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Cognitive interventions for addiction medicine: Understanding the underlying neurobiological mechanisms

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Abstract

Neuroimaging provides a tool for investigating the neurobiological mechanisms of cognitive interventions in addiction. The aim of this review was to describe the brain circuits that are recruited during cognitive interventions, examining differences between various treatment modalities while highlighting core mechanisms, in drug addicted individuals. Based on a systematic Medline search we reviewed neuroimaging studies on cognitive behavioral therapy, cognitive inhibition of craving, motivational interventions, emotion regulation, mindfulness, and neurofeedback training in addiction. Across intervention modalities, common results included the normalization of aberrant activity in the brain's reward circuitry, and the recruitment and strengthening of the brain's inhibitory control network. Results suggest that different cognitive interventions act, at least partly, through recruitment of a common inhibitory control network as a core mechanism. This implies potential transfer effects between training modalities. Overall, results confirm that chronically hypoactive prefrontal regions implicated in cognitive control in addiction can be normalized through cognitive means.

Keywords

Substance use disorders; CBT; Treatment; Psychotherapy; Training; fMRI; EEG; Cognitive control; Emotion regulation; Neurofeedback

1 INTRODUCTION

Addiction is a chronically relapsing disorder, characterized by continued drug-seeking despite reduced pleasure derived from the drug. Its recurring nature poses a substantial economic burden to society, and significant personal distress to the individual and their family (Volkow et al., 2011). Current standard treatment options include cognitive behavioral therapy (CBT) and motivational interventions. Cognitive-behavioral treatment approaches comprise an array of cognitive techniques and behavioral skills trainings aimed at increasing coping skills, which are employed depending on the individual's needs (Carroll, 1998). Motivational interventions aim at enhancing intrinsic motivation to change (Smedslund et al., 2011). Behavioral treatment studies show that both treatment modalities are effective in alleviating craving, preventing relapse and reducing substance use across a

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range of substance use disorders (Dutra et al., 2008). However, the exact neural mechanisms underlying such treatments are not fully known; their better understanding may enhance the further development of therapeutic interventions.

Imaging techniques, such as positron emission tomography (PET), functional magnetic resonance imaging (fMRI), and electroencephalography (EEG), offer a window into the functioning brain, providing a unique opportunity to examine the neurobiological effects of these interventions in addiction. Imaging studies can be used to describe the brain systems involved in select interventions, clarify which mechanisms are dysfunctional, offering the opportunity to explore differences and commonalities between different interventions. Imaging-based neurobiological indicators entail information that goes beyond self-report or behavior alone and have been shown to be good predictors of relapse following treatment (Brewer et al., 2008; Janes et al., 2010; Paulus et al., 2005; Moeller et al., 2015, this volume). They may thus provide unique information, hinting at potential new and efficacious treatment options.

While previous reviews and a meta-analysis of the neurobiological effects of treatment in addiction have broadly discussed the mechanisms underlying current treatment approaches (Konova et al., 2013; Potenza et al., 2011), this review discusses the neurobiological mechanisms of select cognitive and motivational interventions in more depth. To review the current neuroimaging literature on cognitive and motivational interventions in addiction in adults, we performed a systematic Medline search and a manual search of the citation lists of the relevant publications. Keywords used for the Medline search were: *treatment, therapy, psychotherapy, training, intervention, cognitive behavioral therapy, contingency management, cessation, coping, cognitive control, regulation, self-regulation, reappraisal, mindfulness, neurofeedback, and biofeedback*. These treatment keywords were used in a combined search with *substance, drug, cocaine, alcohol, marijuana, nicotine, abuse, dependence, use*, and either *EEG, fMRI, or PET*. This search identified 24 neuroimaging studies of cognitive interventions, investigating the effect of CBT ($n = 2$), cognitive inhibition of craving ($n = 6$), motivational interventions ($n = 7$), emotion regulation ($n = 2$), mindfulness training ($n = 2$), and neurofeedback training ($n = 6$). Neuroimaging studies examining training of working memory ($n = 1$) and attention bias training ($n = 1$) were excluded due to the low number of studies. Of the identified neuroimaging studies seventeen (71%) were conducted with smokers, four (17%) with cocaine users, two (8%) with alcoholics, and one (4%) with a mixed population.

2 COGNITIVE INTERVENTIONS

Generally, two different research approaches were implemented in the selected studies. Either a pre–post study design was employed to investigate posttreatment change in relation to a pretreatment baseline measurement, or participants were scanned while they were actively engaged in a therapeutic intervention.

