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Cognitive Function as a Trans-Diagnostic Treatment Target in Stimulant Use Disorders

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Abstract

Stimulant use disorder is an important public health problem, with an estimated 2.1 million current users in the United States alone. No pharmacological treatments are approved by the U.S. Food and Drug Administration (FDA) for stimulant use disorder and behavioral treatments have variable efficacy and limited availability. Most individuals with stimulant use disorder have other comorbidities, most with overlapping symptoms and cognitive impairments. The goal of this article is to present a rationale for cognition as a treatment target in stimulant use disorder, and to outline potential treatment approaches. Rates of lifetime comorbid psychiatric disorders among people with stimulant use disorders are estimated at 65% - 73%, with the most common being mood disorders (13% - 64%) and anxiety disorders (21% - 50%), as well as non-substance induced psychotic disorders (under 10%). There are several models of addictive behavior, but the dual process model particularly highlights the relevance of cognitive impairments and biases to the development and maintenance of addiction. This model explains addictive behavior as a balance between automatic processes and executive control, which in turn are related to individual (genetics, comorbid disorders, psychosocial factors) and other (craving, triggers, drug use) factors. Certain cognitive impairments, such as attentional bias and approach bias, are most relevant to automatic processes, while sustained attention, response inhibition, and working memory are primarily related to executive control. These cognitive impairments and biases are also common in disorders frequently comorbid with stimulant use disorder, and predict poor treatment retention and clinical outcomes. As such, they may serve as feasible trans-diagnostic treatment targets. There are promising pharmacological, cognitive, and behavioral approaches that aim to enhance cognitive function. Pharmacotherapies target cognitive impairments associated with executive control and include cholinesterase inhibitors (e.g., galantamine, rivastigmine) and monoamine

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transporter inhibitors (e.g., modafinil, methylphenidate). Cognitive behavioral therapy and cognitive rehabilitation also enhance executive control, while cognitive bias modification targets impairments associated with automatic processes. Cognitive enhancements to improve treatment outcomes is a novel and promising strategy, but its clinical value for the treatment of stimulant use disorder, with or without other psychiatric comorbidities, remains to be determined in future studies.

Keywords

attentional retraining; cocaine; cognitive behavioral therapy; cognitive bias modification; cognitive enhancement; cognitive remediation; methamphetamine; pharmacotherapy; psychotherapy

1. Introduction

Stimulants, most notably cocaine and methamphetamine, are widely abused, with an estimated 2.1 million users in the United States and 36 million current users worldwide (SAMHSA, 2014). As defined by the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5), stimulant use disorder encompasses the DSM-IV abuse and dependence diagnoses (APA, 2013). Stimulant use is associated with an increased risk of HIV and hepatitis-C infection, detrimental effects on the unborn and newborn, increased homelessness, unemployment, crime and imprisonment, and many other medical, financial and psychosocial problems (Herbeck, Brecht, & Lovinger, 2015; Stein, 1999).

There is a clear public health need for development of new treatment approaches for stimulant use disorder. Currently available treatments for stimulant use disorder are mainly behavioral, with variable efficacy and availability (Dutra et al., 2008). There are no medications approved by the U.S. Food and Drug Administration (FDA) for treatment of stimulant use disorder, in spite of intense preclinical and clinical research focused on medications development (Forray & Sofuoglu, 2014). Comorbidity is likely the norm rather than the exception for individuals with stimulant use disorder. Studies conducted from treatment and community samples have shown that the majority of individuals with stimulant use disorder have mental health comorbidities that most frequently include other addictions and psychiatric disorders (Conway, Compton, Stinson, & Grant, 2006; Rounsaville et al., 1991). Paradoxically, most preclinical and clinical research for treatment development has focused on stimulant use disorder as a single disorder without considering the impact of commonly observed mental health comorbidities.

As noted by many, mental health disorders (including addictions) have overlapping symptom clusters across different diagnostic categories (Millan et al., 2012; Schumann et al., 2014). As such, new treatment approaches may be developed by using trans-diagnostic treatment targets rather than trying to develop specific treatments for individual mental health disorders and a large number of comorbid conditions (Schumann et al., 2014). This approach is consistent with the Research Domain Criteria (RDoC) initiative of the National Institute of Mental Health (Cuthbert & Insel, 2013) and is endorsed by the Roadmap for Mental Health Research initiative of European Union in response to what some have called “therapeutic stagnation” for mental health disorders. This initiative proposes several

domains that include negative and positive valences, cognitive systems, systems for social processes, and arousal and regulatory systems. Cognitive systems may be particularly relevant to consider as trans-diagnostic treatment targets (Schumann et al., 2014). Specifically, cognitive deficits commonly observed in individuals with psychiatric and addictive disorders have been proposed as viable treatment targets (Goschke, 2014; Sofuoglu, DeVito, Waters, & Carroll, 2013; Sofuoglu, Sugarman, & Carroll, 2010) and may function as trans-diagnostic treatment targets for individuals with stimulant use disorder and comorbid mental health disorders. Cognitive deficits are correlated with patients' daily functioning and are predictive of treatment outcomes across many mental health disorders (Bates, Pawlak, Tonigan, & Buckman, 2006; Keshavan, Vinogradov, Rumsey, Sherrill, & Wagner, 2014; Millan et al., 2012). Cognitive impairments shared across addictive and other psychiatric disorders may be targeted by cognitive-enhancement strategies as an adjunct treatment approach. Strategies that enhance selective cognitive functions hold promise to improve treatment outcomes for many mental health disorders, including stimulant use disorder.

The goal of this article is to provide an overview of cognitive enhancement strategies as a new area of research for stimulant use disorder. We first summarize the prevalence of stimulant use disorder comorbidities followed by a discussion of cognitive models of addiction. We then provide the rationale that supports the potential role of cognitive enhancement in stimulant use disorder and comorbid disorder. Finally, we present an overview of some pharmacological, behavioral and cognitive-training therapy approaches that target cognitive enhancement and are either currently available or under development as treatments for stimulant use disorder. We conclude with a discussion of areas for further research.

2. STIMULANT USE DISORDER AND COMORBID DISORDERS

According to 2013 estimates, there are approximately 1.5 million current cocaine users and 600,000 methamphetamine users in the United States (SAMHSA, 2014). A majority of individuals with stimulant use disorder have comorbidities, which most frequently include other addictions as well as psychiatric disorders.

