2

PSYCHOBIOLOGICAL ASPECTS OF COCAINE DEPENDENCE

Implications for prevention, treatment, and the consequences of use

Mieke H. J. Schulte, Wim van den Brink, and Reinout W. Wiers

Introduction

Cocaine use disorder (CUD) is a global public health concern. In both Europe and the USA, cocaine is one of the most commonly used illicit stimulant drugs. In 2017, 18 million Europeans (5.4%) had ever used cocaine, with 2.6 million Europeans (2.1%) having used cocaine in the last year ("European Monitorin Center for Drugs and Drug Addiction Annual Report," 2019). In the USA, 40 million people (14.9%) had ever used cocaine, with almost 6 million people (2.2%) having used cocaine in the last year (Center for Behavioral Health Statistics and Quality, 2018). There has been an increase in cocaine use over the years, which is mirrored by an increased number of people entering treatment. For instance, there has been an increase of 35% of first-time treatment entries for problematic cocaine use in Europe ("European Monitorin Center for Drugs and Drug Addiction Annual Report," 2019). In addition, 966,000 Americans were diagnosed with CUD in 2017, and 637,000 received treatment for problematic cocaine use (Center for Behavioral Health Statistics and Quality, 2018).

In *DSM-5*, substance use disorders (SUDs), including CUD, are classified on a severity scale based on the number of the defining 11 criteria, such as using more/longer than intended, and inability to cut down or continuing use despite professional or social problems or despite physiological or psychological problems. Patients meeting 2–3 criteria are diagnosed with mild SUD, patients meeting 4–5 criteria are diagnosed with moderate SUD, and patients meeting six or more criteria are diagnosed with severe SUD. In contrast to previous editions of the *DSM*, the fifth edition was expanded with the inclusion of craving as a central component for the persistence of addiction (American Psychological Association, 2013).

Acute cocaine use leads to blocked reuptake of dopamine from the synaptic cleft, causing its pleasurable effect. Additionally, the reuptake of noradrenaline and serotonin from the synaptic cleft are also blocked (Ritz, Lamb, Goldberg, & Kuhar, 1987), resulting in increased activation of the sympathetic nervous system and consequently to symptoms such as increased heart rate and pupil dilation. The development of SUDs has long been attributed to striatal dopamine release, mediating feelings of reward that lead to the development of addiction (Di Chiara, 2002; Volkow, Wang, Fowler, & Tomasi, 2012). However, research has indicated that the involvement of dopamine is more complicated, and can also be linked to incentive sensitization and craving (Berridge & Robinson, 2016). Repeated cocaine use leads to a surplus of dopamine in the synaptic cleft by inhibiting the reuptake by the presynaptic neuron. Therefore, dopamine can bind to the receptor again, creating feelings of euphoria. Chronic use of cocaine leads to disrupted dopamine functioning by decreasing (i.e. blunting) dopamine production and downregulating dopamine receptors. This disrupted functioning is thought to contribute to a decreased ability to experience pleasure in a normally pleasurable activity (anhedonia) and insensitivity to drug rewards (tolerability). At the same time, other brain areas (e.g. ventromedial prefrontal cortex, VMPFC) become more (dopaminergic) sensitive to drug-related stimuli, which is reflected by excessive wanting of the drug (Berridge & Robinson, 2016), leading to enhanced craving and loss of control over drug intake (Volkow, Koob, & McLellan, 2016; Volkow, Wang, Fowler, Tomasi, & Telang, 2011). Although dopamine is involved in SUDs in general, it appears that deviations in the striatal dopaminergic system are specific to the use of stimulants and alcohol (Nutt, Lingford-Hughes, Erritzoe, & Stokes, 2015).

This chapter summarizes the deviating cognitive functions and the neurobiological mechanisms associated with cocaine use. In addition, the factors that moderate these effects will also be considered. Thereafter, existing as well as more experimental interventions to treat CUD and associated neurobiological changes will be discussed. Finally, directions for future research and clinical implication will be discussed.

Neurocognitive correlates of CUD

Cognitive correlates of CUD

Cocaine use leads to an increase of dopamine, serotonin and noradrenalin in several sub-cortical structures, including the nucleus accumbens (NAcc). Due to the connections of the NAcc with brain regions involved in cognitive functioning, the effects of cocaine are dispersed throughout the brain. There is a vast body of literature reporting impaired cognitive functions associated with CUD, including cognitive functions in the domains of attention, executive functioning, learning and memory (Fernández-serrano, Pérez-García, & Verdejo-García, 2011; Jovanovski, Erb, & Zakzanis, 2005; Potvin, Stavro, Rizkallah, & Pelletier, 2014;

Spronk, van Wel, Ramaekers, & Verkes, 2013). Moreover, in addition to the general effects of substance use, including impaired episodic memory, emotional processing and executive functions, psychostimulant use appears to specifically affect impulsivity and cognitive flexibility (Fernández-serrano et al., 2011). However, a recent independent patient data (IPD) mega-analysis showed that inhibition was not affected in active cocaine users (Liu et al., 2019). This is in contrast with a review that concluded that effects of long-term cocaine use is characterized by a general cognitive impairment across functions, rather than by specific cognitive deficits (Spronk et al., 2013). It must be noted that the review by Spronk et al. (2013) included participants with abstinence ranging from several hours to several years, whereas the review by Fernández-serrano et al. (2011) was based on studies with medium- to long-term abstinence. In addition, the extent of deterioration appears to vary between different cognitive functions, with the greatest impairments in cognitive functions including attention, verbal/visual memory and working memory (Jovanovski et al., 2005; Potvin et al., 2014).

In order to get a clear view of the sustained effects of cocaine use and CUD on cognitive functioning, a substantial period of abstinence needs to be considered in order to eliminate possible acute (reversible) effects of cocaine use. For instance, acute effects of cocaine use were considered in the review by Spronk et al. (2013). The results suggest improvements in inhibition and psychomotor speed, whereas other domains including learning/memory and attention appeared unaffected by protracted abstinence. However, it should be noted that the different studies included different types of cocaine users, ranging from experienced frequent users to people diagnosed with CUD. Not only could the acute administration of cocaine have led to masking of any cognitive deteriorations, the variety of included user types may also have distorted the results.

Studies in ex-cocaine users with sustained abstinence can reveal deficits in cognitive functions that were masked by ongoing cocaine use, but also improvements or even recovery of deteriorated cognitive functions after abstinence. For instance, the extent of general and specific cognitive impairments resulting from substance use appears to taper off with prolonged duration of abstinence, but the effects of psychostimulant use appear to be more persistent (Fernández-serrano et al., 2011). A more recent review on the effects of sustained abstinence on cognitive functions reported at least partial recovery in general. Regarding patients with CUD specifically, executive functions showed improvements with sustained abstinence, whereas attentional processes remained impaired (Schulte et al., 2014). A meta-analysis including 46 studies with 1,452 subjects with CUD and 1,411 healthy controls revealed that most cognitive functions show improvements after five months of abstinence from cocaine (Potvin et al., 2014).

In addition to abstinence, several other factors need to be considered to acquire a more comprehensive view on the effects of cocaine use on cognitive functioning. First, cocaine use characteristics influence the extent to which cognitive functions are impaired (Mahoney, 2019). For instance, features such as quantity, frequency and the duration of cocaine use were associated with deficits in

distinct executive functions (Bolla et al., 2004; Madoz-Gúrpide, Blasco-Fontecilla, Baca-García, & Ochoa-Mangado, 2011). Moreover, age of onset appears to affect cognitive performance specifically resulting in distinct patterns of cognitive dysfunctions in early- versus late-onset cocaine use (Lopes et al., 2017). Furthermore, given that cocaine users typically use multiple substances (Connor, Gullo, White, & Kelly, 2014), the effect of polysubstance use should also be considered. Although it is difficult to disentangle the exact effect of cocaine, polysubstance users (also using cocaine) have been found to show greater impairments in neuropsychological functioning compared to alcohol dependents and healthy controls (Selby & Azrin, 1998). Furthermore, polysubstance users (also using cocaine) show greater impulsivity as measured with the Barratt Impulsiveness Scale (BIS-11) compared to cigarette smokers and healthy controls (Schmaal, Veltman, Nederveen, van den Brink, & Goudriaan, 2012; Schulte et al., 2017). Finally, demographic factors also appear to influence the effect of substance use on cognitive functioning (Liu et al., 2019). For instance, age already has a negative effect on cognitive functions (Suutama, Ruoppila, & Stig, 2002), but deviations in cognitive functions appear to further increase after substance use. Indeed, a negative association was reported for several cognitive functions, such as psychomotor speed, attention and short-term memory, indicating that CUD has a more detrimental effect on several cognitive functions in older regular cocaine users (Kalapatapu et al., 2011).

Neurobiological correlates of CUD

Several theories have been proposed for the neurobiological processes involved in addiction. One of those theories states that SUDs are associated with three separate but interacting systems, that mainly involve the prefrontal cortex (PFC), amygdala/striatum and insula (Noël, Brevers, & Bechara, 2013). The system involving the PFC constitutes a hypoactive, reflective system involved in cognitive functions including decision-making and inhibitory control, whereas the system involving the amygdala/striatum constitutes a hyperactive, motivational system involved with cognitive functions such as impulsivity. The system involving the insula can be viewed as a 'gate' system, that translates interoceptive signals into conscious feelings of desire and decision-making processes related to uncertain risk and reward (Bechara, 2005; Noël et al., 2013).

A vast body of literature has indicated that many neurobiological measures to be associated with the deviations in cognitive functions previously mentioned, at the level of brain structure as well as at the level of brain function. Understanding these neurobiological correlates could aid in understanding the development and maintenance of CUD, and consequently in the development of effective prevention and treatment.

It must be noted that a distinction between structural and functional deviations is, to some extent, arbitrary, since changes in brain structure are often related to changes in brain function (Guye, Bartolomei, & Ranjeva, 2008).

However, for the purpose of this review, deviations in structure and function will be discussed separately. In addition, it should be noted that cross-sectional studies, comparing a cocaine-using group with a control group, are not suitable for causal inference with respect to neurobiological correlates of CUD. Second, many studies have used very small samples, limiting the power, generalizability and replicability of these studies and possibly explaining some of the inconsistencies in study results.

Structural brain correlates of CUD

Smaller gray matter volumes in cocaine-using participants have been reported in a broad range of brain areas, including the frontal, temporal and parietal cortices, cingulate cortices, insula, cerebellum, striatum, thalamus and amygdala (Barrós-Loscertales, Garavan, et al., 2011; Ersche et al., 2011; Franklin et al., 2002; Ide et al., 2014; Makris et al., 2004; Moreno-López, Catena, et al., 2012; Sim et al., 2007). In addition to smaller gray matter volumes, smaller cortical volumes and surface areas have been reported in areas including the superior temporal cortex (Kaag et al., 2014). There are also reports of greater gray matter volumes and surface areas in a range of areas including the putamen, caudate nucleus, pallidum, insula and cerebellum (Ersche et al., 2011; Ide et al., 2014; Kaag et al., 2014), as well as no deviations in gray matter, for instance in the hippocampus (Makris et al., 2004). Similarly, smaller white matter volumes have been reported in a broad range of areas including frontal and parietal areas, cingulate cortex, insula, corpus callosum, cerebellum and caudate (Lane et al., 2010; Moreno-López, Catena, et al., 2012; Sim et al., 2007), as well as no deviations in white matter volumes (Franklin et al., 2002).

These deviations in brain structures have also been associated with cognitive functions in CUD, such as impulsivity, decision-making and attentional processes (Ersche et al., 2011; Kaag et al., 2014; Lane et al., 2010; Moreno-López, Catena, et al., 2012; Sim et al., 2007). More specifically, impulsivity has been positively correlated to gray matter volume in the caudate and frontal gyrus (Ersche et al., 2011; Moreno-López, Catena, et al., 2012), as well as negatively correlated with gray matter in insula, temporal gyrus and putamen (Ersche et al., 2011; Moreno-López, Catena, et al., 2012). Additionally, surface area and cortical thickness of the superior temporal cortex, insula and anterior cingulate cortex (ACC) were negatively correlated with impulsivity (Kaag et al., 2014). Decision-making has been negatively associated with white matter integrity in frontal and parietal lobes, and the corpus callosum (Lane et al., 2010). The inconsistencies in the association between cognitive functions and deviations in brain structure could be attributed to differences in the assessment of a particular cognitive function, such as self-report questionnaires versus behavioral tasks, which tap into different aspects of impulsivity (Broos et al., 2012). Another explanation could be the variation in the duration of abstinence of the included participants, ranging from acute users to long-term abstinent ex-users.

Some studies have specifically investigated the effect of abstinence on the normalization of brain structures associated with recovery of cognitive functioning. For instance, increased frontal gray matter was reported in a longitudinal study after six months of abstinence or significantly reduced use in treatment-seeking CUD participants, which was associated with improved decision-making and cognitive flexibility (Parvaz et al., 2017). Another study investigated the effect of abstinence on recovery of brain structure applying a cross-sectional design comparing active cocaine users, one-month abstinent participants and non-drug users. The abstinent ex-users showed larger gray matter volumes in frontal and temporal cortex compared to active users. In contrast to the active users, there was no difference in white matter density between the abstinent ex-users and non-drug users. In addition, the abstinent ex-users outperformed the active users with respect to several cognitive functions and their performance was associated with a larger gray matter volume in the insula and temporal cortices (Hanlon, Dufault, Wesley, & Porrino, 2011). These studies indicate that normalization of brain structure is associated with improvements in cognitive functions after a particular period of cocaine abstinence.

In addition to abstinence, several other factors need to be considered. First, cocaine use characteristics appear to influence the extent of structural deviations. For instance, the duration and severity of CUD was negatively associated with the volume of several brain areas, including frontal cortex, cingulate, cerebellum and insula (Barrós-Loscertales, Garavan, et al., 2011; Ersche et al., 2011; Ide et al., 2014; Sim et al., 2007). In addition, cerebellar gray and white matter volumes were negatively correlated with the duration of cocaine use (Sim et al., 2007). Cortical thickness of the insula and superior temporal cortex were negatively associated with the amount of cocaine use (Kaag et al., 2014). Furthermore, polysubstance use also appears to have a negative effect on the volume of the medial PFC (Kaag et al., 2018). Second, demographic factors also appear to influence the extent of structural deviations. For instance, women were found to show greater loss of gray matter in frontal areas associated with duration of use compared to men (Ide et al., 2014).

