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SUBSTANCE USE AND RELATED DISORDERS (F LEVIN AND E DAKWAR, SECTION EDITORS)

Neuroimaging and Biomarkers in Addiction Treatment

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Abstract Neuroimaging studies have made a significant contribution to the efforts to identify measurable indices, or biomarkers, of addictions and their treatments. Biomarkers in addiction treatment are needed to provide targets for treatment, detect treatment subgroups, predict treatment response, and broadly improve outcomes. Neuroimaging is important to biomarkers research as it relates neural circuits to both molecular mechanisms and behavior. A focus of recent efforts in neuroimaging in addiction has been to elucidate the neural correlates associated with dimensions of functioning in substance-use and related disorders, such as cue-reactivity, impulsivity, and cognitive control, among others. These dimensions of functioning have been related to addiction treatment outcomes and relapse, and therefore, a better understanding of these dimensions and their neural correlates may help to identify brain-behavior biomarkers of treatment response. This paper reviews recent neuroimaging studies that report potential biomarkers in addiction treatment related to cue-reactivity, impulsivity, and cognitive control, as well as recent advances in neuroimaging that may facilitate efforts to determine reliable biomarkers. This important initial work has begun to identify possible mediators and moderators of treatment response, and multiple promising indices are being tested.

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Introduction

Neuroimaging has helped to elucidate that substance-use disorders are associated with changes in brain structure, function, and neurochemistry. Neuroimaging studies have improved our understanding of the neural correlates of addiction and how these relate to addictive behavior. Nevertheless, the potential impact of neuroimaging on treatment development for addictions has yet to be fully realized. Despite substantial advances, treatments are often not fully effective, and addiction continues to be a major public health burden [1]. Neuroimaging has contributed to our appreciation of the complexity of addiction, highlighting the need for measurable indices, or biomarkers, of addiction to improve treatment outcomes. A "biomarker" typically refers to a measurable indicator of normal or abnormal biological processes or response to treatment [2]. In substance-abuse research, biomarkers are needed to clarify how or why a treatment has an effect, on whom and under what circumstances.

Recent advances in neuroimaging are affording greater opportunities to identify brain biomarkers that might be used to improve outcomes of treatment for substance-use disorders. Neuroimaging is a critical tool in biomarker development because it relates neural circuits to both molecular mechanisms and behavior or clinical variation. In particular, neuroimaging studies are central to an emerging research effort to identify cross-diagnostic processes in substance-use and related disorders based on both behavior and neural circuits [3]. In this work, alterations in brain activation patterns related to dimensions of functioning in individuals with addictions may be considered to represent abnormal processing associated with addictive behavior. Such research holds significant

potential for identifying targets for treatment, detecting subgroups for treatment selection, and/or predicting treatment response [4]. As disorder heterogeneity and individual variation pose significant challenges for delivering effective treatment, considering addictions in terms of dimensions of functioning may help to elucidate factors relevant to treatment response and lead to more specific, more effective treatments [4]. This paper reviews neuroimaging research seeking to identify potential biomarkers of treatment response from several dimensions of functioning relevant to addiction: cue-reactivity, impulsivity, and cognitive control.

Reactivity to Drug Cues

Enhanced reactivity to drug-related cues is characteristic of substance-use and related disorders, and cue-reactivity is associated with craving and relapse [5]. A better understanding of the neural correlates of cue-reactivity can provide potential brain biomarkers for substance-abuse treatment [6]. In general, functional neuroimaging signals are derived from changes in oxygenated hemoglobin related to local changes in cerebral blood flow and brain metabolism. As such, they provide an indirect measure of neuronal activity and may be used to track the neural correlates of mental activity [7]. Multiple functional neuroimaging studies have used various cue-reactivity paradigms to measure neural responses to drug cues and craving. Newer methods for quantitative coordinate-based meta-analyses of neuroimaging studies, such as activation-likelihood estimation (ALE, [8]), are being used to establish consensus across studies [9, 10•, 11–13]. The ALE approach identifies brain regions that show consistent changes in brain activation patterns across neuroimaging studies, thereby increasing sample size and factoring out effects due to variations in study design. A recent ALE meta-analysis [10•] found convergence across studies of drug (nicotine, alcohol, cocaine, marijuana, and heroin) and non-drug (gambling) cue-reactivity showing increased activity in the amygdala, ventral striatum, and orbitofrontal cortex (OFC), among other regions, suggesting altered processing in these brain regions associated with potentially maladaptive response to cues in addiction. The insula has also been found in several ALE meta-analyses of smoking cue-reactivity [9, 13], including in studies that correlate cue-reactivity to craving [13]. These studies have also begun to distinguish neural cue-reactivity between subgroups such as treatment-seeking and non-treatment-seeking drug users [10•] or nicotine-deprived and non-nicotine-deprived smokers [9].