2.1 Rates of Co-morbidities with Cocaine Use Disorders

In an epidemiological sample from the US National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) data (N=43,093), 45% of individuals who use cocaine had lifetime mood disorder and 31% had lifetime anxiety disorder (Conway et al., 2006). In a survey of people seeking treatment for cocaine use (N=298), 73.5% met criteria for lifetime psychiatric disorders other than substance use disorder (Rounsaville et al., 1991). A study of 227 people receiving treatment for cocaine use found that 65% reported lifetime history of psychiatric disorders (Vergara-Moragues et al., 2012). Substance-induced mood (21%) and psychotic disorders (11.5%) were more common than primary mood (13%) and psychotic disorders (7.5%), while primary anxiety disorders (20.7%) were more prevalent than substance-induced (5.3%) anxiety disorders. About 60% of patients had lifetime diagnoses of other addictions, most commonly heroin (46%), alcohol (29%), and benzodiazepines

(25%) (Vergara-Moragues et al., 2012). Use of illicit substances is between 4 and 9 times more prevalent among people who smoke cigarettes than among those who do not smoke (age 12-17: 53.9% of cigarette smokers and 6.1% of non-smokers; ages 12 and up: 24.1% of cigarette smokers and 5.4% of non-smokers), according to the population-based 2013 National Household Survey on Drug Abuse (N = 67,500; (SAMHSA, 2014)).

2.2 Rates of Comorbidities with Methamphetamine Use Disorders

Similar to rates for those with cocaine use, lifetime prevalence of mood and anxiety disorders among individuals who use amphetamine were 51% and 39%, respectively, in the NESARC epidemiological sample (Conway et al., 2006). A survey of 189 people with methamphetamine dependence found that 24% had substance-induced psychotic disorder. Other addictions were even more common: 57% had lifetime dependence on other substances (most commonly alcohol 33%, cocaine 27%, cannabis 15% and opioids 12%), and 56% had lifetime history of abuse (cannabis 24%, alcohol 17% and hallucinogens 8%) (Salo et al., 2011). Rates of cigarette smoking among persons who use methamphetamine range from 87 to 92% (Weinberger & Sofuoglu, 2009).

2.3 Implications for Treatment

Overall, these figures indicate that the majority of individuals with stimulant use disorder have comorbid psychiatric conditions or other addictions, many of which (e.g., alcohol use disorder) themselves lead to higher levels of cognitive impairment (Stavro, Pelletier, & Potvin, 2013). The longitudinal relationship between stimulant use disorder and other comorbid conditions is not well studied. One earlier study suggested that attention deficit hyperactivity disorder (ADHD) and anxiety disorders preceded cocaine use while mood disorders followed the onset of cocaine use (Rounsaville et al., 1991). Given the difficulty in accurately diagnosing mental health disorders retrospectively, longitudinal studies would be needed to determine the temporal relationship between stimulant use disorder and other comorbid conditions.

Comorbidities between stimulant use disorder and other mental health disorders have important treatment implications. Among patients receiving treatment for cocaine use, comorbid depression and alcohol dependence are risk factors for relapse (Poling, Kosten, & Sofuoglu, 2007). Similarly, in a one year outcome study following treatment for cocaine use disorder, the severity of psychiatric comorbidity and the presence of alcohol use, predicted poor outcomes (Carroll, Power, Bryant, & Rounsaville, 1993). The presence of stimulant use disorder may also predict poor treatment response to psychiatric treatments. For example, response to antidepressant treatments may be worse among individuals with depression and comorbid stimulant use disorder, compared to those without this comorbidity (Nunes & Levin, 2004). These studies emphasize the importance of psychiatric and addiction comorbidities for the treatment of stimulant use disorder.

3. DIAGNOSIS AND MODELS OF ADDICTION

Models of addiction are important because they shape how we define addiction, its relationship to other mental disorders (i.e., comorbidity), and treatment approaches for addictions.

The diagnosis of stimulant use disorder, similar to other addictions, relies solely on behavioral signs and symptoms, not on objective biological markers. Despite research on potential biomarkers, with the exception of drugs of abuse and their metabolites, there are no biomarkers for addictive disorders that are routinely used in clinical practice for diagnostic classification or treatment assignment. Identifying biomarkers with greater reliability and predictive validity could substantially improve the diagnosis and treatment of addictive disorders (Volkow, Koob, & Baler, 2015).

In the DSM-5, the terms “stimulant abuse” and “stimulant dependence” are no longer used, instead a broad stimulant use disorder diagnosis has been introduced, with severity levels of mild, moderate and severe (APA, 2013). A diagnosis of stimulant use disorder is based on clinical evidence of impaired control over stimulant use, social impairment as a result of use, risky use pattern, and pharmacological criteria (tolerance or withdrawal).

Addiction models can be broadly categorized as drug-centered models, individual-centered models, or a combination of both (Swendsen & Le Moal, 2011). While the drug-centered models are highly dominant in preclinical addiction research, individual-centered approaches are more dominant in clinical and epidemiological models of addiction.

In drug-centered addiction models the main emphasis is the drug’s pharmacological effect in the brain, especially neuroadaptation in response to drug exposure. The strength of these drug-centered models is the focus on identifying neurobiological mechanisms that underlie transition from initial drug use to compulsive drug use behavior (Swendsen & Le Moal, 2011). The main limitation of drug- centered models is the lack of consideration for individual differences in addiction vulnerability. For example, only a minority of those who experiment with drugs become addicted, estimated to be less than 15% for cocaine (Reboussin & Anthony, 2006). These findings emphasize the importance of individual differences in addiction vulnerability and resilience to addiction. Another limitation of drug-centered models is that by focusing on the pharmacology of a specific drug of abuse, different addictions and other mental disorders can be fragmented into separate groups, despite the high rates of comorbidity and overlapping symptoms. Therefore, purely drug-centered addiction models may be less adept at identifying shared mechanisms across disorders that would be helpful targets for trans-diagnostic treatment approaches.

In contrast, individual-centered models emphasize the wide variation in individual vulnerability for addiction. This vulnerability could be due to psychosocial factors (e.g., sex, age, race, socioeconomic status, income and education), biological and genetic factors, and/or presence of comorbid mental health disorders (Swendsen & Le Moal, 2011). Accordingly, the neuro-adaptation in response to drugs of abuse is influenced by a host of intrinsic vulnerability factors.

Many contemporary models of addiction emphasize both the pharmacological aspects of drugs of abuse, as well as individual vulnerability factors. One such model is the dual process model of addiction, as summarized below.

3.1 Dual process as a cognitive model of addiction

The dual process model (Figure 1) includes two processes in balance: neurobiological "bottom-up" processes, which increase the risk of drug taking/relapse, and reflective or executive "top-down" processes, which attempt to inhibit automatic processes or their output (Wiers et al., 2013). This model emphases two qualitatively distinct conceptualizations: automatic (or "implicit") processes and controlled or executive (or "explicit") processes (Kahneman, 2011; Wiers et al., 2013).

