

Neuroimaging the Effectiveness of Substance Use Disorder Treatments

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Received: 19 January 2016 / Accepted: 26 April 2016 / Published online: 16 May 2016
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Abstract Neuroimaging techniques to measure the function and biochemistry of the human brain such as positron emission tomography (PET), proton magnetic resonance spectroscopy (¹H MRS), and functional magnetic resonance imaging (fMRI), are powerful tools for assessing neurobiological mechanisms underlying the response to treatments in substance use disorders. Here, we review the neuroimaging literature on pharmacological and behavioral treatment in substance use disorder. We focus on neural effects of medications that reduce craving (e.g., naltrexone, bupropion hydrochloride, baclofen, methadone, varenicline) and that improve cognitive control (e.g., modafinil, *N*-acetylcysteine), of behavioral treatments for substance use disorders (e.g., cognitive bias modification training, virtual reality, motivational interventions) and neuromodulatory interventions such as neurofeedback and transcranial magnetic stimulation. A consistent finding for the effectiveness of therapeutic interventions identifies the improvement of executive control networks and the dampening of limbic activation, highlighting their values as targets for therapeutic interventions in substance use disorders.

Keywords Addiction · MRI · Neuroimaging · PET · Substance use disorder · Treatment

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Introduction

Addiction is a disease that cycles through steps of intoxication, craving, bingeing, and withdrawal and is mainly characterized by the continuation of drug taking despite awareness of

negative consequences (Goldstein and Volkow 2002). Differing models have been presented to account for the shift from controlled use to the cycle of addiction, and to investigate why this only happens in certain individuals. That is, it has been theorized that addiction is a deficit in bottom-up motivational processes (i.e., increased motivational reactions to drugs and drug cues) as well as a lack of top-down cognitive control over prepotent responses, which lead to increasing drug taking (Bechara 2005; Volkow et al. 2003). At a neural level, drugs of abuse directly produce rewarding effects from increased dopamine release in the mesolimbic pathway (Nestler 2001) and the subsequent stimulation of dopamine D1 and D2 receptors in the nucleus accumbens (NAc) (Volkow and Morales 2015). This pathway includes dopaminergic neurons from the ventral tegmental area to the NAc, which is located in the ventral striatum, and which fire in response to rewarding cues (Koob 1992). In addition, other neurotransmitters, such as glutamate and GABA, are indirectly affected by different drugs, further altering the brain's reward pathway (Parvaz et al. 2011). Importantly, prefrontal cortical (PFC) areas are less active in substance users, a decrease associated with impaired self-control (Goldstein and Volkow 2011; Volkow et al. 1991, 1992, 1988).

Treatments currently available for addiction include both pharmacological interventions as well as behavioral methods. With the variety of brain regions available as targets from treatment, most of these pharmacological interventions aim to accomplish three things: reduce drug craving, increase cognitive control and/or decrease the enhanced stress reactivity and negative moods. Medications that are aimed at attenuating the drug cravings include naltrexone, methadone, varenicline, bupropion, baclofen, amisulpride, and aripiprazole (Konova et al. 2013; Young et al. 2014; Hermann et al. 2006; Myrick et al. 2010). Treatments that aim to increase cognitive control in order to normalize performance include N-acetylcysteine and modafinil (Schmaal et al. 2012; Schmaal et al. 2014). Some of these medications, specifically varenicline and modafinil, were shown to both attenuate craving and improve cognitive performance (Wheelock et al. 2014; Goudriaan et al. 2013). Additionally, antidepressants are used to improve negative moods which are associated with addiction and which significantly contribute to relapse. Behavioral approaches to abstinence include motivation enhancement, cognitive bias modification and virtual reality trainings (Wiers et al. 2015b; Son et al. 2015). Another recently investigated treatment includes the use of real time fMRI neurofeedback where participants are shown the activation of certain regions and asked to manipulate the activation in a certain direction (Li et al. 2013). The use of neuroimaging techniques in capturing treatment effects may provide insight into neurobiological mechanisms of the treatment in the pathology of addiction, which is a unique benefit over behavioral outcome measures of

treatment. In addition, neuroimaging may be more sensitive than behavioral measures in detecting effects of treatment (Linden 2012).

After introducing neuroimaging techniques, we will review the literature on pharmacological treatments effects, which we separated for treatments that target the increase of control versus those that target attenuation of limbic activation to overcome craving and stress reactivity. We then summarize behavioral interventions including cognitive bias modification training, virtual reality, cognitive-behavioral therapy, and motivational interventions. Lastly, we present information on the use of neuroimaging as a treatment method, covering recent studies investigating the benefits of neurofeedback and transcranial magnetic stimulation in addiction. For this review, we searched PubMed for clinical studies done in drug-dependent populations that investigated treatment efficacy, with neuroimaging available for the post-treatment condition. Various studies have investigated neuroimaging mechanisms as predictors of relapse (e.g., Mann et al. 2014) or used neuroimaging methods as the treatment itself assessing its efficacy with behavioral measures (e.g., Alba-Ferrara et al. 2014; Batista et al. 2015; Gorelick et al. 2014). However, this review only concentrates on studies that used neuroimaging to evaluate treatment efficacy in drug addiction.

Neuroimaging Techniques

Over the last two decades neuroimaging techniques have been used to study neural effects of pharmacological and behavioral treatment in substance use disorders. We discuss studies using Positron Emission Tomography (PET), a technique that utilizes positron-emitting compounds, known as radiotracers, to measure various physiological functions. The radioisotope decays over time releasing positrons that collide with electrons. These collisions create gamma rays, which are recorded by the PET scanner, providing information on the uptake of the tracer by location and over time (Michaelides et al. 2012). The radiotracers that are utilized can include ones that mimic endogenous compounds, such as [^{18}F]-flouro-2-deoxyglucose (FDG) which allows for the measurement of glucose metabolism, and others that bind to specific receptors in the brain, such as [^{11}C]raclopride, which binds primarily to the D2 and D3 receptors and allows for the study of the dopamine pathway (Thanos et al. 2008). Studies utilizing PET have been used to study the effects of different substances of abuse (Heinz et al. 2004; Volkow et al. 2009).

A second technique that has been used for the study of treatment effects is proton magnetic resonance spectroscopy (^1H MRS). MRS allows for the measurement of brain metabolites, with the differing levels signaling a variety of potential changes (Chang et al. 2013). The measurement of endogenous compounds, such as glutamate, myoinositol and N-acetyl

aspartate (NAA), allows for clinical applications in investigating psychiatric disorders, including substance dependence (Lyoo and Renshaw 2002).

Third, we discuss functional magnetic resonance imaging (fMRI) in combination with a drug cue reactivity task, the most frequently used imaging technique to study treatment effects. Participants are shown drug-related cues (often pictorial) that are known to induce craving and reward-related brain activation patterns inside the fMRI. The fMRI scanner captures the blood oxygenation level-dependent (BOLD) response, a measure of brain activation (e.g., Courtney et al. 2016). Key brain areas that are activated in drug-users in cue reactivity paradigms are the NAc, medial PFC (mPFC), basolateral amygdala and other PFC areas (for reviews, see Courtney et al. 2016; Schacht et al. 2013). The NAc, mPFC and amygdala have been associated with bottom-up motivational aspects of cue reactivity (Barros-Loscertales et al. 2011), reward processing (Koob and Volkow 2010), subjective drug craving and relapse (Beck et al. 2012; Sinha 2012; Volkow et al. 2004), whereas the dorsolateral PFC (dlPFC) is involved in top-down control over motivational reactions to drug cues in addiction (Baler and Volkow 2006; Bechara 2005; Sinha 2012). Since there is evidence that PFC regions are hypoactive in drug-dependent individuals at baseline when not intoxicated and when performing cognitive tasks (e.g., Volkow et al. 2004; Goldstein and Volkow 2002, 2011), it has been proposed that drug-cue induced activation measured with functional MRI may correspond to an immediate effort to regulate limbic reward responses (Goldstein and Volkow 2011; Hayashi et al. 2013; Lubman et al. 2004). Interestingly, however, PET studies measuring changes in regional brain glucose metabolism (marker of brain function) to cues show reductions in frontal brain areas (i.e., PFC and ACC) in female cocaine abusers following the exposure to cocaine cues (Volkow et al. 2011). This apparent discrepancy in results is likely to reflect the different temporal resolution for PET metabolic measures (30 min) and fMRI (2–5 min) and are consistent with impairment in control capacity following exposure to cues for which females appear to be more vulnerable than males (Volkow et al. 2011). Various studies have focused on cue reactivity and relapse (recently reviewed in Courtney et al. 2016). For example, alcohol cue-induced activation in the mPFC was elevated in alcoholics versus controls (Beck et al. 2012). A recent meta-analysis by Konova et al. (2013) on targets for addiction therapies emphasized the relevance of the ventral striatum (VS), inferior frontal gyrus (IFG), orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), middle frontal gyrus, (MFG) and precuneus in pharmacological and behavioral interventions.

In contrast to task-based fMRI, resting state MRI (rsMRI) measures the spontaneous activity across different regions during a resting scan. The common activation of certain regions is referred to as the functional connectivity, providing an

organizational overview of the connections between different brain regions (Lu and Stein 2014). Resting state functional connectivity is altered in numerous psychiatric and neurological disorders, including in addiction (Ma et al. 2010; Meunier et al. 2012; Tomasi et al. 2010). In particular addicted individuals show decreased functional connectivity in executive control networks, which are responsible for self-regulation and enhanced connectivity in the default mode network (DMN), which is responsible for interoceptive awareness (Pariyadath et al. 2016).

Last, electroencephalography (EEG) is a noninvasive technique that involves the measurement of electrical signals from the brain (Stewart and May 2016). Endogenous event-related potentials (ERPs) are signals that are temporally linked to specific events. A frequently used component of ERPs is the P300, which is an ERP deflection seen between 300 and 600 ms after the initiation of an intervention (Fabiani et al. 2000). P300 has been recognized as a phenotypic marker for drug addiction, as it was altered in individuals with substance use disorder (SUD) on several tasks including reward processing (Goldstein et al. 2008; Parvaz et al. 2012), and was predictive of relapse (reviewed in Stewart and May 2016). As such, the P300 has been used as a potential target for capturing treatment effects of SUDs (Stotts et al. 2006).

Neural Effects of Pharmacological Interventions

Pharmacological Treatment Studies That aim to Reduce Drug Craving

Individuals who are addicted to a drug often report strong cravings in response to drug-related cues or to negative emotions (i.e. stress, boredom, depression). However, self-reported craving is a subjective measure. Researchers are using neuroimaging to objectively quantify brain activation that is the result of drug cues. Neuroimaging can be used to evaluate the treatment utility of different pharmacological agents. Several studies involving different drugs of abuse, including alcohol, nicotine and cocaine, have shown consistent brain areas of increased activation in drug abusers when they view cues of their drug. In addition, pharmacological agents that block dopamine release can erase the increased activation of these cue-craving areas (Courtney et al. 2016).