Multiple functional neuroimaging studies have mapped the relationship between the neural correlates of cue-reactivity and addiction treatment outcomes. This work has shown that cue-reactivity in the limbic cortico-striatal dopamine system is related to craving and relapse [14]. In a recent functional magnetic resonance imaging (fMRI) study, alcohol-dependent individuals showed an increased response to neutral-relaxing cues in the ventromedial prefrontal cortex (vmPFC), anterior cingulate cortex (ACC), ventral striatum, and precuneus, and these activations were associated with higher craving during alcohol or stress cues and a greater likelihood of relapse [15•]. In addition, decreased response in the vmPFC, ACC, precuneus, and insula during stress cue exposure was related to greater relapse severity [15•]. Another recent study [16] found that alcohol-dependent individuals who relapsed showed pre-quit alcohol cue-reactivity-related activation in the medial prefrontal cortex (mPFC) and diminished volumes of the mPFC, OFC, and ACC, whereas abstinent individuals showed increased cue-reactivity-related activation in the midbrain and ventral striatum and increased functional connectivity between the midbrain and amygdala and midbrain and OFC. Another study [17] found that smokers who relapsed showed increased pre-quit cue-reactivity-related activation in the prefrontal cortex (PFC), ACC, insula, and amygdala, as well as reduced functional connectivity between a cue-reactivity network (e.g., insula, amygdala, ACC) and brain regions involved in response inhibition, including the dorsal ACC (dACC) and dorsolateral prefrontal cortex (dlPFC). In that study, smoking cue-reactivity-related activation of the insula and dACC correlated with attentional bias to smoking-related cues, and together, these indices were strongly related to relapse [17]. These and similar studies suggest that neural cue-reactivity, such as dysfunction of the vmPFC, ACC, and related circuits, may represent indicators of substance-abuse relapse [6]. As more studies are conducted, it will be useful to establish consensus on the specific neural correlates of cue-reactivity related to treatment outcomes. An ALE meta-analysis of treatment effects has been attempted [12], but was limited by the small number of studies and by studies reporting correlations only with specific brain regions of interest.

New approaches in neuroimaging are contributing to potential systems-level biomarkers of cue-reactivity and craving. Supervised machine learning or pattern-analysis methods are being used to better define the neural circuits of craving at the level of the individual [18], which may lead to the identification of reliable indicators of treatment outcome. Real-time fMRI is being used to investigate brain states in real time [19], including those related to mental representations of addictive behaviors such as the modulation of craving [18]. Real-time fMRI has also been used to relate with greater temporal specificity subjective experience to objective data [20], and this approach may be used to investigate how first-person experiences such as self-reported craving relate to neural correlates such as those associated with cue-reactivity. Real-time fMRI neurofeedback has also shown potential as a direct clinical neurotherapeutic intervention [21] to target dimensions of functioning in addiction, such as by training

smokers to self-regulate their brain activations and craving experiences in response to drug cues [22, 23].

Impulsivity

Impulsivity—making decisions quickly, without forethought or regard for potential consequences [24]—is associated with most forms of drug taking and clinical disorders including substance abuse and addiction, attention deficit hyperactivity disorder (ADHD), personality disorders, and others [25]. Impulsivity is a multifaceted construct; multiple domains or dimensions are typically identified, with two such domains often identified being impulsive choice/decision-making and impulsive action or rapid response disinhibition [26]. Impulsivity has been associated with poorer addiction treatment outcomes [27, 28]; thus, a better understanding of the neural correlates of impulsivity and its different dimensions may lead to the identification of brain biomarkers related to treatment response. In neuroimaging studies, the neural correlates of impulsivity have been assessed using magnetic resonance imaging (MRI) to correlate individual variations in impulsivity with volumetric measures of specific brain structures; positron emission tomography (PET) to characterize impulsivity-related neurochemistry; and fMRI to measure brain activation patterns during impulsive behaviors such as poor response inhibition, steep temporal discounting, and disadvantageous decision-making [29–31]. From such studies, neurobiological models of impulsivity have been proposed to include networks of brain regions involving the OFC, ACC, vmPFC, and ventral striatum (among other regions), with key roles for dopamine and serotonin (among other neurotransmitters) [24].