Functional brain correlates of CUD

Deviating cognitive functions in a variety of cognitive domains are often associated with brain activity in areas associated with that function. A review on neurocognitive functioning in stimulant users, including cocaine, has shown the association of activity in particular brain areas to specific cognitive functions (Crunelle, Veltman, Booij, Van Emmerik-Van Oortmerssen, & van den Brink, 2012). Based on the literature on both cocaine and ecstasy users, it appeared that there were deviations in activity of frontal, parietal and temporal areas, as well as the ACC and left hippocampus, during working memory performance. When looking specifically at the effects in cocaine users, increased activation was found in the ACC, amygdala and striatal areas (Barrós-Loscertales,

Bustamante, et al., 2011; Moeller et al., 2010; Tomasi et al., 2007b), whereas decreased activation was found in prefrontal and parietal areas (Tomasi et al., 2007b). Regarding deviating brain activity associated with impulsivity, reduced activity in the ACC and supplementary motor area was found to be related to motor impulsivity, whereas reduced activity in the dorsal and ventral system was related to cognitive impulsivity (Crunelle et al., 2012). When looking specifically at the effects in cocaine users, reduced activity in the right PFC, ACC, pre-supplementary motor area and insula was found (Hester & Garavan, 2004; Kaufman, Ross, Stein, & Garavan, 2003). Deviating brain activation has also been reported regarding attentional processes. For instance, decreased activation in the thalamus was reported during a visuospatial attention task, whereas occipital and prefrontal regions showed increased activity (Tomasi et al., 2007a). Furthermore, increased activation in the right orbitofrontal cortex (OFC) was found during performance of a decision-making task, whereas decreased activation in the right dorsolateral PFC (DLPFC) and left medial PFC was found (Bolla et al., 2003). Interestingly, deviations in brain activity are not always accompanied by behavioral deviations. The absence of cognitive dysfunctions in the presence of functional deviations could be attributed to increased activity in some areas, indicating compensatory mechanisms of attention and control processes (Barrós-Loscertales, Bustamante, et al., 2011; Moeller et al., 2010). However, Tomasi et al. (2007b) did find between-group differences in accuracy and reaction times with increasing task difficulty. Moreover, positive correlations of brain activation in the cerebellum with accuracy, and of brain activation in the postcentral gyrus with reaction times, have been reported at higher working memory load conditions. Similarly, greater performance on a decision-making task was associated with increased activation in the right OFC (Bolla et al., 2003). One reason for the discrepancy between studies regarding deviating working memory performance in cocaine users compared to controls could be the use of different working memory tasks.

In addition to deviating activity of individual brain regions, looking at the functional connectivity between the affected areas may give a more comprehensive insight into deviating brain functions associated with CUD. A review by Ma, Steinberg, Moeller, Johns, and Narayana (2015) reported that most studies on brain connectivity reported altered connectivity between different brain areas in CUD compared to health controls. In some cases, this altered connectivity is associated with cognitive functioning. For example, deviations in resting state functional connectivity in patients with CUD compared to control subjects have been reported, with evidence of increased (Hu, Salmeron, Gu, Stein, & Yang, 2015) as well as decreased functional connectivity (Hu et al., 2015; Verdejo-Garcia et al., 2014). Moreover, differences in effective connectivity between several brain areas in CUD compared to healthy controls have been reported during tasks tapping into working memory (Ma et al., 2014), response inhibition (Ma, Steinberg, Cunningham, et al., 2015) or cue reactivity (Ray, Gohel, & Biswal, 2015).

There are many inconsistencies between study results. For instance, increased as well as decreased activity in the rostral ACC has been reported to be related to impulsivity (Bolla et al., 2004; Li et al., 2008). However, there are various factors that could explain this inconsistency. First, it is important to consider the duration of abstinence. Deviations in brain activity during a working memory task were more pronounced in short-term abstinent CUD participants with positive urine screens compared to those with a negative urine screen (Tomasi et al., 2007b). This could indicate the acute effects cocaine use has on brain activity. In addition to the importance of ruling out possible acute effects of cocaine use on brain functioning, some brain functions appear to improve or even recover with prolonged abstinence (Schulte et al., 2014).

Second, demographic factors such as age and gender need to be considered. Aging has a detrimental effect on cognitive functioning and associated brain activity (Rypma & D'Esposito, 2000), making age an important factor to consider. Most studies use age-matched groups in their study design, ruling out any effect of aging on neurobiological functioning. Some studies performed subanalyses to investigate the effect of gender, but did not find such effects (Hester & Garavan, 2004; Moeller et al., 2010). Future research could benefit from thoroughly investigating the effect of aging on cognitive functioning and associated brain activity in CUD. In addition, future research could benefit from taking into account potential gender differences, since there are studies that reported gender differences in neurobiological correlates of cognitive functioning in CUD (Adinoff et al., 2006). However, since there are also studies that reported no gender differences (Moeller et al., 2010), the actual difference in response between gender could be attributed to the use of different tasks. Future research should elucidate if there is a gender difference in the effects of CUD on cognitive functioning and the neurobiological correlates.

Third, cocaine use characteristics do not only influence cognitive functioning (Mahoney, 2019), but also appear to influence associated brain functions (Bolla et al., 2003). Specifically, the amount of cocaine used in the period before testing was negatively correlated with activity in the left OFC during performance of an 'Iowa Gambling Task' (Bolla et al., 2003). Moreover, the lifetime amount of cocaine use was negatively associated with activity in parietal areas during resting state (Moreno-López, Stamatakis, et al., 2012). Similarly, cocaine use characteristics – including duration, amount and frequency of cocaine use – appear to influence functional connectivity (Contreras-Rodríguez et al., 2016; Hu et al., 2015; Ray et al., 2015). It must be noted that none of the aforementioned studies investigated the effect of cocaine use characteristics as primary analyses. There are only a few studies available investigating the effect of cocaine use on brain activity associated with cognitive functioning in CUD. For example, Prisciandaro et al. (2014) investigated the association of years of cocaine use with brain activity and inhibition and reported positive correlations between years of cocaine use and activation in the ventral striatum and with increased activity in the insula and inferior frontal gyrus associated to inhibition.

Neurotransmitter alterations

Cocaine use affects several neurotransmitters, including dopamine, serotonin, noradrenalin, glutamate and gamma-aminobutyric acid (GABA). One way of studying dopaminergic signaling is by positron emission tomography (PET) imaging. Using a radioactive ligand that binds to the dopamine D2 receptor as an agonist or antagonist, PET imaging can be used to assess D2 receptor availability and/or pre-synaptic dopamine release, which is a measure of dopamine transmission. A review by Trifilieff and Martinez (2014) investigated the association of dopamine with impulsivity in SUDs. Based on preclinical and clinical studies, they concluded that deviations in D2 receptor binding and dopamine release were associated with impulsivity. For instance, decreased striatal D2 receptor binding was associated with decreased glucose metabolism in the PFC (Volkow et al., 1993; Volkow, Fowler, & Wang, 2004). Given its key role in impulsivity, reduced glucose metabolism could point to reduced activity of the PFC, and subsequently to a diminished ability to maintain cognitive control. These reductions in D2 receptor availability remained after a period of abstinence. For example, there was no significant improvement in D2 receptor availability in the striatum up to four months of abstinence (Volkow et al., 1993, 2002). Another study reported an association of low pre-synaptic dopamine release in the ventral striatum with increased choice impulsivity (Martinez et al., 2007).

More recently, different neurotransmitters have also been associated with SUDs. Glutamate and GABA, the main excitatory and inhibitory neurotransmitters (respectively), play a key role in the regulation of the excitation/inhibition balance in the brain. The importance of glutamatergic and GABA-ergic modulation of the NAcc in SUDs has been emphasized in animal studies (Kalivas, 2009; Scofield & Kalivas, 2014; Vanderschuren & Kalivas, 2000). Repeated administration of cocaine has been found to decrease extracellular glutamate in the NAcc (Baker et al., 2003) and putamen (Yin & Knowlton, 2006). This results in reduced firing rates of glutamatergic projections from the medial PFC to the NAcc (Sun & Rebec, 2006). Glutamatergic modifications have also been associated with the continuation of and relapse into substance use, by mediating cocaine-induced drug-seeking behavior (Cornish & Kalivas, 2000; McFarland, Lapish, & Kalivas, 2003). In addition, deviations in the GABA system have been associated with abstinence and withdrawal, such as a decrease in the GABA-synthesizing enzyme glutamic acid decarboxylase (Sherif, Tawati, Ahmed, & Sharif, 1997), an upregulation of benzodiazepine-sensitive GABA-A receptors (Staley et al., 2005), and a down-regulation of the expression of gephyrin (an important regulator of GABA-ergic neurotransmission) at postsynaptic density sites of the medial PFC (Yang et al., 2017).

Using proton magnetic resonance spectroscopy (1H-MRS), deviations of glutamate and GABA in various frontal brain regions have been associated with SUDs and associated cognitive functions. Regarding glutamate, mixed effects have been reported for different substances (Bauer et al., 2013; Durazzo et al.,

2016; Gallinat & Schubert, 2007). The findings with respect to CUD are also not straightforward. Increased levels of glutamate have been reported in the dorsal anterior cingulate cortex (dACC) of cocaine-dependent inpatients (Schmaal et al., 2012), but not in active cocaine users (Schulte et al., 2017). Furthermore, although a positive association between glutamate concentrations and impulsivity has been reported by Schmaal et al. (2012), this association was absent in the study of Schulte et al. (2017). Although participants from both studies used multiple substances, the cocaine users in the study of Schmaal et al. (2012) were cocaine-dependent abstinent inpatients, whereas the participants in the study of Schulte et al. (2017) were non-treatment-seeking active users. This discrepancy highlights the importance of considering the effect of prolonged abstinence. Mixed results regarding GABA concentrations have also been reported in a variety of SUDs (Mon, Durazzo, & Meyerhoff, 2012; Prescot, Renshaw, & Yurgelun-Todd, 2013; Silveri et al., 2014). Focusing on CUD, an inverse association between decreased GABA concentrations and cocaine consumption has been reported in polysubstance users (Abé et al., 2013), but a more recent study did not report deviating GABA concentrations (Schulte et al., 2017). As this discrepancy was independent of factors such as MRS or substance use characteristics, future research should focus on how GABA is affected by cocaine use.

Interventions for CUD

There are several treatments available for SUDs, including CUD. More common interventions include psychosocial/psychotherapeutic interventions and pharmacotherapy. However, new treatment strategies are being tested, such as neurocognitive training and neuromodulation. As CUD has not always been the focus of effectiveness studies, the effectiveness in other substances will be regarded to provide an overview on the general effectiveness of a particular treatment strategy. In addition, investigating the neurobiological correlates of treatment could aid in better understanding the effectiveness of a particular treatment and aid in the development of more targeted treatments (Chung et al., 2016).

Psychosocial and psychotherapeutic interventions

A variety of psychosocial and psychotherapeutic interventions are available for the treatment of CUD, including cognitive behavioral therapy (CBT), motivational interviewing, contingency management and the community reinforcement approach. In addition to the effectiveness of a single treatment modality, research has also focused on combining modalities in order to further improve their effectiveness. A recent comprehensive review reported that psychosocial interventions were more effective in achieving abstinence at the end of treatment and at long-term follow up than no treatment or treatment as usual (TAU) (Minozzi, Saulle, De Crescenzo, & Amato, 2016). However, the literature on neurobiological mechanisms of these interventions is scarce.

CBT targets individual and social triggers for relapse via functional analysis of substance use behavior and coping skills training to support the individual to abandon dysfunctional thoughts and behaviors. A recent meta-analysis including 30 randomized controlled trials (RCTs) with 5,398 participants focused on CBT for alcohol and other substances. CBT was found to be more effective than minimal treatment and non-specific therapies (e.g. psychoeducation or supportive therapy), but not compared to other specific therapies (e.g. motivational interviewing or contingency management). Only when compared to minimal treatments was CBT was still more effective at long-term follow up (Magill et al., 2019). However, the effectiveness of CBT in the treatment of CUD is ambiguous, with reports of greater effectiveness compared to other interventions (Carroll, Rounsaville, & Gawin, 1991) and similar effectiveness compared to other interventions (McKay et al., 2010). Although the body of research on the neurobiological mechanisms of the effectiveness of CBT in the treatment for cocaine dependence is small, there is some evidence that CBT has a positive effect on cognitive functions and brain activity in areas associated with cognitive functions in SUD (e.g. DeVito et al., 2012). However, more studies are needed to clarify if the effects of CBT with respect to cocaine use correlate with changes in neurobiological measures.

Related to CBT, the community reinforcement approach (CRA) combines operant conditioning with a social system approach (Hunt & Azrin, 1973). Through functional analysis of triggers and consequences of specific behaviors, strategies are developed to either avoid or address those behaviors. CRA uses various incentives of a vocational, social and recreational nature in order to change patients' circumstances. The effectiveness has been investigated with or without other treatment modalities added on, but the evidence for the effectiveness of CRA in the treatment for various SUDs – including alcohol, heroin and cocaine – is limited (Roozen et al., 2004). Specifically regarding CRA to obtain cocaine abstinence, there was strong evidence of greater effectiveness of CRA in combination with contingency management compared to TAU (Higgins et al., 1993, 1991). In addition, there was strong evidence of greater effectiveness of CRA with contingency management than CRA without contingency management (Higgins et al., 1994) or with non-abstinence contingent incentives (Higgins, Wong, Badger, Haug Ogden, & Dantona, 2000). The effects of CRA have been found to last up to one year post-treatment (Higgins et al., 2000; Secades-Villa et al., 2011).

Contingency management (CM) is a behavioral change method based on positive reinforcement which has been found to be effective to change behaviors, including the treatment of SUDs (Petry, Alessi, Olmstead, Rash, & Zajac, 2017; Prendergast, Podus, Finney, Greenwell, & Roll, 2006). More specifically, CM has been found to be a promising add-on intervention for the treatment of CUD (Schierenberg, van Amsterdam, van den Brink, & Goudriaan, 2012). For example, CM as add-on to CBT was found to be more effective to maintain cocaine abstinence compared to CM alone, CBT alone and TAU at long-term follow-ups (McKay et al., 2010).

However, CM appears to be effective for the promotion of abstinence, but not for its long-term maintenance as the effects gradually taper off over time (Benishek et al., 2014; Prendergast et al., 2006). Despite a vast body of research on the effectiveness of CM as treatment for CUD, there are no studies available that investigate the associated neurobiological mechanisms. No studies have focused on the neurobiological mechanisms of CM for the treatment of CUD or SUDs in general.