Naltrexone, an opioid antagonist, is one of the medications currently approved to treat alcohol as well as opioid use disorders. Naltrexone blocks the NAc-activated release of dopamine in response to alcohol (Gonzales and Weiss 1998) and it is expected that serotonin 3 antagonists, such as ondansetron, might have a similar action (Grant 1995; Johnson et al. 2000). Previous behavioral studies showed that these medications, in combination with psychotherapy, reduced craving, reduced number of drinks per drinking day, and increased time to

relapse (Anton et al. 1999; Johnson et al. 2000). A study by Weerts et al. (2008) utilized PET to study the availability of two of the opioid receptor (OR) subtypes, μ - and δ -OR, before and during a standard naltrexone treatment using [^{11}C]carfentanil and [^{11}C]methylnaltrindole, respectively. Alcohol dependent subjects scanned during treatment (after their fourth dose) showed complete inhibition of the μ -OR, which was hypothesized to be responsible for the craving reduction seen with the medication. The δ -OR, however, was only partially inhibited by naltrexone. The degree of inhibition was highly variable between subjects and correlated with blood levels of naltrexone. This variability in δ -OR inhibition may explain the differences in treatment success with this medication (Weerts et al. 2008). In an additional study, Myrick et al. (2008) measured brain activation in craving areas after alcohol dependent subjects were given two acute pharmacological treatments: naltrexone and ondansetron hydrochloride. Subjects treated with naltrexone showed reduced VS activation compared to placebo-treated controls. However, subjects treated with only ondansetron showed a non-significant reduction in VS activation compared to placebo-treated controls. The acute combination of naltrexone and ondansetron not only significantly reduced subjective craving in alcoholics, but also decreased VS cue-related activation during fMRI as compared to placebo-treated alcoholics. In addition, subjective craving significantly correlated with VS activation (Myrick et al. 2008). These results provide evidence supporting the effectiveness of an acute combination treatment for reducing alcohol-related cravings in alcohol use disorders (AUD).

Studies have also been done with an extended-release naltrexone (XRNTX) injection, which improves compliance over that of oral medication. Drug cue reactivity was evaluated before and between 10 and 14 days after a single XRNTX injection, in both heroin and alcohol dependent patients (Langleben et al. 2014; Lukas et al. 2013). Both of the study populations reported decreases in drug craving. In the heroin dependent subjects, the post treatment scans showed decreased activation in the amygdala, caudate, precentral gyrus, and cuneus, which are related to drug conditioning, self-regulation and craving. Increased activation was seen in MFG and precuneus, which are involved in “self-referential processes”. These changes suggest that the XRNTX regulates the drug cue responses by increasing inhibitory control (Langleben et al. 2014). The alcohol-dependent patients in the other study were exposed to both visual and olfactory cues. The XRNTX decreased activation in cue related regions known to be involved in cognition, reward processing, and memory, altering the responsiveness to drug cues (Lukas et al. 2013). XRNTX has been shown to have similar results as oral naltrexone as far as treatment potential, but with the added advantage of facilitating treatment compliance.

Two antipsychotics, amisulpride and aripiprazole, have been considered for addiction treatment due to their

dopamine-D2/D3 receptor blocking effects. The utility of these treatments has also been studied through the imaging of cue-induced craving. An fMRI study by Hermann et al. (2006) looked at amisulpride, a dopamine D2/D3 receptor antagonist, and reported reduced activation in the right thalamus during alcohol cues compared to placebo. Further, Myrick et al. (2010) found that in alcoholics, aripiprazole reduced activation in VS compared to placebo. For the alcoholics given aripiprazole, right VS activity and heavy drinking during the 14-day medication period significantly decreased compared to alcoholics given placebo. However, there were no significant differences in subjective cravings between aripiprazole and placebo (Myrick et al. 2010). In another study, the combination of aripiprazole and escitalopram given to alcoholics with co-morbid major depressive disorder increases activation of the left ACC on a cue reactivity task compared to escitalopram alone (Han et al. 2013). Increases in left ACC activation were negatively associated with subjective craving. Because the ACC is a mediator of depressive symptoms, the authors suggest that the negative association may be due to the co-morbidity of depression in these subjects.

Baclofen has also been proposed as a treatment for addiction. One study reported that cocaine-dependent individuals given baclofen had reduced activation of VS, ventral pallidum, amygdala, midbrain, and OFC in response to cocaine cues compared to cocaine-dependent individuals given a placebo (Young et al. 2014). This study used subliminal cues—the cocaine stimuli were presented for 33 ms only and were followed by longer masking stimuli to prevent visual processing of the cocaine cues. The brain areas where activation decreased after treatment (i.e., ventral pallidum, amygdala, and OFC), were previously reported to be activated during subliminal cue tasks in drug abusers at baseline before treatment (Childress et al. 2008). This study reveals a potential target for evaluating pharmacotherapies by utilizing subliminal cues to test unconscious drug cue processing.

Varenicline is a partial agonist to nicotinic acetylcholine receptors that is used as a smoking cessation medication. It has an indirect action on mesolimbic dopamine (DA) release, reducing the rewarding effects of nicotine. Functional neuroimaging studies in smokers revealed reduced activation of the VS and medial OFC, and increased activation of the ACC, lateral OFC, posterior cingulate cortex (PCC), superior frontal gyrus (SFG), and dorsolateral PFC (dlPFC) (Franklin et al. 2011). The combination of varenicline and naltrexone reduced activation in bilateral ACC compared to a placebo in heavy drinking smokers (Ray et al. 2015). Varenicline also reduced cue-induced OFC activation bilaterally in alcohol-dependent individuals, although it had no effect on reducing drinking behavior (Schacht et al. 2014). A preliminary study by Wheelock et al. (2014) utilized both ^1H -MRS and fMRI with the Stroop task, a color-naming paradigm that can be used to

measure cognitive control, on smokers before and after treatment with varenicline. MRS showed a reduction in glutamine and glutamate levels in the ACC after treatment, with the baseline levels associated with craving and nicotine dependence. Decreases in BOLD signal in fMRI occurred in the rostral ACC, medial OFC, and precuneus/PCC. Functional connectivity analysis revealed changes between the dorsal ACC and the DMN, specifically in the rostral ACC and PCC (Wheelock et al. 2014) suggesting that varenicline exerts its actions through changes in glutamine/glutamate decrease and alterations of the functional connectivity of the dorsal ACC and the DMN.

Another smoking cessation medication, bupropion hydrochloride modulates DA and norepinephrine levels by blocking reuptake transporters. This action may reduce nicotine reward and withdrawal (Foley et al. 2006). A study using PET-FDG in the presence of cigarette-related cues showed decreased glucose metabolism in the perigenual and ventral ACC in bupropion-treated smokers compared to non-treated smokers (Brody et al. 2004). An fMRI study by Culbertson et al. (2011) reported reduced self-reported craving and cue-activation in limbic and PFC areas in bupropion-treated smokers. Reduced activation in bilateral medial OFC and left ACC correlated with self-reported craving (Culbertson et al. 2011). There was also decreased cue-induced activation in left VS in bupropion-treated subjects, consistent with the studies of other craving-reducing medications (e.g., Courtney et al. 2016).

Methadone, an opioid receptor agonist, is effective in the treatment of opioid use disorder and is the most widely used pharmacological treatment for heroin addiction (Wang et al. 2014). Methadone prevents withdrawal symptoms and reduces craving upon cessation of heroin use (Shi et al. 2008). Multiple studies have utilized fMRI and a heroin-related cue paradigm to investigate the effects of methadone maintenance treatment (MMT). A study by Wang et al. (2014) investigated differences in brain activations in heroin users with different treatment durations of MMT (less than a year vs treatment for at least 2 years) and also compared them with healthy controls. MMT patients, regardless of treatment length, had increased activity in both the mesolimbic reward and the visuospatial attention circuits compared to controls, consistent with results from a previous study (Wang et al. 2011). The MMT patients with longer treatments exhibited a reduction in activity compared to patients with shorter treatment lengths in the bilateral caudate, supporting the idea that long term MMT decreases the risk of relapse in heroin dependent patients by reducing the activation in reward-related regions (Wang et al. 2014). Further, Tabatabaei-Jafari et al. (2014) studied heroin users undergoing MMT, heroin users undergoing opiate abstinence, and healthy volunteers. Their results suggest that while both opiate abstinence and MMT both decrease craving, the craving reductions seemed to be caused by different patterns of activations. Although a number of regions were activated in

both conditions, opiate abstinence led to an additional increase in activation in ACC and IFG, suggesting that these regions are involved in drug processing and aversion. MMT patients had higher activation in cerebellum and right lingual gyrus, implicating this enhanced activation as a medication effects (Tabatabaei-Jafari et al. 2014). In a study by Langleben et al. (2008), heroin dependent patients on MMT were scanned before and after their daily methadone dose. At the post-dose scanning sessions, MMT patients had increased activation to drug-related cues in OFC, insula, and left hippocampal complex. Pre-dose scans showed similar significant responses in these same regions, to an even greater degree, as well as increased response in ACC and the amygdala. This difference between the pre-dose and post-dose conditions suggests that MMT patients are most vulnerable in the time just before their dose (Langleben et al. 2008). These increases in activation persist even though the self-reported craving scores are not significantly different between any of the groups, a result also replicated by other studies (Tabatabaei-Jafari et al. 2014; Wang et al. 2011; Wang et al. 2014).

Resting state functional connectivity (RFC) has also been used to study MMT's effects. Ma et al. (2010) used fMRI to investigate RFC changes in chronic heroin users (majority undergoing treatment with methadone) compared to healthy controls. The heroin users had increased connectivity in regions related to reward and craving including between NAcc and ACC, NAcc and OFC, and amygdala and OFC. Reduced connectivity between the PFC and both the ACC and OFC suggests impaired cognitive control (Ma et al. 2010). The combination of increased activation in reward and craving related regions with decreased cognitive restraint provides evidence of the shifts in functional connectivity that occur in chronic heroin users, even when undergoing methadone treatment or controlled heroin-maintenance.

Studies have also utilized PET and MRS to learn more about other aspects of MMT. It was proposed that chronic opiates disrupt dopamine transporters (DAT) in brain and that methadone counteracts this, accounting for the anti-craving effects. To test this hypothesis, a study used PET and [^{11}C]-2 β -carbomethoxy-3 β -aryltropane ([^{11}C]CFT), a DAT radioligand, to compare DAT between abstinent heroin abusers on methadone treatment, heroin abusers in prolonged abstinence (no methadone), and controls (Shi et al. 2008). The results revealed that subjects on MMT had lower than normal DAT in caudate and putamen. Abstinent (with or without methadone) heroin users had even lower DAT in caudate when compared to controls. The lower DAT in the caudate was associated with subjective anxiety only in MMT subjects. Further, MMT subjects had lower DAT levels in the putamen compared to the prolonged abstinence subjects, illustrating a restoration of DAT levels for the subjects who were cleared from all types of opioids, both heroin and methadone. This study concluded that long-term heroin use (presumably also

methadone) can reduce DAT in striatum. Although methadone does reduce craving for heroin, sustained abstinence from the opioids in general can facilitate DAT restoration to a greater extent (Shi et al. 2008). In another PET study using FDG, Galynker et al. (2007) studied three similar groups: opiate-abstinent former opiate-dependent patients, MMT patients, and controls. While both experimental groups showed atypical relative activity patterns in similar regions, the opiate-abstinent group showed decreased activity in a greater number of regions including the bilateral perigenual ACC, left mid-cingulate, left insula, and right SFG. Some of these regions, specifically the left perigenual ACC and mid-cingulate cortex, play an important role in mood processing. These findings suggest that MMT may normalize activity in mood processing regions, even in non-depressed patients, decreasing the probability of relapse (Galynker et al. 2007). A ^1H MRS study measured glutamate levels in the ACC in heroin-dependent subjects, at both high (100 mg/day) and low (10–25 mg/day) dose MMT. Subjects first received a high dose and were then tapered off to a lower dose. The shift from high to low MMT led to an increase in ACC glutamate in the heroin-dependent subjects. This shift in glutamate levels, which approached control levels, suggests that the lower dose MMT might help normalize glutamate levels in ACC (Greenwald et al. 2015).