Reduced dopamine function in the striatum has been associated with decreased metabolism in prefrontal regions implicated in impulsivity including the OFC and ACC, and impaired dopaminergic modulation of these prefrontal regions has been postulated to underlie impulsive drug taking in addiction [32]. One approach to testing whether the neural correlates of impulsivity relate to treatment outcomes has been to assess dopamine function (receptor availability and displacement) in the striatum. A recent PET study [33] found that lower pretreatment dopamine transmission in the limbic striatum of cocaine-addicted individuals was associated with poorer treatment outcomes, although the behavioral treatment did not change dopamine transmission in treatment responders. Along similar lines, low pretreatment striatal dopamine function was prospectively related to relapse in methamphetamine-addicted individuals [34]. Both studies used raclopride and focused on D2/D3 receptors in the striatum. Although these striatal receptors have been linked to addictions in preclinical and clinical studies of drug addictions and have been related to impulsivity [35], a broader range of studies involving other brain regions and other neurotransmitter systems is needed to identify neurochemical and neural targets for treatment development. Another approach has been to use fMRI to test whether alterations in the neural correlates of reward processing, a central component of addictions that has been related to impulsivity, are related to treatment response. Two recent small fMRI studies have found that heightened pretreatment reward response in the ventral striatum relates prospectively to relapse in treatment for cocaine [36] and cannabis [37] use disorders. These findings suggest the need for larger longitudinal studies in which neuroimaging measures of reward processing, impulsive behavior, and other factors are examined with respect to treatment outcomes.

Neuroimaging studies are also helping to elucidate the mechanisms by which dimensions of function such as impulsivity may moderate the effects of behavioral and pharmacological treatments in substance-use and related disorders [28]. For example, in alcohol-dependent individuals, poorer response inhibition prior to treatment with modafinil, a cognitive enhancer, was associated with better outcomes [e.g., 38], indicating that modafinil may only be a useful treatment for alcohol in individuals with greater impulsivity. Modafinil has been found to improve response inhibition in alcohol-dependent individuals by influencing activations in brain regions involved in successful inhibition, including the thalamus and supplementary motor area, but only in those with poor initial response inhibition [39]. These and similar studies are generating preliminary data that impulsivity and the related neural correlates may relate importantly to treatment outcomes in addiction.

Cognitive Control

Most forms of substance abuse and addiction are associated with impairments in cognitive control—broadly defined as goal-directed guidance of information processing and behavior [40]—including deficits in response inhibition, cognitive flexibility, working memory, and attention, among others [27]. Cognitive deficits have been associated with poorer treatment retention and, in some cases, poorer outcomes in addiction treatment [41]. Cognitive deficits are therefore relevant to determining potential indices of treatment response. Brain regions implicated in cognitive control include the ACC for conflict monitoring, dlPFC for conflict resolution, right inferior frontal gyrus (IFG) for inhibitory control, and regions in the midbrain and striatum for reward-related learning [42]. Neuroimaging studies indicate that drug-addicted individuals show altered function [e.g., 43], structure [e.g., 44], and connectivity [e.g., 45] across these brain regions and that these changes are associated with cognitive deficits.

Few neuroimaging studies have directly tested whether the neural correlates of cognitive control are related to treatment

outcomes and relapse [42, 46; reviews]. Several of these have measured error processing, a critical component of cognitive control that is disrupted in substance-use and related disorders [42]. A recent fMRI study found that reduced activity in the dACC during error processing related prospectively to cocaine relapse and earlier time to relapse, as did activity in the thalamus and left insula in females and males, respectively [47•]. Another recent study found that reduced baseline error-related negativity, an electrophysiological index of cognitive control in electroencephalography (EEG), was associated with cocaine use after treatment [48]. These studies suggest that reduced brain activity related to error processing may be a marker of relapse risk [46].

Other studies have tested the Stroop color-word interference task [49] to determine how cognitive control deficits are related to treatment response. fMRI Stroop is associated with activation of the dACC, dlPFC, insula, striatum, and thalamus [50]. A behavioral intervention for substance-use disorders resulted in improved Stroop performance and lower task-related activations in the ACC, dlPFC, rIFG, and midbrain [51]. Although no relation to treatment response was reported, in earlier studies, Stroop-related activations have been associated with treatment outcomes [e.g., 52]. In a more recent study [53], adolescent smokers with greater pretreatment Stroop-related activity in the ACC, IFG, insula, and thalamus showed a greater reduction in smoking with a behavioral intervention. In a study of pathological gamblers [50], lower pretreatment Stroop-related activity in the vmPFC, ventral striatum, and other brain regions correlated with improved outcomes from a behavioral intervention. Given the small sample sizes in these studies, more work is needed to test the relationship between the neural correlates associated with individual differences in cognitive control and treatment outcomes.