With motivational interviewing (MI), the patient, rather than the practitioner, voices the arguments for behavior change (Miller & Rollnick, 2012). The practitioner provides psychoeducation on the negative effects of the behavior and facilitates the patients' awareness of ambiguous behaviors, awareness of certain goals and the development of strategies to reach those goals. In an umbrella review, it was shown that MI is effective in the treatment of SUDs, but the evidence is less strong for CUD compared to other substances (DiClemente, Corno, Graydon, Wiprovnick, & Knoblach, 2017). It was argued that MI might be effective for increasing motivation to enter treatment or adhere to treatment, specifically in participants with low initial motivation, but not to affect drug use outcomes. Although many studies have focused on the effect of MI on the use of several substances, less have focused specifically on CUD, with even fewer studies focusing on associated neurobiological mechanisms.

Despite the vast body of research into psychosocial and behavioral interventions for the treatment of CUD, the literature on associated neurobiological mechanisms is scarce. Only one study focused on the neurobiological mechanisms of psychosocial and behavioral interventions for CUD (DeVito et al., 2012). More studies have focused on neurobiological mechanisms of psychosocial and behavioral interventions in a broader range of substances, and the results showed that CBT results in less reward sensitivity, whereas MI result in an increase in cognitive control (Zilverstand, Parvaz, Moeller, & Goldstein, 2016). This might argue for combining treatment modalities to acquire more effective treatments. Future research should focus on the increased effectivity of combining treatment modalities with respect to clinical outcomes and associated neurobiological mechanisms. Furthermore, a better understanding of the involved underlying mechanisms could be gained by investigating functional connectivity between areas (Feldstein Ewing et al., 2017).

Pharmacotherapy

Despite the many studies on a broad range of chemical compounds, currently there is no medication proven effective or registered for the treatment of CUD. However, there are some compounds that are more promising than others. Until now, the range of tested medications includes anticonvulsants, antidepressants, antipsychotics, stimulants and some other medications such as disulfiram, naltrexone and N-acetylcysteine.

Regarding anticonvulsants, a systematic review and meta-analysis with 20 RCTs with 2,068 patients (Minozzi et al., 2015) evaluated several anticonvulsants,

including carbamazepine (six studies), topiramate (five studies), tiagabine (three studies), gabapentin (three studies), lamotrigine (two studies), vigabatrin (two studies), and phenytoin (one study). It was concluded that anticonvulsants are generally more effective neither than placebo in the promoting of retention nor in the reduction of cocaine use. A possible exception should be made for topiramate (150–300 mg/day) which might be effective in the reduction of cocaine use. Similar findings were reported in some other RCTs that were not included in this review or were published after this review, including positive studies on topiramate (Baldaçara et al., 2016; Mariani et al., 2012), and negative studies on carbamazepine (Brady et al., 2002), and gabapentin (Mancino et al., 2014). Thus, anticonvulsants – with the possible exception of topiramate – are not effective in the treatment of CUD.

Regarding antidepressants, a systematic review and meta-analyses with 37 RCTs with 3,552 patients (Pani, Trogu, Vecchi, & Amato, 2011) evaluated several antidepressants, including desipramine (17 studies), fluoxetine (five studies), bupropion (three studies), nefazodone (two studies), ritanserin (two studies) and buspirone, gepirone, paroxetine, citalopram, venlafaxine, selegiline, tryptophan, sertraline and imipramine (one study each). Although some studies suggested a small positive effect, the authors concluded that antidepressants as a group have no effect on the reduction of cocaine use, although among patients with a comorbid depression, these compounds generally had a positive effect on depressive symptoms. A possible exception should be made for bupropion, which might be effective in the reduction of cocaine use. Since bupropion also has stimulating effects, its effectiveness in the treatment of patients with CUD will be discussed more extensively under this heading. Similar findings were reported in some other RCTs that were not included in this review or were published after this review, including negative studies on buspirone (Winhusen et al., 2014), venlafaxine (Raby et al., 2014), sertraline (Mancino et al., 2014; Oliveto et al., 2012), and mirtazapine (Afshar et al., 2012; Raby et al., 2015). Thus antidepressants – apart from bupropion – are not effective in the treatment of CUD.

Regarding antipsychotics, a systematic review and meta-analyses with 14 RCTs with 719 patients (Indave, Minozzi, Pani, & Amato, 2016) evaluated several antipsychotics, including risperidone (three studies), olanzapine (three studies), quetiapine (two studies), lamotrigine (one study) and reserpine (one study). In addition, in three studies, different antipsychotics were compared with each other: olanzapine vs. haloperidol, olanzapine vs. risperidone, and aripiprazole vs. ropinirole. Although most studies were small and of low quality, with high dropout rates, the authors concluded that antidepressants are not effective in the treatment of CUD. Moreover, the authors warned against the increased risk of malignant neuroleptic syndrome and parkinsonism.

Regarding psychostimulants, there is increasing interest in using these in the treatment of CUD, similar to methadone and buprenorphine in the treatment of opioid use disorders and nicotine replacement therapy in tobacco dependence. In a systematic review and meta-analyses with 26 RCTs with 2,366 participants

(Castells, Cunill, Pérez-Mañá, Vidal, & Capellà, 2016), the following psychostimulants were evaluated: modafinil (eight studies), methylphenidate (four studies), dexamphetamine (four studies), mazindol (four studies), bupropion (three studies) and lis-dexamphetamine, mixed amphetamine salts and selegiline (one study each). Overall, psychostimulants were effective in terms of reduced cocaine use and longer periods of cocaine abstinence. Possible benefits were observed for bupropion (in combination with CM) and the best effects were seen for robust doses (>60 mg/day) of sustained release (sr) dexamphetamine and for mixed amphetamine salts. In a study among CUD patients with comorbid ADHD, mixed amphetamine salts had a beneficial effect on both ADHD symptoms and reductions in cocaine use, with the best effect on cocaine use in the highest dose group (80 mg/day). In a recent study, not included in the review, it was shown that sr-dexamphetamine significantly reduced cocaine use in cocaine-dependent patients currently in heroin assisted treatment (Nuijten, Blanken, Van den Brink, & Hendriks, 2011). Thus, certain psychostimulants in robust doses seem to be effective in the treatment of CUD.

Several other compounds have also been investigated. In a systematic review with seven studies and 492 patients, disulfiram was compared with no treatment, placebo or naltrexone. The findings were inconsistent but showed some promise for disulfiram in the treatment of CUD (Pani et al., 2010). Since then, another five RCTs were published comparing different doses of disulfiram with placebo and mainly in patients with a comorbid opioid use disorder treated with methadone or buprenorphine (Carroll et al., 2016; Carroll, Nich, Shi, Eagan, & Ball, 2012; Nielsen, Harding, Hamon, Huang, & Kosten, 2012; Oliveto et al., 2012; Schottenfeld et al., 2014). Again, the findings were inconsistent with some of the studies showing a significant beneficial effect on some of the outcomes. Thus, disulfiram (250 mg/day) might be effective in the treatment of CUD.

Between 2001 and 2015, at least eight RCTs were published on the effectiveness of naltrexone for the treatment of CUD and often with a comorbid alcohol use disorder (Kampman & Jarvis, 2015; Pettinati et al., 2014; Pettinati, Kampman, Lynch, Suh, et al., 2008; Pettinati, Kampman, Lynch, Xie, et al., 2008; Schmitz et al., 2014, 2009; Schmitz, Stotts, Rhoades, & Grabowski, 2001; Schmitz, Stotts, Sayre, DeLaune, & Grabowski, 2004). Overall, the effects were disappointing and thus, naltrexone should be regarded not effective in the treatment of CUD.

There also many compounds with only one or two studies of sufficient quality suggesting that these compounds are probably not effective in the treatment of patients with CUD, including acamprosate (Kampman et al., 2011), atomoxetine (Walsh et al., 2013), citicoline (Brown, Gorman, & Hynan, 2007; Brown et al., 2015; Licata et al., 2011), memantine (Bisaga et al., 2010), carvedilol (Oliveto et al., 2014; Sofuoglu et al., 2017), and baclofen (Kahn et al., 2009; Shoptaw et al., 2003). Finally, there are promising compounds without enough evidence to draw firm conclusions, including biperiden (Dieckmann et al., 2014), ondansetron (Johnson et al., 2006), varenicline (Plebani et al., 2012; Poling, Rounsaville,

Gonsai, Severino, & Sofuoglu, 2010), n-acetylcysteine (Schmaal et al., 2012; Schulte et al., 2018) and doxazosin (Shorter, Lindsay, & Kosten, 2013).

In summary, more than 100 compounds have been studied for the treatment of CUD but only some of these have shown (probable) effectiveness (sr-dexamphetamine, bupropion, topiramate, disulfiram), and none of these compounds is currently registered for the indication CUD.

Neurocognitive training

In line with the observation that deteriorated cognitive functioning is associated with SUDs, several studies have aimed to retrain these cognitive functions. Conceptually, two broad types of cognitive training can be distinguished (Wiers, 2018): training of general cognitive functions such as working memory or inhibition (training without substance cues) and cognitive bias modification, which is aimed at changing maladaptive cognitive biases in decision-making, in which cues relating to the addictive substance or activity (e.g., in gambling) are used.

Regarding the training of general cognitive functions, most studies have tested the effects of working memory training (often considered the most general of executive control functions [Kane & Engle, 2002]). One of the first studies was conducted by Bickel and colleagues (Bickel, Yi, Landes, Hill, & Baxter, 2011) with 27 stimulant-dependent patients (mostly cocaine). No effects on treatment outcome or cocaine use were reported, but active training led to reduced delay discounting (a facet of impulsivity). Similarly, a more recent study did not report effects on drinking or treatment outcome in alcohol-dependent patients, but did report improved future episodic thinking in the active group (Snider et al., 2018). Effects on use have been reported for alcohol in problem drinkers, but only in problem drinkers with relatively strong positive alcohol associations, moderated mediation (Houben, Wiers, & Jansen, 2011) and on opioid use in a small study (N = 28). The largest clinical study so far (N = 181, 50 cocaine users) found no effects on substance use (Wanmaker et al., 2018). Some studies have also investigated the neurobiological mechanisms of working memory training. For instance, Schulte et al. (2019, 2018) investigated the effect of working memory training on cocaine use, cognitive functions and neurobiological correlates. Working memory did not have an effect on cocaine use, impulsivity, cue reactivity and activity in several brain areas including the DLPFC, ventrolateral prefrontal cortex (VLPFC) and dACC. However, the absence of an effect of working memory training could be attributed to the small sample size and high dropout rates. Overall, general training of cognitive control functions is possible, but the problem is generalization to real-world behaviors (including substance use related behaviors). Nevertheless, effects on other cognitive functions (impulsivity, future episodic thinking) can be beneficial in a therapeutic context (Wiers, 2018) and active training and improving general cognitive functions can be motivating in recovery (Bates, Buckman, & Nguyen, 2013).

Regarding the effects of cognitive bias modification (CBM), it should be noted that CBM was first developed as an experimental manipulation to test the hypothetical causal role of cognitive biases in addiction by directly manipulating a bias and then testing direct effects on the corresponding addictive behavior (typically in students). For example, it was demonstrated that training students' attentional bias toward alcohol compared with away from alcohol, resulted in increased craving for alcohol (Field & Eastwood, 2005), with similar effects for manipulating an automatically activated approach bias (Wiers, Rinck, Kordts, Houben, & Strack, 2010). After these proof-of-principle studies, several RCTs were performed in which CBM was added to regular treatment of alcohol use disorders (Eberl et al., 2013; Rinck, Wiers, Becker, & Lindenmeyer, 2018; Schoenmakers et al., 2010; Wiers, Eberl, Rinck, Becker, & Lindenmeyer, 2011). These studies consistently found improved treatment outcomes: approximately 10% less relapse one year after treatment discharge. Note that an early meta-analysis with 25 RCTs with 3,176 participants concluded that there was no evidence of a clinical effect of CBM in addiction (Cristea, Kok, & Cuijpers, 2016), but this study included both proof-of-principle studies in volunteers not motivated to change and clinical RCTs, which constitute different phases of experimental health research (Sheeran, Klein, & Rothman, 2017; Wiers, Boffo, & Field, 2018). Once this is taken into account, the picture becomes clear: short-lived effects on behavior directly after the manipulation in case the bias is successfully manipulated and consistent (but small) add-on effects in clinical RCTs (Wiers et al., 2018). The latter conclusion was further supported by a Bayesian IPD meta-analysis including 14 clinical studies with 2,435 participants (Boffo et al., 2019). We are aware of one study testing one form of CBM (attentional retraining) in cocaine users (Mayer et al., 2016), which found no effects. One other study tested a different variety of attentional retraining in methadone users (some of whom also used crystals), which reported more promising effects, regarding effects on attentional bias at post-test (Ziaee, Fadardi, Cox, & Yazdi, 2016). In summary, there is promise in adding CBM to clinical treatment of addiction (with replicated add-on effects in the treatment of alcohol use disorders), but research on potential (add-on) effects in the treatment of CUD is still lacking. Some studies have focused on neurobiological correlates of CBM. For instance, attentional bias modification resulted in a reduced approach bias which was associated with reduction in activation of the medial PFC (Wiers et al., 2015).

Neuromodulation

In recent years, there has been growing interest in the effect of neurostimulation as treatment for SUDs. Studies applying non-invasive neuromodulation strategies such as repetitive transcranial magnetic current stimulation (rTMS) and transcranial direct current stimulation (tDCS), as well as the more invasive deep brain stimulation (DBS), have found promising results with respect to the treatment of SUDs (Bari et al., 2018; Luigjes, Segrave, de Joode, Figee, &

Denys, 2019). With both rTMS and tDCS, an electrical current can be passed through the cortical surface to increase or decrease its activity (George & Aston-Jones, 2010) and consequently alter cognitive functioning (Schluter, Daams, van Holst, & Goudriaan, 2018). Depending on specific stimulation parameters, the after-effects can be long lasting. For instance, after-effects of 90 minutes have been reported for rTMS (Klomjai, Katz, & Lackmy-Vallée, 2015), whereas after-effects of 40 minutes have been reported for tDCS (Nitsche et al., 2005). With DBS, an electrode is implanted in the brain to stimulate deeper brain areas. The stimulation of several brain areas has been found to have positive clinical effects, including the NAcc (Luigjes et al., 2012) and the ventral anterior limb of the internal capsule (vALIC; Liebrand et al., 2019).