A study in patients undergoing protracted heroin-maintenance also showed increased RFC of the putamen, which was associated with the reported effects of the drug (Schmidt et al. 2015a). Another study by the same group investigated changes in connectivity with fMRI in response to fearful faces to test differences in stress reactivity. Heroin-maintained participants increased amygdala connectivity in response to the task after placebo administration, whereas the connectivity after heroin administration was similar to that of controls (Schmidt et al. 2015b). The combination of increased activation in reward and craving related regions with decreased cognitive restraint provides evidence of the shifts in functional connectivity that occur in chronic heroin users, even during MMT or controlled heroin-maintenance. A structural imaging study also on patients undergoing heroin-maintenance treatment revealed decreased gray matter volume in frontal areas. Decreased gray matter volume was associated with lower perfusion, an index of cerebral blood flow (CBF), which serves as marker of brain function. Reduced frontal CBF is consistent with impaired executive function in heroin addicted subjects (Denier et al. 2013).

Pharmacological Treatment Studies That aim to Increase Cognitive Control

Modafinil, *N*-acetylcysteine, methylphenidate and amphetamine and others are cognition enhancing drugs that aim to boost control processes in SUD. Modafinil is a mild stimulant

that is marketed for the treatment of narcolepsy, to inhibit bouts of daytime drowsiness. Modafinil modulates DA signaling in the human brain (Volkow et al. 2009). In a study by Ghahremani et al. (2011), a learning task performed in the fMRI was used to evaluate the effect of modafinil in methamphetamine (METH) dependent patients. METH dependent patients and healthy controls underwent two scanning sessions, with modafinil or placebo in random order. Modafinil increased performance during the task in METH group, reaching levels similar to those seen in controls. Activation in ACC and bilateral insula/ventrolateral PFC also increased after modafinil administration, possibly reflecting the increased activation of these regions in the learning and cognitive processes activated during the MRI task (Ghahremani et al. 2011). The normalization of performance after one dose of modafinil supports its use as a therapy for METH dependence.

In AUD, modafinil improves impulsive decision making on a delay discounting task measured using an fMRI paradigm (Schmaal et al. 2014). Alcohol dependent (AD) patients and healthy controls underwent two fMRI sessions, either with a placebo or modafinil administration. For the AD patients, activation in frontoparietal regions was enhanced whereas ventromedial PFC activation was reduced after modafinil administration. Modafinil also enhanced functional connectivity between the SFG and VS and this was associated with behavioral improvement in task performance (Schmaal et al. 2014). This study supports the suggestion that modafinil enhances coupling of PFC control regions and reward areas thereby decreasing impulsive decision-making.

In another publication, Schmaal et al. (2013b) explored whether modafinil could play a role in enhancing response inhibition, which is typically compromised in AUD. Similar to their previous study, AD patients and healthy controls completed two fMRI sessions with either a placebo or modafinil. Response inhibition performance was measured from stop signal reaction times during a stop signal task performed during the scans. For AD subjects, modafinil enhanced response inhibition only for those subjects whose inhibition was already significantly compromised at baseline. In contrast, modafinil actually worsened performance for those AD patients with more regular response inhibition at baseline. For healthy controls with adept baseline response inhibition abilities, the drug caused no significant modulation in the task across the two conditions. Modafinil did, however, improve response inhibition for healthy controls with a more deficient baseline measurements. For the AD patients who improved their response inhibition as a result of modafinil, a larger activation of the thalamus and supplementary motor area was observed in parallel with diminished communication between the thalamus and the primary motor cortex (Schmaal et al. 2013a). This indicates that modafinil can improve response inhibition for AD patients, although baseline measurements

of the ability should be taken into consideration before relying on modafinil as a means of treatment. A follow up study investigated the effect the dose of modafinil had on functional connectivity in the DMN in AD patients and controls as they completed the Stroop task. Modafinil increased functional coupling between DMN and both the salience network and the central executive network in AD patients. These two networks are involved in cognitive tasks, with the increased association providing a potential mechanism by which modafinil improved cognitive performance (Schmaal et al. 2013a).

Modafinil is also used for reducing craving in cocaine addicts upon exposure to drug-related cues. A study by Goudriaan et al. (2013) sought to investigate the modulations in cerebral activity, if any, that are present in response to substance-related cues under the influence of modafinil. Cocaine-dependent patients and healthy controls participated in two fMRI scans separated by 1 week, receiving either a placebo or modafinil. While in the scanner observing cocaine-related cues, the cocaine-dependent individuals exhibited large activations of the “MFG, ACC, angular gyrus, left OFC, and ventral tegmental area” during the baseline condition compared to controls. There were no activation differences for these reward and motivation centers between groups with treated with modafinil. In addition, in cocaine-dependent subjects, there was less activation in the ventral tegmental area and more activation in the right ACC and putamen with modafinil than with placebo. This variation did not occur in healthy controls. The overall findings indicate that modafinil plays a role in dampening the activity of motivational and subjective craving centers of the brain for cocaine-dependent individuals upon exposure to cocaine-related stimuli (Goudriaan et al. 2013)

In a placebo-controlled trial by Volkow et al. (2009), Fig. 1, the effects of oral modafinil on DA release and DAT occupancy were measured in healthy subjects using PET with [¹¹C]raclopride and [¹¹C]cocaine, respectively. PET results revealed that DA was significantly increased in the VS after modafinil administration due to the ability of modafinil to block DAT. Moreover modafinil decreases the binding of [¹¹C]cocaine which is evidence that both modafinil and cocaine bind to the same site. The results of this study suggest that modafinil might hold some abuse potential due to the DA increases in VS following the blockade of DAT, similar to other drugs of abuse such as cocaine (Volkow et al. 2009). However modafinil is much less potent than cocaine in its ability to block DAT, which is likely to explain its low abuse potential. A recent study with [¹¹C]-N-(3-iodopro-2E-enyl)-2beta-carbomethoxy-3beta-(4'-methylphenyl) nortropine ([¹¹C]-PE2I), a DAT radiotracer, measured DAT availability in cocaine-dependent subjects administered either modafinil or placebo who underwent two PET scans during a 17-day period. While the modafinil treated patients showed a

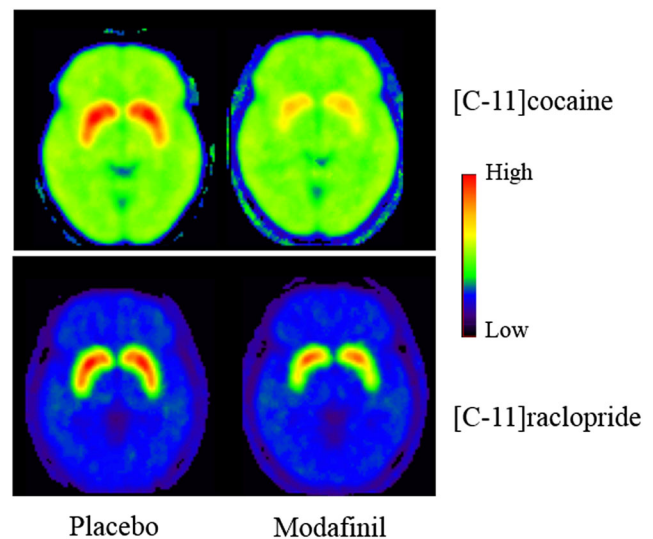


Fig 1 Adapted from Volkow et al. (2009). Modafinil blocks DAT ([¹¹C]cocaine) and increases dopamine release ([¹¹C]raclopride)

significant decrease in binding of the tracer, the medication failed to show greater abstinence levels than the placebo. This argues against the use of modafinil to treat cocaine abuse (Karila et al. 2016).

Addictive disorders have been associated with disruptions in the homeostasis of glutamate, an excitatory neurotransmitter in the brain, which may underlie vulnerability to drug-seeking behavior, such as craving and impulsivity (see Reissner and Kalivas (2010) for a review). For example, studies using ¹H MRS found decreased levels of glutamate in the rostral ACC in patients with cocaine dependence (Yang et al. 2009), whereas increased levels of glutamate were found in the putamen of monkeys on long-term cocaine treatment (Liu et al. 2011). The administration of the drug *N*-acetylcysteine normalized glutamate levels in cocaine-treated rats (Baker et al. 2003). Whether this result is consistent in drug dependent humans was the focus of a study by Schmaal et al. (2012) that recruited cocaine dependent individuals as well as healthy controls to undergo two ¹H MRS scans, with each individual receiving either no drug or *N*-acetylcysteine 1 h before the scan. Study results confirmed that baseline glutamate levels in the dorsal ACC of cocaine dependent individuals are significantly higher than in healthy controls. Following *N*-acetylcysteine, however, a significant reduction of dorsal ACC glutamate was observed in cocaine dependent subjects while no change was seen in the brains of healthy controls. These results imply that *N*-acetylcysteine is responsible for the normalization of abnormal glutamate levels seen in cocaine dependent individuals (Schmaal et al. 2012) and suggests an alternative treatment method for cocaine dependent individuals. Whether *N*-acetylcysteine is effective for reducing impulsivity and craving for cocaine-dependent individuals, as well as potentially benefiting abusers of other drugs, requires additional investigation.

Neural Effects of Behavioral Interventions

Cognitive Behavioral Therapy

Cognitive Behavioral Therapy (CBT) aims to change unhelpful thinking and behavior, and has been shown to decrease drug consumption in various SUD (Dutra et al. 2008). However, surprisingly few studies have investigated the effects of CBT with neuroimaging. A preliminary study by DeVito et al. (2012) evaluated the effect of CBT using an fMRI Stroop task (task that measures cognitive control) and compared BOLD response before and after treatment for subjects with SUD. After treatment, the patients exhibited decreased activation of ACC, IFG, dlPFC, and midbrain during the Stroop task. Compared to healthy controls who also underwent two scans, patients had a greater signal change in the subthalamic nucleus and midbrain after the second scan. These regions are involved in cognitive processes and impulse control, providing a mechanism by which this intervention method may help treat SUD (DeVito et al. 2012). A second study in heavy smokers compared the effects of CBT vs placebo on glucose metabolism using FDG PET. CBT, but not placebo, reduced FDG uptake in the posterior cingulate cortex (PCC), an area involved in value-based decision making (Costello et al. 2010).