2.1 COGNITIVE BEHAVIORAL THERAPY

Standard CBT comprises an array of approaches directed toward modifying dysfunctional thinking and behavior. The two critical components are analysis of thoughts, feelings, and

behaviors, as well as skills training for achieving active behavior and thought modification (Carroll, 1998). Skills training, considered essential to treatment, includes interventions to enhance motivation and coping with craving, and dealing with high-risk situations. Additional skills training depends on the patient's needs and includes self-monitoring, emotion regulation, relaxation, and building a social support network (Carroll, 1998). Standard CBT has been shown to be effective in reducing drug use in individuals addicted to nicotine, alcohol, cannabis, cocaine, and opiates and in polysubstance use disorders (Dutra et al., 2008).

Although CBT has been used in addiction treatment for over two decades, not many studies have employed neuroimaging to demonstrate the neurobiological changes associated with treatment. We identified two studies that used neuroimaging to investigate its effects. Both studies, performed in smokers and a mixed population of drug users prior to and after 2 months of CBT, reported a reduction in drug use and an improvement on relevant behavioral measures (Costello et al., 2010; DeVito et al., 2012; Table 1). Both employed a pre–post design to compare brain activation before and after treatment in a within-subjects design, while controlling for treatment-unrelated changes over time by including a control group. The first study investigated PET resting glucose metabolism, comparing the CBT group (nicotine smokers) to another group of smokers receiving placebo treatment (Costello et al., 2010). The PET resting data analysis revealed reduced glucose metabolism in the posterior cingulate cortex (PCC) in the CBT group compared to the placebo group after treatment. This region encodes subjective valuation of potential rewards (Schacht et al., 2012), and is associated with attentional bias toward drug cues (Kang et al., 2012) and attentional control (Leech and Sharp, 2014). The second study used fMRI to investigate brain function during the Stroop color–word task, a neuropsychological task designed to probe cognitive control (DeVito et al., 2012). In comparison to healthy controls, drug users displayed a greater decrease in brain activation levels in the ventral tegmental area (VTA) and globus pallidus after treatment relative to the pretreatment baseline. Both regions are part of the brain's dopaminergic reward system involved in reinforcement learning, which has been linked to the core symptoms of addiction (Everitt and Robbins, 2005). This study also reported treatment-related changes in the subthalamic nucleus (STN) (as well as the thalamus and hypothalamus) (DeVito et al., 2012), which has been proposed to play a role in impulse control (Bari and Robbins, 2013). Overall, results suggest that treatment with CBT over the course of 2 months led to a reduced recruitment of regions involved in reward processing, attention, and impulse control. The normalized aberrant activation in the brain's reward circuitry could indicate reduced reward sensitivity and reactivity after treatment.

However, since CBT is a multimodal treatment, results cannot be used to ascertain the precise components that may have contributed to the observed changes. Neuroimaging during the use of the select interventions is therefore necessary to achieve a better understanding of the underlying mechanisms.

2.2 COGNITIVE INHIBITION

Cognitive inhibition of craving is one of the cognitive control techniques practiced within standard CBT to enhance the patient's ability to cope with craving and prevent relapse

(Carroll, 1998). The deployment of effective cognitive control strategies for reducing craving is also associated with longer periods of abstinence in smokers (Bliss et al., 1989; Swan et al., 1996). Cognitive techniques most commonly used intuitively by abstinent smokers include self-talk, contemplating the adverse effects of drug use and the positive effects of abstinence, and distraction (Bliss et al., 1989). Similar strategies, along with talking about and reliving craving, are included in standard treatment protocols (Carroll, 1998).

We identified six neuroimaging studies (five fMRI studies in smokers and one PET study in cocaine users) that implemented a cognitive inhibition task within the scanner, to image participants while they were actively engaged in the use of a therapeutic technique. All six studies employed a within-subjects design comparing conditions where craving is induced by visual cues to those where craving is volitionally controlled during cue exposure. Two of the fMRI studies asked smokers to “resist” their urge to smoke using a strategy of their own choice (Brody et al., 2007; Hartwell et al., 2011). In both these studies distraction and ignoring smoking cues were reported as being the most commonly used strategy, but only participants in the second study reported that they also contemplated the adverse effects of their addiction. Importantly, only participants of this second study achieved a significant reduction in craving. The remaining four studies used explicit instructions for implementing cognitive control. These instructions included the following: “ignore your thoughts,” “do not recall how it felt,” “try to relax,” or “shift attention away” during PET imaging in cocaine users (Volkow et al., 2010); “think about long-term consequences associated with smoking” (Kober et al., 2010); “conjure a soothing image from nature” (Zhao et al., 2012); and “reinterpret” (Tabibnia et al., 2014) during fMRI imaging in smokers. Participants in all four studies with explicit instructions achieved a significant reduction of craving during the regulation condition (Table 1).