Regarding TMS, several studies have shown the potential of rTMS in the treatment of CUD (for a review see Bolloni, Badas, Corona, & Diana, 2018). For instance, one session of high frequency (10Hz) stimulation of the right DLPFC was found to decrease craving (Camprodon, Martínez-Raga, Alonso-Alonso, Shih, & Pascual-Leone, 2007). However, different strategies have been investigated that resulted in promising effects; bilateral stimulation of the PFC resulted in decreased cocaine intake (Bolloni et al., 2016), high frequency stimulation (10Hz) of the PFC resulted in a greater reduction of cocaine use compared to low frequency stimulation (1Hz) or sham (Martinez et al., 2018), and intermittent theta burst stimulation (iTBS), a more tolerable protocol administered at lower intensities and shorter intervals, of the PFC was found to be equally effective (Sanna et al., 2019).

Studies on the effect of tDCS in CUD have predominantly focused on the effect of craving, with mixed effects. For example, bilateral right anode/left cathode stimulation of the DLPFC has been found to have positive effects on craving (Batista, Klauss, Fregni, Nitsche, & Nakamura-Palacios, 2015), whereas it has also been reported to have no effect on craving (Klauss et al., 2018). Klauss et al. (2018) is one of the few studies including the effect on cocaine use, but found no effects of tDCS.

Due to its invasiveness, the literature on the effect of DBS on SUDs has mainly focused on animal studies, with mixed results depending on the specific area and stimulation protocol (see Luigjes et al., 2012). Human studies on the effect of DBS are very scarce. Studies have predominantly focused on substances other than cocaine, with mixed results. To the best of our knowledge, only one case study has focused on the effect of DBS on refractory CUD, which found positive effects on CUD severity up to two years post-surgery (Gonçalves-Ferreira et al., 2016).

All in all, neuromodulation for the treatment of CUD appears to be a promising approach. However, more research is needed to establish how neurostimulation can be most effective to treat CUD, as there is a lot of heterogeneity between studies with respect to methodology and results. The inconsistency in study results could be attributed to differences in stimulation parameters, study populations and outcome measures (Naish, Vedelago, MacKillop, & Amlung,

2018). Differences in stimulation parameters (e.g. specific target area, unilateral vs. bilateral stimulation, stimulation frequency) can substantially influence study results. Future research could benefit from taking a uniform approach to investigate the effectiveness of neuromodulation taking into account demographic factors and cocaine use characteristics. (See Ekhtiari et al. (2019) for suggestions on how to bridge the current caveats and guidelines for best practices for non-invasive stimulation.) Future DBS research could benefit from study with greater sample sizes. However, the facts that DBS is still a new indication for SUD treatment, requires a high degree of expertise and is expensive, hamper scientific research and this field and consequently reduces the probability of DBS as a treatment for SUD (Luigjes et al., 2019). However, the great lack in RCTs on the efficacy of DBS for the treatment of SUDs, especially CUDs, greatly questions the feasibility of DBS for the treatment of SUD (Luigjes, van den Brink, Schuurman, Kuhn, & Denys, 2015).

Directions for future research and clinical implications

Many opportunities remain for future research. First, studies into the psychobiological effects of CUD could benefit from taking a more standardized approach. The discrepancy in current study results could be clarified by using identical cognitive test batteries, larger sample sizes, normative scores, and clinical significance. The latter is important to consider, because only considering statistical significance without clinical significance could potentially lead to an overestimation of the effects (Frazer, Richards, & Keith, 2018). Further, especially neuroimaging studies could benefit from increasing sample sizes to increase power, generalizability and reproducibility. In recent years, a consensus has been developed on the minimum number of participants needed in neuroimaging studies (see for example Murphy & Garavan, 2004), as well as several approaches and tools to actually perform an a prior power analysis (see for example Mumford, 2012).

Second, the use of imaging techniques provides a more detailed understanding of the neurobiological changes that underlie deviations in behavior. However, investigating neurobiological correlates (e.g. brain structure or function) without investigating associated deviations in the actual behavior (e.g. task performance) provides an incomplete picture. As has been shown by the literature, there can be increased or decreased activity in several brain areas associated to deviating as well as intact cognitive functioning possibly due to compensating mechanisms. Therefore, future research could benefit from investigating neurobiological measures in addition to cognitive functioning. Moreover, as has been argued by Ma, Steinberg, Moeller, Johns, and Narayana (2015), future research could benefit from simultaneously using a variety of neuroimaging modalities as it provides more information.

In addition to assessing the cognitive and neurobiological correlates of CUD, future research could benefit from investigating moderating factors, including

demographic characteristics such as age and gender, but also cocaine use characteristics such as duration, quantity, age of onset, CUD severity and polysubstance use. Moreover, a uniform approach in the consideration of the effect of abstinence would lead to a better understanding into which cognitive functions are affected, and which functions improve or even recover (Fernández-serrano et al., 2011; Schulte et al., 2014). This could be achieved by comparing groups with differing lengths of abstinence or by applying a longitudinal design in which participants are tracked for longer time periods. However, prospective studies that include assessments before, during and after the development of a SUD are needed to clarify if observed differences are cause or consequence of SUD. Identifying factors that predispose people to develop a SUD could benefit the development of preventative strategies.

The current overview also provides some clinical implications. For instance, having a clear view of the cognitive functions and associated neurobiological mechanisms at different stages of abstinence could aid in the development of more suitable treatments, possibly comprising multiple treatment strategies. Specific dysfunctions could be addressed by supplying treatment strategies that aim to improve these functions; for example, improving working memory to increase cognitive control or modifying attentional bias to decrease craving. Another approach could be to target underlying neurobiological mechanisms to improve brain activity to mediate changes in cognitive functioning. Possibilities include neurostimulation of the PFC to improve its activity and consequently increase cognitive control or by DBS of the NAcc or vALIC. Newly developed treatment strategies could be added in a stepped care approach, where first the least invasive and least expensive strategy is added before proceeding to the more invasive and expensive strategies.

Summary

This chapter focused on the cognitive effects of cocaine use disorder (CUD) and associated neurobiological mechanisms, as well as on their moderating factors. In addition, existing as well as more experimental interventions for the treatment of CUD were discussed. The chapter closed by addressing directions for future research and clinical implications.

Cognitive functions that have found to be affected with CUD include functions in the domains of attention, executive functioning and learning and memory. Several moderating factors have been found to influence the extent to which certain functions are affected. First, abstinence appears to reverse cognitive dysfunctions, either by improvements or by complete recovery. Second, cocaine use characteristics (e.g. quantity or frequency) exacerbate the extent to which cognitive functions are affected. In addition, although the effects specific to a certain type of drug are difficult to disentangle, polysubstance use has been found to lead to greater deterioration of cognitive functions. Last, certain demographic factors (e.g. age) also appear to have a greater detrimental effect on cognitive functions.

Several neurobiological measures, such as brain structure, brain function and neurotransmitter systems, are associated with cognitive functions in CUD. First, several deviations in measures of gray and white matter have been implicated in CUD. Deviations in brain structure have been associated with cognitive functions, albeit with great heterogeneity. Second, deviations in brain function have been associated with cognitive dysfunctions in CUD. Decreased activation in a broad range of brain areas have been associated with deviating cognitive functions. In addition, some increases in activity of some brain areas have also been reported, allegedly reflecting compensatory mechanisms to maintain cognitive functioning. All in all, also regarding associated deviations in brain activity, there is great heterogeneity in study results. Third, deviations in neurotransmitter systems have been associated with cognitive functions in CUD. Dopamine has long been the main neurotransmitter of interest in research on substance use disorders (SUDs), and decreased receptor availability and dopamine release have been found to be associated with deviations in cognitive functions. More recently, the focus has broadened to investigate other neurotransmitters, such as glutamate and GABA. Although the results with regard to glutamate and GABA concentrations are mixed, associations with cognitive functions have been reported. The inconsistent findings on neurobiological correlates of cognitive functions in CUD can, again, be explained by several factors such as abstinence (duration), cocaine use characteristics and demographic factors. In addition to the differences in operationalization of outcome measures, the majority of neuroimaging studies applied a cross-sectional design, limiting the interpretation of cause and effect, and used small sample sizes, limiting power, generalizability, and replicability.

Several interventions are available for the treatment of SUDs, including psychosocial/psychotherapeutic interventions, pharmacological treatments, neurocognitive training and neuromodulation. Common psychosocial/psychotherapeutic interventions include cognitive behavioral therapy (CBT), community reinforcement approach, contingency management and motivational interviewing. Mainly in combination with other treatment approaches, these treatment approaches have shown positive effects on the treatment of CUD. However, the literature on neurobiological mechanisms of treatment is scarce; only one study focused on the neurobiological mechanisms of psychosocial/behavioral interventions (CBT). Despite the many studies on a broad range of chemical compounds, including anticonvulsants, antidepressants, antipsychotics, psychostimulants and other compounds, currently there is no medication proven effective or registered for the treatment of CUD. Among the more than 100 compounds that have been investigated, only some have shown (probable) effectiveness for the treatment of CUD, including sr-dexamphetamine, bupropion, topiramate and disulfiram. However, none of these compounds is currently registered for the treatment of CUD.

In line with the observation that cognitive deficits are associated with SUDs, several studies have aimed to retrain these cognitive functions. Two

types of neurocognitive training can be distinguished: training general cognitive functions and cognitive bias modification (CBM). Studies investigating the effect of training of general cognitive functions mainly investigated working memory training. Although some effects have been found for alcohol use and opioid use, no effects have been reported for cocaine use. In addition, no effects of working memory training on neurobiological mechanisms have been reported. CBM is aimed at changing cognitive biases which play a role in addictive behaviors. The results of adding CBM to clinical treatment of SUDs have been promising, but are still lacking for CUD. Some studies have reported neurobiological correlates of CBM, including reductions in activation in the medial prefrontal cortex.

Future research could benefit from considering several suggestions. First, future research could benefit from standardizing the approach in testing cognitive functions and associated neurobiological mechanisms in CUD. Second, it is advised that studies on the neurobiological mechanisms of CUD are always combined with cognitive functioning to better facilitate their interpretation. Third, several factors should be considered, including demographic factors, cocaine use characteristics and abstinence. The current overview also provides some clinical implications, such as a better tailoring of treatment strategies to the neurocognitive profile of a patient.

References

Abé, C., Mon, A., Durazzo, T. C., Pennington, D. L., Schmidt, T. P., & Meyerhoff, D. J. (2013). Polysubstance and alcohol dependence: Unique abnormalities of magnetic resonance-derived brain metabolite levels. *Drug and Alcohol Dependence*, *130*(1–3), 30–37. https://doi.org/10.1016/j.drugalcdep.2012.10.004

Adinoff, B., Williams, M. J., Best, S. E., Harris, T. S., Chandler, P., & Devous, M. D. (2006). Sex differences in medial and lateral orbitofrontal cortex hypoperfusion in cocaine-dependent men and women. *Gender Medicine*, *3*(3), 206–222. https://doi.org/10.1016/S1550-8579(06)80209-3

Afshar, M., Knapp, C. M., Sarid-Segal, O., Devine, E., Colaneri, L. S., Tozier, L.,... Ciraulo, D. A. (2012). The efficacy of mirtazapine in the treatment of cocaine dependence with comorbid depression. *American Journal of Drug and Alcohol Abuse*, *38*(2), 181–186. https://doi.org/10.3109/00952990.2011.644002

American Psychological Association (2013). *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.). Arlington, VA: Author.

Baker, D. A., McFarland, K., Lake, R. W., Shen, H., Toda, S., & Kalivas, P. W. (2003). N-acetyl cysteine-induced blockade of cocaine-induced reinstatement. *Annals of the New York Academy of Sciences*, *1003*, 349–351. https://doi.org/10.1196/annals.1300.023

Baldaçara, L., Cogo-Moreira, H., Parreira, B. L., Diniz, T. A., Milhomem, J. J., Fernandes, C. C., & Lacerda, A. L. T. (2016). Efficacy of topiramate in the treatment of crack cocaine dependence: A double-blind, randomized, placebo-controlled trial. *The Journal of Clinical Psychiatry*, *77*(3), 398–406. https://doi.org/10.4088/JCP.14m09377

Bari, A., DeCisare, J., Babayan, D., Runcie, M., Sparks, H., & Wilson, B. (2018). Neuromodulation for substance addiction in human subjects: A review. *Neuroscience and Biobehavioral Reviews*, *95*, 33–43. https://doi.org/10.1016/j.neubiorev.2018.09.013

Barrós-Loscertales, A., Bustamante, J. C., Ventura-Campos, N., Llopis, J. J., Parcet, M. A., & Ávila, C. (2011). Lower activation in the right frontoparietal network during a counting Stroop task in a cocaine-dependent group. *Psychiatry Research: Neuroimaging*, *194*(2), 111–118. https://doi.org/10.1016/j.pscychresns.2011.05.001

Barrós-Loscertales, A., Garavan, H., Bustamante, J. C., Ventura-Campos, N., Llopis, J. J., Belloch, V.,... Ávila, C. (2011). Reduced striatal volume in cocaine-dependent patients. *NeuroImage*, *56*(3), 1021–1026. https://doi.org/10.1016/j.neuroimage.2011.02.035

Bates, M. E., Buckman, J. F., & Nguyen, T. T. (2013). A role for cognitive rehabilitation in increasing the effectiveness of treatment for alcohol use disorders. *Neuropsychology Review*, *23*(1), 27–47. https://doi.org/10.1007/s11065-013-9228-3

Batista, E. K., Klauss, J., Fregni, F., Nitsche, M. A., & Nakamura-Palacios, E. M. (2015). A randomized placebo-controlled trial of targeted prefrontal cortex modulation with bilateral tDCS in patients with crack-cocaine dependence. *International Journal of Neuropsychopharmacology*, *18*(12), 1–11. https://doi.org/10.1093/ijnp/pyv066

Bauer, J., Pedersen, A., Scherbaum, N., Bening, J., Patschke, J., Kugel, H.,... Ohrmann, P. (2013). Craving in alcohol-dependent patients after detoxification is related to glutamatergic dysfunction in the nucleus accumbens and the anterior cingulate cortex. *Neuropsychopharmacology*, *38*(8), 1401–1408. https://doi.org/10.1038/npp.2013.45

Bechara, A. (2005). Decision making, impulse control and loss of willpower to resist drugs: A neurocognitive perspective. *Nature Neuroscience*, *8*(11), 1458–1463. https://doi.org/10.1038/nn1584

Benishek, L. A., Dugosh, K. L., Kirby, K. C., Matejkowski, J., Clements, N. T., Seymour, B. L., & Festinger, D. S. (2014). Prize-based contingency management for the treatment of substance abusers: A meta-analysis. *Addiction (Abingdon, England)*, *109*(9), 1426–1436. https://doi.org/10.1111/add.12589