Motivational Interventions

Motivational intervention is another treatment option available for SUD. Through a variety of techniques, including public service announcements (PSAs), personally tailored messages, or motivational interviewing, motivational interventions can increase the chances of drug use cessation (Zilverstand et al. 2016). An fMRI study by Feldstein Ewing et al. (2011) in AUD subjects investigated two different types of client speech during motivational interviewing and their effectiveness at altering neural activation following alcohol cue presentation. Change talk (CT), where the participant addresses the need for modified behavior, was compared with counterchange talk (CCT), where participants believed they did not have to alter their behavior regarding drinking. After CCT and alcohol cue presentation, activation was seen in OFC, insula, NAcc, caudate, and putamen. However, there were no significant increases in activation following CT supporting the importance of CT during motivational interviewing as well as other behavioral interventions (Feldstein Ewing et al. 2011). Another study by Wilson et al. (2013) investigated differences in coping strategies during cue exposure in smokers: self-focused (with the focus being on personal benefit) versus other-focused (benefits presented in terms of another individual). Self-focused strategies, in contrast to other-focused strategies, produced an increase in activation in medial PFC, precuneus, and insula, all regions

involved in self-referential processes (Wilson et al. 2013). These studies support the careful selection of specific strategies for therapies, with the best results seen with strategies that are more self-focused.

Two studies investigated the use of PSAs, frequently viewed on television, as a form of motivational intervention. Langleben et al. (2009) studied the brain responses of regular smokers to two types of anti-tobacco PSAs, those with high message sensation value (MSV) compared to those with low MSV, as well as neutral cues. MSV is a measure of intensity of the response to the different features of the video, such as visual and audio components. Frames from the PSAs, both high and low MSV, were more accurately identified during a “Frame Recognition Test” compared to those from the neutral videos, with the low MSV frames being those most accurately recognized. The activation elicited by the low MSV PSAs in the PFC and temporal cortex was greater than that of the high MSV PSAs, suggesting that higher intensity videos may not directly lead to greater retention (Langleben et al. 2009). A second study by Wang et al. (2013), investigated anti-smoking PSAs using fMRI in smokers while in the scanner. Smokers viewed PSAs with either high or low “argument strength (AS)”, i.e., the strength of the content and its persuasiveness with the audience. Smokers’ brain responses to AS and MSV strength interacted in the inferior parietal lobule, left IFG, left fusiform gyrus, right dorsomedial PFC (dmPFC), and precuneus. These results show the importance of processing the PSAs in these regions, with activation in the dmPFC also correlating to nicotine metabolite levels after a 1 month follow-up (Wang et al. 2013). These studies show the differences in brain activation by the varying types of PSAs, helping elucidate which types may be more beneficial for anti-tobacco PSAs.

Three studies by the same group investigated the use of tailored messages as a motivational intervention for smoking, by measuring brain responses to high-tailored, low-tailored, and generic smoking cessation messages. High-tailored messages produced greater activation of rostral mPFC and precuneus/PCC compared to low-tailored response, while the two tailored conditions produced greater activation in these regions compared to the generic messages (Chua et al. 2009a). A second study investigated the difference between neutral messages and three types of tailored messages: personalization/feedback, motivational, and instructional. The 3 types of messages each activated different areas: instructional messages activated the dlPFC, the personalized/feedback messages activated the mPFC and precuneus/PCC, and the motivational messages activated the ventral mPFC. The areas activated are involved in instructional processing, self-referential processes, and reward expectation, providing options for targets for the messages (Chua et al. 2009b). A more recent study investigated the neural changes seen with the tailored messages and its association with continued smoking

cessation (Chua et al. 2011). After viewing tailored messages, participants showed increased activation in dmPFC, precuneus, and angular gyrus. The activations of dmPFC and precuneus were correlated with smoking cessation after a 4 month follow-up visit (Chua et al. 2011). The increased activation in mPFC and precuneus in the 3 studies in response to the tailored messages and its association with smoking cessation provides support for the use of tailored messages for smoking cessation treatments.

Cue-Exposure Treatment

Cue-exposure treatment (CET) aims at reducing conditioned responses towards drugs in individuals with SUD, which may reduce their risk of relapse (Drummond et al. 1990). A meta-analysis by Conklin and Tiffany (2002) showed no evidence for efficacy of CET for SUD, whereas Loeber et al. (2006) showed that CET decreased craving in AUD. Vollstädt-Klein et al. (2011) investigated the effects of CET on alcohol cue reactivity using fMRI in abstinent AUD patients. After treatment, the CET group exhibited stronger cue-reactivity reductions in VS, dorsal striatum, ACC, precentral gyrus, and insula compared to controls, which correlated with subjective craving.

Cognitive Bias Modification Training

Automatic processes may play a large role in drug addiction, and drug users have shown behavioral cognitive biases for drug cues, i.e., selective attention (attentional bias) and the tendency to approach drug cues faster than to avoid them (drug approach bias). The attentional bias can be measured with the addiction Stroop task (Cox et al. 2006), in which individuals with a SUD respond slower to drug-related words compared to neutral words, suggesting distraction by drug cues and the visual probe task; SUD participants generally fixate longer on a drug picture than a neutral picture (Field et al. 2013). The drug approach bias can be assessed with the Stimulus–Response Compatibility (SRC) task and a joystick Approach Avoidance Task (AAT). In the SRC, drug users moved a manikin faster towards drug cues than towards neutral cues (Bradley et al. 2008). In the AAT, participants push and pull pictorial cues that appear on a computer screen (drug-related/neutral) with a joystick in response to the format of the cue. The behavioral approach bias is calculated as the reaction time of pushing – pulling cues, with higher approach bias scores corresponding to stronger tendencies to pull than push certain cues. Patients with AUD (Wiers et al. 2014), cannabis use disorders (Cousijn et al. 2011), opiate use disorder (Zhou et al. 2012) and tobacco smokers (Wiers et al. 2013), have an approach bias for drug cues compared to control groups on the AAT; i.e., faster approach than avoidance. Attentional and approach biases for drugs correlated positively with explicit

craving scores (Mogg et al. 2003; Mogg et al. 2005; Watson et al. 2013), and predicted relapse (Janes et al. 2010) and drug consumption (Volkow et al. 2005). These studies highlight the clinical importance of automatic biases in drug addiction.

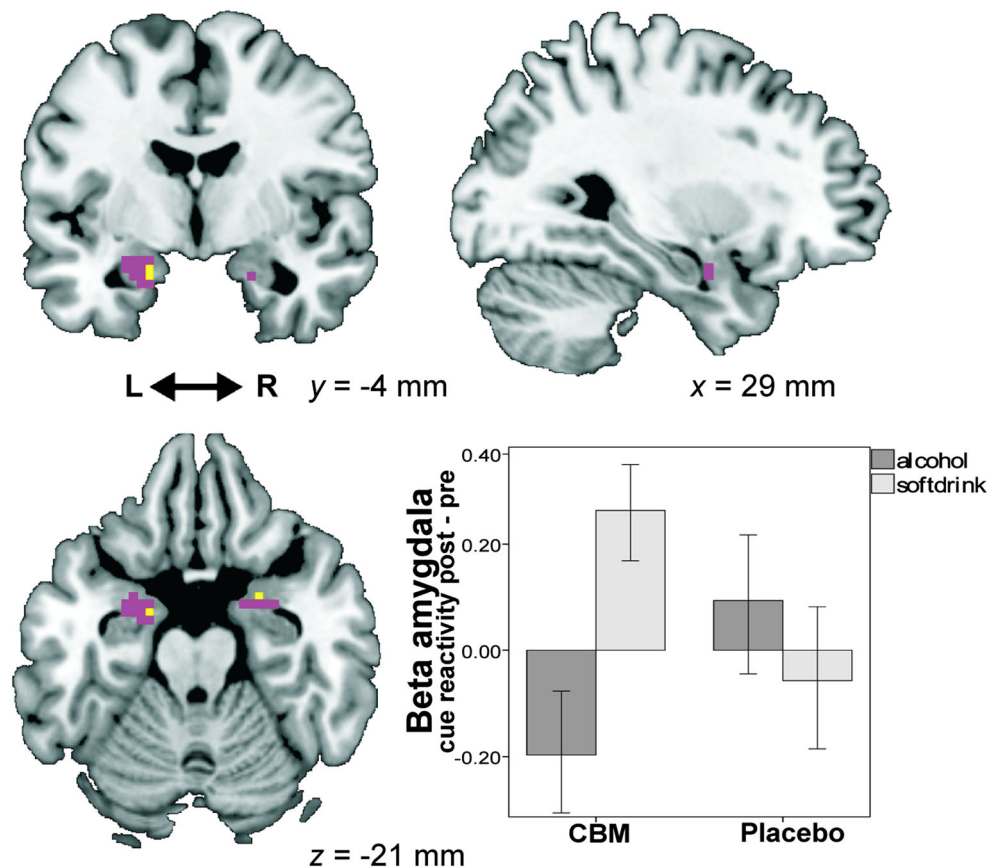
Automatic biases can be “re-trained” by means of cognitive bias modification (CBM) training. The first study investigating CBM adapted a visual probe task for anxiety (MacLeod et al. 2002), in which probes follow neutral cues in the majority of cases, therefore disengaging attention from anxious cues and reducing attentional bias. CBM also decreased attentional biases for drug cues compared to neutral cues in heavy drinkers (Fadardi and Cox 2009), alcohol-dependent patients (Schoenmakers et al. 2010) and smokers (Field et al. 2009). Some of these studies found generalization to new stimuli, i.e., attention was not only disengaged from the drug cues that were used for CBM training, but reduced attentional biases also occurred for drug cues that participants hadn’t seen before (Fadardi and Cox 2009). This suggests that CBM may affect attentional biases for drug-related cues in general, which may influence other behavioral processes such as drug craving and drug seeking behavior.

In the AAT-based version of CBM participants systematically but implicitly push away drug cues with a joystick to decrease the drug approach bias. Typically a CBM group pushes away drug cues in 90 % of trials and pulls 10 % of alcohol cues towards them. Some study designs use a sham training group that pushes and pulls alcohol in 50 %/50 % of the cases. In two recent randomized-controlled trials, CBM reduces relapse rates up to 13 % in patients with AUD, compared with a placebo-training group (Wiers et al. 2011) and compared with a non-training group (Eberl et al. 2013), showing its clinical potential in alcohol addiction.

Two studies have investigated the neural effects of CBM in addicted populations. First, Wiers et al. (2015b) investigated recently detoxified patients with AUD on a blocked design alcohol cue reactivity task (Fig. 2). After the task, patients were randomly assigned to either a CBM group or a placebo group, and performed six sessions of CBM/sham training for 3 weeks. Before training, alcohol cue-evoked activation was observed in bilateral amygdala and right NAc, which correlated with craving and arousal ratings of alcohol stimuli. After training, the CBM group showed greater reductions in cue-evoked activation in amygdala and in behavioral arousal ratings of alcohol pictures, compared with the placebo training group. Decreases in right amygdala activity correlated with decreases in craving in the CBM but not the placebo training group.