3.1.1 Automatic/implicit processes—Automatic cognitive processes are fast, parallel, effortless, and may not engage conscious awareness. Cognitive biases pertinent to stimulant use disorder involve automatic cognitive processes. "Approach bias" is the tendency to automatically approach drug-related stimuli. "Attentional bias" is the tendency to automatically attend to, and maintain attention on, drug-related stimuli (Cox, Fadardi, Intriligator, & Klinger, 2014). These biases may increase exposure to drug cues and provoke craving and use. It is important to note that craving is neither necessary nor sufficient for drug use behavior. For example, some behavioral therapies encourage patients to recognize drug cravings while they are occurring but then resist the urge to act upon the cravings. However, as suggested by many studies with different drugs, craving (especially cue-induced craving) increases the likelihood of relapse (Galloway & Singleton, 2009; Sinha et al., 2011; Sinha, Garcia, Paliwal, Kreek, & Rounsaville, 2006). Individual differences in cognitive biases may reveal which individuals are at risk for continued drug use, and individual differences in the propensity to acquire such biases may predict drug use escalation. Importantly, attentional biases are observed in many comorbid psychiatric conditions including anxiety disorders (e.g., Van Bockstaele et al., 2014) and depression (Browning, Holmes, & Harmer, 2010). Interventions that target multiple attentional biases may be particularly useful in stimulant use disorder

3.1.2 Executive/explicit processes—Executive function, rather than being a unitary function, is best conceptualized as a collection of related but separable functions (Friedman et al., 2008) including response inhibition, working memory, attention, problem solving, decision making, and cognitive flexibility (e.g., set-shifting). As with the cognitive biases, individual differences in one or more of these functions may be associated with the risk of drug use initiation or maintenance. Among these functions, response inhibition, working memory, and sustained attention are particularly relevant to stimulant use disorder and many comorbid psychiatric conditions, such as depression and attention deficit hyperactivity disorder (Sofuoglu et al., 2013).

Response inhibition refers to the ability to voluntarily inhibit a dominant, automatic, or pre-potent response (Friedman et al., 2008). It can be assessed with a number of tasks including the Stop-Signal Task (SST) and the Go/No-Go task (Eagle, Bari, & Robbins, 2008). Working memory refers to the ability to keep in mind an event that had just been

experienced or to retrieve information from long-term memory storage and manipulate this information or use this information to regulate behavior (Arnsten, Wang, & Paspalas, 2015). There are many measures of working memory including auditory or visuo-spatial span tasks, which require information to be kept in mind while it is actively updated or manipulated. Working memory function may be linked to inhibitory control in that high working memory demand or reduced working memory function may provoke drug craving or relapse (Chambers, Garavan, & Bellgrove, 2009).

Sustained attention is controlled by both bottom-up and top-down processes (Posner & Rothbart, 1998). Bottom-up processing, also known as exogenous or stimulus-driven attention, is an automatic process driven by external stimuli (e.g. visual drug cues). Top-down processing, also known as the endogenous or executive attention, is controlled via engagement of prefrontal cortical neural circuitry and is closely linked to working memory and response inhibition functions (Rueda et al., 2005). These functions have been operationalized by separate tasks and may serve as potential treatment targets for cognitive-enhancement approaches.

4. RATIONALE FOR COGNITIVE ENHANCEMENT FOR STIMULANT USE DISORDER

4.1 Cognitive deficits are associated with stimulant use disorder

Many studies have examined the cognitive deficits associated with stimulant use disorder. A meta-analysis comparing persons who use methamphetamine (N=487) with those who do not (N=464) found moderate effect sizes ($0.8 > d \geq 0.5$) for learning, executive function, memory, and speed of information processing domains, and small effect sizes ($0.5 > d \geq 0.2$) for motor skills, attention, working memory, visuo-construction, and language domains (Scott et al., 2007). Another meta-analysis (Jovanovski, Erb, & Zakzanis, 2005) that compared people who do (n=481) and do not (n=586) use cocaine reported large effect sizes (Cohen's $d \geq 0.8$) for attentional function, moderate effect sizes for visual and working memory, and small effect sizes for language and sensory-perceptual functions (Cohen, 1988). These findings were replicated in a more recent meta-analysis of studies examining cognitive function and cocaine use (Potvin, Stavro, Rizkallah, & Pelletier, 2014).

While acute drug and withdrawal effects contribute to cognitive deficits associated with stimulant use disorder, many of these cognitive deficits are not fully ameliorated by abstinence from stimulants. In one study, individuals with methamphetamine dependence failed to demonstrate significant improvement in cognitive performance following one month of abstinence (Simon, Dean, Cordova, Monterosso, & London, 2010). Similarly, individuals with methamphetamine dependence who were abstinent displayed persistent neurocognitive deficits despite nearly full recovery from dopamine transporter (DAT) deficiency (Volkow et al., 2001)..

The origins and stability of cognitive deficits in stimulant use disorder are likely multifaceted. While acute stimulant use or withdrawal temporarily disrupts aspects of cognition and chronic stimulant exposure may cause persistent cognitive deficits, individuals

with pre-existing cognitive deficits (e.g., response inhibition) may also be more vulnerable to initiating drug use and/or becoming dependent (de Wit, 2009; Ersche et al., 2012; Wagner et al., 2012). Given the high prevalence of psychiatric comorbidity in individuals with stimulant use disorder, cognitive deficits primarily accounted for by these comorbid disorders would also be present in many individuals with stimulant use disorder.

4.1 Cognitive deficits are associated with comorbid mental health disorders

In this section, we briefly review cognitive deficits in psychiatric disorders that are frequently comorbid with stimulant use disorder (for a broader review see Keshavan et al., 2014 or Millan et al., 2012).

Cumulating evidence from hundreds of studies with thousands of patients with and without schizophrenia have demonstrated the association of schizophrenia with generalized cognitive deficits across multiple cognitive domains (Bora, Yucel, & Pantelis, 2010; Fioravanti, Bianchi, & Cinti, 2012; Irani, Kalkstein, Moberg, & Moberg, 2011). While the severity of cognitive deficits in schizophrenia is modestly associated with symptom severity, it is closely associated with measures of daily functioning (Leifker, Patterson, Bowie, Mausbach, & Harvey, 2010). A recent meta-analysis of 100 studies with 9048 patients with, and 8814 without, schizophrenia, found large effect sizes ($d \geq 0.8$) for verbal fluency, working memory, episodic memory, sustained attention and executive functioning, and moderate effect sizes ($0.8 > d \geq 0.5$) for visuospatial/problem solving deficits (Schaefer, Giangrande, Weinberger, & Dickinson, 2013). Across studies, male sex and earlier onset was associated with greater cognitive impairment, and treatment with antipsychotics did not seem to affect the severity of cognitive deficits (Schaefer et al., 2013).