The most consistent finding across all studies was the recruitment of the dorsal anterior cingulate cortex (dACC) and inferior frontal gyrus (IFG), both core regions of the inhibitory control network (Luijten et al., 2014), during successful cognitive inhibition of craving. All studies reported upregulation of at least one region in this network, which has been reported to be activated during tasks requiring inhibition of a behavioral response (Luijten et al., 2014). Increased activation was also found in areas involved in executive functioning, including the medial superior frontal gyrus (SFG) (Nee et al., 2013) and precentral gyrus, and areas supporting language processing, such as the superior temporal gyrus (STG). Downregulation of regions in the brain’s reward circuitry, including VTA, nucleus accumbens (NAcc), striatum, and parahippocampal gyrus (Everitt and Robbins, 2005; Koob and Volkow, 2010), was the second most consistent result across all studies. This downregulatory effect extended into regions that encode value signals in emotion regulation (vlPFC) (Kohn et al., 2014), represent expected value (OFC) (Chase et al., 2015), and self-relevance during emotional processing (rACC) (Moeller and Goldstein, 2014). Importantly, metabolism/activation levels in a core region of the reward network, the NAcc/striatum, was negatively correlated with metabolism in the inhibitory control network (IFG), and positively correlated with craving (Kober et al., 2010; Volkow et al., 2010). As the NAcc has been most consistently linked to subjective craving (Schacht et al., 2012), this suggests that recruitment of the inhibitory control network is closely associated with reduced reward

processing. Third, regions involved in motivated attention (precuneus, PCC), and self-referential emotional processing (rACC), were not consistently up- or downregulated. Finally, while the dorsolateral prefrontal cortex (dlPFC) has been implicated as a core region in inhibitory control of negative affect (Kober et al., 2010), none of the six studies showed involvement of the dlPFC during cognitive inhibition of craving in a whole-brain analysis (Table 1). In summary, results suggest that the same inhibitory control network as that activated during tasks requiring inhibition of a behavioral response is recruited during cognitive inhibition of craving, thereby exerting regulatory influence on regions in the brain's reward circuitry.

Overall results from these cognitive inhibition studies are comparable to the studies utilizing the CBT approach. Both lines of research suggest that cognitive techniques can be employed to inhibit the reward system of the brain. Importantly, the cognitive inhibition results demonstrate that substance abusers can cognitively recruit their inhibitory control network to enhance control over craving. This suggests that inhibitory control regions, which are chronically hypoactive in addiction (Luijten et al., 2014), can be reactivated through cognitive effort at least in a supervised, explicitly instructed, and monitored environment.

2.3 MOTIVATIONAL INTERVENTIONS

Another technique used in standard treatment is motivational enhancement. Motivational interventions are designed to increase the commitment to make behavioral and psychological changes. Motivational interviewing is one form of intervention that is effective in reducing drug use in addiction (Smedslund et al., 2011). It enhances the motivation for change through reflective listening, analyzing the discrepancy between goals and current behavior, and supporting self-efficacy. A different form of motivational intervention, designed as a stand-alone intervention, uses public service announcements (PSAs) that are broadcasted to modify public behavior. Evidence for the efficacy of these advertisements is mixed (Wang et al., 2013). However, when change messages are tailored to provide individualized support, they do have a measurable effect on drug use behavior in smokers (Lancaster and Stead, 2002).

We found seven fMRI studies that implemented a motivational intervention during imaging, six in smokers and one in alcoholics. All studies contrasted a stronger intervention condition with a weaker intervention or no intervention. Five studies employed a within-subjects design. The first contrasted smoking PSA ads with neutral videos (Langleben et al., 2009); three other studies compared individually tailored verbal smoking cessation messages to low tailored, untailored, and neutral messages, respectively (Chua et al., 2009a,b, 2011); and the fifth study investigated verbal change messages developed during a motivational interview ("I need to stop drinking—it is ruining my life") in comparison to counter change messages ("drinking is not a problem") in alcoholics (Feldstein Ewing et al., 2011). While the direct effects on drug use behavior could not be evaluated with these within-subjects designs, a recognition test administered after the intervention showed improved retention of stronger messages, confirming that stronger interventions had an enhanced effect (Chua et al., 2011; Langleben et al., 2009). To directly evaluate the effects of motivational intervention on smoking behavior, the remaining two studies used a between-subjects design. In one study

participants watched strong or weak smoking PSA ads, as categorized by independent raters (Wang et al., 2013). This study reported differences in smoking behavior after the intervention, with the stronger PSA ad group demonstrating a reduction in smoking after treatment (Table 1). However, the study which compared the effects of “self-focused” versus “other-focused” motivational messages did not find a significant impact on cigarette use behavior (Wilson et al., 2013). This study was the only study that, in both the self-relevant and the control conditions, presented motivational messages which were exclusively focused on the positive effects of quitting rather than the negative consequences of drug use.

