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Review

Factors modulating neural reactivity to drug cues in addiction: A survey of human neuroimaging studies

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ABSTRACT

Human neuroimaging studies suggest that neural cue reactivity is strongly associated with indices of drug use, including addiction severity and treatment success. However, little is known about factors that modulate cue reactivity. The goal of this review, in which we survey published fMRI and PET studies on drug cue reactivity in cocaine, alcohol, and tobacco cigarette users, is to highlight major factors that modulate brain reactivity to drug cues. First, we describe cue reactivity paradigms used in neuroimaging research and outline the brain circuits that underlie cue reactivity. We then discuss major factors that have been shown to modulate cue reactivity and review specific evidence as well as outstanding questions related to each factor. Building on previous model-building reviews on the topic, we then outline a simplified model that includes the key modulatory factors and a tentative ranking of their relative impact. We conclude with a discussion of outstanding challenges and future research directions, which can inform future neuroimaging studies as well as the design of treatment and prevention programs.

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Abbreviations: ACC, anterior cingulate cortex; AMY, amygdala; AUDIT, Alcohol Use Disorder Identification Test; CER, cerebellum; DA, dopamine; DLPFC, dorsolateral prefrontal cortex; DMPFC, dorsomedial prefrontal cortex; DS, dorsal striatum; DMS, dorsomedial striatum; DLS, dorsolateral striatum; FG, fusiform gyrus; FG/VC, fusiform gyrus/visual cortex; fMRI, functional magnetic resonance imaging; FTND, Fagerström Test for Nicotine Dependence; HIPP/PH, hippocampus/parahippocampal gyrus; IFG, inferior frontal gyrus; INS, insula; IPC/SPC, inferior/superior parietal cortex; ITC, inferior temporal cortex; MC, motor cortex; MPFC, medial prefrontal cortex; NAc, nucleus accumbens; OFC, orbitofrontal cortex; PCC, posterior cingulate cortex; PET, positron emission tomography; PFC, prefrontal cortex; PMC, premotor cortex; pMTG, posterior middle temporal gyrus; ROI, region of interest; SC, somatosensory cortex; SMA, supplementary motor area; SN, substantia nigra; THAL, thalamus; VLPFC, ventrolateral prefrontal cortex; VMPFC, ventromedial prefrontal cortex; VS, ventral striatum; VTA, ventral tegmental area.

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1. Introduction

Growing evidence suggests that drug cue reactivity, as assessed with functional MRI (fMRI), positron emission tomography (PET), and related neuroimaging techniques, as well as behavioral and autonomic measures, is strongly associated with a number of indices of drug use, including addiction severity and treatment success. However, factors that modulate cue reactivity remain incompletely understood and in some cases the direction of causal influence unclear, impeding a translation of this knowledge to clinical practice. Therefore, our goal in this review is to identify and characterize major factors that modulate brain reactivity to drug cues, which may inform future neuroimaging studies as well as the design, selection, and tailoring of treatment and prevention programs. Toward that goal, we survey published fMRI and PET studies on drug cue reactivity in cocaine, alcohol, and tobacco cigarette users, with the focus on identifying and characterizing specific factors that modulate this reactivity. We first describe cue reactivity paradigms used in human neuroimaging research and outline the brain circuits that underlie drug cue reactivity. We then discuss major factors that have been shown to modulate cue reactivity and review specific evidence as well as outstanding questions related to each factor. In light of recent findings, we highlight the importance of implicit and explicit cognitive regulation over drug cue reactivity and the conditioned drug-seeking behavioral responses that these cues engender. Building on previous model-based reviews (Field and Cox, 2008; Franken, 2003; Wilson et al., 2004), we then provide a simplified model that includes the key modulatory factors and offer a tentative ranking of their relative impact on neural drug-cue reactivity in drug users. We conclude with a discussion of outstanding challenges and future research directions.

2. Drug cue reactivity paradigms in human neuroimaging research

A number of different neuroimaging paradigms have been used to investigate the neural correlates of drug cue reactivity in human drug users. The shared feature of these paradigms is that drug users are exposed to stimuli associated with their respective drug of abuse. These drug-related cues may be visual (seeing words, pictures or silent videos) (Janes et al., 2010; Luijten et al., 2011), auditory (e.g., listening to imagery scripts) (Kilts et al., 2001; Seo et al., 2011), audiovisual (Childress et al., 1999; Garavan et al., 2000; Maas et al., 1998), tactile or haptic (handling the corresponding paraphernalia) (Filbey et al., 2009; Wilson et al., 2005, 2013; Yalachkov et al., 2013), olfactory or gustatory (smelling or tasting the substance) (Claus et al., 2011; Schneider et al., 2001); increasingly often, multi-sensory drug cues are also employed (e.g., holding a cigarette while watching audio-videos of smoking) (Brody et al., 2007; Franklin et al., 2007; Grant et al., 1996). Subjects may be instructed to passively experience the drug cues or, alternatively, they may be required to actively respond to these stimuli. Drug cues may also be presented subliminally and never enter the subjects' conscious perception (Childress et al., 2008). In addition, drug-related stimuli can be presented either as task-related targets and the focus of attention (Wilcox et al., 2011; Zhang et al., 2011), or as task-irrelevant distracters (Artiges et al., 2009; Due et al., 2002; Fryer et al., 2012; McClernon et al., 2005). Subjects may also be required to ignore the drug-related attributes of a complex stimulus while responding to a non-drug-related attribute of the same stimulus (e.g., indicate the number of horizontal lines in the image while ignoring whether the scene depicts smokers or not) (Luijten et al., 2011). Matched, neutral and non-drug-related stimuli in the same sensory domain are often used as control stimuli.

The critical within-subject comparison, yielding a measure of neural cue reactivity, is therefore between the neural response to drug-related cues vs. the neural response to control cues in drug users (*drug cues – control cues* contrast) (Chase et al., 2011; Kuhn and Gallinat, 2011). Often, a secondary between-group comparison of neural cue reactivity is conducted between drug users vs. matched non-using control subjects (David et al., 2005; Garavan et al., 2000; Goudriaan et al., 2010; Luijten et al., 2011), or between highly dependent, heavy drug users vs. less dependent or non-dependent drug users (Fryer et al., 2012; Goudriaan et al., 2010; Tapert et al., 2003). In addition to studies of drug cue reactivity per se, fMRI has also been used to investigate the neural correlates of effortful, cognitive regulation of cue-induced craving (Brody et al., 2007; Hartwell et al., 2011; Kober et al., 2010). In these studies, drug-related cues are initially attentional targets but subjects are asked to control or suppress their drug craving in response to these cues using different strategies, with the goal of identifying the neural correlates of regulation and its impact on the neural circuits underlying cue reactivity.

Experimental tasks, where behavioral reactions are measured, allow for correlating the degree of brain activation with objective performance (e.g., reaction time, error rate, skin conductance, etc.) or subjective reports (craving, drug urges, cue-related valence and arousal, etc.). The subjective reports can be collected during the neuroimaging experiment, for example after each trial, which provides higher validity of the measurements but carries the risk that the presentation of drug cues during the rating sessions can influence subsequent experimental runs. Alternatively, cues can be rated "offline," e.g., prior to or after the experiment, which would reduce that risk but diminish the external validity of the correlations between subjective reports and brain activations.