In contrast to more persistent forms of cognitive deficits in schizophrenia, cognitive deficits in mood disorders, most notably bipolar disorder and major depressive disorder, could be seen as state dependent with return to normal cognitive functioning upon remission (Hasselbalch, Knorr, & Kessing, 2011). However, many studies with patients who were diagnosed with bipolar disorder or major depressive disorder but were euthymic at the time of cognitive testing indicated that cognitive deficits may persist beyond mood symptoms and may reflect functional abnormalities in the hippocampus or prefrontal cortex region (Arnone, McIntosh, Ebmeier, Munafo, & Anderson, 2012; Malykhin & Coupland, 2015). A recent re-analysis of previously conducted studies, including a total of 1276 with euthymic bipolar disorder and 1609 without it, found moderate effect size for deficits in verbal memory and small effect sizes for visual scanning speed, working memory, and response inhibition function (Bourne et al., 2013). The severity of cognitive deficits did not appear to be affected by medication treatment or residual mood symptoms.

A similar meta-analysis examined cognitive function among patients with major depressive disorder who were euthymic at the time of testing (Rock, Roiser, Riedel, & Blackwell, 2014). The study included 895 patients with, and 993 without, major depressive disorder from 27 studies. This meta-analysis found moderate effect sizes for visual memory, verbal memory, executive functions and attention. For working memory, the effect size was small. While the majority of patients were on antidepressant medication, the study reported that

cognitive impairments associated with major depressive disorder were not explained by psychotropic medication treatment (Rock et al., 2014).

Cognitive deficits are also increasingly recognized in individuals with posttraumatic stress disorder (PTSD). A meta-analysis investigated the cognitive deficits associated with PTSD based on data from 60 studies including participants with PTSD (n=1,779), with trauma exposure (n=1,446), and with no trauma history (n= 895) (Scott, Matt, Wrocklage, Crnich, Jordan, Southwick, Krystal, & Schweinsburg, 2015). Analyses revealed cognitive deficits associated with PTSD, within the medium effect size range for verbal learning, speed of information processing, and attention/working memory, and within the small effect size range for verbal memory. This study did not find any evidence suggesting that these cognitive deficits could be due to comorbid depression, drug and alcohol use, traumatic brain injury or medication treatment (Scott et al., 2015).

Cognitive deficits associated with adult ADHD were investigated in a meta-analysis, which included 24 studies with a total of 867 people with ADHD and 806 without ADHD (Schoechlin & Engel, 2005). Although inclusion/exclusion criteria varied across the studies, the majority excluded individuals who had comorbid psychiatric disorders including substance abuse or who were being treated with psychotropic medications. The study found moderate effect sizes for verbal memory, focused attention, sustained attention, visual/verbal fluency, abstract problem solving, and working memory deficits (Schoechlin & Engel, 2005).

Studies examining cognitive functions across different psychiatric disorders have many limitations, including variation in diagnostic criteria, comorbid conditions that were included, documentation of psychotropic medication use, and selection of cognitive tests (Nuechterlein et al., 2008. In spite of these limitations, studies support the presence of cognitive impairments associated with psychiatric disorders that are frequently comorbid with stimulant use disorder. For example, working memory deficits have been demonstrated in major depression, bipolar disorder, schizophrenia, and ADHD, while deficits in attention function have been observed in bipolar disorder, major depression, schizophrenia, ADHD and PTSD (Keshavan et al., 2014; Millan et al., 2012). An important gap in the literature is whether the presence of stimulant use disorder changes the cognitive impairments associated with comorbid disorders. Longitudinal studies are needed to understand the relationship between stimulant use disorder and comorbid psychiatric disorders on cognitive function.

4.2. Relevance of cognitive function to stimulant use disorder treatment

Cognitive impairments have been associated with poorer treatment retention in patients with substance use disorders, including those with stimulant use disorder (Brewer, Worhunsky, Carroll, Rounsaville, & Potenza, 2008; Streeter et al., 2008; Turner, LaRowe, Horner, Herron, & Malcolm, 2009). An early study among 56 patients offered cognitive behavioral therapy for cocaine use found that those who did not complete treatment performed significantly worse on laboratory measures of attention, memory, spatial ability, speed, accuracy, global functioning, and cognitive proficiency compared with those who did complete treatment (Aharonovich, Nunes, & Hasin, 2003). More recently, baseline executive function in 131 individuals with cocaine dependence significantly predicted treatment

retention (Verdejo-Garcia et al., 2012). Another study raised questions about the independent contribution of cognitive function as a treatment outcome predictor. These researchers reported that measures of cognitive function predicted treatment outcome and study retention among 60 patients with methamphetamine dependence, although less robustly than an indicator of baseline methamphetamine use (urine drug screening) (Dean et al., 2009). As suggested by Bates and colleagues, cognitive deficits may mediate outcome by interfering with the individual's ability to effectively engage in treatment (Bates, Buckman, & Nguyen, 2013).

As described above, stimulant use disorder is associated with multiple cognitive deficits, although the causes and stability of these deficits remain uncertain. They could reflect persistent brain dysfunction arising secondary to chronic substance use; acute drug effects; short-term withdrawal effects; or pre-existing vulnerability factors for addiction including comorbid psychiatric conditions. However from a treatment perspective, if cognitive deficits negatively influence substance use outcomes and general functioning, then cognitive enhancement for these deficits would seem to be an important treatment target, regardless of their cause (Sofuoglu, 2010).

5. TREATMENT APPROACHES TARGETING COGNITIVE FUNCTIONS

A range of treatment approaches could target different aspects of cognitive function (see Figure 1). Several pharmacological treatments for stimulant use disorder have shown some initial promise and may function by improving executive control processes. Similarly, behavioral therapies, such as cognitive behavioral therapy (CBT), are thought to exert their effects, at least in part, through enhancement of executive control. Improved executive control would then be expected to improve drug use outcomes both directly and indirectly, by enabling greater regulation of automatic cognitive processes, which are linked with drug use behavior. Cognitive Bias Modification (CBM) training directly targets automatic cognitive processes to improve drug use outcomes. Different combinations of these treatment approaches may be appropriate depending on the cognitive capacity of the patient at baseline or the presence of comorbid disorders.

