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Review

Common and distinct neural targets of treatment: Changing brain function in substance addiction

Anna B. Konova[a,b], Scott J. Moeller[a], Rita Z. Goldstein[a,*]

[a] Departments of Psychiatry & Neuroscience, Icahn School of Medicine at Mount Sinai, New York, NY 10029, United States
[b] Department of Psychology, Stony Brook University, Stony Brook, NY 11794, United States

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ABSTRACT

Neuroimaging offers an opportunity to examine the neurobiological effects of therapeutic interventions for human drug addiction. Using activation likelihood estimation, the aim of the current meta-analysis was to quantitatively summarize functional neuroimaging studies of pharmacological and cognitive-based interventions for drug addiction, with an emphasis on their common and distinct neural targets. More exploratory analyses also contrasted subgroups of studies based on specific study and sample characteristics. The ventral striatum, a region implicated in reward, motivation, and craving, and the inferior frontal gyrus and orbitofrontal cortex, regions involved in inhibitory control and goal-directed behavior, were identified as common targets of pharmacological and cognitive-based interventions; these regions were observed when the analysis was limited to only studies that used established or efficacious interventions, and across imaging paradigms and types of addictions. Consistent with theoretical models, cognitive-based interventions were additionally more likely to activate the anterior cingulate cortex, middle frontal gyrus, and precuneus, implicated in self-referential processing, cognitive control, and attention. These results suggest that therapeutic interventions for addiction may target the brain structures that are altered across addictions and identify potential neurobiological mechanisms by which the tandem use of pharmacological and cognitive-based interventions may yield synergistic or complementary effects. These findings could inform the selection of novel functional targets in future treatment development for this difficult-to-treat disorder.

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* Corresponding author. Tel.: +1 212 824 9312; fax: +1 212 996 8931.
E-mail address: rita.goldstein@mssm.edu (R.Z. Goldstein).

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1. Introduction

Addiction is characterized by continued drug-seeking and drug use despite reduced pleasure derived from the drug and often in the face of catastrophic social, emotional, and legal consequences. The recurrent nature of the disease poses a large economic burden to society and significant personal distress to the individual and their family (Volkow et al., 2011). Limited treatment options are available, and many are only effective in a subset of individuals. Thus, a critical step toward improving treatments for addiction is to clarify the neurobiological mechanisms of therapeutic interventions that are currently used or under investigation.

Addiction affects a distributed set of brain regions and neurotransmitter systems. Although different drugs of abuse have different mechanisms of action, they all increase dopamine release in what has traditionally been labeled as the brain's reward circuit to exert their reinforcing effects (Chen et al., 2010; Sulzer, 2011). Regions comprising this circuit include midbrain (ventral tegmental area and substantia nigra) and basal ganglia structures including the ventral (nucleus accumbens) and dorsal striatum. Chronic drug use modifies dopamine signaling in these regions, facilitating the transition from recreational to habitual use that characterizes addiction (Everitt and Robbins, 2005). These changes result in a state of impaired motivational drive and difficulty with inhibiting conditioned responses to drug-related cues, undermining more goal-directed behavior (Kalivas and Volkow, 2005). Following protracted use, exposure to drug-related cues activates the ventral striatum (among other regions like the cingulate cortices and amygdala) across substance addictions (Chase et al., 2011; Kuhn and Gallinat, 2011) in ways that may facilitate relapse to drug use (Grusser et al., 2004; Kosten et al., 2006). In addition to craving, the negative emotional state of withdrawal during periods of abstinence may also involve the reward circuit (Treadway and Zald, 2011), as well as the amygdala and autonomic structures (Koob and Volkow, 2010).

