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Abnormal reward functioning across substance use disorders and major depressive disorder: Considering reward as a transdiagnostic mechanism

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ABSTRACT

A common criticism of the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2013) is that its criteria are based more on behavioral descriptions than on underlying biological mechanisms. Increasingly, calls have intensified for a more biologically-based approach to conceptualizing, studying, and treating psychological disorders, as exemplified by the Research Domain Criteria Project (RDoC). Among the most well-studied neurobiological mechanisms is reward processing. Moreover, individual differences in reward sensitivity are related to risk for substance abuse and depression. The current review synthesizes the available preclinical, electrophysiological, and neuroimaging literature on reward processing from a transdiagnostic, multidimensional perspective. Findings are organized with respect to key reward constructs within the Positive Valence Systems domain of the RDoC matrix, including initial responsiveness to reward (physiological 'liking'), approach motivation (physiological 'wanting'), and reward learning/habit formation. In the current review, we (a) describe the neural basis of reward, (b) elucidate differences in reward activity in substance abuse and depression, and (c) suggest a framework for integrating these disparate literatures and discuss the utility of shifting focus from *diagnosis* to *process* for understanding liability and co-morbidity. Ultimately, we believe that an integrative focus on abnormal reward functioning across the full continuum of clinically heterogeneous samples, rather than within circumscribed diagnostic categories, might actually help to refine the phenotypes and improve the prediction of onset and recovery of these disorders.

1. Introduction

Substance use disorders (SUD) and major depressive disorder (MDD) rank among the most widespread illnesses nationwide, with 12-month prevalence rates of 6.6% and 9.0%, respectively (Aldworth, 2009; Kessler & Wang, 2009). In the United States, they are also among the leading causes of disability (Mathers et al., 2008), with an estimated annual economic burden of $83.1 billion for MDD and $428.1 billion for SUD (Greenberg et al., 2003; Rice, 1999). Importantly, there exists significant psychiatric comorbidity between MDD and SUD, such that the presence of one disorder increases the risk of onset of the other. Among individuals with lifetime MDD, a history of comorbid SUD is common: 40.3% also have a history of an alcohol use disorder, 17.2% have a history of a drug use disorder, and 30.0% have a history of nicotine dependence (Hasin et al., 2005). Compared to individuals without any SUD, the odds of having current MDD are 2.5 times higher among individuals with a current SUD, 3.7 times higher with current alcohol dependence, and 9.0 times higher with current drug dependence (Grant et al., 2004). These epidemiological data indicate that MDD and SUD are closely related illnesses, with reciprocal impacts on the development of each disorder.

In addition to this well-documented comorbidity, both SUD and MDD are characterized by marked dysfunction in reward-seeking behavior (American Psychiatric Association, 2013). A cardinal symptom of MDD is anhedonia, a pervasive lack of interest or pleasure in activities that are normally enjoyable. A defining feature of SUD, meanwhile, is excessive pursuit and use of a substance that is disproportionate to the hedonic impact derived from it. For each disorder, there is considerable interest in integrating findings from the basic affective neuroscience literature on reward, with the ultimate goal of clarifying how dysfunction in neural circuits known to be involved in reward processing may give rise to these clinical phenomena (Forbes & Dahl, 2012; Pizzagalli et al., 2011; Volkow et al., 2009, 2011). Not only is functioning in the reward circuitry important for the etiopathogenesis of these disorders, but it has also been shown to change in response to treatment of

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these disorders, suggesting potentially novel targets for treatment (Heller et al., 2013; Kreek et al., 2002; Schlaepfer et al., 2008).

Despite this growing interest in utilizing a translational approach to understand reward processing abnormalities *within* SUD and MDD, the extant literatures are limited by the fact that these disorders have not been systematically contrasted with one another; that is, the nature of reward dysfunction *across* SUD and MDD remains largely unexplored. A broader research scope is warranted to substantiate the clinical utility of neurobiological indicators of reward dysfunction, one that: (a) contrasts SUD directly with MDD, and (b) considers the impact of comorbid SUD/MDD. Such an approach would address whether observed neurobiological abnormalities have diagnostic specificity, clarifying whether effects are unique to either MDD or SUD, or instead span both disorders, indicating possible transdiagnostic mechanisms of illness.

A second limitation of research that has been conducted to date is the tendency for individual studies to focus on a single outcome related to reward processing, rather than considering reward as a multi-faceted process. Human (e.g., neuroimaging, psychophysiological studies) and basic animal (e.g., conditioning and drug administration studies) neuroscience literatures indicate that reward is not a unitary construct, but instead is composed of three primary components with distinct neural circuitry: 'liking', which refers to the hedonic impact of reward consumption; 'wanting' or incentive salience, which refers to the motivation to pursue a reward; and learning, or the acquisition of reward–outcome contingencies (Berridge et al., 2009). Thus, rather than conceptualizing abnormal reward processing in SUD or MDD as a relatively global dysfunction (i.e., decreased vs. increased reactivity to rewards overall), the existing evidence indicates that a more nuanced pattern is likely (Treadway & Zald, 2011).