5.1 Pharmacological Treatments

Many medications with cognitive-enhancing properties have been examined as potential treatments for neuropsychiatric disorders (Sofuoglu et al., 2013; Wallace, Ballard, Pouzet, Riedel, & Wettstein, 2011). Only a few medications have been examined as cognitive enhancers for stimulant use disorder. Before initiation of such a treatment, interactions with other psychotropic medications should be carefully considered (Buchanan et al., 2005).

5.1.1 Cholinesterase inhibitors—Cholinesterase inhibitors are marketed for the treatment of Alzheimer's disease and have been under investigation to improve cognitive function in neuropsychiatric disorders, including schizophrenia and traumatic brain injury Deutsch et al., 2013; Kim, Kim, Shin, Park, & Lee, 2009). These medications increase the synaptic concentrations of acetylcholine (ACh), resulting in increased acetylcholine transmission. Acetylcholine mediates many cognitive functions including attention, working memory, motivation, and reward (Mark, Shabani, Dobbs, & Hansen, 2011; Sarter, Lustig,

Howe, Gritton, & Berry, 2014; Sofuoglu & Mooney, 2009), and its release in the prefrontal cortex is especially relevant for attentional functions (Howe, Berry, Francois, Gilmour, Carp, Tricklebank, Lustig, & Sarter, 2013). Two cholinesterase inhibitors, galantamine and rivastigmine, showed promising results in pilot studies for stimulant use disorder (Mahoney et al., 2014; Sofuoglu & Carroll, 2011).

5.1.1.1 Galantamine: Galantamine is an acetylcholinesterase inhibitor and an allosteric potentiator of the nicotinic acetylcholine receptor (nAChR), especially α7 and α4β2 nAChR subtypes (Schilstrom et al., 2007). The potential use of galantamine as a cognitive-enhancing treatment for stimulant use disorder was examined in two separate double-blind, placebo-controlled pilot studies. In one study, individuals who were abstinent from cocaine use (n=28) were randomized to ten days of 8 mg/day galantamine treatment or placebo. The group receiving galantamine, as compared to placebo, demonstrated improved sustained attention and working memory functions, assessed by the Rapid Visual Information Processing (RVP) task (Sofuoglu et al., 2011). In the other study, participants with opioid and cocaine dependence (n=14) who received 8 weeks of 16 mg/day galantamine treatment had fewer self-reported or urine-confirmed cocaine use days, relative to placebo, and the medication was well-tolerated (Sofuoglu & Carroll, 2011). These preliminary studies support the safety and potential efficacy of galantamine as a cognitive enhancer in stimulant use disorder. Randomized clinical trials are underway to determine whether cognitive improvement by galantamine will reduce cocaine use in patients with cocaine dependence.

Galantamine has also been examined as a cognitive-enhancer in other psychiatric disorders, most notably in schizophrenia. Earlier studies showed inconsistent effects of galantamine as a cognitive enhancer for schizophrenia (Buchanan et al., 2008; Dyer et al., 2008; Lindenmayer & Khan, 2011; Schubert, Young, & Hicks, 2006). In a recent clinical trial, galantamine was combined with CDP-choline (a dietary source of choline), to enhance its efficacy. Forty-three participants with schizophrenia who were on second generation antipsychotics were randomized to either galantamine plus CDP-choline or placebo for 16 weeks. While the treatment groups did not differ for negative symptoms, the active treatment group showed improvement in overall functioning and cognitive measures of recall and memory (Deutsch et al., 2013).

5.1.1.2 Rivastigmine: Rivastigmine, another cholinesterase inhibitor, may also enhance cognitive function. A recent study randomly assigned individuals with cocaine dependence who were not seeking treatment to receive placebo (n=16), 3mg/day rivastigmine (n=13), or 6mg rivastigmine (n=12) for 7 days. Those assigned to either rivastigmine dose showed modest improvement in working memory, as measured by an N-back task, relative to placebo (Mahoney, Kalechstein, Verrico, Arnoudse, Shapiro, & De La Garza, 2014). These findings, together with those reported for galantamine (Sofuoglu et al., 2011), support the potential use of cholinesterase inhibitors to enhance selected cognitive functions in individuals with cocaine use disorders. Only a few studies examined the efficacy of rivastigmine's cognitive-enhancing effects in other psychiatric disorders. In one small pilot study, 21 patients with schizophrenia were randomized to rivastigmine (n=11) or placebo

(n=10) as an add-on to antipsychotic treatment for 24 weeks. The study did not find any group differences in cognitive outcomes (Sharma, Reed, Aasen, & Kumari, 2006).

5.1.2 Monoamine Transporter Inhibitors

5.1.2.1 Modafinil: Modafinil is a cognitive enhancer with weak stimulant-like properties, approved for the treatment of sleep apnea, narcolepsy and shift work-induced sleep disorder. It is a weak inhibitor of dopamine and norepinephrine transporters and has additional actions on brain γ-Aminobutyric acid (GABA), glutamate, and orexin (Mereu, Bonci, Newman, & Tanda, 2013). In an inpatient study, patients with cocaine dependence were randomized to receive 200 mg/day modafinil (n=16), 20 mg/day escitalopram (n=16), modafinil plus escitalopram (n=15), or placebo (n=14) for 5 days. Modafinil treatment, but not escitalopram, modafinil plus escitaloram, or placebo, improved working memory function (Kalechstein, Mahoney, Yoon, Bennett, & De la Garza, 2013). Several randomized clinical trials have also found some support for modafinil's efficacy in reducing cocaine use in various groups (Anderson et al., 2009; Dackis, Kampman, Lynch, Pettinati, & O'Brien, 2005; Dackis et al., 2012).

In a series of studies, the cognitive enhancing effects of modafinil were examined in individuals with methamphetamine dependence. In a small inpatient study, 7 days of modafinil treatment improved immediate verbal memory function in 14 patients with methamphetamine dependence who were undergoing 7-day withdrawal (Hester, Lee, Pennay, Nielsen, & Ferris, 2010). In another study, 3 days of modafinil (400 mg/day) treatment improved working memory function in individuals with methamphetamine dependence (n=11) who had impaired working memory function at baseline (Kalechstein, De La Garza, & Newton, 2010). Further, in response to a single 200 mg dose of modafinil, individuals with methamphetamine dependence who were abstinent (n=16), compared to individuals with no methamphetamine use (n=19), showed greater activation of the ventrolateral prefrontal cortex and anterior cingulate cortex (Ghahremani et al., 2011), brain regions implicated in executive functions including response inhibition and attentional control. However, modafinil's efficacy for reducing methamphetamine use remains to be demonstrated (Anderson et al., 2012; Lee et al., 2013).