Berridge, K. C., & Robinson, T. E. (2016). Liking, wanting, and the incentive-sensitization theory of addiction. *American Psychologist*, *71*(8), 670–679. https://doi.org/10.1037/amp0000059

Bickel, W. K., Yi, R., Landes, R. D., Hill, P. F., & Baxter, C. (2011). Remember the future: Working memory training decreases delay discounting among stimulant addicts. *Biological Psychiatry*, *69*(3), 260–265. https://doi.org/10.1016/j.biopsych.2010.08.017

Bisaga, A., Aharonovich, E., Cheng, W. Y., Levin, F. R., Mariani, J. J., Raby, W. N., & Nunes, E. V. (2010). A placebo-controlled trial of memantine for cocaine dependence with high-value voucher incentives during a pre-randomization lead-in period. *Drug and Alcohol Dependence*, *111*(1–2), 97–104. https://doi.org/10.1016/j.drugalcdep.2010.04.006

Boffo, M., Zerhouni, O., Gronau, Q. F., van Beek, R. J. J., Nikolaou, K., Marsman, M., & Wiers, R. W. (2019, March 15). Cognitive bias modification for behavior change in alcohol and smoking addiction: Bayesian meta-analysis of individual participant data. *Neuropsychology Review*, *29*, 52–78. https://doi.org/10.1007/s11065-018-9386-4

Bolla, K. I., Eldreth, D. A., London, E. D., Kiehl, K. A., Mouratidis, M., Contoreggi, C.,... Ernst, M. (2003). Orbitofrontal cortex dysfunction in abstinent cocaine abusers performing a decision-making task. *NeuroImage*, *19*(3), 1085–1094. https://doi.org/10.1016/S1053-8119(03)00113-7

Bolla, K. I., Ernst, M., Kiehl, K., Mouratidis, M., Eldreth, D., Contoreggi, C.,... London, E. (2004). Prefrontal cortical dysfunction in abstinent cocaine abusers. *Journal of Neuropsychiatry and Clinical Neurosciences*, *16*(4), 456–464. https://doi.org/10.1176/jnp.16.4.456

Bolloni, C., Badas, P., Corona, G., & Diana, M. (2018). Transcranial magnetic stimulation for the treatment of cocaine addiction: Evidence to date. *Substance Abuse and Rehabilitation*, *9*, 11–21. https://doi.org/10.2147/sar.s161206

Bolloni, C., Panella, R., Pedetti, M., Frascella, A. G., Gambelunghe, C., Piccoli, T.,... Diana, M. (2016). Bilateral transcranial magnetic stimulation of the prefrontal cortex reduces cocaine intake: A pilot study. *Frontiers in Psychiatry*, 7(133). https://doi.org/10.3389/fpsyt.2016.00133

Brady, K. T., Sonne, S. C., Malcolm, R. J., Randall, C. L., Dansky, B. S., Simpson, K.,... Brondino, M. (2002). Carbamazepine in the treatment of cocaine dependence: Subtyping by affective disorder. *Experimental and Clinical Psychopharmacology*, *10*(3), 276–285. https://doi.org/10.1037/1064-1297.10.3.276

Broos, N., Schmaal, L., Wiskerke, J., Kostelijk, L., Lam, T., Stoop, N.,... Goudriaan, A. E. (2012). The relationship between impulsive choice and impulsive action: A cross-species translational study. *PLoS One*, 7(5), e36781. https://doi.org/10.1371/journal.pone.0036781

Brown, E. S., Gorman, A. R., & Hynan, L. S. (2007). A randomized, placebo-controlled trial of citicoline add-on therapy in outpatients with bipolar disorder and cocaine dependence. *Journal of Clinical Psychopharmacology*, *27*(5), 498–502. https://doi.org/10.1097/JCP.0b013e31814db4c4

Brown, E. S., Todd, J. P., Hu, L. T., Schmitz, J. M., Carmody, T. J., Nakamura, A.,... Lo, A. (2015). A randomized, double-blind, placebo-controlled trial of citicoline for cocaine dependence in bipolar I disorder. *The American Journal of Psychiatry*, *172*(10), 1014–1021. https://doi.org/10.1176/appi.ajp.2015.14070857

Camprodon, J. A., Martínez-Raga, J., Alonso-Alonso, M., Shih, M. C., & Pascual-Leone, A. (2007). One session of high frequency repetitive transcranial magnetic stimulation (rTMS) to the right prefrontal cortex transiently reduces cocaine craving. *Drug and Alcohol Dependence*, *86*(1), 91–94. https://doi.org/10.1016/j.drugalcdep.2006.06.002

Carroll, K. M., Nich, C., Petry, N. M., Eagan, D. A., Shi, J. M., & Ball, S. A. (2016). A randomized factorial trial of disulfiram and contingency management to enhance cognitive behavioral therapy for cocaine dependence. *Drug and Alcohol Dependence*, *160*, 135–142. https://doi.org/10.1016/j.drugalcdep.2015.12.036

Carroll, K. M., Nich, C., Shi, J. M., Eagan, D., & Ball, S. A. (2012). Efficacy of disulfiram and twelve step facilitation in cocaine-dependent individuals maintained on methadone: A randomized placebo-controlled trial. *Drug and Alcohol Dependence*, *126*(1–2), 224–231. https://doi.org/10.1016/j.drugalcdep.2012.05.019

Carroll, K. M., Rounsaville, B. J., & Gawin, F. H. (1991). A comparative trial of psychotherapies for ambulatory cocaine abusers: Relapse prevention and interpersonal psychotherapy. *American Journal of Drug and Alcohol Abuse*, *17*(3), 229–247. https://doi.org/10.3109/00952999109027549

Castells, X., Cunill, R., Pérez-Mañá, C., Vidal, X., & Capellà, D. (2016, September 27). Psychostimulant drugs for cocaine dependence. *Cochrane Database of Systematic Reviews*, *2016*. https://doi.org/10.1002/14651858.CD007380.pub4

Center for Behavioral Health Statistics and Quality (2018). *2017 National Survey on Drug Use and Health: Detailed Tables*. Rockville, MD: Substance Abuse and Mental Health Services Administration. (n.d.).

Chung, T., Noronha, A., Carroll, K. M., Potenza, M. N., Hutchison, K., Calhoun, V. D.,... Feldstein Ewing, S. W. (2016). Brain mechanisms of change in addictions treatment: Models, methods, and emerging findings. *Current Addiction Reports*, *3*(3), 332–342. https://doi.org/10.1007/s40429-016-0113-z

Connor, J. P., Gullo, M. J., White, A., & Kelly, A. B. (2014). Polysubstance use: Diagnostic challenges, patterns of use and health. *Current Opinion in Psychiatry*, *27*(4), 269–275. https://doi.org/10.1097/YCO.0000000000000069

Contreras-Rodríguez, O., Albein-Urios, N., Vilar-López, R., Perales, J. C., Martínez-Gonzalez, J. M., Fernández-Serrano, M. J.,... Verdejo-García, A. (2016). Increased

corticolimbic connectivity in cocaine dependence versus pathological gambling is associated with drug severity and emotion-related impulsivity. *Addiction Biology*, *21*(3), 709–718. https://doi.org/10.1111/adb.12242

Cornish, J. L., & Kalivas, P. W. (2000). Glutamate transmission in the nucleus accumbens mediates relapse in cocaine addiction. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *20*(15), 1–5.

Cristea, I. A., Kok, R. N., & Cuijpers, P. (2016). The effectiveness of cognitive bias modification interventions for substance addictions: A meta-analysis. *PLoS One*, *11*(9), e0162226. https://doi.org/10.1371/journal.pone.0162226

Crunelle, C. L., Veltman, D. J., Booij, J., Van Emmerik-Van Oortmerssen, K., & van den Brink, W. (2012). Substrates of neuropsychological functioning in stimulant dependence: A review of functional neuroimaging research. *Brain and Behavior*, *2*(4), 499–523. https://doi.org/10.1002/brb3.65

DeVito, E. E., Worhunsky, P. D., Carroll, K. M., Rounsaville, B. J., Kober, H., & Potenza, M. N. (2012). A preliminary study of the neural effects of behavioral therapy for substance use disorders. *Drug and Alcohol Dependence*, *122*(3), 228–235. https://doi.org/10.1016/j.drugalcdep.2011.10.002

Di Chiara, G. (2002). Nucleus accumbens shell and core dopamine: Differential role in behavior and addiction. *Behavioural Brain Research*, *137*(1–2), 75–114. https://doi.org/10.1016/S0166-4328(02)00286-3

DiClemente, C. C., Corno, C. M., Graydon, M. M., Wiprovnick, A. E., & Knoblach, D. J. (2017). Motivational interviewing, enhancement, and brief interventions over the last decade: A review of reviews of efficacy and effectiveness. *Psychology of Addictive Behaviors*, *31*(8), 862–887. https://doi.org/10.1037/adb0000318

Dieckmann, L. H. J., Ramos, A. C., Silva, E. A., Justo, L. P., Sabioni, P., Frade, I. F.,... Galduróz, J. C. F. (2014). Effects of biperiden on the treatment of cocaine/crack addiction: A randomised, double-blind, placebo-controlled trial. *European Neuropsychopharmacology*, *24*(8), 1196–1202. https://doi.org/10.1016/j.euroneuro.2014.06.001

Durazzo, T. C., Meyerhoff, D. J., Mon, A., Abé, C., Gazdzinski, S., & Murray, D. E. (2016). Chronic cigarette smoking in healthy middle-aged individuals is associated with decreased regional brain n-acetylaspartate and glutamate levels. *Biological Psychiatry*, *79*(6), 481–488. https://doi.org/10.1016/j.biopsych.2015.03.029

Eberl, C., Wiers, R. W., Pawelczack, S., Rinck, M., Becker, E. S., & Lindenmeyer, J. (2013). Approach bias modification in alcohol dependence: Do clinical effects replicate and for whom does it work best? *Developmental Cognitive Neuroscience*, *4*, 38–51. https://doi.org/10.1016/j.dcn.2012.11.002

Ekhtiari, H., Tavakoli, H., Addolorato, G., Baeken, C., Bonci, A., Campanella, S.,... Hanlon, C. A. (2019, July). Transcranial electrical and magnetic stimulation (tES and TMS) for addiction medicine: A consensus paper on the present state of the science and the road ahead. *Neuroscience and Biobehavioral Reviews*, *104*, 118–140. https://doi.org/10.1016/j.neubiorev.2019.06.007

Ersche, K. D., Barnes, A., Simon Jones, P., Morein-Zamir, S., Robbins, T. W., & Bullmore, E. T. (2011). Abnormal structure of frontostriatal brain systems is associated with aspects of impulsivity and compulsivity in cocaine dependence. *Brain*, *134*(7), 2013–2024. https://doi.org/10.1093/brain/awr138

European Monitoring Centre for Drugs and Drug Addiction (2019). *European Drug Report 2019: Trends and Developments*. Luxembourg: Publications Office of the European Union.

Feldstein Ewing, S. W., Chung, T., Caouette, J. D., Ketcherside, A., Hudson, K. A., & Filbey, F. M. (2017). Orbitofrontal cortex connectivity as a mechanism of adolescent behavior change. *NeuroImage*, *151*, 14–23. https://doi.org/10.1016/j.neuroimage.2016.12.076

Fernández-serrano, M. J., Pérez-García, M., & Verdejo-García, A. (2011). What are the specific vs. generalized effects of drugs of abuse on neuropsychological performance? *Neuroscience and Biobehavioral Reviews*, *35*, 377–406. https://doi.org/10.1016/j.neubiorev.2010.04.008

Field, M., & Eastwood, B. (2005). Experimental manipulation of attentional bias increases the motivation to drink alcohol. *Psychopharmacology*, *183*(3), 350–357. https://doi.org/10.1007/s00213-005-0202-5

Franklin, T. R., Acton, P. D., Maldjian, J. A., Gray, J. D., Croft, J. R., Dackis, C. A.,... Childress, A. R. (2002). Decreased gray matter concentration in the insular, orbitofrontal, cingulate, and temporal cortices of cocaine patients. *Biological Psychiatry*, *51*(2), 134–142. https://doi.org/10.1016/S0006-3223(01)01269-0

Frazer, K. M., Richards, Q., & Keith, D. R. (2018, April). The long-term effects of cocaine use on cognitive functioning: A systematic critical review. *Behavioural Brain Research*, *348*, 241–262. https://doi.org/10.1016/j.bbr.2018.04.005

Gallinat, J., & Schubert, F. (2007). Regional cerebral glutamate concentrations and chronic tobacco consumption. *Pharmacopsychiatry*, *40*(2), 64–67. https://doi.org/10.1055/s-2007-970144

George, M. S., & Aston-Jones, G. (2010, January). Noninvasive techniques for probing neurocircuitry and treating illness: Vagus nerve stimulation (VNS), transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). *Neuropsychopharmacology*, *35*, 301–316. https://doi.org/10.1038/npp.2009.87

Gonçalves-Ferreira, A., Do Couto, F. S., Rainha Campos, A., Lucas Neto, L. P., Gonçalves-Ferreira, D., & Teixeira, J. (2016). Deep brain stimulation for refractory cocaine dependence. *Biological Psychiatry*, *79*(11), e87–e89. https://doi.org/10.1016/j.biopsych.2015.06.023

Guye, M., Bartolomei, F., & Ranjeva, J. P. (2008). Imaging structural and functional connectivity: Towards a unified definition of human brain organization? *Current Opinion in Neurology*, *21*(4), 393–403.

