from WM training. This finding aligns with the view that WM training can be particularly useful to reduce impulsive behaviors given neurobiological overlap in lateral prefrontal cortex regions.66,67 Furthermore, Eberl et al.68 demonstrated that older alcohol-dependent patients and patients with a strong pre-training approach-bias benefitted most from CBM.

**Biological approaches**

**Pharmacotherapy**

Cognitive enhancing pharmacotherapies are based on the premise that cognitive processes may be important targets for the treatment of SUD.68,69 From this point of view, pharmacotherapies that aim at improving cognition can be considered as potential transdiagnostic intervention, i.e., enhancing cognitive processes underlying different types of addictions and associated psychiatric disorders. Broadly two categories of approaches can be identified: mnemonic-enhancing drugs (acetylcholinesterase inhibitors) and stimulants.

Increasing synaptic concentrations of acetylcholine has shown potential to improve cognitive function in neuropsychiatric disorders, e.g., dementia and schizophrenia.7071 In different, small-scale and short studies, galantamine and rivastigmine showed positive effects both on cognitive function (sustained attention, working memory) and clinical outcome in patients with stimulant SUDs (amphetamine, cocaine).72-74 These results provide at least preliminary evidence of mnemonic future research.
Modafinil is a cognitive enhancer with a complex pharmacological profile, ie, inhibitor of dopamine and norepinephrine transporters, and additional actions on GABA, glutamate, and Orexin. Within cocaine-dependent patients, modafinil has shown improvement of cognitive function (working memory) and clinical (reduction of cocaine use) effects. Of interest, in a recent study baseline cognitive functioning, ie, im pulsivity and attentional bias, predicted clinical outcome in mesial fusiform treated crack-cocaine dependent patients. In alcohol-dependent patients, modafinil improved impulse decision-making, response inhibition, and working memory and had a positive effect on clinical outcome (time to relapse percentage of abstinent days). However, both the positive clinical effect and the effect on working memory were limited to those patients with high impulsivity and low working memory. In reverse, patients with a normal-to-low baseline impulsivity had an adverse effect on their drinking outcome when using modafinil.

These findings indicate the importance of baseline cognitive performance in differentiating the effect of modafinil and possibly other cognitive-enhancing medications.

Methylphenidate is another stimulant drug with a pharmacological profile similar to amphetamine and cocaine, ie, increasing dopamine, norepinephrine, and serotonin. Different studies show its efficacy in improving decision-making, working memory, and set-shifting in ADHD patients. Recent studies show a positive effect of high dosages of methylphenidate on amphetamine and cocaine use in stimulant-dependent ADHD patients. Interestingly, other associated substance use in these patients, eg, alcohol and cannabis, diminished in these trials. This finding may indicate a substance “transdiagnostic” effect of high-dose methylphenidate. Overall, amphetamine-like drugs have been shown to have a positive effect on different cognitive functions. In healthy participants, D-amphetamine increases cognitive performance in processing speed, inhibition, and vigilance tasks. However, the cognitive enhancing properties of these substances have been until recently hardly explored as a treatment for SUDs. The potential addictive properties of these substances play an important role here. In a recent study, high-dosed sustained-release dexamphetamine has shown positive clinical effects (fewer days of cocaine use) in cocaine-dependent heroin patients.

Taken together, treatment with cognitive enhancing drugs does seem to carry promise both in enhancing cognitive function and clinical outcome in SUD patients. However, the interrelation between these two outcome domains remains largely unexplored. Most studies focus on either cognition or SUD outcome and do not explore their intercorrelation or temporal (causal) interaction with cognitive outcome. The complexity of this interrelation is highlighted in a recent study. In cocaine-dependent ADHD patients, the effect of extended-release methylphenidate (MAS-XR) on cocaine use, and response inhibition, and working memory and had a positive effect on clinical outcome (time to relapse percentage of abstinent days). However, both the positive clinical effect and the effect on working memory were limited to those patients with high impulsivity and low working memory. In reverse, patients with a normal-to-low baseline impulsivity had an adverse effect on their drinking outcome when using methylphenidate.

Neuromodulation: transcranial stimulation

Transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) are two types of neuromodulation with potential therapeutic utility in the treatment of a broad variety of psychiatric disorders, including SUDs. Studies have been published showing positive results (active versus sham condition), ie, reduction of craving and substance use, of TMS and tDCS in alcohol, nicotine, cocaine, obesity, and food addiction. Of interest, for both techniques the produced effects are temporary, ie, long-term benefits would likely require chronic (repetitive) administration. The exact underlying working mechanism of these interventions remains to be clarified, eg, whether these effects (craving, substance use) are direct or via the strengthening of cognitive functions. Indeed, studies using neuromodulation techniques such as transcranial direct current stimulation (tDCS) have demonstrated promising effects in modulating cognitive and motor functions. In healthy individuals, tDCS and rTMS induce alterations of cognitive functions, eg, reducing impulsivity and risk-taking. Modification of these cognitive deficits that have been suggested to play a role in the pathogenesis of addictive behaviors may, at least from a theoretical stance, reduce these behaviors. In a broad variety of SUD patients, excitatory stimulation over the left DLPFC was associated with increased inhibitory control, lower risk-taking, decreased delay-discounting, reduced attention towards alcohol cues, and im proved executive functioning. Right DLPFC stimulation was less studied, but also showed a reduction of risk-taking and improved cognitive performance in patients with high impulsivity and inhibitory control. However, findings were not consistent with some studies showing no or even negative effect. Of
interest, studies suggest that SUD severity may differentiate the effects of neuromodulation, ie, a more significant effect on executive functioning in patients with more severe AUD. Also, in different studies, baseline cognitive task performance proved to modulate the effectiveness of neuromodulation. Baseline impulsivity is likely to be an essential determinant of neuromodulation effectiveness. Besides, earlier studies in SUDs populations showed rate-dependent effects for manipulations targeting delay discounting, suggesting that for future neuromodulation studies rate-dependent analysis should be considered.

Taken together, transcranial stimulation interventions seem to have both an effect on clinical outcome variables and cognitive functions within SUD patients. However, as yet no information is available on the question of whether these cognitive impairments are the drivers of the clinical effect.

**Conclusion**

The reviewed evidence supports the central role of cognition in SUD symptomology, clinical prognosis, and potential therapeutic targets. Growing evidence about the relevance of attention, impulsivity, and decision-making for prediction and moderation of the outcome of different cognitive and pharmacological approaches suggests that cognitive phenotyping and modulatory intervention will penetrate future treatment options. Future research is warranted to evaluate if this line of research can pave the way to precision medicine approaches. In the interim, we propose a tentative model in which deep phenotyping of cognitive processes can lead to phenotype-matched cognitive and pharmacological approaches and putatively better SUD treatment outcomes. Current evidence suggests that cognitive approaches involving CBM, WM training, and Goal Management Training can be optimally suited for patients with strong automatic biases, high impulsivity levels, and deficient decision-making skills. Biological therapies, ie, pharmacotherapy and neuromodulation aiming at strengthening cognitive functions, are shown to be increasingly important, specifically for patients with high impulsivity and poor executive functioning. Meaningful combinations of cognitive and biological approaches can be particularly useful for patients with extreme presentations of identified phenotypes (eg, WM training and left dorsolateral prefrontal cortex stimulation for highly impaired patients).

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