Modafinil has been tested as a potential cognitive enhancer in psychiatric disorders including depression, schizophrenia and ADHD (Goss, Kaser, Costafreda, Sahakian, & Fu, 2013; Tsapakis, Dimopoulou, & Tarazi, 2015). A meta-analysis examined the efficacy of modafinil as an augmentation treatment for individuals with unipolar (N=568) or bipolar (N=342) depression. The meta-analysis found significant effects of modafinil on improvements in overall depression scores (point estimate = −0.35; 95% CI [−0.61, −0.10]) and remission rates (odds ratio = 1.61; 95% CI[1.04, 2.49]). This meta-analysis also found significant effects of modafinil on fatigue symptoms (Goss et al., 2013). In a recent study, patients with schizophrenia or schizoaffective disorder who were stable on atypical antipsychotics were randomized to modafinil (n=12) or placebo (n=12) for 8 weeks. While modafinil treatment did not improve psychiatric symptoms, daytime sleepiness or cognitive function, it did improve parkinsonian symptoms (Lohr et al., 2013).

5.1.2.2 Methylphenidate: Methylphenidate is a stimulant drug with action similar to amphetamines and cocaine. It increases synaptic dopamine levels by inhibiting reuptake of monoamines including dopamine, norepinephrine and serotonin (Sulzer, Sonders, Poulsen, & Galli, 2005). Methylphenidate is marketed for the treatment of ADHD and has been repeatedly shown to improve response inhibition as well as other cognitive functions such as decision-making, working memory and set-shifting in individuals with ADHD (DeVito et al., 2009; DeVito et al., 2008; Turner, Blackwell, Dowson, McLean, & Sahakian, 2005). In a functional MRI study (Goldstein et al., 2010), a single 20 mg oral dose of methylphenidate improved behavioral measures of response inhibition and anterior cingulate cortex hypoactivation in individuals with cocaine dependence who were not in treatment (n=13), compared to individuals with no cocaine use (n=14). In another study, individuals with cocaine dependence (n=10) who were abstinent for a minimum of 5 days showed improvement in response inhibition, as assessed with a Stop Signal Task, which was associated with changes in prefrontal cortical activation, in response to a single dose of 0.5mg/kg intravenous methylphenidate, relative to placebo (Li et al., 2010). Clinical trials testing the efficacy methylphenidate for cocaine use disorder have provided inconsistent results (Dursteler et al., 2015).

A 14-week clinical trial tested the efficacy of methylphenidate, compared to placebo, in treating 106 individuals with ADHD and cocaine dependence. While there were no significant treatment effects on the severity of ADHD symptoms, those assigned to methylphenidate had greater reduction in cocaine use (Levin, Evans, Brooks, & Garawi, 2007).

To summarize, although several cognitive-enhancing medications are available for clinical use, only a few studies have been conducted in patients with stimulant use disorder or comorbid disorders. Thus, it remains to be determined whether these medications can reduce stimulant use through improvement of selective cognitive functions.

5.2 Behavioral Treatments

Accumulating data on cognitive deficits among substance users has also led to articulation of how behavioral approaches might be developed or modified to address these issues in clinical samples.

5.2.1 Cognitive Behavioral Therapy—Cognitive Behavioral Therapy (CBT) for drug abuse is often thought of as achieving its efficacy through the teaching of specific coping strategies. However, more recent conceptions emphasize its role as a ‘cognitive control therapy’. One mechanism of action of CBT may be its capacity to enhance executive control over behavior. CBT has shown efficacy across many drugs of abuse, including stimulant use disorder, with effect sizes in the low-moderate range (Dutra et al., 2008). Unfortunately, high drop-out rate is common among those in treatment for stimulant use disorder, about 40 to 45% drop out across different behavioral treatments, including CBT. Contingency management has shown the lowest drop-out rate (29.4%) and has been used in conjunction with CBT improve treatment retention for patients with substance use disorders (Dutra et al., 2008).

CBT has also shown efficacy for major depression and bipolar depression but not for the treatment of schizophrenia (Hofmann, Asnaani, Vonk, Sawyer, & Fang, 2012). Recent systematic reviews and meta-analysis examining the efficacy of behavioral interventions for comorbid serious mentally illness and substance use disorder, including stimulant use disorder, did not find evidence for the efficacy of CBT. One caveat was the small number of studies, all with limited sample sizes (Bradizza, Stasiewicz, & Dermen, 2014).

One of the key problems for substance use disorders and other psychiatric disorders is that only a minority of patients who could potentially benefit actually receive evidence-based treatments. Computer-assisted delivery of CBT could potentially increase the availability, cost, and quality of CBT in a multitude of settings. Our group has developed a system which delivers computer-based cognitive behavioral therapy (CBT4CBT; http://www.cbt4cbt.com/) using a multimedia platform (interactive quizzes, video, minimal reading with accompanying audio) to provide an opportunity for self-paced learning across different learning styles. We recently tested the efficacy of CBT4CBT in 101 patients with cocaine dependence who receiving methadone maintenance treatment in an 8-week trial. Patients were randomized to CBT4CBT plus methadone maintenance or methadone maintenance alone. Those assigned to CBT4CBT were more likely to achieve three or more consecutive weeks of abstinence from cocaine (36% compared with 17%; $p<0.05$, odds ratio=0.36). Participants maintained these improvements six months after the completion of the trial, supporting the durability of the treatment gains (Carroll, Kiluk, Nich, Gordon, Portnoy, Marino, & Ball, 2014). CBT4CBT remains to be tested in stimulant use disorder with comorbid psychiatric disorders.

5.2.2. Cognitive Rehabilitation—Cognitive rehabilitation training, which aims to enhance cognitive function in certain domains, may enhance the efficacy of other treatment approaches. Using cognitive rehabilitation training prior to the onset of other treatments could provide a helpful cognitive ‘boost’ to patients with cognitive impairments, which could enable them to comprehend and adhere to their treatment more effectively. Inclusion of cognitive rehabilitation treatment as an adjunct during the treatment period would not interfere with other treatment delivery and could help to maintain cognitive gains throughout treatment, when optimal executive control over problematic cognitions, drug-seeking behavior, and learning capacity are sorely needed. Most cognitive rehabilitation approaches encourage several hours of practice on cognitive tasks per week for several months. The specific tasks trained can be chosen to target an individual patient’s problem areas or to target the same cognitive domains for all patients, wherein those domains are chosen based on their particular importance to treatment outcome (e.g., memory, problem-solving, response inhibition). These domains are typically executive control functions which strengthen ‘top down’ control over automatic processes or overlearned behaviors.

