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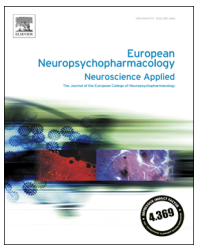

Largely overlapping neuronal substrates of reactivity to drug, gambling, food and sexual cues: A comprehensive meta-analysis

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Abstract
Cue reactivity to natural and social rewards is essential for motivational behavior. However, cue reactivity to drug rewards can also elicit craving in addicted subjects. The degree to which drug and natural rewards share neural substrates is not known. The objective of this study is to conduct a comprehensive meta-analysis of neuroimaging studies on drug, gambling and natural stimuli (food and sex) to identify the common and distinct neural substrates of cue reactivity to drug and natural rewards. Neural cue reactivity studies were selected for the meta-analysis by means of activation likelihood estimations, followed by sensitivity and clustering analyses of averaged neuronal response patterns. Data from 176 studies (5573 individuals) suggests largely overlapping neural response patterns towards all tested reward modalities. Common cue reactivity to natural and drug rewards was expressed by bilateral neural responses within anterior cingulate gyrus, insula, caudate head, inferior frontal gyrus, middle frontal gyrus and cerebellum. However, drug cues also generated distinct activation patterns in medial frontal gyrus, middle temporal gyrus, posterior cingulate gyrus, caudate body and putamen. Natural (sexual) reward cues induced unique activation of the pulvinar in thalamus. Neural substrates of cue reactivity to alcohol, drugs of abuse, food, sex and gambling are largely overlapping and comprise a network that processes reward, emotional responses and habit formation. This suggests that cue-mediated craving involves mechanisms that are not exclusive for addictive disorders but rather resemble the intersection of information pathways for processing reward, emotional responses, non-declarative memory and obsessive-compulsive behavior.
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1. Introduction

Craving is a critical and ambiguous psychiatric term that in its core refers to a subjective state of urge or desire to gain pleasure (positive reinforcement) or to terminate distress (negative reinforcement) from drug use or other activities (Wise, 1988). This phenomenon is often associated with neurophysiological response patterns to an acute presentation of stimuli also referred to as "cue reactivity" (Drummond, 2000; Sinha, 2013).

Despite the numerous issues involved in the conceptualization of craving (Wise, 1988; Sinha, 2013), the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) now includes craving as a diagnostic criteria for alcohol and substance use disorders (AUD and SUDs) (Cherpitel et al., 2010). However, craving remains to be an ill-defined term, especially if it comes to the underlying neurobiolological mechanisms. As said neural cue reactivity captures at least one dimension of craving and as such a quantitative and comprehensive evaluation of the neurobiological substrates of cue reactivity across all drug and natural rewards may provide a better understanding of the neurobiological underpinnings of craving. In addition comprehensive meta-analyses of cue reactivity across all drug and natural rewards will also provide a reliable framework to define cue-mediated craving by objective measures and dimensions. Studies concerning with cue reactivity paradigms commonly assume that the experiments reflect cue-mediated craving and assume that drug, sexual desire and food may share common neural pathways (Childress et al., 1999; Garavan et al., 2000).

In the past two decades, a growing number of studies have utilized functional neuroimaging techniques such as functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and single-photon emission computed tomography (SPECT) to characterize the cue-induced neural response patterns in healthy and addicted individuals. While numerous meta-analyses have restrictively investigated the activation patterns and influencing factors for specific stimulus types (Kuhn and Gallinat, 2011a; Engelmann et al., 2012; Heckman et al., 2013; Schacht et al., 2013; Wray et al., 2013; Hanlon et al., 2014; Chase et al., 2011) and occasionally across different cues (Kuhn and Gallinat, 2011b; Tang et al., 2012), no attempts have been made yet to provide a robust and comprehensive characterization of the specific features of drug- and natural cues in order to identify the universal substrates of cue reactivity in general. Such a global analysis is critical to evaluate whether cue reactivity constitutes an appropriate and one-dimensional indicator of AUD and SUDs (and gambling). Furthermore it enables us to ultimately construct quantitative approaches towards the ambiguous term craving based on neurobiological measures.

Therefore, the aim of the present study is to conduct validated and comprehensive meta-analyses following MOOSE (Meta-analysis Of Observational Studies in Epidemiology) guidelines (Stroup et al., 2000) to assess the common and distinct neural activation patterns across all previously published functional neuroimaging studies of drug (alcohol, cocaine, nicotine, heroin and cannabis), natural (sexual, food), and gambling cue reactivity using the activation likelihood estimation (ALE) approach (Turkeltaub et al., 2002). This approach provides weighted averages of stereotactic coordinates of clusters with respect to each particular cue. In addition, we performed a two-step clustering technique to identify brain regions that either directly overlap or converge for different stimulus types and to determine group differences in activation patterns between drug-induced and natural cue reactivity.

To evaluate the methodological quality of the primary research underlying the meta-analyses and minimize the biases (Laird et al., 2005), an 83-item checklist (Poldrack et al., 2008) was used. Furthermore, sensitivity analyses were performed to estimate the level of robustness of the meta-analyses with respect to demographic and experimental parameters.

2. Experimental procedures

2.1. Search strategy

The online portal of the National Library of Medicine (http://www.ncbi.nlm.nih.gov/pubmed/) including PubMed, PubMed Central and MEDLINE was used as the platform for literature research. A systematic screening of the original research articles published until March 2015 was performed based on the keywords: alcohol (OR) Ethanol (OR) cannabis (OR) THC (OR) joint (OR) cocaine (OR) crack (OR) amphetamine (OR) methamphetamine (OR) nicotine (OR) smoking (OR) smoke (OR) tobacco (OR) cigarettes (OR) heroin (OR) opiates (OR) food (OR) sex (OR) sexual (OR) gamble/gambling (OR) gaming (OR) internet (AND) addiction (OR) dependence (OR) abuse (OR) consumption (OR) craving (AND) cue (OR) stimulus (OR) stimuli (OR) reactivity (AND) fMRI (OR) PET (OR) neuroimaging (OR) SPECT. In addition, the reference sections of identified papers as well as review and meta-analysis articles were then screened for further relevant citations.

2.1. Study selection

Reviewers, in pairs, independently screened titles and abstracts of articles and reviewed the full-text of any title or abstract deemed potentially eligible by either reviewer. Reviewers resolved disagreements by discussion. Among these studies, only peer-reviewed original research articles in English language were chosen for data mining if they provided analysis of brain responses (i.e. exact coordinates or explicit identification of the reactive brain regions) to drug and natural stimuli either within a pathological user group or between such individuals and control subjects or in case of natural cues within a group of healthy individuals. All pathological users fulfilled DSM-IV criteria for alcohol or drug dependence and no other axis I disorders. Pathological gamblers were either currently under treatment or met at least five of the ten criteria for pathological gambling provided by DMS-IV. Pathological gamers had to meet at least three of the six criteria of computer game addiction (Grüsser and Thalemann, 2006): craving, impaired control of playing, withdrawal, development of tolerance, progressive neglect of other pleasures and playing despite harmful consequences. Exclusion criteria for both groups as well as individuals exposed to natural rewarding stimuli were: lifetime diagnosis of schizophrenia or psychotic episodes; diagnosis of manic disorder, obsessive-compulsive disorder, alcohol use disorders, substance dependent disorder or post-traumatic stress disorder; treatment for mental disorders other than pathological gambling in the past 12 months; use of psychotropic medication; history or current treatment for neurological disorders, major internal disorders, brain

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