Hanlon, C. A., Dufault, D. L., Wesley, M. J., & Porrino, L. J. (2011). Elevated gray and white matter densities in cocaine abstainers compared to current users. *Psychopharmacology*, *218*(4), 681–692. https://doi.org/10.1007/s00213-011-2360-y

Hester, R., & Garavan, H. (2004). Executive dysfunction in cocaine addiction: Evidence for discordant frontal, cingulate, and cerebellar activity. *Journal of Neuroscience*, *24*(49), 11017–11022. https://doi.org/10.1523/JNEUROSCI.3321-04.2004

Higgins, S. T., Budney, A. J., Bickel, W. K., Foerg, F. E., Donham, R., & Badger, G. J. (1994). Incentives improve outcome in outpatient behavioral treatment of cocaine dependence. *Archives of General Psychiatry*, *51*(7), 568–576. https://doi.org/10.1001/archpsyc.1994.03950070060011

Higgins, S. T., Budney, A. J., Bickel, W. K., Hughes, J. R., Foerg, F., & Badger, G. (1993). Achieving cocaine abstinence with a behavioral approach. *American Journal of Psychiatry*, *150*(5), 763–769. https://doi.org/10.1176/ajp.150.5.763

Higgins, S. T., Delaney, D. D., Budney, A. J., Bickel, W. K., Hughes, J. R., Foerg, F., & Fenwick, J. W. (1991). A behavioral approach to achieving initial cocaine abstinence. *American Journal of Psychiatry*, *148*(9), 1218–1224. https://doi.org/10.1176/ajp.148.9.1218

Higgins, S. T., Wong, C. J., Badger, G. J., Haug Ogden, D. E., & Dantona, R. L. (2000). Contingent reinforcement increases cocaine abstinence during outpatient treatment and 1 year of follow-up. *Journal of Consulting and Clinical Psychology*, *68*(1), 64–72. https://doi.org/10.1037/0022-006X.68.1.64

Houben, K., Wiers, R. W., & Jansen, A. (2011). Getting a grip on drinking behavior: Training working memory to reduce alcohol abuse. *Psychological Science*, *22*(7), 968–975. https://doi.org/10.1177/0956797611412392

Hu, Y., Salmeron, B. J., Gu, H., Stein, E. A., & Yang, Y. (2015). Impaired functional connectivity within and between frontostriatal circuits and its association with compulsive drug use and trait impulsivity in cocaine addiction. *JAMA Psychiatry*, *72*(6), 584–592. https://doi.org/10.1001/jamapsychiatry.2015.1

Hunt, G. M., & Azrin, N. H. (1973). A community-reinforcement approach to alcoholism. *Behaviour Research and Therapy*, *11*(1), 91–104. https://doi.org/10.1016/0005-7967(73)90072-7

Ide, J. S., Zhang, S., Hu, S., Sinha, R., Mazure, C. M., & Li, C.-S. R. (2014). Cerebral gray matter volumes and low-frequency fluctuation of BOLD signals in cocaine dependence: Duration of use and gender difference. *Drug and Alcohol Dependence*, *134*(1), 51–62. https://doi.org/10.1016/j.drugalcdep.2013.09.004

Indave, B. I., Minozzi, S., Pani, P. P., & Amato, L. (2016). Antipsychotic medications for cocaine dependence. *The Cochrane Database of Systematic Reviews*, *3*, CD006306. https://doi.org/10.1002/14651858.CD006306.pub3

Johnson, B. A., Roache, J. D., Ait-Daoud, N., Javors, M. A., Harrison, J. M., Elkashef, A.,... Bloch, D. A. (2006). A preliminary randomized, double-blind, placebo-controlled study of the safety and efficacy of ondansetron in the treatment of cocaine dependence. *Drug and Alcohol Dependence*, *84*(3), 256–263. https://doi.org/10.1016/j.drugalcdep.2006.02.011

Jovanovski, D., Erb, S., & Zakzanis, K. K. (2005). Neurocognitive deficits in cocaine users: A quantitative review of the evidence. *Journal of Clinical and Experimental Neuropsychology*, *27*, 189–204. https://doi.org/10.1080/13803390490515694

Kaag, A. M., Crunelle, C. L., van Wingen, G., Homberg, J., van den Brink, W., & Reneman, L. (2014). Relationship between trait impulsivity and cortical volume, thickness and surface area in male cocaine users and non-drug using controls. *Drug and Alcohol Dependence*, *144*, 210–217. https://doi.org/10.1016/j.drugalcdep.2014.09.016

Kaag, A. M., Schulte, M. H. J., Jansen, J. M., van Wingen, G., Homberg, J., van den Brink, W.,... Reneman, L. (2018). The relation between gray matter volume and the use of alcohol, tobacco, cocaine and cannabis in male polysubstance users. *Drug and Alcohol Dependence*, *187*, 186–194. https://doi.org/10.1016/j.drugalcdep.2018.03.010

Kahn, R., Biswas, K., Childress, A. R., Shoptaw, S., Fudala, P. J., Gorgon, L.,... Elkashef, A. (2009). Multi-center trial of baclofen for abstinence initiation in severe cocaine-dependent individuals. *Drug and Alcohol Dependence*, *103*(1–2), 59–64. https://doi.org/10.1016/j.drugalcdep.2009.03.011

Kalapatapu, R. K., Vadhan, N. P., Rubin, E., Bedi, G., Cheng, W. Y., Sullivan, M. A., & Foltin, R. W. (2011). A pilot study of neurocognitive function in older and younger cocaine abusers and controls. *American Journal on Addictions*, *20*(3), 228–239. https://doi.org/10.1111/j.1521-0391.2011.00128.x

Kalivas, P. W. (2009). The glutamate homeostasis hypothesis of addiction. *Nature Reviews Neuroscience*, *10*(8), 561–572. https://doi.org/10.1038/nrn2515

Kampman, K. M., Dackis, C., Pettinati, H. M., Lynch, K. G., Sparkman, T., & O'Brien, C. P. (2011). A double-blind, placebo-controlled pilot trial of acamprosate for the treatment of cocaine dependence. *Addictive Behaviors*, *36*(3), 217–221. https://doi.org/10.1016/j.addbeh.2010.11.003

Kampman, K. M., & Jarvis, M. (2015, December 1). American Society of Addiction Medicine (ASAM) national practice guideline for the use of medications in the treatment of addiction involving opioid use. *Journal of Addiction Medicine*, *9*, 358–367. https://doi.org/10.1097/ADM.0000000000000166

Kane, M. J., & Engle, R. W. (2002). The role of prefrontal cortex in working-memory capacity, executive attention, and general fluid intelligence: An individual-differences perspective. *Psychonomic Bulletin & Review*, *9*(4), 637–671.

Kaufman, J. N., Ross, T. J., Stein, E. A., & Garavan, H. (2003). Cingulate hypoactivity in cocaine users during a GO-NOGO task as revealed by event-related functional magnetic resonance imaging. *The Journal of Neuroscience*, *23*(21), 7839–7843. https://doi.org/10.1523/JNEUROSCI.23-21-07839.2003

Klauss, J., Anders, Q. S., Felippe, L. V., Buback Ferreira, L. V., Cruz, M. A., Nitsche, M. A., & Nakamura-Palacios, E. M. (2018). Lack of effects of extended sessions of transcranial direct current stimulation (tDCS) over dorsolateral prefrontal cortex on craving and relapses in crack-cocaine users. *Frontiers in Pharmacology*, *9*(1198). https://doi.org/10.3389/fphar.2018.01198

Klomjai, W., Katz, R., & Lackmy-Vallée, A. (2015, September 1). Basic principles of transcranial magnetic stimulation (TMS) and repetitive TMS (rTMS). *Annals of Physical and Rehabilitation Medicine*, *58*, 208–213. https://doi.org/10.1016/j.rehab.2015.05.005

Lane, S. D., Steinberg, J. L., Ma, L., Hasan, K. M., Kramer, L. A., Zuniga, E. A.,... Moeller, F. G. (2010). Diffusion tensor imaging and decision making in cocaine dependence. *PLoS One*, *5*(7), e11591. https://doi.org/10.1371/journal.pone.0011591

Li, C.-S. R., Huang, C., Yan, P., Bhagwagar, Z., Milivojevic, V., & Sinha, R. (2008). Neural correlates of impulse control during stop signal inhibition in cocaine-dependent men. *Neuropsychopharmacology*, *33*(8), 1798–1806. https://doi.org/10.1038/sj.npp.1301568

Licata, S. C., Penetar, D. M., Ravichandran, C., Rodolico, J., Palmer, C., Berko, J.,... Lukas, S. E. (2011). Effects of daily treatment with citicoline: A double-blind, placebo-controlled study in cocaine-dependent volunteers. *Journal of Addiction Medicine*, *5*(1), 57–64. https://doi.org/10.1097/ADM.0b013e3181d80c93

Liebrand, L. C., Caan, M. W. A., Schuurman, P. R., van den Munckhof, P., Figee, M., Denys, D., & van Wingen, G. A. (2019). Individual white matter bundle trajectories are associated with deep brain stimulation response in obsessive-compulsive disorder. *Brain Stimulation*, *12*(2), 353–360. https://doi.org/10.1016/j.brs.2018.11.014

Liu, Y., van den Wildenberg, W. P. M., de Graaf, Y., Ames, S. L., Baldacchino, A., Bø, R.,... Wiers, R. W. (2019). Is (poly-) substance use associated with impaired inhibitory control? A mega-analysis controlling for confounders. *Neuroscience & Biobehavioral Reviews*, *105*, 288–304. https://doi.org/10.1016/j.neubiorev.2019.07.006

Lopes, B. M., Gonçalves, P. D., Ometto, M., dos Santos, B., Cavallet, M., Chaim-Avancini, T. M.,... Cunha, P. J. (2017). Distinct cognitive performance and patterns of drug use among early and late onset cocaine users. *Addictive Behaviors*, *73*(August, 2016), 41–47. https://doi.org/10.1016/j.addbeh.2017.04.013

Luigjes, J., Segrave, R., de Joode, N., Figee, M., & Denys, D. (2019, March 15). Efficacy of invasive and non-invasive brain modulation interventions for addiction. *Neuropsychology Review*, *29*, 116–138. https://doi.org/10.1007/s11065-018-9393-5

Luigjes, J., Van Den Brink, W., Feenstra, M., Van Den Munckhof, P., Schuurman, P. R., Schippers, R.,... Denys, D. (2012, June). Deep brain stimulation in addiction: A review of potential brain targets. *Molecular Psychiatry*, *17*, 572–583. https://doi.org/10.1038/mp.2011.114

Luigjes, J., van den Brink, W., Schuurman, P. R., Kuhn, J., & Denys, D. (2015). Is deep brain stimulation a treatment option for addiction? *Addiction*, *110*(4), 547–548. https://doi.org/10.1111/add.12773

Ma, L., Steinberg, J. L., Cunningham, K. A., Lane, S. D., Bjork, J. M., Neelakantan, H.,... Moeller, F. G. (2015). Inhibitory behavioral control: A stochastic dynamic causal modeling study comparing cocaine dependent subjects and controls. *NeuroImage: Clinical*, *7*, 837–847. https://doi.org/10.1016/j.nicl.2015.03.015

Ma, L., Steinberg, J. L., Hasan, K. M., Narayana, P. A., Kramer, L. A., & Moeller, F. G. (2014). Stochastic dynamic causal modeling of working memory connections in cocaine dependence. *Human Brain Mapping*, *35*(3), 760–778. https://doi.org/10.1002/hbm.22212

Ma, L., Steinberg, J. L., Moeller, F. G., Johns, S. E., & Narayana, P. A. (2015). Effect of cocaine dependence on brain connections: Clinical implications. *Expert Review of Neurotherapeutics*, *15*(11), 1307–1319. https://doi.org/10.1586/14737175.2015.1103183

Madoz-Gúrpide, A., Blasco-Fontecilla, H., Baca-García, E., & Ochoa-Mangado, E. (2011). Executive dysfunction in chronic cocaine users: An exploratory study. *Drug and Alcohol Dependence*, *117*(1), 55–58. https://doi.org/10.1016/j.drugalcdep.2010.11.030

Magill, M., Ray, L., Kiluk, B., Hoadley, A., Bernstein, M., Tonigan, J. S., & Carroll, K. M. (2019). A meta-analysis of cognitive-behavioral therapy for alcohol or other drug use disorders: Treatment efficacy by contrast condition. *Journal of Consulting and Clinical Psychology*. https://doi.org/10.1037/ccp0000447

Mahoney, J. J. (2019). Cognitive dysfunction in individuals with cocaine use disorder: Potential moderating factors and pharmacological treatments. *Experimental and Clinical Psychopharmacology*, *27*(3), 203–214. https://doi.org/10.1037/pha0000245

Makris, N., Gasic, G. P., Seidman, L. J., Goldstein, J. M., Gastfriend, D. R., Elman, I.,... Breiter, H. C. (2004). Decreased absolute amygdala volume in cocaine addicts. *Neuron*, *44*(4), 729–740. https://doi.org/10.1016/j.neuron.2004.10.027

Mancino, M. J., McGaugh, J., Chopra, M. P., Guise, J. B., Cargile, C., Williams, D. K.,... Oliveto, A. (2014). Clinical efficacy of sertraline alone and augmented with gabapentin in recently abstinent cocaine-dependent patients with depressive symptoms. *Journal of Clinical Psychopharmacology*, *34*(2), 234–239. https://doi.org/10.1097/JCP.0000000000000062

Mariani, J. J., Pavlicova, M., Bisaga, A., Nunes, E. V, Brooks, D. J., & Levin, F. R. (2012). Extended-release mixed amphetamine salts and topiramate for cocaine dependence: A randomized controlled trial. *Biological Psychiatry*, *72*(11), 950–956. https://doi.org/10.1016/j.biopsych.2012.05.032

Martinez, D., Narendran, R., Foltin, R. W., Slifstein, M., Hwang, D. R., Broft, A.,... Laruelle, M. (2007). Amphetamine-induced dopamine release: Markedly blunted in cocaine dependence and predictive of the choice to self-administer cocaine. *American Journal of Psychiatry*, *164*(4), 622–629. https://doi.org/10.1176/ajp.2007.164.4.622

Martinez, D., Urban, N., Grassetti, A., Chang, D., Hu, M. C., Zangen, A.,... Nunes, E. V. (2018). Transcranial magnetic stimulation of medial prefrontal and cingulate cortices reduces cocaine self-administration: A pilot study. *Frontiers in Psychiatry*, *9*(80). https://doi.org/10.3389/fpsyt.2018.00080

Mayer, A. R., Wilcox, C. E., Dodd, A. B., Klimaj, S. D., Dekonenko, C. J., Claus, E. D., & Bogenschutz, M. (2016). The efficacy of attention bias modification therapy in cocaine use disorders. *The American Journal of Drug and Alcohol Abuse*, *42*(4), 459–468. https://doi.org/10.3109/00952990.2016.1151523

McFarland, K., Lapish, C. C., & Kalivas, P. W. (2003). Prefrontal glutamate release into the core of the nucleus accumbens mediates cocaine-induced reinstatement of drug-seeking behavior. *Journal of Neuroscience*, *23*(8), 3531–3537.

McKay, J. R., Lynch, K. G., Coviello, D., Morrison, R., Cary, M. S., Skalina, L., & Plebani, J. (2010). Randomized trial of continuing care enhancements for cocaine-dependent patients following initial engagement. *Journal of Consulting and Clinical Psychology*, *78*(1), 111–120. https://doi.org/10.1037/a0018139

Miller, W. R., & Rollnick, S. (2012). *Motivational Interviewing: Helping People Change* (3rd ed.). New York: Guilford.