There is evidence that addressing cognitive deficits may improve treatment outcome. Behavioral and pharmacological therapies targeting cognitive functioning have shown promise in the treatment of substance-use and related disorders [41]. Short-term treatment of nicotine dependence with varenicline has been associated with increased working-memory-related activations in the dACC/mPFC and dlPFC and the activations correlated with improved task performance in heavy smokers [54]. Modafinil has been found to boost learning in methamphetamine-addicted individuals and increase task-related activations in the ACC, IFG, and insula [55]. The stimulant methylphenidate has been found to improve performance on cognitive tasks in cocaine-dependent individuals and increase task-related activations in the ACC [56], or reduce activations in the vmPFC [57], suggesting greater task-related engagement. Galantamine treatment has been found to improve sustained attention in abstinent chronic cocaine users [58], and a recent pilot study suggests the possible efficacy of galantamine in reducing cocaine use [59]. These pharmacotherapies offer brain-behavior enhancement that may have clinical utility by targeting cognitive control dimensions in addiction treatment [41], and more studies are warranted to investigate this possibility.

Resting-State Networks

Resting-state functional connectivity has potential to provide systems-level biomarkers of addictions and their treatment. Spontaneous, correlated fluctuations in brain activity at rest, as measured by resting-state fMRI, represent functional brain networks, and alterations in these networks may underlie addictive processes. Studies have related resting-state functional connectivity to genetic, neural, and behavioral measures of cue-reactivity [60], impulsivity [61], and cognitive control [62], among others [63], and beginning work has related alterations in resting-state functional connectivity to treatment outcomes in addictions [e.g., 64, 65]. Other studies provide evidence for pharmacological modulation of resting-state networks as a mechanism of drug effects in the treatment of substance-use and related disorders [66•, 67, 68]. In a recent study, the relative strength of resting-state interactions between three major brain networks—salience, default mode, and executive control—was related to craving and cognitive deficits during withdrawal in smokers [69•]. These findings suggest that the salience network may toggle resources between the default-mode and executive-control networks, and abstinence-related craving may bias this coupling toward the default-mode network, such that less suppression of default-mode activity combined with decreased executive control results in cognitive deficits [69•]. These findings were based on a proposed metric, the resource allocation index, which integrates network dynamics and is an example of a potential brain biomarker of addiction to be derived from resting-state data.

Looking forward, the integration of large resting-state functional connectivity datasets (e.g., 1000 Functional Connectomes Project, www.nitrc.org/projects/fcon_1000, as in [70], and Human Connectome Project, www.humanconnectomeproject.org [71–73]) and data sharing (e.g., International Neuroimaging Data-sharing Initiative, http://fcon_1000.projects.nitrc.org/) have enormous potential to elucidate brain connectivity patterns related to addictions and their treatment.

Moderators and Mediators

The extent to which a factor may influence or moderate treatment outcome versus operate through or mediate treatment outcome may be tested with neuroimaging data. Mediation analyses have been used to examine different dimensions of function related to addiction. For example,

activity in the ventral striatum has been found to mediate fully the relationship between dlPFC activity and regulation of craving, suggesting that the inverse relationship between dlPFC activity and craving operates through dlPFC effects on ventral striatum [74]. These findings suggest a neural mechanism for the effects of therapies targeting craving. Likewise, hippocampal volume has been found to mediate the relationship between pre-treatment cocaine use and within-treatment cocaine abstinence in cocaine-dependent individuals receiving cognitive behavioral therapy (CBT) [75]. These findings suggest that hippocampal structure (and possibly function, although this possibility warrants direct investigation) may be particularly relevant to the mechanisms by which CBT operates and may represent an important neural target for treatment development for cocaine and possibly other addictions. More generally, neural correlates of dimensions of functioning derived from neuroimaging studies may indicate moderators and mediators of addiction treatment response (Fig. 1).