With the exception of one study (Feldstein Ewing et al., 2011), all of these studies showed the recruitment of a self-referential processing network (Table 1). This network includes regions such as the medial prefrontal cortex (mPFC) and precuneus, and areas involved in motivated attention (e.g., PCC). Activation in the mPFC has been linked to self-referential processing and self-awareness in healthy subjects (D’Argembeau et al., 2007), with abnormalities in this region contributing to self-awareness deficits in addiction (Moeller and Goldstein, 2014). Similarly, the precuneus has been linked to first-person perspective taking and experience of agency (Cavanna and Trimble, 2006), and has been implicated in addiction (Engelmann et al., 2012; Schacht et al., 2012). The involvement of the PCC suggests high motivated attention during internally directed cognition (Kang et al., 2012; Leech and Sharp, 2014; Schacht et al., 2012). Activation of this self-referential processing network during strong motivational intervention conditions indicates that the presented information was processed with regard to its self-relevance during the intervention. Importantly, activation levels in the precuneus were correlated with the intention to quit smoking in one study (Wang et al., 2013), supporting the notion that the information processed was indeed relevant to therapeutic change. Furthermore, the majority of studies demonstrated recruitment of the inhibitory control network (e.g., IFG and dACC) during strong interventions, suggesting that self-referential information was updated in a way that strengthened inhibitory control. Additionally, imaging results showed the involvement of regions involved in executive functioning (e.g., SFG) (Nee et al., 2013) and the semantic network, including MTG, STG, and IPL, involved in verbal and semantic processing (Binder et al., 2009; Rauschecker, 2011). Evidence for activation level changes in other regions, such as the insula and dlPFC, was limited and inconsistent. Finally, none of the studies reported reduced activation in regions associated with the reward circuit, indicating that there was no immediate impact of motivational interventions on reward sensitivity. Overall, only one study diverged from this very consistent activation pattern, showing reduced activation of the semantic network during the change intervention (Feldstein Ewing et al., 2011). This single study in alcoholics, which used completely individualized messages, comprised of the smallest sample size among all other studies of motivational intervention. The diverging results, which may be driven by differences in procedure and population, should therefore be interpreted with caution.

The imaging results thus generally confirm the efficacy of the motivational intervention. Stronger interventions enhanced self-referential processing, and were associated with a strengthening of inhibitory control networks. This further suggests that cognitive motivational strategies, which in contrast to cognitive inhibition strategies do not directly train self-control of craving, can nevertheless be effective in recruiting inhibitory control.

2.4 AFFECT REGULATION

Addiction is associated with elevated negative affect and deficits in emotion regulation (Cheetham et al., 2010). Importantly, effective affect regulation plays a role in maintaining abstinence, as high negative affect has been shown to predict drug use and relapse (Albein-Urios et al., 2014; Cheetham et al., 2010). Skill training for improving self-regulation of affect is therefore an optional component of standard CBT treatment. The aim of such training is to find strategies for reducing the intensity of the affective response. Cognitive reappraisal, which reduces the intensity of the emotional response through reinterpretation of the situation (Gross, 1998), is one possible cognitive strategy.

We identified two fMRI studies that investigated cognitive reappraisal of negative emotions in addiction. Both studies employed a within-subjects design, contrasting a “regulation” condition with a “watch” condition during presentation of unpleasant high arousing pictures from the International Affective Picture System (IAPS) (Albein-Urios et al., 2014; Tabibnia et al., 2014). Participants were instructed to either look passively at the IAPS pictures during the “watch” condition, or to regulate emotional stress by reinterpreting or distancing themselves from the pictures’ content during the “regulation” condition. The first study was performed in smokers (Tabibnia et al., 2014); and the second in cocaine users, additionally comparing them with healthy controls (Albein-Urios et al., 2014). In both studies participants successfully downregulated subjective emotion during the regulation condition (Table 1), with the cocaine users performing the regulation task equally well as healthy controls, but showing slightly higher overall negative affect according to self-report.

During reappraisal, smokers activated the inhibitory control network (e.g., IFG and dACC), as well as the dlPFC involved in goal setting during motivated behavior (Ballard et al., 2011), and supplementary motor area (SMA) activated during motor planning (Luijten et al., 2014; Table 1). Both inhibitory control regions and the dlPFC have been previously implicated in the regulation of negative affect (Diekhof et al., 2011). Cocaine users, however, did not show any increased activation during affect regulation, but instead showed reduced recruitment of the inhibitory control network (e.g., IFG), areas involved in goal setting, working memory, arousal and attention (e.g., dlPFC, insula, and PCC), thalamus, and the OFC when compared to healthy controls (Table 1). Thus, the cocaine users did not activate the network known to be involved in the regulation of negative affect in healthy subjects (Diekhof et al., 2011), supporting previous behavioral studies on affective dysregulation in addiction (Cheetham et al., 2010). This impaired recruitment of the emotion control network in cocaine users may be related to reported higher overall levels of affect, as similar impairment of recruitment of inhibitory control regions and dlPFC has been shown in patients with pathologically increased negative affect levels (Manber-Ball et al., 2013; New et al., 2009).