Minozzi, S., Cinquini, M., Amato, L., Davoli, M., Farrell, M. F., Pani, P. P., & Vecchi, S. (2015). Anticonvulsants for cocaine dependence. *The Cochrane Database of Systematic Reviews*, (4), CD006754. https://doi.org/10.1002/14651858.CD006754.pub4

Minozzi, S., Saulle, R., De Crescenzo, F., & Amato, L. (2016). Psychosocial interventions for psychostimulant misuse. *Cochrane Database of Systematic Reviews*, (9). https://doi.org/10.1002/14651858.CD011866.pub2.www.cochranelibrary.com

Moeller, F. G., Steinberg, J. L., Schmitz, J. M., Ma, L., Liu, S., Kjome, K. L.,... Narayana, P. A. (2010). Working memory fMRI activation in cocaine-dependent subjects: Association with treatment response. *Psychiatry Research: Neuroimaging*, *181*(3), 174–182. https://doi.org/10.1016/j.pscychresns.2009.11.003

Mon, A., Durazzo, T. C., & Meyerhoff, D. J. (2012). Glutamate, GABA, and other cortical metabolite concentrations during early abstinence from alcohol and their associations with neurocognitive changes. *Drug and Alcohol Dependence*, *125*(1–2), 27–36. https://doi.org/10.1016/j.drugalcdep.2012.03.012

Moreno-López, L., Catena, A., Fernández-Serrano, M. J., Delgado-Rico, E., Stamatakis, E. A., Pérez-García, M., & Verdejo-García, A. (2012). Trait impulsivity and prefrontal gray matter reductions in cocaine dependent individuals. *Drug and Alcohol Dependence*, *125*(3), 208–214. https://doi.org/10.1016/j.drugalcdep.2012.02.012

Moreno-López, L., Stamatakis, E. A., Fernández-Serrano, M. J., Gómez-Río, M., Rodríguez-Fernández, A., Pérez-García, M., & Verdejo-García, A. (2012). Neural correlates of the severity of cocaine, heroin, alcohol, MDMA and cannabis use in polysubstance abusers: A resting-PET brain metabolism study. *PLoS One*, 7(6). https://doi.org/10.1371/journal.pone.0039830

Mumford, J. A. (2012). A power calculation guide for FMRI studies. *Social Cognitive and Affective Neuroscience*, 7(6), 738–742. https://doi.org/10.1093/scan/nss059

Murphy, K., & Garavan, H. (2004). An empirical investigation into the number of subjects required for an event-related fMRI study. *NeuroImage*, *22*(2), 879–885. https://doi.org/10.1016/j.neuroimage.2004.02.005

Naish, K. R., Vedelago, L., MacKillop, J., & Amlung, M. (2018, August). Effects of neuromodulation on cognitive performance in individuals exhibiting addictive behaviors: A systematic review. *Drug and Alcohol Dependence*, *192*, 338–351. https://doi.org/10.1016/j.drugalcdep.2018.08.018

Nielsen, D. A., Harding, M. J., Hamon, S. C., Huang, W., & Kosten, T. R. (2012). Modifying the role of serotonergic 5-HTTLPR and TPH2 variants on disulfiram treatment of cocaine addiction: A preliminary study. *Genes, Brain, and Behavior*, *11*(8), 1001–1008. https://doi.org/10.1111/j.1601-183X.2012.00839.x

Nitsche, M. A., Seeber, A., Frommann, K., Klein, C. C., Rochford, C., Nitsche, M. S.,... Tergau, F. (2005). Modulating parameters of excitability during and after transcranial direct current stimulation of the human motor cortex. *Journal of Physiology*, *568*(1), 291–303. https://doi.org/10.1113/jphysiol.2005.092429

Noël, X., Brevers, D., & Bechara, A. (2013). A neurocognitive approach to understanding the neurobiology of addiction. *Current Opinion in Neurobiology*, *23*(4), 632–638. https://doi.org/10.1016/j.conb.2013.01.018

Nuijten, M., Blanken, P., Van den Brink, W., & Hendriks, V. (2011). Cocaine addiction treatments to improve control and reduce harm (CATCH): New pharmacological treatment options for crack-cocaine dependence in the Netherlands. *BMC Psychiatry*, *11*. https://doi.org/10.1186/1471-244X-11-135

Nutt, D. J., Lingford-Hughes, A., Erritzoe, D., & Stokes, P. R. A. (2015). The dopamine theory of addiction: 40 years of highs and lows. *Nature Reviews Neuroscience*, *16*(5), 305–312. https://doi.org/10.1038/nrn3939

Oliveto, A., McGaugh, J., Thostenson, J., Guise, J. B., Kosten, T. R., & Mancino, M. J. (2014). Effects of carvedilol in recently abstinent, cocaine dependent patients: A randomized, double blind, placebo-controlled pilot study. [Abstract]. *ACNP 53RD Anual Meeting.*

Oliveto, A., Poling, J., Mancino, M. J., Williams, D. K., Thostenson, J., Pruzinsky, R.,... Kosten, T. R. (2012). Sertraline delays relapse in recently abstinent cocaine-dependent patients with depressive symptoms. *Addiction*, *107*(1), 131–141. https://doi.org/10.1111/j.1360-0443.2011.03552.x

Pani, P. P., Trogu, E., Vacca, R., Amato, L., Vecchi, S., & Davoli, M. (2010). Disulfiram for the treatment of cocaine dependence. *Cochrane Database of Systematic Reviews*. https://doi.org/10.1002/14651858.CD007024.pub2

Pani, P. P., Trogu, E., Vecchi, S., & Amato, L. (2011). Antidepressants for cocaine dependence and problematic cocaine use. *Cochrane Database of Systematic Reviews*. https://doi.org/10.1002/14651858.cd002950.pub3

Parvaz, M. A., Moeller, S. J., d'Oleire Uquillas, F., Pflumm, A., Maloney, T., Alia-Klein, N., & Goldstein, R. Z. (2017). Prefrontal gray matter volume recovery in treatment-seeking cocaine-addicted individuals: A longitudinal study. *Addiction Biology*, *22*(5), 1391–1401. https://doi.org/10.1111/adb.12403

Petry, N. M., Alessi, S. M., Olmstead, T. A., Rash, C. J., & Zajac, K. (2017). Contingency management treatment for substance use disorders: How far has it come, and where does it need to go? *Psychology of Addictive Behaviors*, *31*(8), 897–906. https://doi.org/10.1037/adb0000287

Pettinati, H. M., Kampman, K. M., Lynch, K. G., Dundon, W. D., Mahoney, E. M., Wierzbicki, M. R., & O'Brien, C. P. (2014). A pilot trial of injectable, extended-release naltrexone for the treatment of co-occurring cocaine and alcohol dependence. *The American Journal on Addictions*, *23*(6), 591–597. https://doi.org/10.1111/j.1521-0391.2014.12146.x

Pettinati, H. M., Kampman, K. M., Lynch, K. G., Suh, J. J., Dackis, C. A., Oslin, D. W., & O'Brien, C. P. (2008). Gender differences with high-dose naltrexone in patients with co-occurring cocaine and alcohol dependence. *Journal of Substance Abuse Treatment*, *34*(4), 378–390. https://doi.org/10.1016/j.jsat.2007.05.011

Pettinati, H. M., Kampman, K. M., Lynch, K. G., Xie, H., Dackis, C., Rabinowitz, A. R., & O'Brien, C. P. (2008). A double blind, placebo-controlled trial that combines disulfiram and naltrexone for treating co-occurring cocaine and alcohol dependence. *Addictive Behaviors*, *33*(5), 651–667. https://doi.org/10.1016/j.addbeh.2007.11.011

Plebani, J. G., Lynch, K. G., Yu, Q., Pettinati, H. M., O'Brien, C. P., & Kampman, K. M. (2012). Results of an initial clinical trial of varenicline for the treatment of cocaine dependence. *Drug and Alcohol Dependence*, *121*(1–2), 163–166. https://doi.org/10.1016/j.drugalcdep.2011.08.025

Poling, J., Rounsaville, B., Gonsai, K., Severino, K., & Sofuoglu, M. (2010). The safety and efficacy of varenicline in cocaine using smokers maintained on methadone: A pilot study. *American Journal on Addictions*, *19*(5), 401–408. https://doi.org/10.1111/j.1521-0391.2010.00066.x

Potvin, S., Stavro, K., Rizkallah, É., & Pelletier, J. (2014). Cocaine and cognition: A systematic quantitative review. *Journal of Addiction Medicine*, *8*(5), 368–376. https://doi.org/10.1097/ADM.0000000000000066

Prendergast, M., Podus, D., Finney, J., Greenwell, L., & Roll, J. (2006). Contingency management for treatment of substance use disorders: A meta-analysis. *Addiction*, *101*(11), 1546–1560. https://doi.org/10.1111/j.1360-0443.2006.01581.x

Prescot, A. P., Renshaw, P. F., & Yurgelun-Todd, D. A. (2013). γ-Amino butyric acid and glutamate abnormalities in adolescent chronic marijuana smokers. *Drug and Alcohol Dependence*, *129*(3), 232–239. https://doi.org/10.1016/j.drugalcdep.2013.02.028

Prisciandaro, J. J., Joseph, J. E., Myrick, H., Mcrae-Clark, A. L., Henderson, S., Pfeifer, J., & Brady, K. T. (2014). The relationship between years of cocaine use and brain

activation to cocaine and response inhibition cues. *Addiction*, *109*(12), 2062–2070. https://doi.org/10.1111/add.12666

Raby, W. N., Dylan, B., Glass, A., Pavlikova, M., Nunes, E. V., & Kleber, H. D. (2015). Absence of stress dysregulation predicts cocaine and mood outcomes in a study of mirtazapine for depressed cocaine-dependent patients. *Drug and Alcohol Dependence*, *146*, e74. https://doi.org/10.1016/j.drugalcdep.2014.09.571

Raby, W. N., Rubin, E. A., Garawi, F., Cheng, W., Mason, E., Sanfilippo, L.,... Nunes, E. V. (2014). A randomized, double-blind, placebo-controlled trial of venlafaxine for the treatment of depressed cocaine-dependent patients. *American Journal on Addictions*, *23*(1), 68–75. https://doi.org/10.1111/j.1521-0391.2013.12065.x

Ray, S., Gohel, S., & Biswal, B. B. (2015). Altered functional connectivity strength in abstinent chronic cocaine smokers compared to healthy controls. *Brain Connectivity*, *5*(8), 476–486. https://doi.org/10.1089/brain.2014.0240

Rinck, M., Wiers, R. W., Becker, E. S., & Lindenmeyer, J. (2018). Relapse prevention in abstinent alcoholics by cognitive bias modification: Clinical effects of combining approach bias modification and attention bias modification. *Journal of Consulting and Clinical Psychology*, *86*(12), 1005–1016.

Ritz, M., Lamb, R., Goldberg, & Kuhar, M. (1987). Cocaine receptors on dopamine transporters are related to self-administration of cocaine. *Science*, *237*(4819), 1219–1223. https://doi.org/10.1126/science.2820058

Roozen, H. G., Boulogne, J. J., Van Tulder, M. W., Van Den Brink, W., De Jong, C. A. J., & Kerkhof, A. J. F. M. (2004). A systematic review of the effectiveness of the community reinforcement approach in alcohol, cocaine and opioid addiction. *Drug and Alcohol Dependence*, *74*(1), 1–13. https://doi.org/10.1016/j.drugalcdep.2003.12.006

Rypma, B., & D'Esposito, M. (2000). Isolating the neural mechanisms of age-related changes in human working memory. *Nature Neuroscience*, *3*(5), 509–515. https://doi.org/10.1038/74889

Sanna, A., Fattore, L., Badas, P., Corona, G., Cocco, V., & Diana, M. (2019). Intermittent theta burst stimulation of the prefrontal cortex in cocaine use disorder: A pilot study. *Frontiers in Neuroscience*, *13*(765). https://doi.org/10.3389/fnins.2019.00765

Schierenberg, A., van Amsterdam, J., van den Brink, W., & Goudriaan, A. E. (2012). Efficacy of contingency management for cocaine dependence treatment: A review of the evidence. *Current Drug Abuse Reviews*, *5*(4), 320–331. https://doi.org/10.2174/1874473711205040006

Schluter, R. S., Daams, J. G., van Holst, R. J., & Goudriaan, A. E. (2018). Effects of non-invasive neuromodulation on executive and other cognitive functions in addictive disorders: A systematic review. *Frontiers in Neuroscience*, *12*(642). https://doi.org/10.3389/fnins.2018.00642

Schmaal, L., Veltman, D. J., Nederveen, A., van den Brink, W., & Goudriaan, A. E. (2012). N-acetylcysteine normalizes glutamate levels in cocaine-dependent patients: A randomized crossover magnetic resonance spectroscopy study. *Neuropsychopharmacology*, *37*(9), 2143–2152. https://doi.org/10.1038/npp.2012.66

Schmitz, J. M., Green, C. E., Stotts, A. L., Lindsay, J. A., Rathnayaka, N. S., Grabowski, J., & Moeller, F. G. (2014). A two-phased screening paradigm for evaluating candidate medications for cocaine cessation or relapse prevention: Modafinil, levodopa-carbidopa, naltrexone. *Drug and Alcohol Dependence*, *136*, 100–107. https://doi.org/10.1016/j.drugalcdep.2013.12.015

Schmitz, J. M., Lindsay, J. A., Green, C. E., Herin, D. V, Stotts, A. L., & Gerard Moeller, F. (2009). High-dose naltrexone therapy for cocaine-alcohol dependence. *American Journal on Addictions*, *18*(5), 356–362. https://doi.org/10.3109/10550490903077929

Schmitz, J. M., Stotts, A. L., Rhoades, H. M., & Grabowski, J. (2001). Naltrexone and relapse prevention treatment for cocaine-dependent patients. *Addictive Behaviors*, *26*(2), 167–180. https://doi.org/10.1016/S0306-4603(00)00098-8

Schmitz, J. M., Stotts, A. L., Sayre, S. L., DeLaune, K. A., & Grabowski, J. (2004). Treatment of cocaine: Alcohol dependence with naltrexone and relapse prevention therapy. *American Journal on Addictions*, *13*(4), 333–341. https://doi.org/10.1080/10550490490480982