However, brain regions (and their corresponding functions) outside the reward system also appear affected by chronic drug use. In particular, drug addicted individuals exhibit alterations in the anterior cingulate, orbitofrontal, and dorsolateral prefrontal cortices, where abnormalities are linked to impaired emotion regulation and inhibitory control (Goldstein and Volkow, 2011). Thus, the ability of addicted individuals to achieve abstinence may be diminished both by pathologically strengthened drug-seeking behavior and impairments in the capacity to regulate such behavior (Everitt and Robbins, 2005; Kalivas, 2009). The effectiveness of therapeutic interventions may consequently depend on the ability of these interventions to target and normalize addiction-related deficits in reward regions to decrease motivation for drugs (e.g., craving and withdrawal) and in control regions to increase inhibitory control, respectively. Furthermore, while different drugs of abuse share common neurobiological substrates (e.g., in reward and cognitive control regions), differences also exist and these differences may have implications for addiction treatment. For example, the influence of contextual triggers on relapse to drug use, supported by the medial prefrontal cortex, appears to be more profoundly impacted by stimulant use than by opiate use (Badiani et al., 2011); similarly, visuospatial attention, supported by occipital, parietal, and medial temporal lobe regions, appears to be more profoundly impacted by alcohol use; impulsivity and cognitive flexibility, supported by the orbitofrontal cortex, striatum, and thalamus, by alcohol and stimulant use; and fluency and working memory, supported by inferior frontal and parietal regions, by opiate use than by use of other substances, respectively [for review, see (Crunelle et al., 2012; Fernandez-Serrano et al., 2011; van Holst and Schilt, 2011)]. Thus, therapeutic interventions for addiction may share a common neural mechanism across addictions, and/or a unique mechanism by specific addiction type.

A number of therapeutic interventions for addiction have been put forth and some have been tested in clinical trials with the goal of reducing the amount or frequency of drug use, or extending time to relapse. These interventions can be broadly divided into pharmacological and cognitive-based (psychosocial) strategies [for review, see (Potenza et al., 2011)]. Briefly, pharmacological interventions are proposed to primarily target the reward circuit and influence neural processes that mediate negative mood and craving. Most pharmacological interventions for addiction block or mimic the reinforcing effects of drugs (Potenza et al., 2011). For example, among others, studies have tested the efficacy of nicotinic receptor agonists (e.g., varenicline, nicotine patch) and antagonists (e.g., bupropion) for nicotine addiction (Cahill et al., 2010; Eisenberg et al., 2008), opioid receptor agonists (e.g., methadone, buprenorphine) and antagonists (e.g., naltrexone) for opioid (Johansson et al., 2006) and alcohol (Srisurapanont and Jarusuraisin, 2005) addiction, and dopamine and norepinephrine agonists (e.g., psychostimulants including modafinil and methylphenidate) for stimulant addictions (Anderson et al., 2009; Castells et al., 2010; Dackis et al., 2005, 2012; Longo et al., 2010). Cognitive-based interventions are proposed to primarily target executive control processes dependent on the prefrontal cortex. These interventions aim to help addicted individuals recognize and implement strategies to change cognitions and behaviors associated with drug use, and to increase motivation for change (Carroll and Onken, 2005). Interventions that have been tested in their efficacy for motivating change include motivational interventions (e.g., smoking cessation messages), psychoeducation (e.g., health-related information), and contingency management (e.g., receiving monetary incentives) (Burke et al., 2003; Dutra et al., 2008). Interventions that provide strategies for change include cognitive behavioral therapy (CBT) and its active components (e.g., self-regulation strategies, exposure therapy) (Dutra et al., 2008; Magill and Ray, 2009). Interventions that motivate individuals to quit and remain abstinent after quitting may involve the reward circuit and regions such as the ventromedial prefrontal cortex, anterior and posterior cingulate cortex, and insula that are involved in delay discounting (Luhmann, 2009), or the drive for immediate at the expense of delayed yet larger rewards, and effort (Prevost et al., 2010; Treadway et al., 2012). Taken together, pharmacological interventions may primarily target brain reward regions, while cognitive-based interventions may target *both* reward and control regions.