The patients also performed the AAT in a 3 T fMRI scanner pre and post training (Wiers et al. 2015a). The relevant neuroimaging contrast for the alcohol approach bias was the difference between approaching versus avoiding alcohol cues relative to soft drink cues: [(alcohol pull > alcohol push) > (soft drink pull > soft drink push)]. Before training,

Fig 2 Adapted from Wiers et al. (2015b). Cue-induced amygdala reactivity reduced after 3 weeks of CBM training compared to the placebo training group ($p < 0.05$ family-wise error corrected). Decreases in amygdala cue reactivity covaried with decreases in craving in the CBM group, but not in the placebo group



both groups showed significant alcohol approach bias-related activation in mPFC (Wiers et al. 2014). After training, patients in the CBM group showed stronger reductions in mPFC activation compared with the placebo group. Moreover, these reductions correlated with reductions in approach bias scores (but not with craving) in the CBM group only. Together, these findings provide evidence that CBM affects alcohol cue-induced mesolimbic brain activity and neural mechanisms involved in the automatic alcohol approach bias. This may be an important underlying mechanism of the therapeutic effectiveness of this training. Interestingly, two studies investigating the effects of CBM in anxious individuals also found effects of the amygdala for fear processing (Britton et al. 2015; Taylor et al. 2014). Since protocols for the neural effects of CBM have already been published (Attwood et al. 2014), more studies on the neural effects of CBM in the drug-dependent populations are to be expected.

Virtual Reality

Virtual reality (VR) therapy allows for the immersion into a three dimensional world, which can be altered to show any type of environment. When compared to the previous techniques, using videos or pictures, VR provides a different approach to cue exposure treatment (CET) for addiction. As it

aims at cue extinction, the VR system can produce environments containing alcoholic drinks, drugs, advertisements, and even other people consuming drugs (Moon and Lee 2009). In recent years, this technology has been most effectively used to treat patients suffering from anxiety disorders including a range of phobias and PTSD (Bohil et al. 2011).

Recent studies utilized VR technology as a therapy for SUD in conjunction with fMRI. Using a VR approach that was previously shown to produce greater levels of craving than still photographs (Lee et al. 2003), VR was paired with 6 sessions of CET for smoking with MRI scanning before and after treatment completion. The combined treatment method, while not impacting craving, did result in a decrease in the urge to smoke. Craving reductions were also associated with a decreased activation of regions in PFC, specifically IFG and SFG (Moon and Lee 2009). In a recent preliminary study by Son et al. (2015), AUD subjects received 5 weeks of VR therapy, undergoing FDG-PET before and after treatment. At baseline prior to starting VR treatment, AUD subjects exhibited elevated metabolism in basal ganglia compared to controls. This finding is consistent with previous studies suggesting that elevated limbic activation in AUD subjects is associated with increased sensitivity to drug cues (Lee et al. 2013). After VR treatment completion, the metabolism in basal ganglia decreased suggesting a stabilization of the cue responses.

This study was preliminary, however, since a small number of subjects was used ($N=12$ AUD patients) and the control group did not undergo treatment, only a baseline scan (Son et al. 2015). Future expansion of this VR therapy into a larger number of subjects as well as inclusion of a healthy control group in the VR treatment would provide further evidence into its potential for AUD treatment. Nevertheless, the study stresses the potential of VR for addiction therapy. Since VR is a computer-based intervention, it also has strong potential for combination with neuroimaging techniques since VR can be done within the fMRI environment, whereas other behavioral treatments such as CBT cannot.

Neuromodulatory Techniques for Treatment

Neurofeedback

Neurofeedback through the use of fMRI has been investigated in nicotine-dependent smokers. In a study by Li et al. (2013), real time fMRI (rtfMRI) neurofeedback was tested on a nicotine-dependent population. Utilizing changes in BOLD response during rtfMRI in specific regions, the ACC and PFC, participants were trained to attempt to regulate the response during two separate states: a “reduce craving” state and an “increase resistance” state, respectively. Participants were shown a bar referred to as a “thermometer”, which monitored BOLD responses in either the ACC or the PFC, whose level they had to decrease or increase respectively, during separate sessions. The results suggest that the participants were able to possess control over the ACC and reduce its activation, a reduction that was also correlated with decreased craving. Canterberry et al. (2013) also investigated neurofeedback in nicotine-dependent cigarette smokers, in the ACC. A study by Hanlon et al. (2013), used a similar approach, except they merged the two instructions of reducing craving and increasing resistance into the same neurofeedback session, utilizing 2 thermometers with opposing instructions. Both the Canterberry et al. (2013) and the Hanlon et al. (2013) studies had similar findings as the Li et al. (2013). In a recently published study, Hartwell et al. (2016) further studied the aforementioned rtfMRI neurofeedback paradigm. A matched sample of smokers that did not receive neurofeedback but underwent scanning allowed for direct interpretation of the results of the treatment. Personalized ROI neurofeedback for each participant increased the potential benefit. After completing the 3 treatment visits, the rtfMRI neurofeedback group exhibited both lower craving scores and ROI activation, as observed in the previous studies (Li et al. 2013; Hanlon et al. 2013). The decrease in ACC activity found in all three rtfMRI studies discussed above is similar to those observed with nicotine-dependent patients receiving bupropion. This provides further validation for these findings and its treatment

potential (Brody et al. 2004; Culbertson et al. 2011). The question of whether this approach would apply to normal, daily life has to still be answered before the true potential of this treatment for nicotine-dependent smokers or other SUD populations can be assessed.

Neurofeedback has recently been used in conjunction with rtfMRI to investigate its potential as a treatment for AUD. In a study by Kirsch et al. (2015), neurofeedback was used in heavy social drinkers to investigate its potential in reducing the response to alcohol stimuli. Compared to both no feedback and sham feedback control groups, the real feedback group had reduced activation of VS after treatment. These results were similar to those reported by Karch et al. (2015), who utilized two different control groups, one with false feedback and another with no feedback. The real feedback group exhibited lower activation in ACC, dlPFC, inferior temporal gyrus, MFG, and insula. The decrease in ACC activation in heavy drinkers is similar to that seen in the studies involving nicotine-dependent smokers (Hanlon et al. 2013; Hartwell et al. 2016; Li et al. 2013). Although both studies are preliminary and questions remain on the right type of control groups to be used, regarding if no feedback or false feedback are adequate control conditions, the results suggest a potential benefit in using neurofeedback treatment for AUD.

Neurofeedback as a treatment for SUD has also been investigated through EEG. Neurofeedback using EEG was utilized as treatment for AUD by Peniston and Kulkosky (1989). The AUD participants in the experimental group were able to increase their alpha and theta brain rhythms after treatment completion. In addition, depression scores and relapse percentage were lower in the biofeedback group compared to the control groups. Lastly, the biofeedback group failed to show the elevated beta-endorphin serum levels, which are related to stress, that was seen in AUD patients undergoing traditional treatment (Peniston and Kulkosky 1989). A study by Horrell et al. (2010) investigated a combined intervention of neurofeedback with motivational interviewing in cocaine abusers. The neurofeedback training aimed to increase sensorimotor rhythm (SMR) amplitude and/or decrease theta band frequency. Following treatment completion, the participants showed increased SMR amplitude while managing to maintain the theta band levels at a stable level. In a cue reactivity task after neurofeedback, participants decreased EEG gamma activation (Horrell et al. 2010). In a second study also using a combination of EEG neurofeedback and motivational interviewing in cocaine abusers, the treatment group showed the typical P300 amplitude decrease seen in retest (Stotts et al. 2006). Since the healthy controls had higher P300 in the baseline condition, this stabilization of the P300 indicates a difference in engagement during the visual task. The combined beneficial effects of neurofeedback and motivational interviewing provide support for a combination of treatments.

In a study combining two different approaches previously described, Sokunbi et al. (2014) present a “motivational neurofeedback” approach with an approach/avoidance visual feedback system. Using food to study the motivational neurofeedback paradigm, subjects were instructed to decrease the size of the image presented by decreasing the activation in an individualized target brain area using a localizer (e.g., amygdala, putamen and caudate), measured through fMRI. When compared to a passive session, the neurofeedback session lowered the region activation, providing evidence to the usefulness of this approach. This motivational neurofeedback approach can be further developed into one similar to the AAT where images increase or decrease in size as they are pulled towards or pushed away, respectively. This approach may be beneficial in the addiction field, as it adds a sense of direct involvement in the treatment. However, whether the approach works for addiction has not yet been explored.

Transcranial Magnetic Stimulation

Transcranial magnetic stimulation (TMS) is another neuromodulatory technique that stimulates the brain. TMS is noninvasive technique using a high intensity magnetic pulse to alter the excitability of a specific brain area. Repetitive TMS (rTMS), which utilizes multiple currents, can provide a more lasting modulation (Bellamoli et al. 2014). While a number of studies have investigated TMS and shown its treatment potential for SUD, the majority had non-imaging outcome measures, such as craving scores or urine drug screen results (Amiaz et al. 2009; Mishra et al. 2010; Terraneo et al. 2016; Trojak et al. 2015). A recent study investigated differences in RFC in control and motivational networks after rTMS in AUD patients and controls. Participants received rTMS to the right dlPFC or sham stimulation. Overall, AUD patients showed greater functional connectivity within the left fronto-parietal cognitive control network, a change which was further increased after receiving rTMS. AUD patients also exhibited higher connectivity within the fronto-striatal motivational network and between the left and right fronto-parietal networks compared to controls. These findings suggest that rTMS may help increase connectivity in control-related regions, which can help in the cognitive processes needed to resist relapse (Jansen et al. 2015). Herremans et al. (2016) investigated accelerated high-frequency rTMS (HF-rTMS) in AUD patients using an fMRI cue-exposure paradigm. Patients received a total of 15 sessions of HF-rTMS over a 5 day period. While the majority of AUD patients relapsed, those who abstained had greater dACC activation during the cue-exposure paradigm. Those who abstained at the end of the treatment period showed decreased dACC activation after HF-rTMS while those who relapsed had an inverse relationship (Herremans et al. 2016). A preliminary study on one AUD patient utilized rTMS on the dACC to attempt to reduce severe cravings.

Following the TMS, craving-related increases in EEG ACC and PCC connectivity in both beta and gamma bands as well as fMRI activation of the NAc, ACC, mPFC, and PCC were normalized. At a follow-up visit after the patient relapsed, the fMRI again showed increases in NAc, ACC, and PCC. The EEG increases in ACC and PCC connectivity also returned, but only in the gamma bands (De Ridder et al. 2011). While this provides evidence for the treatment potential of TMS in some patients, it suggests the need for continued study. A study by Pripfl et al. (2014) compared HF-rTMS using EEG on the left dlPFC with a sham condition in smokers. After the treatment sessions, both craving and resting state EEG delta power, which is related to the activity of the reward system, decreased (Pripfl et al. 2014). This reduction in a short term condition provides evidence supporting the use of HF-rTMS for treatment of cigarette smoking.