Schoenmakers, T. M., De Bruin, M., Lux, I. F. M., Goertz, A. G., Van Kerkhof, H. A. T., & Wiers, R. W. (2010). Clinical effectiveness of attentional bias modification training in abstinent alcoholic patients. *Drug and Alcohol Dependence*, *109*, 30–36. https://doi.org/10.1016/j.drugalcdep.2009.11.022

Schottenfeld, R. S., Chawarski, M. C., Cubells, J. F., George, T. P., Lappalainen, J., & Kosten, T. R. (2014). Randomized clinical trial of disulfiram for cocaine dependence or abuse during buprenorphine treatment. *Drug and Alcohol Dependence*, *136*(1), 36–42. https://doi.org/10.1016/j.drugalcdep.2013.12.007

Schulte, M. H. J., Cousijn, J., den Uyl, T. E., Goudriaan, A. E., van den Brink, W., Veltman, D. J.,... Wiers, R. W. (2014). Recovery of neurocognitive functions following sustained abstinence after substance dependence and implications for treatment. *Clinical Psychology Review*, *34*(7), 531–550. https://doi.org/10.1016/j.cpr.2014.08.002

Schulte, M. H. J., Kaag, A. M., Boendermaker, W. J., Brink, W. van den, Goudriaan, A. E., & Wiers, R. W. (2019, April). The effect of N-acetylcysteine and working memory training on neural mechanisms of working memory and cue reactivity in regular cocaine users. *Psychiatry Research: Neuroimaging*, *287*, 56–59. https://doi.org/10.1016/j.pscychresns.2019.03.011

Schulte, M. H. J., Kaag, A. M., Wiers, R. W., Schmaal, L., van den Brink, W., Reneman, L.,... Goudriaan, A. E. (2017, February). Prefrontal Glx and GABA concentrations and impulsivity in cigarette smokers and smoking polysubstance users. *Drug and Alcohol Dependence*, *179*, 117–123. https://doi.org/10.1016/j.drugalcdep.2017.06.025

Schulte, M. H. J., Wiers, R. W., Boendermaker, W. J., Goudriaan, A. E., van den Brink, W., van Deursen, D. S.,... Waters, A. J. (2018, March). Reprint of The effect of N-acetylcysteine and working memory training on cocaine use, craving and inhibition in regular cocaine users: Correspondence of lab assessments and ecological momentary assessment. *Addictive Behaviors*, *83*, 79–86. https://doi.org/10.1016/j.addbeh.2018.03.023

Scofield, M. D., & Kalivas, P. W. (2014). Astrocytic dysfunction and addiction. *The Neuroscientist*, *20*(6), 610–622. https://doi.org/10.1177/1073858413520347

Secades-Villa, R., García-Rodríguez, O., García-Fernández, G., Sánchez-Hervás, E., Fernandez-Hermida, J. R., & Higgins, S. T. (2011). Community reinforcement approach plus vouchers among cocaine-dependent outpatients: Twelve-month outcomes. *Psychology of Addictive Behaviors*, *25*(1), 174–179. https://doi.org/10.1037/a0021451

Selby, M. J., & Azrin, R. L. (1998). Neuropsychological functioning in drug abusers. *Drug and Alcohol Dependence*, *50*(1), 39–45. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed4&NEWS=N&AN=1998128383

Sheeran, P., Klein, W. M. P. P., & Rothman, A. J. (2017). Health behavior change: Moving from observation to intervention. *Ssrn*, *68*, 573–600. https://doi.org/10.1146/annurev-psych-010416-044007

Sherif, F. M., Tawati, A. M., Ahmed, S. S., & Sharif, S. I. (1997). Basic aspects of GABA-transmission in alcoholism, with particular reference to GABA-transaminase. *European Neuropsychopharmacology*, *7*(1), 1–7. https://doi.org/10.1016/S0924-977X(96)00383-5

Shoptaw, S., Yang, X., Rotheram-Fuller, E. J., Hsieh, Y. C. M., Kintaudi, P. C., Charuvastra, V. C., & Ling, W. (2003). Randomized placebo-controlled trial of baclofen for cocaine dependence: Preliminary effects for individuals with chronic patterns of cocaine use. *Journal of Clinical Psychiatry*, *64*(12), 1440–1448. https://doi.org/10.4088/JCP.v64n1207

Shorter, D., Lindsay, J. A., & Kosten, T. R. (2013). The alpha-1 adrenergic antagonist doxazosin for treatment of cocaine dependence: A pilot study. *Drug and Alcohol Dependence*, *131*(1–3), 66–70. https://doi.org/10.1016/j.drugalcdep.2012.11.021

Silveri, M. M., Cohen-Gilbert, J. E., Crowley, D. J., Rosso, I. M., Jensen, J. E., & Sneider, J. T. (2014). Altered anterior cingulate neurochemistry in emerging adult binge drinkers with a history of alcohol-induced blackouts. *Alcoholism: Clinical and Experimental Research*, *38*(4), 969–979. https://doi.org/10.1111/acer.12346

Sim, M. E., Kyoon Lyoo, I., Streeter, C. C., Covell, J., Sarid-Segal, O., Ciraulo, D. A.,... Renshaw, P. F. (2007). Cerebellar gray matter volume correlates with duration of cocaine use in cocaine-dependent subjects. *Neuropsychopharmacology*, *32*, 2229–2237. https://doi.org/10.1038/sj.npp.1301346

Snider, S. E., Deshpande, H. U., Lisinski, J. M., Koffarnus, M. N., LaConte, S. M., & Bickel, W. K. (2018). Working memory training improves alcohol users' episodic future thinking: A rate dependent analysis. *Biological Psychiatry Cognitive Neuroscience and Neuroimaging*, *3*, 160–167.

Sofuoglu, M., Poling, J., Babuscio, T., Gonsai, K., Severino, K., Nich, C., & Carroll, K. M. (2017). Carvedilol does not reduce cocaine use in methadone-maintained cocaine users. *Journal of Substance Abuse Treatment*, *73*, 63–69. https://doi.org/10.1016/j.jsat.2016.11.005

Spronk, D. B., van Wel, J. H. P., Ramaekers, J. G., & Verkes, R. J. (2013). Characterizing the cognitive effects of cocaine: A comprehensive review. *Neuroscience and Biobehavioral Reviews*, *37*(8), 1838–1859. https://doi.org/10.1016/j.neubiorev.2013.07.003

Staley, J. K., Gottschalk, C., Petrakis, I. L., Gueorguieva, R., O'Malley, S., Baldwin, R.,... Krystal, J. H. (2005). Cortical γ-aminobutyric acid type A-benzodiazepine receptors in recovery from alcohol dependence: Relationship to features of alcohol dependence and cigarette smoking. *Archives of General Psychiatry*, *62*(8), 877–888. https://doi.org/10.1001/archpsyc.62.8.877

Sun, W. L., & Rebec, G. V. (2006). Repeated cocaine self-administration alters processing of cocaine-related information in rat prefrontal cortex. *Journal of Neuroscience*, *26*(30), 8004–8008. https://doi.org/10.1523/JNEUROSCI.1413-06.2006

Suutama, T., Ruoppila, I., & Stig, B. (2002). Changes in cognitive functioning from 75 to 80 years of age: A 5-year follow-up in two Nordic localities. *Aging Clinical and Experimental Research*, *14*(Suppl. 3), 29–36.

Tomasi, D., Goldstein, R. Z., Telang, F., Maloney, T., Alia-Klein, N., Caparelli, E. C., & Volkow, N. D. (2007a). Thalamo-cortical dysfunction in cocaine abusers: Implications in attention and perception. *Psychiatry Research: Neuroimaging*, *155*(3), 189–201. https://doi.org/10.1016/j.pscychresns.2007.03.002

Tomasi, D., Goldstein, R. Z., Telang, F., Maloney, T., Alia-Klein, N., Caparelli, E. C., & Volkow, N. D. (2007b). Widespread disruption in brain activation patterns to a working memory task during cocaine abstinence. *Brain Research*, *1171*, 83–92. https://doi.org/10.1016/j.brainres.2007.06.102

Trifilieff, P., & Martinez, D. (2014). Imaging addiction: D 2 receptors and dopamine signaling in the striatum as biomarkers for impulsivity. *Neuropharmacology*, *76*(Part B), 498–509. https://doi.org/10.1016/j.neuropharm.2013.06.031

Vanderschuren, L. J. M. J., & Kalivas, P. W. (2000). Alterations in dopaminergic and glutamatergic transmission in the induction and expression of behavioral sensitization:

A critical review of preclinical studies. *Psychopharmacology*, *151*(2–3), 99–120. https://doi.org/10.1007/s002130000493

Verdejo-Garcia, A., Contreras-Rodríguez, O., Fonseca, F., Cuenca, A., Soriano-Mas, C., Rodriguez, J.,... De La Torre, R. (2014). Functional alteration in frontolimbic systems relevant to moral judgment in cocaine-dependent subjects. *Addiction Biology*, *19*(2), 272–281. https://doi.org/10.1111/j.1369-1600.2012.00472.x

Volkow, N. D., Fowler, J. S., Wang, G. -J, Hitzemann, R., Logan, J., Schlyer, D. J.,... Wolf, A. P. (1993). Decreased dopamine D2 receptor availability is associated with reduced frontal metabolism in cocaine abusers. *Synapse*, *14*(2), 169–177. https://doi.org/10.1002/syn.890140210

Volkow, N. D., Fowler, J. S., & Wang, G. J. (2004). The addicted human brain viewed in the light of imaging studies: Brain circuits and treatment strategies. *Neuropharmacology*, *47*(Suppl. 1), 3–13. https://doi.org/10.1016/j.neuropharm.2004.07.019

Volkow, N. D., Koob, G. F., & McLellan, A. T. (2016). Neurobiologic advances from the brain disease model of addiction. *New England Journal of Medicine*, *374*(4), 363–371. https://doi.org/10.1056/NEJMra1511480

Volkow, N. D., Wang, G., Fowler, J. S., & Tomasi, D. (2012). Addiction circuitry in the human brain. *Annual Review of Pharmacology and Toxicology*, *52*, 321–326. https://doi.org/10.1146/annurev-pharmtox-010611-134625

Volkow, N. D., Wang, G. J., Fowler, J. S., Tomasi, D., & Telang, F. (2011). Addiction: Beyond dopamine reward circuitry. *Proceedings of the National Academy of Sciences of the United States of America*, *108*(37), 15037–15042. https://doi.org/10.1073/pnas.1010654108

Volkow, N. D., Wang, G. J., Maynard, L., Fowler, J. S., Jayne, B., Telang, F.,... Pappas, N. (2002). Effects of alcohol detoxification on dopamine D2 receptors in alcoholics: A preliminary study. *Psychiatry Research: Neuroimaging*, *116*(3), 163–172. https://doi.org/10.1016/S0925-4927(02)00087-2

Walsh, S. L., Middleton, L. S., Wong, C. J., Nuzzo, P. A., Campbell, C. L., Rush, C. R., & Lofwall, M. R. (2013). Atomoxetine does not alter cocaine use in cocaine dependent individuals: A double blind randomized trial. *Drug and Alcohol Dependence*, *130*(1–3), 150–157. https://doi.org/10.1016/j.drugalcdep.2012.10.024

Wanmaker, S., Leijdesdorff, S. M. J., Geraerts, E., van de Wetering, B. J. M., Renkema, P. J., & Franken, I. H. A. (2018). The efficacy of a working memory training in substance use patients: A randomized double-blind placebo-controlled clinical trial. *Journal of Clinical and Experimental Neuropsychology*, *40*(5), 473–486. https://doi.org/10.1080/13803395.2017.1372367

Wiers, C. E., Ludwig, V. U., Gladwin, T. E., Park, S. Q., Heinz, A., Wiers, R. W.,... Bermpohl, F. (2015). Effects of cognitive bias modification training on neural signatures of alcohol approach tendencies in male alcohol-dependent patients. *Addiction Biology*, *20*(5), 990–999. https://doi.org/10.1111/adb.12221

Wiers, R. W. (2018). Cognitive training in addiction: Does it have clinical potential? *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, *3*(2). https://doi.org/10.1016/j.bpsc.2017.12.008

Wiers, R. W., Boffo, M., & Field, M. (2018). What's in a trial? On the importance of distinguishing between experimental lab studies and randomized controlled trials: The case of cognitive bias modification and alcohol use disorders. *Journal of Studies on Alcohol and Drugs*, *79*(3), 333–343. https://doi.org/10.15288/jsad.2018.79.333

Wiers, R. W., Eberl, C., Rinck, M., Becker, E. S., & Lindenmeyer, J. (2011). Retraining automatic action tendencies changes alcoholic patients' approach bias for alcohol

and improves treatment outcome. *Psychological Science*, *22*(4), 490–497. https://doi.org/10.1177/0956797611400615

Wiers, R. W., Rinck, M., Kordts, R., Houben, K., & Strack, F. (2010). Retraining automatic action-tendencies to approach alcohol in hazardous drinkers. *Addiction*, *105*(2), 279–287. https://doi.org/10.1111/j.1360-0443.2009.02775.x

Winhusen, T. M., Kropp, F., Lindblad, R., Douaihy, A., Haynes, L., Hodgkins, C.,... Brigham, G. S. (2014). Multisite, randomized, double-blind, placebo-controlled pilot clinical trial to evaluate the efficacy of buspirone as a relapse-prevention treatment for cocaine dependence. *Journal of Clinical Psychiatry*, *75*(7), 757–764. https://doi.org/10.4088/JCP.13m08862

Yang, W., He, H., Pan, Y., Duan, F., Zhao, D., Hu, B.,... Liu, W. (2017). Cocaine withdrawal reduces gamma-aminobutyric acid-ergic transmission and gephyrin expression at medial prefrontal cortex in cocaine-conditioned place-preference rats, which shows increased cocaine seeking. *European Addiction Research*, *23*(1), 28–36. https://doi.org/10.1159/000452657

Yin, H. H., & Knowlton, B. J. (2006). The role of the basal ganglia in habit formation. *Nature Reviews Neuroscience*, *7*(6), 464–476. https://doi.org/10.1038/nrn1919

Ziaee, S. S., Fadardi, J. S., Cox, W. M., & Yazdi, S. A. A. (2016). Effects of attention control training on drug abusers' attentional bias and treatment outcome. *Journal of Consulting and Clinical Psychology*, *84*(10), 861.

Zilverstand, A., Parvaz, M. A., Moeller, S. J., & Goldstein, R. Z. (2016). Cognitive interventions for addiction medicine: Understanding the underlying neurobiological mechanisms. In *Progress in Brain Research* (1st ed., Vol. 224). https://doi.org/10.1016/bs.pbr.2015.07.019