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Toward biomarkers of the addicted human brain: Using neuroimaging to predict relapse and sustained abstinence in substance use disorder☆

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ABSTRACT

The ability to predict relapse is a major goal of drug addiction research. Clinical and diagnostic measures are useful in this regard, but these measures do not fully and consistently identify who will relapse and who will remain abstinent. Neuroimaging approaches have the potential to complement these standard clinical measures to optimize relapse prediction. The goal of this review was to survey the existing drug addiction literature that either used a baseline functional or structural neuroimaging phenotype to longitudinally predict a clinical outcome, or that examined test-retest of a neuroimaging phenotype during a course of abstinence or treatment. Results broadly suggested that, relative to individuals who sustained abstinence, individuals who relapsed had (1) enhanced activation to drug-related cues and rewards, but reduced activation to non-drug-related cues and rewards, in multiple corticolimbic and corticostriatal brain regions; (2) weakened functional connectivity of these same corticolimbic and corticostriatal regions; and (3) reduced gray and white matter volume and connectivity in prefrontal regions. Thus, beyond these regions showing baseline group differences, reviewed evidence indicates that function and structure of these regions can prospectively predict – and normalization of these regions can longitudinally track – important clinical outcomes including relapse and adherence to treatment. Future clinical studies can leverage this information to develop novel treatment strategies, and to tailor scarce therapeutic resources toward individuals most susceptible to relapse.

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1. Introduction

Drug addiction is a chronic disorder marked by high rates of relapse even after months or years of abstinence, long after self-reported craving and withdrawal have abated (Dennis et al., 2007). Accordingly, clinical self-report measures only modestly predict relapse and future drug use in the laboratory (Paliwal et al., 2008) and the clinic (Miller and Gold, 1994), are subject to a range of problems and biases that may reduce their reliability and validity (Crowne and Marlowe, 1960; Moeller and Goldstein, 2014; Williamson, 2007), and present challenges of translation between human and preclinical studies (Moeller and Stoops, 2015; Sinha et al., 2011). For these reasons, and in recognition that the persistence of drug-seeking and relapse may at least partly stem from underlying neurobiological alterations associated with chronic consumption of the drug, more recent studies of relapse prediction have incorporated neuroimaging approaches. These neuroimaging procedures, which include magnetic resonance imaging (MRI), electroencephalography (EEG), and positron emission tomography (PET) (among others), allow researchers to examine noninvasively how structural and/or functional brain abnormalities may contribute to relapse and other important clinical outcomes.

To date, studies correlating brain phenotypes with abstinence mainly have been cross-sectional, for example testing whether active/recent users and abstinent users differ on neuroimaging markers associated with inhibitory control, cue-reactivity, or gray matter volume (GMV) (Bell et al., 2014; Castelluccio et al., 2014; Connolly et al., 2013; Ersche et al., 2005; Li et al., 2013; Parvaz et al., 2016b). However, a growing number of studies have begun employing longitudinal designs, examining whether a particular neuroimaging phenotype *predicts* future clinical outcomes. Importantly, longitudinal studies can both inform the direction of association and can account for at least some of the extraneous variables (beyond abstinence) that may differ between active and former users. For example, active users and former users studied cross-sectionally may additionally differ on treatment motivation (Prisciandaro et al., 2014), self-regulation (Heatherton and Wagner, 2011), recent drug use that may prime further use (Donny et al., 2004), the expectation of receiving an imminent drug reward (Wilson et al., 2012), and potentially many other factors. In longitudinal studies, addicted individuals ostensibly begin the study with equivalent motivation and underlying neurobiology, and only later diverge on abstinence. For this reason, longitudinal studies are putatively less likely than cross-sectional studies to yield epiphenomenal neural signatures of abstinence.

These longitudinal prediction designs were the focus of the current review. The goal was to examine the extent to which neuroimaging phenotypes [i.e., structural and functional MRI (fMRI), EEG, and PET] can prospectively predict clinical relapse in human drug addiction. Animal studies were not included in this review because, although animal models are vital for cause-and-effect understanding of addiction pathophysiology, animal abstinence can be easily and externally enforced compared with human abstinence (Garavan and Weierstall, 2012). PubMed was searched on August 1, 2016 for the following keywords: "addiction and (brain imaging or biomarker) and (relapse or abstinence)"; relevant citations were also gleaned from prior reviews on broadly similar topics [e.g., (Courtney et al., 2016; Garavan and Weierstall, 2012; Garrison and Potenza, 2014; Hanlon et al., 2013; Marhe et al., 2014)]. To be included in the current review, studies must have incorporated at least one baseline neuroimaging assessment of brain structure or function that was then used to predict a ≥1 month relapse-relevant outcome variable (e.g., relapse, abstinence length, drug use frequency, or adherence to a particular clinical approach or course of treatment) and/or a ≥1 month follow-up neuroimaging assessment (during a time span where treatment was sought and/or drug use was absent or reduced); we did not include studies examining short-term abstinence or withdrawal that occurred over several hours or days [e.g., (Lerman et al., 2014; Moeller et al., 2013)]. As this field has evolved over time to use larger sample sizes with better statistical power, studies included in this review were required to have ≥15 study participants per group (i.e., ≥15 total if conducting within-group/correlational analyses; ≥15 per group if conducting between-group analyses of relapsers and abstainers). Our goal was not to list all regions and activations for each study, but rather to identify a manageable number of relevant regions that appeared across multiple studies of a particular task or modality (see Table 1 for summaries of the longitudinal studies reviewed here). The neuroimaging phenotypes identified in this review, then, potentially could serve as targets for future therapeutic interventions, and could help identify which individuals might be most susceptible to relapse and most in need of additional resources to sustain abstinence.

2. Functional imaging phenotypes

2.1. Task-based activation

Neural activations elicited during a range of cognitive and emotional tasks have been used to predict clinical outcomes. Tasks have principally included cue-reactivity, response inhibition, monetary reward, and decision-making.

2.1.1. Drug cue-reactivity

Cue-reactivity tasks assess the degree to which drug-related cues, including actual drug paraphernalia or more abstract stimuli such as words and images, capture attention and evoke a craving response in drug-addicted individuals (Jasinska et al., 2014). These tasks are meant to tap into the excessive motivational significance carried by drugs and their associated cues (Goldstein and Volkow, 2011; Robinson and Berridge, 2008). Most studies have contrasted brain activation to drug stimuli against activation to neutral, non-drug-related stimuli; a subset of studies has contrasted activation to drug stimuli against activation to other appetitive reinforcers (e.g., sexual images, serene beaches, etc.). Most tasks have entailed passive cue exposure; fewer have incorporated an additional executive function such as inhibitory control [e.g., whether addicted individuals have the ability to halt a (presumably) prepotent tendency to respond to drug stimuli].

One region consistently engaged by cue-reactivity is the medial prefrontal cortex (PFC), extending into the rostral anterior cingulate cortex