In a study by Bickel et al., 27 individuals with stimulant use disorder, who were enrolled in treatment, were randomized to receive either 15 working memory training or control training sessions (Bickel, Yi, Landes, Hill, & Baxter, 2011). Participants assigned to the working memory training condition, compared to those assigned to control condition, showed less impulsive performance on a delay discounting task (in which ‘choice impulsivity’ is indicated by preference for a smaller immediate reward over a larger delayed reward) after

memory training (Bickel et al., 2011). This study did not address whether training on a working memory task would reduce drug use behavior.

In addition, cognitive rehabilitation training has been demonstrated to improve aspects of cognition in a range of disorders, including some commonly comorbid with substance use disorders, such as major depressive disorder, bipolar disorder, and schizophrenia (Bowie, Gupta, & Holshausen, 2013a; Elliott & Parente, 2014; Revell, Neill, Harte, Khan, & Drake, 2015; Wykes, Huddy, Cellard, McGurk, & Czobor, 2011). In a meta-analysis of cognitive enhancement treatments for schizophrenia that included 2,104 participants, durable effects on global cognition and functioning were reported (Wykes et al., 2011). Improvements were observed across a broad range of cognitive domains, including attention/vigilance, speed of processing, verbal working memory, reasoning/problem solving, and social cognitions, with effect sizes ranging from 0.25 to 0.65. Treatment was more effective when combined with other established treatments (e.g., psychiatric rehabilitation) and when patients were clinically stable (Wykes et al., 2011).

In contrast to schizophrenia, there have been only a few studies testing the efficacy of cognitive enhancement treatments for bipolar disorder or major depressive disorder. In a recent study, 46 patients with bipolar disorder who were in full or partial remission and had subjective cognitive complaints were randomized to a 12-week cognitive rehabilitation or standard treatment (Demant, Vinberg, Kessing, & Miskowiak, 2015). While there were no group differences for the functional and main cognitive outcomes, those assigned to cognitive rehabilitation had improved subjective sharpness at week 12, and quality of life and verbal fluency at week 26 follow-up (Demant et al., 2015). A small pilot study examined the efficacy of a 10-week cognitive rehabilitation program in 33 patients with major depressive disorder who had not improved after other treatment (Bowie, Gupta, Holshausen, et al., 2013). Those who were randomized to cognitive rehabilitation, which was given online daily, compared to the wait list controls showed improvement in verbal memory, attention and processing speed. There were no group differences for everyday functional skills and behavior (Bowie et al., 2013b). Several functional MRI studies have also shown functional changes associated with cognitive rehabilitation treatment, most notably functional normalization in brain regions including the prefrontal cortex, a region thought to be linked with many cognitive functions including executive and working memory function (Meusel, Hall, Fougere, McKinnon, & MacQueen, 2013; Penades et al., 2013). Taken together, these studies support the feasibility and potential utility of cognitive rehabilitation for patients with bipolar disorder or major depressive disorder and warrant further controlled studies to test the efficacy of these treatments.

As summarized in this section, there is a clear need for future studies examining the efficacy of cognitive rehabilitation for stimulant use disorder. Further, there are no published studies on the efficacy of cognitive rehabilitation training for those with stimulant use disorder and psychiatric comorbidity (Keshavan et al., 2014).

5.2.3 Cognitive Bias Modification—In contrast to cognitive rehabilitation training (typically focused on ‘top down’ executive control-related domains), other cognitive training approaches directly target cognitive biases, which are conceptualized more as ‘bottom up’

automatic processes. Cognitive Bias Modification (CBM) involves training with modified cognitive tasks with the goal of changing cognitive biases. Biases targeted by CBM include attentional bias (Cox et al., 2014) and approach bias (Wiers, Eberl, Rinck, Becker, & Lindenmeyer, 2011). Although in its infancy, CBM to address approach bias has shown promise in the treatment of addiction (Wiers et al., 2011).

Attentional retraining is one type of CBM and refers to the use of "modified" tasks to change attentional bias. Individuals with substance use disorders tend to show an attentional bias towards drug-related stimuli and people who are depressed tend to show an attentional bias towards negative stimuli. These biases are thought to further reinforce exposure to these classes of stimuli, so the logic of attentional retraining is that training to reorient away from problematic stimuli classes could actually improve clinical outcomes. It is most often conducted using modified visual probe tasks (Cox et al., 2014; Field & Cox, 2008), which usually rely on a tendency for individuals to respond faster to probes (e.g., small dots) when they are attending to them (Posner, Snyder, & Davidson, 1980). Individuals tend to respond more quickly to probes that replace motivationally salient stimuli (either positive or negative) than those that replace neutral stimuli (Mogg & Bradley, 1998). This tendency is interpreted as an attentional bias in the "standard" version of the visual probe task, administered for assessment. In the retraining version of the (modified) visual probe task, the dot always replaces neutral stimuli, thus directing attention away from drug stimuli toward neutral stimuli over the course of many trials. By reducing attentional bias, less attention is paid to drug stimuli, resulting in less craving and decreased drug use.

Attentional retraining has shown promise in substance use disorders, including those involving alcohol and nicotine (Attwood, O'Sullivan, Leonards, Mackintosh, & Munafò, 2008; Kerst & Waters, 2014; Schoenmakers et al., 2010). Currently there are no published attentional retraining studies for stimulant use disorder. Findings suggest a strong attentional bias to cocaine (see Leeman, Robinson, Waters, & Sofuoglu, 2014 for a review) and methamphetamine cues (Hester et al., 2010). In addition, there are stronger associations between attentional bias and craving for cocaine and opioids than for tobacco or alcohol (Field, Munafo, & Franken, 2009). This suggests that diminishing attentional bias for cocaine cues via attentional retraining may reduce craving and use of these drugs. Further, executive function deficits observed among people who use cocaine and opioids (e.g., (Jovanovski et al., 2005) may make attentional retraining particularly appropriate for this population.

CBM was first developed in the anxiety literature (MacLeod, Rutherford, Campbell, Ebsworthy, & Holker, 2002). It is a trans-diagnostic intervention approach in that the same methodology can be applied to any disorder. Four meta-analyses have examined the effect of CBM on both cognitive biases and psychiatric symptoms (Beard, Sawyer, & Hofmann, 2012; Hakamata, Lissek, Bar-Haim, Britton, Fox, Leibenluft, Ernst, & Pine, 2010; Hallion & Ruscio, 2011; Mogoaşe, David, & Koster, 2014). All four meta-analyses reported a significant effect of attentional retraining on attentional bias and symptoms. The effect of attentional retraining on attentional bias tended to be larger than the effect on symptoms, which is expected because the effect of attentional retraining on symptoms (e.g., anxiety or depression) should be mediated through its effect on attentional bias. The effect sizes on

symptoms appeared to be small (Mogoaşe et al., 2014), or small-to-medium (Beard et al., 2012) (see also (Cristea, Kok, & Cuijpers, 2015).