Transcranial Direct Current Stimulation

Transcranial direct current stimulation (tDCS) utilizes currents to alter the resting membrane potential of specific brain areas. This alteration effects neuronal excitability (da Silva et al. 2013). For addiction, it has been shown that stimulation of the dlPFC with tDCS decreased craving in heavy drinkers (den Uyl et al. 2015) and patients with AUD (Boggio et al. 2008) who were exposed to alcohol cues. Den Uyl, however, did not find evidence for changes in cognitive biases for alcohol. Another study by Conti et al. (2014) utilized this method in crack-cocaine dependent individuals. Patients either received 5 sessions of bilateral tDCS over the dlPFC or sham tDCS, with brain activity measured through P3 event related potentials (ERP) collected through EEG and low-resolution brain electromagnetic tomography (LORETA). Following one session, the P3 activity was already altered differently compared to those in the sham group. After the 5 treatment sessions, the subjects in the tDCS group showed increased intensity during drug-cue presentation in a variety of PFC areas, which included dlPFC, OFC, ACC, and frontopolar cortex. These results indicate that changes in neural activity are already present after a single session, expanding as the number of tDCS applications is increased (Conti et al. 2014). Another study by Conti and Nakamura-Palacios (2014) also studied tDCS on cocaine-addicted individuals. Increased activity in ACC was seen in the sham group while the tDCS group showed a decrease in activity. These results show that tDCS can alter activity in the ACC, an area important in drug-cue processing, suggesting its potential application in treatment (Conti and Nakamura-Palacios 2014). A study by da Silva et al. (2013) also investigated the effects of tDCS using ERPs in AUD patients, randomized into either a real tDCS group or a sham group. The sham group showed increased activation in response to alcohol-cues, a change not seen in the tDCS group. While the tDCS group also exhibited

Table 1 Studies assessing neural effects of pharmacological/behavioral treatment

Authors (Year)	Study group	Treatment	Imaging task	Results
Pharmacological treatment studies that aim to reduce drug craving				
Weerts et al. (2008)	<i>N</i> = 21 recently abstinent AUD subjects	5 days of NTX (50 mg)	[¹¹ C]carfentanil (CAR) PET and [¹¹ C] Methyl naltrindole (MeNTI) PET before and after 4 days of treatment	<ul style="list-style-type: none"> - Complete inhibition of μ-OR binding potential as measured by [¹¹C]CAR - Partial inhibition of δ-OR binding potential as measured by [¹¹C] MeNTI with more variability among subjects - Peak serum levels of NTX positively correlated to % inhibition of δ-OR binding potential but not % inhibition of μ-OR binding potential
Myrick et al. (2008)	<i>N</i> = 90 non-treatment-seeking AUD <i>N</i> = 17 social drinking	7 days of NTX (50 mg), ondansetron hydrochloride (0.5 mg), or combination of both, double-blind, randomized	Cue reactivity with alcohol vs. neutral beverage visual cues (1.5 T fMRI)	<ul style="list-style-type: none"> - NTX reduced alcohol cue-induced activation of VS, both with and without ondansetron hydrochloride - Combination of NTX and ondansetron hydrochloride significantly reduced subjective craving for alcohol
Langleben et al. (2014)	<i>N</i> = 17 abstinent I.V. heroin users	XR-NTX injection (352 mg)	cue reactivity with heroin vs. neutral audiovisual cues (3 T fMRI)	<ul style="list-style-type: none"> - fMRI response to cues was decreased in amygdala, cuneus, caudate and precentral gyrus and increased in the medial frontal gyrus and precuneus after 10–14 days from XRNTX injection - Higher plasma levels of 6-beta-naltrexol associated with a larger reduction of fMRI response to drug cues in precentral, caudate amygdala areas
Lukas et al. (2013)	<i>N</i> = 28 detoxified AUD subjects	XR-NTX injection (380 mg) or placebo, double-blind	Cue reactivity with alcohol vs. neutral visual and olfactory cues (3 T fMRI)	<ul style="list-style-type: none"> - XRNTX-treated subjects showed a significant reduction in cue-induced craving compared to a placebo - XRNTX showed decreased responses to alcohol odors compared to placebo in SFG, supramarginal gyrus, post central gyrus and angular gyrus -XRNTX showed decreased responses to alcohol-related pictures compared to placebo in orbital gyri, cingulate gyrus, IFG, and middle frontal gyrus
Hermann et al. (2006)	<i>N</i> = 10 male abstinent AUD patients (1–3 weeks post detox) <i>N</i> = 10 healthy males	Single dose of amisulpride (400 mg)	Cue reactivity with alcohol vs. neutral visual cues (1.5 T fMRI)	<ul style="list-style-type: none"> - Alcohol cues initially elicited an increased BOLD response in the left frontal lobe, left OFC, left cingulate gyrus, bilateral lobe, and bilateral hippocampus in AUD patients versus healthy controls, but following amisulpride administration there was no significant difference in BOLD response -Amisulpride reduced cue-induced activation of the thalamus of the AUD patients
Myrick et al. (2010)	<i>N</i> = 30 non-treatment-seeking AUD patients	14 days of aripiprazole (15 mg) or placebo, randomized	Cue reactivity with alcohol vs. neutral beverage visual cues (3 T fMRI)	<ul style="list-style-type: none"> - Aripiprazole-treated subjects showed decreased right VS activity compared to placebo-treated subjects
Han et al. (2013)	<i>N</i> = 35 subjects with major depressive disorder and AUD subjects	6 weeks or escitalopram (10–20 mg) or aripiprazole (5–15 mg) and escitalopram (10–20 mg) combination, randomized	Cue reactivity with alcohol drinking scene vs. control scene (1.5 T fMRI)	<ul style="list-style-type: none"> - Increased activity in the ACC in response to alcohol drinking scenes following treatment with aripiprazole and escitalopram combination - Change of activity in ACC was negatively correlated with change in craving for alcohol

Table 1 (continued)

Authors (year)	Study group	Treatment	Imaging task	Results
Young et al. (2014)	N = 20 cocaine-dependent patients	7–9 days of bupropion (60 mg) or placebo, double-blind, randomized	Backward-masked cue task with subliminally presented cocaine, sexual, aversive and neutral cues (3 T fMRI)	- Reduced activation in response to cocaine cues versus neutral, but not sexual or aversive cues, in bupropion-treated subjects compared to placebo-treated subjects in VS, ventral pallidum, amygdala, midbrain, and OFC
Franklin et al. (2011)	N = 19 smokers	18 days of VAR (1 mg) or placebo, double-blind, randomized	Cue reactivity with smoking-related vs. non-smoking-related audiovisual video cues (CASL perfusion fMRI)	- Reduced response to smoking cues in VS and medial OFC following VAR treatment, no change in response for placebo-treated subjects - VAR treatment increased activity of the lateral OFC at rest, which predicted the reduced response to smoking cues in the medial frontal cortex - VAR treatment also showed increased activity in ACC, PCC, SFG and dlPFC
Ray et al. (2015)	N = 40 heavy drinking smokers	12 days of VAR (2 mg), NTX (25 mg), VA (1 mg twice daily) and NTX (25 mg) combination (VAR + NTX), or placebo, double-blind, randomized	Cue reactivity with smoking vs. control audiovisual cues (3 T fMRI)	- VAR + NTX combination treatment reduced activation of ACC compared to placebo and NTX alone - VAR alone, NTX alone, and VAR + NTX combination all decreased NAcc activation compared to the placebo
Schacht et al. (2014)	N = 35 non-treatment-seeking AUD patients	14 days of VAR (2 mg) or placebo, randomized	Cue reactivity with alcohol vs. neutral beverage cues (3 T fMRI)	- VAR treatment reduced response to alcohol cues in the bilateral OFC compared to placebo - VAR treatment showed no effect in reducing drinking behavior
Wheeler et al. (2014)	N = 11 healthy smokers	12 weeks of VAR	¹ H MRS and 3 T fMRI with the Stroop Task (before and after treatment)	- Reduction in glutamate and glutamine levels in the dACC
Brody et al. (2004)	N = 37 healthy smokers	4 weeks of bupropion HCl (300 mg) or untreated	Cue reactivity with cigarette-related vs. neutral video cues (2 [¹⁸ F]-FDG PET scans)	- BOLD signal reduction in rACC, mOFC, precuneus, and PCC - Changes in the functional connectivity between DMN (rACC and PCC) and the dACC - Bupropion-treated smokers showed significantly lower activation of perigenual/ventral ACC metabolism in response to cigarette-related cues than untreated smokers
Culbertson et al. (2011)	N = 30 healthy nicotine-dependent smokers	8 weeks of bupropion HCl (300 mg) or placebo, double-blind, randomized	Cue reactivity with smoking vs. neutral video cues, before and after treatment (1.5 T fMRI)	- Bupropion-treated smokers showed reduced activation in the left ventral striatum, right medial OFC and bilateral ACC when actively resisting craving, compared to pre-treatment - Placebo-treated smokers did not show significant changes in activation following treatment period
Wang et al. (2014)	N = 15 former heroin addicts on short term MMT N = 15 former heroin addicts on long term MMT N = 17 healthy controls	Subjects on short term MMT (less than 1 year) or long term MMT (2–3 years)	3 T fMRI with heroin-cue paradigm	- MMT patients, regardless of treatment duration, had increased activity in the mesolimbic and visuospatial circuitry. - Long term MMT had decreased activation in the caudate compared to short-term MMT patients.
Wang et al. (2011)	N = 14 former heroin-dependent patients	Patients undergoing long-term MMT(5–24 months)	3 T fMRI with heroin-cue paradigm	- Patients on MMT had increased activity in mesocorticolimbic, PFC, and visuospatial-attention regions after viewing heroin-related cues - Heroin-cues did not significantly change cravings

Table 1 (continued)

Authors (year)	Study group	Treatment	Imaging task	Results
Tabatabaie-Jafari et al. (2014)	N = 20 abstinent crystalline-heroin smokers N = 20 crystalline-heroin smokers on MMT N = 20 controls	Heroin smokers on MMT or opiate abstinent for at least 3 months	1.5 T fMRI with heroin-cue paradigm	- The opiate-abstinent group had higher activation in the ACC and IFG compared to controls and higher IFG and superior temporal gyrus compared to MMT patients. - MMT group exhibited increased activity to cues in the lingual gyrus and cerebellum
Langleben et al. (2008)	N = 25 former heroin users on MMT	Patients receiving daily methadone dose	3 T fMRI with heroin-cue paradigm (scanned before and after daily dose)	- After the daily dose of methadone, activation in the insula, amygdala, and hippocampal complex decreased compared to activation before the dose of methadone.
Ma et al. (2010)	N = 14 chronic heroin N = 13 controls	12 of the 14 chronic heroin users were receiving a methadone treatment	3 T fMRI	- Functional connectivity between the NAcc and ACC, the NAcc and OFC, and the amygdala and OFC increased in the heroin users - Heroin users also had decreased functional connectivity between PFC and both the ACC and OFC
Shi et al. (2008)	N = 11 former heroin users in prolonged abstinence N = 10 MMT patients N = 10 healthy controls	Patients in MMT for at least 6 months. Patients in prolonged abstinence were abstinent from heroin for 6 months	[¹¹ C]-2-β-carbomethoxy-3-β-aryltropine ([¹¹ C] CFT) PET, which measures	- MMT patients had decreased DAT uptake in the putamen compared to the two other groups and decreased DAT uptake in the caudate compared to controls. - MMT patients exhibited an association between DAT uptake in the caudate and subjective anxiety. - Prolonged abstinence subjects had decreased DAT uptake in the caudate compared to controls.
Galyunker et al. (2007)	N = 15 opiate-abstinent former opiate-dependent patients N = 12 MMT opiate dependent subjects N = 13 controls	Opiate abstinent subjects had received MMT for more than a year, but stopped at least 6 months before study. MMT patients had been on methadone for over 1 year with stable dose for 6 months	[¹⁸ F]-FDG PET	- Opiate-abstinent patients exhibited decreased metabolism in perigenual ACC, left mid-cingulate cortex, left insula, and right superior frontal cortex compared to controls. - Compared to health controls, MMT patients had lower metabolism in the thalamus and left insula. - Depression scores correlated with metabolism of the perigenual ACC and mid-cingulate cortex in the opiate-abstinent groups
Greenwald et al. (2015)	N = 7 heroin-dependent patients N = 5 controls	100 mg/day MMT (minimum of 2 weeks), then 3 week dose taper, and low dose 10–25 mg/day MMT (minimum of 2 weeks)	¹ H MRS	- Compared to the high dose, the low dose scans had increased glutamate levels in the ACC - ACC glutamate levels were inversely correlated in the healthy controls with cigarette smoking duration and in heroin users with heroin use.
Schmidt et al. (2015a)	N = 20 heroin-dependent participants N = 20 healthy controls	Patients in heroin-assisted treatment for at least 6 month with stable dose last 3 months	3 T fMRI with acute infusion of heroin and placebo (control received placebo only)	- In heroin-assisted patients, the heroin administration increased the functional connectivity of the putamen within the basal ganglia. - Increase in functional connectivity of the putamen in patients correlated with subjective “rush” and the plasma levels of the metabolite morphine.
Schmidt et al. (2015b)	N = 22 opioid-dependent participants N = 17 healthy controls	Patients in heroin-assisted treatment for at least 6 month with stable dose last 3 months	3 T fMRI with acute infusion of heroin and placebo (control received placebo only) with fearful face paradigm	- In opioid dependent patients, heroin administration before the fearful face paradigm reduced alterations in the connectivity between the left fusiform gyrus to the left amygdala and the right amygdala to right OFC, which exhibited increased connectivity after placebo administration.;