The imaging results therefore demonstrate that brain circuits involved in regulation of negative affect partly overlap with brain systems involved in cognitive control of craving, suggesting that recruitment of the inhibitory control network is relevant both during affect regulation and cognitive control of craving. This further implies that disruption in affect regulation may be related to impaired inhibitory control in addiction.

2.5 MINDFULNESS TRAINING

Mindfulness training is a systematic training of attention and self-control (Tang et al., 2013). Participants are asked to attend to any thought, feeling, or sensation that occurs by simply acknowledging it, without attempting to regulate emotions (Westbrook et al., 2013). This technique is designed to help participants maintain a state of inner ease through taking a neutral stance, therefore reducing craving by reducing reactivity to drug-related cues (Westbrook et al., 2013). While mindfulness techniques have not been integrated into standard treatment protocols of addiction, a recent randomized controlled trial shows their effectiveness in reducing smoking behavior (Brewer et al., 2011).

We found two fMRI studies which implemented a mindfulness intervention in smokers. One study compared a group of smokers participating in a 2-week mindfulness training with a second group taking part in a 2-week relaxation training (Tang et al., 2013). As compared to smokers in the relaxation group, smokers in the mindfulness group achieved a reduction in self-reported craving and smoking as measured with carbon monoxide monitor after the 2-week intervention. Changes in brain activation were evaluated with a pre–post training fMRI resting state scan. Brain imaging results largely demonstrated involvement of the same networks as in the other cognitive interventions. After the 2-week mindfulness training participants showed increased recruitment of the inhibitory control network (e.g., IFG and dACC), the self-referential processing network (medial PFC), and a region involved in encoding value signals in emotion regulation (e.g., vlPFC) (Table 1). The second study implemented a within-subjects design to directly investigate the mechanisms of mindfulness techniques during cue-induced craving (Westbrook et al., 2013). Participants reported lower level of craving and distress during mindful attention to smoking cues, which was accompanied by reduced activation level in the subgenual ACC (sgACC) and adjacent vmPFC (Table 1). This reduction in sgACC activation levels likely reflects the reported reduction in craving, as sgACC has been generally implicated in increased craving in smokers (Engelmann et al., 2012; Kober et al., 2010). There was no evidence for an involvement of prefrontal control regions during mindful attention (Westbrook et al., 2013), suggesting that mindfulness may act through a different mechanism than other cognitive interventions. Importantly, brain imaging also demonstrated that mindful attention to drug cues led to a reduced correlation between activation levels in the sgACC and striatum, a core region implicated in reward processing. This indicates that reduced reactivity to drug cues may be the main therapeutic mechanism, as opposed to enhancement of cognitive control in other interventions.

The results therefore suggest that while mindfulness interventions may overall strengthen the same networks implicated in other cognitive interventions, the mechanisms involved may be different.

2.6 NEUROFEEDBACK TRAINING

Neurofeedback training allows participants to self-regulate their own brain response. Participants are presented with either fMRI- or EEG-based feedback derived from select relevant brain processes. Thus, subjects receive instant feedback regarding potentially pathological brain processes, hypothesized to aid in shaping one’s own brain activation in a

desired direction, and thereby improving symptoms. Neurofeedback training can be used either as a stand-alone intervention to modify dysfunctional brain activation patterns without explicit instruction, or as a tool to enhance learning of cognitive and behavioral strategies. A significant advantage of neurofeedback training is its ability to be customized for each participant as the feedback is dependent on the participant's own neural activity. While there is limited evidence for efficacy of EEG neurofeedback training in addiction (Sokhadze et al., 2008), the clinical effectiveness of fMRI neurofeedback awaits to be explored empirically.

We identified six neurofeedback training studies (three fMRI and three EEG) which used neuroimaging to evaluate treatment success. The fMRI neurofeedback training studies were performed in smokers, and comprised two or three training sessions employing a within-subjects paradigm to compare a self-regulation feedback condition with a craving condition (Canterberry et al., 2013; Hanlon et al., 2013; Li et al., 2013). Specifically, participants were asked to use a self-selected strategy to downregulate sgACC activation levels (Canterberry et al., 2013; Li et al., 2013), as a measure of craving-related brain processes, and/or upregulate dorsal mPFC/ middle frontal gyrus (MFG) activation levels to increase prefrontal control over craving (Hanlon et al., 2013; Li et al., 2013). Results showed that participants were able to downregulate the sgACC signal, leading to an associated reduction in craving (Canterberry et al., 2013; Li et al., 2013). Similarly, when smokers were instructed to downregulate sgACC activation while simultaneously upregulating dorsal mPFC/MFG signal, the sgACC reduction was correlated with a respective reduction in craving (Hanlon et al., 2013; Table 1). This demonstrates that regions implicated in increased craving in smokers (Engelmann et al., 2012; Kober et al., 2010) can be controlled by voluntary self-regulation guided by neural feedback only. Results further showed that participants were not able to increase the dorsal mPFC/MFG signal, when presented separately or displayed simultaneously with the sgACC signal. They also did not experience a change in subjective craving during upregulation of dorsal mPFC/MFG (Hanlon et al., 2013; Li et al., 2013). In a future extension and in larger sample sizes it will be important to inspect brain networks that are recruited to support neurofeedback-enhanced self-regulation and investigate the overlap with neurobiological mechanisms of explicitly instructed cognitive inhibition of craving.