Although some of the effect sizes may be small, the possibility that attentional retraining may be beneficial across multiple disorders indicates that it may be useful for treating stimulant use disorder with comorbid mental health disorders, such as PTSD. One study administered attentional retraining in conjunction with evidence-based cognitive behavioral therapies to military personnel diagnosed with PTSD (Kuckertz, Amir, Boffa, Warren, Rindt, Norman, Ram, Ziajko, Webb-Murphy, & McLay, 2014). Compared to the control group, participants in the attentional retraining group had lower PTSD symptoms and depressive symptoms at follow-up. Additionally, the effect of attentional retraining on trauma symptoms was mediated by change in attentional bias. Currently, there are no published studies using attentional retraining for the treatment of stimulant use disorder.

6. CONCLUSIONS

No FDA-approved pharmacological treatments are available for stimulant use disorder and behavioral treatments have variable efficacy and limited availability. Further complicating matters, the majority of individuals with stimulant use disorder have other comorbidities including other addictions, depression, psychotic disorder and anxiety disorders. These comorbid disorders have many overlapping symptoms with stimulant use disorder, supporting the need for trans-diagnostic treatment approaches. One such approach may be development of treatments targeting cognitive function. Accumulating evidence suggests that stimulant use disorder is associated with a wide range of cognitive impairments, including response inhibition, working memory, and sustained attention functions. Many patients with stimulant use disorder also show attentional bias for drug-related stimuli. Individuals with psychiatric disorders have been shown to have deficits in cognitive function including disorder-specific cognitive biases. Accordingly, cognitive deficits and cognitive biases could be potential trans-diagnostic treatment targets for stimulant use disorder and comorbid disorders. Both pharmacological and behavioral approaches are available to enhance specific cognitive functions and ameliorate cognitive biases. However, there is a dearth of research directly assessing the capacity for cognitive enhancing treatments to improve drug use outcomes that are mediated by improvement in cognitive function and this gap in our knowledge represents a clinically important topic for future research. If the efficacy of these cognitive enhancement approaches can be demonstrated in clinical trials, future research could further refine which patients are most likely to benefit from which approaches. Overall, cognitive enhancement is a promising treatment for stimulant use disorder and comorbid conditions, but much work needs to be done.

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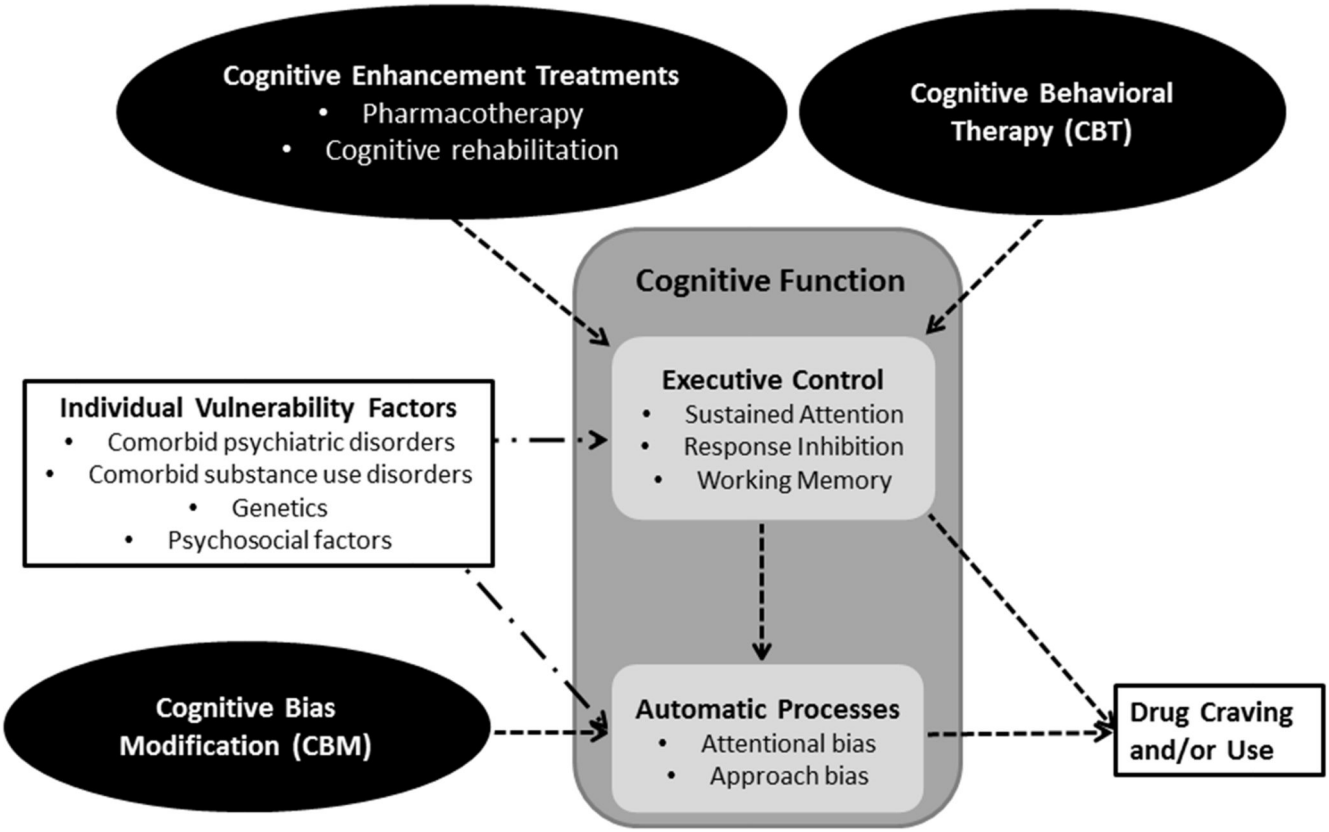

Figure 1.

Dual Process Model of Addiction: Schematic of Potential Therapeutic Mechanisms. Cognitive function is proposed as a trans-diagnostic treatment target, expected to reduce stimulant use in individuals with stimulant use disorders (SUD). Executive control functions are proposed to modulate drug use directly and indirectly via regulation of automatic thoughts. Co-morbid conditions are expected to influence both executive control and automatic process components of cognitive function. Proposed interventions include pharmacological interventions and cognitive behavioral therapy (CBT), both of which are expected to act via their strengthening of executive control. Cognitive Bias Modification (CBM) is expected to work directly on automatic processes. Black ovals= proposed interventions; grey squares= trans-diagnostic cognitive targets.