In order for progress to be made in linking abnormalities in reward processing to clinical phenomena in SUD and MDD, a multidimensional approach is required both in procedures for diagnosing these conditions and in the manner in which reward is assessed. Indeed, such an approach is highly consistent with the aims of the National Institute of Mental Health's Research Domain Criteria (RDoC) project (Cuthbert & Insel, 2013; Insel et al., 2010), an initiative which seeks to reclassify psychiatric illness based on quantifiable dysfunction in biologically-based constructs—irrespective of traditional diagnostic boundaries. A primary domain of functioning within RDoC is that of Positive Valence Systems, which delineates reward into constituent constructs of Initial/Sustained Responsiveness to Reward (i.e., 'liking'), Approach Motivation (i.e., 'wanting'), and Reward Learning/Habit. In addition to adopting a transdiagnostic perspective, a significant advantage of RDoC is the integration of multiple units of analysis, incorporating information from genetic, psychophysiological, behavioral, and self-report measures. RDoC provides a highly promising framework, yet there is little work to date aimed at developing a comprehensive understanding of reward function across multiple units of analysis and across multiple disorders.

Here, we seek to integrate the literatures on reward dysfunction in SUD and MDD with specific reference to the RDoC framework. While pertinent evidence remains incomplete, the goals of our review are to synthesize findings that currently exist, identify promising psychophysiological indicators of reward dysfunction using candidate analytic methods in relation to SUD/MDD, and outline how future studies may address critical gaps in our knowledge. We focus primarily on psychophysiological evidence (e.g., electroencephalography, or EEG; event-related potentials, or ERPs; functional magnetic resonance imaging, or fMRI), while also linking these with other units of analysis wherever possible (e.g., animal studies). First, we provide a brief overview of the basic neuroscience literature on reward. Next, we review the specific abnormalities in reward processing that have been identified to date within SUD and MDD. Finally, we suggest a framework for integrating these disparate literatures and discuss the utility of shifting investigative focus from individual clinical disorders to processes relevant to understanding broad liability and diagnostic co-morbidity. An integrative focus on abnormal reward functioning across the full clinical continuum, rather than solely within circumscribed diagnostic categories, may contribute to the refinement of clinical phenotypes such as SUD and MDD, and better predict the onset of and recovery from these disorders.

2. The neurobiology of reward

Recently, significant progress been made not only in parsing the psychological components of reward, but also in identifying the underlying neural mechanisms associated with each component. Overall, reward processes are represented in the brain by a complex network involving many cortical structures, including the orbitofrontal cortex (OFC) and anterior cingulate (ACC), as well as subcortical structures such as the nucleus accumbens (NAc), ventral tegmentum, ventral pallidum, amygdala, and mesolimbic dopamine projections. Evidence from animal studies, fMRI, and EEG/ERP suggests that interactive networks in this circuitry bridge processes such as cognition, emotion, and goal-directed behavior (Haber & Knutson, 2010; Dragnanski et al., 2008; Belin & Everitt, 2008). Though there is inherent complexity in the interrelationships of specific brain regions within this network, certain structures have been principally associated with distinct reward processes of 'liking', 'wanting', and learning, respectively (Berridge et al., 2009). It is important to note that physiological 'liking' and 'wanting' are not the same as perceived liking and wanting. The former represent heuristics that can be useful in guiding theories about the distinct effects of discrete neurobiological systems on behavior. Therefore, activation of 'liking' and 'wanting' can be associated with perceived feelings of liking (e.g., enjoyment) or wanting (e.g., desire), but these reward-related processes may also occur implicitly without palpable awareness (Berridge, 2007). Simply put, an individual with an SUD may report that s/he no longer likes using a substance or experiences a desire for it; however, the underlying neural processes linked to 'liking' and 'wanting' may still be at play and contribute to maintenance of his/her disorder. Similarly, an individual with MDD may report improvement in perceived anhedonia and other depressive symptoms, but persistent abnormalities in 'liking' or 'wanting' may place him/her at increased risk for future recurrence of the disorder.

2.1. 'Liking': the hedonic impact of rewards

The process of 'liking' is a basic evolutionary function that represents the hedonic impact of information. Though liking is commonly linked to perceived pleasure, 'liking' is a process that represents a neurophysiological response to hedonic stimuli that is not necessarily accompanied by a perceived sense of pleasure. 'Liking' reactions can be elicited by a variety of stimuli ranging from tastes (e.g., sweet) to drug-mediated rewards, money, and sex (Beaver et al., 2006; Berridge, 2007; Wheeler & Carelli, 2006). However, in human research, self-report assessments (e.g., rating scales) along with other measures (e.g., ERP) in response to various rewards are commonly used as proxies for liking/'liking' functioning, and combined may tap the hedonic impact of rewards in non-preclinical studies. Within the RDoC framework, this concept of 'liking' may be mapped onto the Initial/Sustained Responsiveness to Reward, as both are associated with hedonic responses and the culmination of reward seeking.

Much of the initial research used to identify and define 'liking' came from conditioning studies with animals. Using measures such as palatability, lever pressing, and neural reactions to conditioned sweet tastes in animals, Berridge and colleagues identified a number of hedonic hotspots in the ventral pallidum and the shell of the NAc that mediate pleasure. Opioid, endocannabinoid, and GABA-benzodiazepine neurotransmitter systems are important for enhancing the hedonic perception of rewards, particularly at specific sites in limbic hedonic hotspots (Berridge & Robinson, 2003). Activation of these hotspots closely relates

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