The first EEG neurofeedback training study in addiction compared a neurofeed-back training group with treatment as usual in alcoholics (Peniston and Kulkosky, 1989). Neurofeedback training was comprised of eight sessions relaxation training, "autogenic training," in combination with temperature biofeedback and subsequently 15 sessions of EEG neurofeedback training. The EEG feedback signal was derived from alpha and theta EEG frequencies, which are associated with a tranquil/calm/serene state of mind (Peniston and Kulkosky, 1989). At the end of training, neurofeedback participants were able to control the feedback signal, showed an increase in alpha and theta frequencies in comparison to baseline measurement and control participants, and reported a reduction in depression symptoms (Peniston and Kulkosky, 1989; Table 1). Furthermore, they relapsed less often during 13 months of follow-up.

The other two EEG neurofeedback training studies combined a motivational intervention with neurofeedback training in cocaine users. The goal of these training studies was to enhance attention during cognitive involvement rather than induce a relaxed state as in the

previous study with alcoholics. One study employed a between-subjects design to investigate the effect of adding two sessions of neurofeedback to treatment as usual (Stotts et al., 2006). Feedback was provided from the P300 signal, as an index of cognitive involvement, while participants were attending to visual stimuli. The neurofeedback group showed increased P300 signal feedback after training, and reported higher engagement in adjacent treatment in comparison to the control group following treatment as usual. The other EEG neurofeedback training study employed a pre- and posttraining design to investigate change after 12 sessions of neurofeedback based on a sensorimotor rhythm (SMR) protocol (Horrell et al., 2010). Participants were instructed to increase amplitude of SMR frequency, as high SMR amplitude has been linked to improved attention (Horrell et al., 2010). At the end of training, cocaine users demonstrated increased SMR signal, reported reduction in stress and depression symptoms, and tested collaborated reports of decreased drug use (Table 1).

In summary, while the neurobiological mechanisms of neurofeedback training cannot be critically evaluated due to the diverging approaches, limited sample sizes and low number of studies, the reviewed studies do suggest that learning to self-regulate brain signals has the potential to reduce drug-related behaviors.

3 SUMMARY

Overall, results suggest that imaging is a suitable tool to investigate the mechanisms underlying cognitive and motivational interventions in addiction. Imaging studies have shown that CBT dampens reward sensitivity to drug-related cues, whereas cognitive inhibition and motivational interventions recruit and strengthen the inhibitory control network (Fig. 1). Cognitive inhibition reactivates the chronically hypoactive inhibitory control network, leading to an associated reduction in the reactivity of the brain’s reward circuitry. Motivational interventions enhance self-referential processing, and increase activation in inhibitory control regions. Affect regulation activates an overlapping inhibitory network. The mechanism of neurofeedback training remains to be explored. Interestingly, mindfulness training was the only intervention showing a reduction of activation in craving-related brain systems, without direct involvement of prefrontal control regions.

This pattern of results generally confirms that chronically hypoactive regions implicated in prefrontal control in drug addiction (Goldstein and Volkow, 2011) can be normalized through cognitive and motivational/emotional interventions. Results also demonstrate that different cognitive interventions act, at least partly, through a common mechanism, supporting a previous meta-analysis that posited the recruitment of the inhibitory control network as a shared therapeutic mechanism between cognitive and pharmacological interventions (Konova et al., 2013). Importantly, this conclusion implies that learned coping mechanisms may partially generalize across different methods for skills training. It would therefore be valuable to investigate directly if there are transferable effects between different modalities of training, and to systematically compare different mechanisms within one study sample. Overall, the low number of implemented training protocols warrants further research in all reviewed training modalities.

4 CONCLUSION AND FUTURE DIRECTIONS

Two-thirds of the reviewed treatment studies were performed in smokers. Given this clear gap between research in nicotine addiction as compared to other substance use disorders, this review cannot generalize conclusions to other substance use disorders. Aside from extending results to additional substance abusing populations and optimizing study paradigms, future studies should draw on new analysis methods to investigate the interaction between regions, and understand dynamic reconfigurations within networks. Studies investigating how changes in the recruitment of brain networks over time predict treatment success are necessary. Understanding the reconfiguration of brain networks during cognitive interventions may allow us to build a theoretical model of the relevant neurobiological mechanisms of treatment in addiction. Such a theoretical model may guide the development of effective treatment strategies in substance use disorders in the future.