Limitations

Neuroimaging studies indicate that dimensions of functioning in addiction are multifaceted constructs with multiple dimensions that rely on distinct but overlapping neural mechanisms and show variation across individuals. These factors contribute to considerable complexity in treatment, but should inform the development of more specific and more effective treatments. Moreover, dysfunction in neural circuits may predispose to or represent a consequence of substance use or both [e.g., 76•, 77]. Thus, it is informative to investigate the neural correlates of dimensions of functioning in other disorders that do not share the same pharmacological or neurotoxic effects as drugs (e.g., gambling disorder). Further investigation of the neural factors associated with specific components of addictions will aid in determining which may be most predictive of treatment responses.

The use of neuroimaging to identify biomarkers of treatment outcomes is challenged by limitations of neuroimaging. Reproducibility in neuroimaging is limited by both differences in methods and designs across studies, as well as by heterogeneity in patient groups and differences in substances, treatments, and outcome indicators, among other factors [78]. Another challenge to determining biomarkers from these studies is that findings in neuroimaging are typically derived from group-level analyses that may not hold at the level of the individual. Many of these limitations may be overcome with recent advances in neuroimaging, such as those described in this review. For example, quantitative meta-analyses allow for testing of brain-behavior hypotheses across diverse tasks and groups [8, 79, 80] (with the possible added benefit of better predicting mental states from brain activation patterns [81]). Such efforts should help to determine more precisely the reproducibility and generalizability of findings. Resting-state fMRI enables task-independent measures to characterize the intrinsic functional organization of addicted and non-addicted brains. The use of supervised machine learning provides more information on the whole-brain neural correlates of addictive processes that may be applied at the level of the individual. Nevertheless, large, well-controlled longitudinal studies are needed to determine whether insights from neuroimaging are able to provide reliable brain biomarkers of addictions and their treatment.

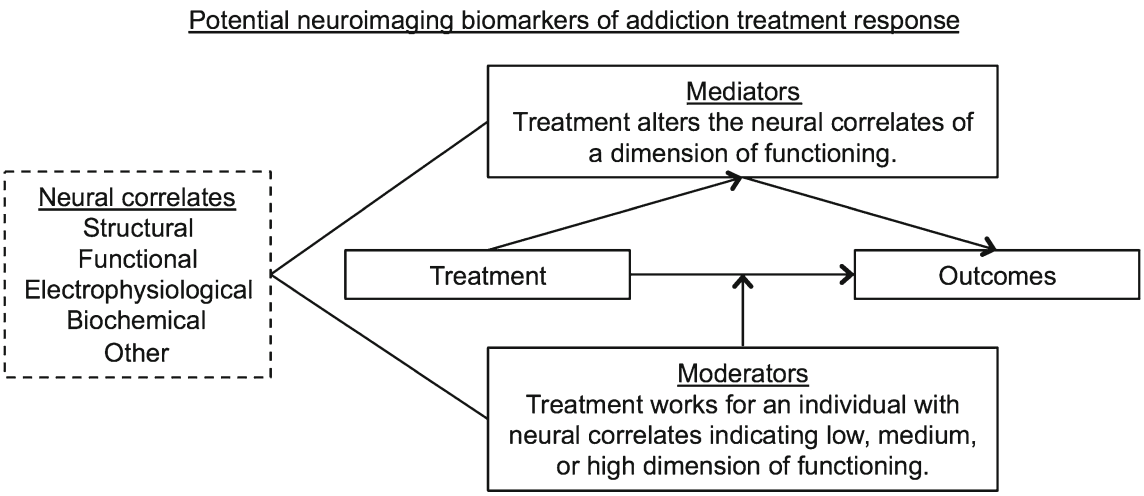

Fig. 1 Schematic diagram describing the role of neural correlates derived from neuroimaging studies as potential biomarkers of addiction treatment response. Brain structure, function, electrophysiology, neurochemistry, and other biological measures related to dimensions of functioning may be indices of mediators or moderators of addiction treatment outcomes

Conclusions

Recent technological and computational advances in neuroimaging have the potential to impact significantly the identification of biomarkers of addictions and their treatment. Neuroimaging has been used to better understand the dimensions of functioning—such as cue-reactivity, impulsivity, and cognitive control, among others—relevant to treatment outcomes in addiction. Although brain biomarkers of treatment response have yet to be identified to date, efforts have investigated mediators and moderators of treatment response, and multiple promising indices are being tested. These advances, as well as integration across neuroimaging modalities and other measures, will be important with respect to improving outcomes in addiction.

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Compliance with Ethics Guidelines

Conflict of Interest Kathleen A. Garrison declares that she has no conflict of interest.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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