Table 1 (continued)

Authors (year)	Study group	Treatment	Imaging task	Results
Denier et al. (2013)	N = 14 heroin-dependent patients	Patients in heroin-assisted treatment for at least 6 months with stable dose last 3 months	3 T fMRI with acute infusion of heroin and placebo	<ul style="list-style-type: none"> - Results suggest that heroin maintenance treatment may help normalized stress response in dependent patients - Low gray matter volume in the frontal brain regions in patients correlated with decreased perfusion
Pharmacological treatment studies that aim to increase cognitive control				
Ghahremani et al. (2011)	N = 22 Methamphetamine dependent subjects and N = 28 healthy controls	Single dose of modafinil (200 mg) or placebo (randomized order) 2 h before scanning	Deterministic associative learning task (3 T fMRI)	<ul style="list-style-type: none"> - Modafinil boosted learning in Methamphetamine dependent subjects, bringing them to the same performance level as control subjects; whereas the control group did not show changes in performance with modafinil. - Methamphetamine dependent subjects showed a greater effect of modafinil on brain activation in bilateral insula/ventrolateral prefrontal cortex and ACC than control participants
Schmaal et al. (2014)	N = 14 AUD patients N = 16 healthy controls	Single dose of modafinil (200 mg) or placebo (randomized order) 2 h before scanning	Delay-discounting task (3 T fMRI)	<ul style="list-style-type: none"> - Modafinil improved behavioral performance (impulsive decision making) in AUD - Behavioral improvement was accompanied by enhanced activation of frontoparietal regions but reduced activation of the ventromedial prefrontal cortex and enhancement of functional connectivity between the SFG and VS
Schmaal et al. (2013a)	N = 15 AUD patients N = 16 healthy controls	Single dose of modafinil (200 mg) or placebo (randomized order) 2 h before scanning	Stroop Task (3 T fMRI)	<ul style="list-style-type: none"> - AUD patients had increased functional coupling between the DMN and both the salience and central executive networks - Change in coupling in AUD patients correlated with increased cognitive control
Schmaal et al. (2013b)	N = 16 abstinent AUD patients N = 16 healthy controls	Single dose of modafinil (200 mg) or placebo (randomized order) 2 h before scanning	Stop Signal Task (3 T fMRI)	<ul style="list-style-type: none"> - In AUD patients modafinil improved response inhibition in those with initial poor response inhibition, whereas response inhibition was diminished in better performing subjects - In AUD patients with initial poor response inhibition, modafinil-induced improvement of response inhibition was accompanied by greater activation in the thalamus and SMA and reduced connectivity between the thalamus and the primary motor cortex - Baseline response inhibition and modafinil-induced behavioral improvement was mediated by these changes in thalamus and SMA activation
Goudriaan et al. (2013)	N = 13 treatment-seeking cocaine-dependent patients N = 16 healthy controls	Single dose of modafinil (200 mg) or placebo (randomized order) 2 h before scanning	Cocaine Cue Reactivity Task (3 T fMRI)	<ul style="list-style-type: none"> - Placebo: higher brain activation in the mPFC, ACC, angular gyrus, left OFC, and VTA in the cocaine dependent group compared to controls - Modafinil: no differences in brain activation patterns were found between cocaine dependent patients and HCs - Decreased activity in the VTA and increased activity in the right ACC and putamen in the modafinil condition relative to

Table 1 (continued)

Authors (year)	Study group	Treatment	Imaging task	Results
Karila et al. (2016)	N = 29 cocaine-dependent male patients	Modafinil administration: 400 mg/day for 26 days, then 300 mg/day for 30 days, and 200 mg/day for 31 days	PET and [¹¹ C]-PE2I	<p>the placebo condition in cocaine-dependent subjects, but not in controls</p> <ul style="list-style-type: none"> - Decreases in self-reported craving when watching cocaine-related cues after modafinil administration compared to placebo were associated with modafinil-induced increases in ACC and putamen activation - Baseline [¹¹C]-PE2I-binding potential covaried with risk taking and craving index in striatal and extrastriatal regions - Decrease (65.6 %) of binding potential was detected in patients receiving modafinil for 2 weeks, whereas placebo induced no significant change - During hospitalization, an equivalent improvement in clinical outcomes was observed in both treatment groups, and during the outpatient follow-up there were more therapeutic failures in the modafinil-treated group
Schmaal et al. (2012)	N = 8 cocaine-dependent patients N = 14 healthy controls	Single dose of 2400 mg N-acetylcysteine or no compound	¹ H MRS while resting	<ul style="list-style-type: none"> - At baseline glutamate levels in the dACC were significantly higher in cocaine-dependent patients compared with healthy controls - NAcc reduced glutamate levels in the cocaine dependent group, whereas NAcc had no effect in healthy controls - Higher baseline glutamate levels were associated with higher impulsivity, and both were predictive of greater N-acetylcysteine-induced glutamate reduction
Behavioral Interventions				
1. Cognitive Behavioral Therapy				
De Vito et al. (2012)	N = 6 SUD individuals receiving CBT N = 6 SUD individuals receiving treatment as usual	Treatment as usual included 8 weeks of weekly individual and group sessions (CBT group had additional twice a week computer-assisted CBT)	3 T fMRI with Stroop task	<ul style="list-style-type: none"> - At the post-treatment scan, SUD patients showed decreased ACC, IFG, and midbrain BOLD signal during the Stroop task. - Compared to the healthy controls, the subthalamic nucleus showed more decrease on the retest.
Costello et al. (2010)	N = 12 healthy controls N = 17 smokers receiving bupropion N = 20 smokers in CBT group N = 17 smokers in placebo group	Bupropion group started on 150 mg per day and increased to twice a day on fourth day. CBT group attended twice a week hour-long practical group sessions	[¹⁸ F]-FDG PET	<ul style="list-style-type: none"> - Both treatment groups had decreased metabolism in the PCC after treatment compared to the placebo group. - CBT group had greater decreases than the bupropion group.
2. Motivational Interventions				
Feldstein Ewing et al. (2011)	N = 10 AUD participants	Received motivational interviewing, with 2 types of client talk: CT and CCT	3 T fMRI with alcohol cue paradigm	<ul style="list-style-type: none"> - Significant activation following the alcohol cues was seen in the OFC, insula, NAcc, caudate, and putamen following CCT. - No significant changes in activation seen after CT.
Wilson et al. (2013)	N = 57 treatment seeking smokers	Engaged in either self-focused or other-focused coping	3 T fMRI with smoking cue presentation	<ul style="list-style-type: none"> - After cue exposure, participants that underwent self-focused coping had higher activation in the mPFC, precuneus, and insula.

Table 1 (continued)

Authors (year)	Study group	Treatment	Imaging task	Results
Langleben et al. (2009)	N= 18 smokers	Viewed 8 PSAs and 8 neutral videos, performed Frame Recognition Test after	3 T fMRI	<ul style="list-style-type: none"> - Low MSV PSAs recognized more accurately than high MSV videos, with both types of PSAs being more accurately recognized than the neutral videos. - Low MSV PSAs video produced greatest activation in the prefrontal and temporal cortices. - Activation of the temporal and prefrontal cortices associated with the recognition accuracy during the Frame Recognition Test.
Wang et al. (2013)	N=71 smokers	Viewed either high or low AS PSAs group and completed Frame Recognition Test	3 T fMRI	<ul style="list-style-type: none"> - MSV helped with frame recognition only in videos with high AS. - Interaction of MSV and AS PSA rating associated with activation in the inferior parietal lobule, left IFG, left fusiform gyrus, right dorsomedial PFC, and precuneus.
Chua et al. (2009a)	N= 24 smokers	Within-subject design, each receiving high-tailored, low-tailored, and generic messages in mixed blocked and event-related design	3 T fMRI	<ul style="list-style-type: none"> - During both the blocked and event-related conditions, high-tailored messages showed increased activation of the rostral mPFC and precuneus/PCC compared to the low-tailored messages.
Chua et al. (2009b)	N= 41 smokers	Web-based smoking cessation messages: personalization/feedback, motivational, and instructional as well as neutral messages	3 T fMRI	<ul style="list-style-type: none"> - Compared to neutral messages, each of the various types of tailored messages activated different regions: personalized/feedback messages increased activity in the mPFC and precuneus/PCC, motivational messages increased activity in the ventral mPFC, and instructional messages increased activation in dIPFC.
Chua et al. (2011)	N=91 smokers	Completed 2 tasks in fMRI: 1) subjects received tailored and untailored smoking-cessation messages and neutral messages with surprise memory task after 2) self-appraisal task	3 T fMRI	<ul style="list-style-type: none"> - Participants performed better in the memory task for the tailored messages compared to both the untailored and neutral messages. - The dmPFC, precuneus, and angular gyrus were activated during both the self-appraisal task and tailored messages. - The increased activation in the dmPFC and precuneus to the tailored messages predicting smoking cessation after a 4 month follow-up.
3. Cue-exposure Treatment				
Vollstädt-Klein et al. (2011)	N= 15 AUD patients received CET N= 15 AUD patients in control group	CET patients had 9 sessions over 3 weeks	3 T fMRI with cue-reactivity task	<ul style="list-style-type: none"> - CET group showed greater cue-reactivity reduction in the ACC, insula, limbic and frontal regions at post-treatment compared to the control group. - CET also showed decreased activation in the left VS.
4. Cognitive Bias modification training				
Wiers et al. (2015b)	N= 32 abstinent AUD inpatients N= 26 abstinent AUD inpatients	6 sessions (3 weeks) of AAT-based CBM: (1) n = 15 CBM (2) n = 17 placebo training	Alcohol cue reactivity with alcohol and soft drink cues (3 T fMRI) Implicit alcohol joystick AAT with alcohol and soft drink cues	<ul style="list-style-type: none"> - Pre-post: stronger reductions in alcohol cue-induced cue reactivity in the amygdala for CBM versus placebo, which correlated with decreases in craving (DAQ) and arousal ratings - Pre-post: mPFC activation for [(alcohol pull > alcohol push) > (soft drink pull > soft drink push)] decreased after