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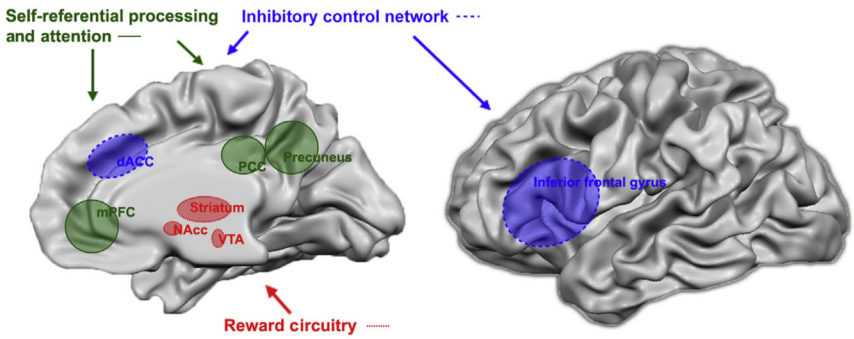

FIGURE 1.

Brain circuits in cognitive interventions in addiction. Common results across intervention modalities were the normalization of aberrant activity in the brain's reward circuitry, and the recruitment and strengthening of the brain's inhibitory control network (regions involved in reward processing are depicted in red (light gray in the print version): e.g., striatum; NAcc, nucleus accumbens; VTA, ventral tegmental area; inhibitory control network is shown in blue (dark gray in the print version): e.g., IFG, inferior frontal gyrus; dACC, dorsal anterior cingulate). During motivational interventions regions involved in self-referential processing and motivated attention were activated (in green (light gray in the print version): mPFC, medial prefrontal cortex; PCC, posterior cingulate cortex, precuneus).

Table 1

Reviewed Studies

First Author	Year	Treatment Modality	Intervention	Subjects	Addiction	Behavioral Effects	Imaging	Main Contrast	Brain Effects
Costello	2010	CBT	8 week	EG = 20 PG = 17	Nicotine	↓ Smoking, craving	FDG PET	Group * treatment interaction	Resting state: ↓ PCC
DeVito	2012	CBT	8 week	EG = 12 HC = 12	Mixed	↓ Drug use, Stroop interference	3T fMRI	Group * treatment interaction	Stroop task: ↓ VTA, globus pallidus, STN, thalamus, hypothalamus
Brody	2007	Cognitive inhibition	Self-select	EG = 42	Nicotine	NS on craving	1.5T fMRI	Resist>crave	↑ dACC, medial SFG, rACC, precuneus, PCC; ↓ cuneus, MOG, MTG, postcentral
Hartwell	2011	Cognitive inhibition	Self-select	EG = 32	Nicotine	↓ Craving	3T fMRI	Resist>crave	↑ IFG, STG, precentral; ↓ mid cingulate, precuneus, cuneus
Volkow	2010	Cognitive inhibition	Four strategies	EG = 24	Cocaine	↓ Craving	FDG PET	Inhibit>watch	↓ NAcc, OFC; ↓ NAcc negatively correlated with ↑ IFG
Kober	2010	Cognitive inhibition	Consequences	EG = 21	Nicotine	↓ Craving	3T fMRI	Later>now	↑ Medial SFG, IFG, postcentral, STG, MTG, ITG; ↓ striatum (correlated with craving), VTA, OFC, rACC, insula, parahippocampal, dACC, dlPFC, PCC, MTG, IPL
Zhao	2012	Cognitive inhibition	Soothing	EG = 16	Nicotine	↓ Craving	3T fMRI	Reappraise>watch	↑ dACC, cuneus, parietal, paracentral, cerebellum; ↓ vlPFC
Tabibnia	2014	Cognitive inhibition	Reappraise	EG = 25	Nicotine	↓ Craving	3T fMRI	Reappraise>watch	↑ dACC, precentral, thalamus, insula
Langleben	2009	Motivational intervention	PSA	EG = 18	Nicotine	↑ Recognition	3T fMRI	Ad>neutral video	↑ mPFC, STG, parahippocampal, precuneus,

First Author	Year	Treatment Modality	Intervention	Subjects	Addiction	Behavioral Effects	Imaging	Main Contrast	Brain Effects
									lingual, caudate, cerebellum; ↓ insula, dlPFC, SPL, occipital
Wang	2013	Motivational intervention	PSA	Strong = 33 Weak = 30	Nicotine	↓ Smoking	3T fMRI	Strong ad>weak ad	↑ mPFC (predicted reduced smoking), precuneus correlated with intention to quit smoking
Ghua	2009a	Motivational intervention	Tailored messages	EG = 24	Nicotine	NA	3T fMRI	High tailored>low tailored>generic	↑ mPFC, medial SFG, IFG, lingual, precentral, MTG, STG, precuneus, PCC
Ghua	2009b	Motivational intervention	Tailored messages	EG = 41	Nicotine	NA	3T fMRI	Tailored (3 sorts)> neutral	↑ mPFC, medial SFG (personalized), precuneus/PCC (personalized), vmPFC (motivational), dlPFC (instructional)
Ghua	2011	Motivational intervention	Tailored messages	EG = 91	Nicotine	↑ Recognition	3T fMRI	Tailored> untailored>neutral	↑ mPFC, medial SFG, IFG, MTG, STG, precuneus, PCC, IPL, cerebellum
Feldstein Ewing	2011	Motivational intervention	Individual message	EG = 10	Alcohol	NA	3T fMRI	Change message>counter change message	↓ SFG, postcentral, IPL
Wilson	2013	Motivational intervention	Self-focused	Self = 28 Other = 29	Nicotine	NS	3T fMRI	Self-focused > other-focused	↑ mPFC, IFG, rACC, dACC, insula, precuneus, IPL, cerebellum
Tabibnia	2014	Emotion regulation	Reappraisal	EG = 25	Nicotine	↓ Negative emotion	3T fMRI	Reappraise>watch	↑ IFG, dACC, dlPFC, pre-SMA
Albein-Urious	2014	Emotion regulation	Reappraisal	EG = 17 HC = 18	Cocaine	↓ Negative emotion	3T fMRI	Group * reappraisal interaction	↓ IFG, dlPFC, OFC, insula, thalamus, PCC, cuneus, occipital, cerebellum

First Author	Year	Treatment Modality	Intervention	Subjects	Addiction	Behavioral Effects	Imaging	Main Contrast	Brain Effects
Tang	2013	Mindfulness	Meditation	EG = 15 PG = 12	Nicotine	↓ Smoking, craving	3T fMRI	Post>pre	Resting state: ↑ IFG, dACC, mPFC, vlPFC
Westbrook	2013	Mindfulness	Mindful attention	EG = 47	Nicotine	↓ Craving, distress	3T fMRI	Mindful>watch	↓ sgACC (↓ correlation sgACC with striatum), vmPFC
Hanlon	2013	Neurofeedback	↓ sgACC ↑ dmPFC simultaneous	EG = 15	Nicotine	NS	3T fMRI	Regulate>crave	↓ sgACC (↓ sgACC correlated with decrease in craving)
Li	2013	Neurofeedback	↓ sgACC alternating with ↑ dmPFC/MFG	EG = 10	Nicotine	↓ Craving (↓ sgACC)	3T fMRI	Regulate>crave	↓ sgACC (↓ sgACC correlated with decrease in craving)
Canterberry	2013	Neurofeedback	↓ sgACC	EG = 9	Nicotine	↓ Craving	3T fMRI	Regulate>crave	↓ sgACC
Peniston	1989	Neurofeedback	Autogenic training+↑ alpha/theta	EG = 10 PG = 10	Alcohol	↓ Relapse, depression	EEG	Group * treatment interaction	↑ % alpha, % theta, amplitude alpha (parietal)
Stotts	2006	Neurofeedback	Motivational+↑ P300	EG = 17 PG = 14	Cocaine	↑ Adherence to treatment	EEG	Group * treatment interaction	↑ P300
Horrell	2010	Neurofeedback	Motivational+↑ SMR	EG = 10	Cocaine	↓ Drug use, stress, depression	EEG	Neurofeedback > baseline	↑ SMR; ↓ gamma (during cue exposure)

CBT, cognitive behavioral therapy; EG, experimental group; PG, placebo patient group; HC, healthy control group; VTA, ventral tegmental area; NAcc, nucleus accumbens; STN, subthalamic nucleus; IFG, inferior frontal gyrus; SFG, superior frontal gyrus; OFC, orbitofrontal cortex; vmPFC, ventromedial prefrontal cortex; vlPFC, ventrolateral prefrontal cortex; mPFC, medial prefrontal cortex; dmPFC, dorsal medial prefrontal cortex; sgACC, subgenual anterior cingulate cortex; rACC, rostral anterior cingulate; dACC, dorsal anterior cingulate cortex; dlPFC, dorsolateral prefrontal cortex; ITG, inferior temporal gyrus; MTG, middle temporal gyrus; STG, superior temporal gyrus; PCC, posterior cingulate cortex; IPL, inferior parietal lobe; SPL, superior parietal lobe; MOG, middle occipital gyrus; P300, positive 300; SMR, sensory motor rhythm.