Table 1 (continued)

Authors (year)	Study group	Treatment	Imaging task	Results
Wiers et al. (2015a)		6 sessions (3 weeks) of AAT-based CBM; (1) $n = 13$ CBM (2) $n = 13$ placebo training	(3 T fMRI)	CBM versus placebo, which correlated with decreases in behavioral bias scores in CBM group only
5. Virtual Reality				
Moon and Lee (2009)	$N = 8$ smokers	6 sessions of virtual environment-cue exposure therapy	1.5 T fMRI with smoking-related and neutral cues	- After treatment, smoking related cues had reduced activation in the IFG and SFG
Son et al. (2015)	$N = 12$ AUD subjects $N = 15$ healthy control subjects	Virtual reality therapy on the AUD subjects twice a week for 5 weeks	PET-FDG before and after treatment (controls only at baseline)	- Baseline scans showed increased metabolism in the AUD subjects in the right lentiform nucleus and right temporal lobe. - Baseline metabolism in left ACC lower in AUD subjects. - After treatment, AUD patients decreased metabolism in the basal ganglia.
Neuromodulatory techniques for treatment				
Neurofeedback				
Li et al. (2013)	$N = 10$ smokers	2 rtfMRI neurofeedback paradigms: "reduce craving" or "increase resistance"	3 T fMRI	- During the "reduce craving" paradigm, subjects successfully decreased activation of the ACC - Decrease in craving ratings was correlated with the reduction in ACC BOLD signal.
Hanlon et al. (2013)	$N = 15$ treatment seeking nicotine-dependent smokers	3 visits with 4 paradigms: 2 to isolate ROI while "crave" and "resist" and 2 using neurofeedback	3 T fMRI with nicotine-cue paradigm	- Participants were able to alter the activity of the vACC during the "crave" task, but had no success with the dmPFC during the "resist" task. - Activation of the vACC was correlated with craving scores.
Canterberry et al. (2013)	$N = 9$ smokers	3 visits consisting of one ROI run and 3 neurofeedback runs	3 T fMRI	- After neurofeedback to the ACC with the instructions to reduce craving, patients decreased both craving scores and ACC activation
Hartwell et al. (2016)	$N = 16$ smokers in neurofeedback group $N = 17$ smokers in no-feedback control group	3 neurofeedback visits each with 1 ROI run and 3 neurofeedback runs	3 T fMRI with smoking-cue paradigm	- After completion of all visits, smokers in the neurofeedback group were able to reduce neural activation to smoking-related cues compared to the smokers in the control group.
Kirsch et al. (2015)	$N = 38$ heavy social drinkers (real feedback $n = 13$, yoke feedback $n = 13$, no feedback $n = 12$)	3 neurofeedback blocks with alcohol cues	3 T fMRI	- The real feedback group exhibited a significant decrease in activation in the VS after the neurofeedback treatment. In the real feedback group, the downregulation of the VS activation was associated with activation of prefrontal regions.
Karch et al. (2015)	$N = 13$ AUD patients in true neurofeedback group $N = 14$ health volunteers in true neurofeedback group $N = 2$ AUD patients in sham neurofeedback group $N = 5$ controls in sham neurofeedback group	1 session of either true or sham neurofeedback with activation of individual ROI for each patient while viewing alcohol or neutral cues	3 T fMRI	- For the AUD subjects receiving real neurofeedback, activity in the ACC, inferior temporal gyrus, medial frontal gyrus, and insula was significantly decreased.
Peniston and	$N = 10$ AUD participants in experimental group		EEG	

Table 1 (continued)

Authors (year)	Study group	Treatment	Imaging task	Results
Kulkosky (1989)	N = 10 AUD participants with traditional treatment N = 22 healthy controls	Experimental group received 15 30-min sessions of alpha-theta biofeedback training		<ul style="list-style-type: none"> - After completing the biofeedback training, the experimental group showed an increase in alpha and theta brain rhythms. - Biofeedback group also had significant reductions of their depression scores compared to those of both control groups. - Biofeedback receiving group failed to show the increase in beta-endorphin seen in the AUD participants undergoing traditional treatment. - Less relapse was seen in the biofeedback group.
Horrell et al. (2010)	N = 10 current cocaine abusers	Motivational Interviewing (2 or 3 sessions) with 12 sessions of increasing SMR amplitude and/or decreasing theta band frequency neurofeedback	EEG	<ul style="list-style-type: none"> - SMR amplitude decreased following treatment while the theta band frequency remained the same. - Participants had decreased EEG gamma activation in the post-treatment cue-reactivity task.
Stotts et al. (2006)	N = 17 Cocaine dependent participants in the experimental group N = 14 Cocaine dependent participants in a control group N = 18 healthy control group	Motivational interviewing (2 sessions) with 2 sessions of EEG feedback	EEG	<ul style="list-style-type: none"> - While both control groups exhibited decreased P300 amplitudes upon retest, the experimental group failed to show the amplitude reduction.
Transcranial Magnetic Stimulation				
Jansen et al. (2015)	N = 38 AUD patients N = 37 healthy controls	Randomized into one of two groups: 1) right dlPFC stimulation with rTMS 2) sham group	3 T fMRI	<ul style="list-style-type: none"> - The AUD patients exhibited increased connectivity within the fronto-parietal network and within the fronto-striatal motivational network. - AUD patients also showed increased connectivity between the left and right fronto-parietal network, which was associated with a reduced number of alcohol-related problems.
Herremans et al. (2016)	N = 19 AUD patients	5 day period consisting of first single sham-controlled session, followed by 14 right dlPFC session	3 T fMRI with cue-exposure paradigm	<ul style="list-style-type: none"> - 68 % patients relapsed during the 4 week period following the sessions - AUD patients that relapsed showed decreased dACC before treatment during the cue-exposure paradigm. - BOLD response change in the dACC after high frequency rTMS was negatively correlated with baseline activation.
De Ridder et al. (2011)	N = 1 AUD patient	TMS over medial frontal cortex	fMRI and EEG	<ul style="list-style-type: none"> - After TMS, craving-related increases in EEG ACC and PCC connectivity in both beta and gamma bands. Activation of the NAc, ACC, mPFC, and PCC during the fMRI were also normalized. - After relapse, the fMRI showed recurrent increases in NAc, ACC, and PCC. The EEG increases in ACC and PCC connectivity were seen only in the gamma bands.
Pripfl et al. (2014)	N = 14 smokers	Within-subject design, two TMS sessions (left dlPFC or sham)	EEG	<ul style="list-style-type: none"> - After HF-rTMS, subjects showed significantly lower craving scores and EEG delta power.

Table 1 (continued)

Authors (year)	Study group	Treatment	Imaging task	Results
Transcranial Direct Current Stimulation				
Conti et al. (2014)	N= 13 crack-cocaine users	Received either 5 sessions of bilateral tDCS or sham tDCS	EEG with cue-paradigm	<ul style="list-style-type: none"> - The decreases in craving and EEG delta power were not associated. - P3 intensity in the subjects after 1 session of tDCS was decreased during drug cues while being increased during neutral cues. The reverse was observed in the sham group. - After the 5 sessions, P3 intensity was increased in the dlPFC, frontopolar cortex, OFC, and ACC when presented drug-cues. - Results for the tDCS group showed decreased activation after viewing drug-cues in the ACC while the sham group had increased ACC activation.
Conti and Nakamura-Palacios (2014)	N= 13 crack-cocaine addicted subjects	Received either real tDCS or sham tDCS over the dlPFC	EEG with low-resolution brain electromagnetic tomography (LORETA)	<ul style="list-style-type: none"> - Sham group exhibited increased activation after cue presentation. The real-tDCS group failed to show this increase. - Real tDCS group had reduced craving and depressive symptoms. - There was a trend in the real tDCS group towards more relapses.
da Silva et al. (2013)	N= 13 AUD subjects	Randomized into either sham-tDCS group or real tDCS treatment (once a week for a 5 week period)	EEG	

AAV approach avoidance task, *ACC* anterior cingulate cortex, *AUD* alcohol use disorder, (*dACC*) (dorsal) anterior cingulate cortex, *AS* argument strength, *CBM* cognitive bias modification training, *CBT* cognitive behavioral therapy, *CE* Cue exposure treatment, *CT* change talk, *CCT* counterchange talk, *DAQ* desire for alcohol questionnaire, *DAT* dopamine transporter, *dlPFC* dorsolateral prefrontal cortex, *DMN* default mode network, *FDG* [18 F]-flouro-2-deoxyglucose, *EEG* Electroencephalography, *fMRI* functional magnetic imaging, *IFG* inferior frontal gyrus, *MMT* methadone maintenance treatment, *miPFC* medial prefrontal cortex, *MRS* magnetic resonance spectroscopy, *MSV* message sensation value, *Nacc* nucleus accumbens, *NTX* naltrexone, *OFC* orbitofrontal cortex, *OR* Opioid Receptor, *PCC* posterior cingulate cortex, *PET* Positron Emission Tomography, *PSA* public service announcement, *rACC* rostral anterior cingulate cortex, *SMA* supplementary motor area, *SFG* superior frontal gyrus, *SMR* sensorimotor rhythm, *tDCS* transcranial direct current stimulation, (*rTMS*) (repetitive) transcranial magnetic stimulation, *vACC* ventral anterior cingulate cortex, *VTA* ventral tegmental area, *XR-NTX* Extended-release naltrexone, 3 T 3 Tesla

reduced craving and depression symptoms compared to the sham group, the tDCS group had a greater number of relapsers (da Silva et al. 2013). Nevertheless, tDCS has shown potential as being a valuable treatment strategy for drug dependence.

Summary and Conclusions

In summary, neuroimaging techniques have advanced our understanding of neural processes involved in the treatment of SUD as seen in Table 1. Some techniques, such as the virtual reality and neurofeedback, are still in early stages of clinical treatment investigations and further studies are needed. The expansion of the studies mentioned above to incorporate the follow-up of some of the populations studied at later time points is needed to determine whether some of the treatments, such as the neurofeedback training (Hanlon et al. 2013; Li et al. 2013), retain their effect following the initial study visits. In addition, pharmacological treatments, as the recent XRNTX, have been studied with neuroimaging only after a single injection (Langleben et al. 2014; Lukas et al. 2013). There remains a need to investigate its potential in the long term for both alcohol and heroin dependence. Other drugs such as bupropion hydrochloride, have been established as treatments for certain SUD, i.e., tobacco smoking.

In addition, there are other potential treatments for SUD that can be explored further. The brain can be stimulated using and deep brain stimulation (DBS), which also has potential in the treatment of SUDs (reviewed by Kravitz et al. 2015).

Acknowledgments The authors thank Dr. Joanna Fowler for proofreading.

This work was supported by NIH/NIAAA intramural grant Y1AA-3009 to NDV.

Compliance with ethical standards

Conflicts of Interest The authors declare that they have no conflict of interest.

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