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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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to increases in 'liking' reactions, such as palatability and lever pressing in rats elicited by oral infusions of sucrose, whereas damage to these regions correspond to a 'disliking' reaction (e.g., gaping, pre-vomiting, reaction to bitter *and* sweet tastes; Pecina, 2008). In humans, the core neural components of 'liking' include the ventral pallidum and the ventral striatum, specifically the shell regions of the NAc. The ventral pallidum is a primary target for NAc outputs. In particular, the activation of mu-opiod and endogenous cannabinoid receptors in the NAc and ventral pallidum enhances the hedonic perception of rewards. Other components of neural circuitry, including GABA-receptor feedback and mesolimbic outputs to certain locations in the NAc shell and the ventral pallidum, also modulate 'liking' (Berridge & Robinson 2003).

While dopamine traditionally has been linked to sensory pleasure, research indicates that this neurotransmitter is insufficient for initiating a 'liking' response (Berridge & Robinson, 1998). For example, during Pavlovian conditioning paradigms with rats, activation of dopamine in the NAc through amphetamine microinjection does not alter the 'liking' response (e.g., affective reaction to conditioned reward), but does increase the motivational component of a reward (Wyvell & Berridge, 2000). As such, the primary role of dopamine has been linked to incentive salience, learning, and other reward-related functions (Berridge, 2007).

A psychophysiological candidate for quantifying 'liking' in humans is the feedback negativity (FN) elicited by reward delivery in simple gambling/guessing tasks.[2] In two such studies—in which rewards were randomly delivered and did not require contingency learning—FN amplitude was correlated with self-reported consummatory pleasure (Bress & Hajcak, 2013; Liu et al., 2014), thereby linking it with both perceived liking and the RDoC constructs of Initial Responsiveness and Sustained Responsiveness to Reward Attainment. Moreover, multimodal studies combining ERP and fMRI data indicate that FN amplitude covaries with reward-related BOLD signal within the NAc (Becker et al., 2014; Carlson et al., 2011). Insofar as the FN occurs within 250–300 ms following reward delivery, it appears to reflect the relatively automatic and binary evaluation of outcomes as either favorable or unfavorable (Hajcak et al., 2006; Proudfit, in press), thereby providing an objective indicator of hedonic impact related to 'liking.'

2.2. 'Wanting': the motivational salience of rewards

While 'liking' and 'wanting' may seem tightly coupled, these processes are neurobiologically and psychologically separable. 'Wanting' refers to incentive salience that motivates approach toward rewards—and is delineated within RDoC as the construct of Approach Motivation and, more specifically, the sub-construct of Expectancy. It is often mediated by the reward stimulus itself, and does not require elaborate cognitive expectations. As such, physiological or implicit 'wanting' is distinct from perceived wanting, which relates more to explicit and elaborative expectations and goals. 'Wanting' can occur in the face of innate incentives (e.g., unconditioned stimuli) or to learned stimuli (e.g., conditioned stimuli, reward cues). Research on the neural systems responsible for 'wanting' has used a variety of rewards ranging from drug administration, to stimuli representing sex and food, to monetary rewards.

Across these reward elicitors, the midbrain dopamine (DA) system appears primarily responsible for mediating the motivation to obtain the signaled rewards (Berridge & Robinson, 2003). Specifically, DA projections from the ventral tegmentum to the ventral striatum, largely the NAc core (Di Chiara, 2002), fire in response to unpredicted rewards and cues that predict rewards. Additionally, dopamine cell firing is diminished when predicted rewards do not occur (Schultz, 1998). Thus, it is hypothesized that one function of dopamine is to connect incentive value to the cues that predict reward.

In addition to DA, opioid receptors in the amygdala, specifically the basolateral amygdala, are involved in the evaluation of rewards (Murray, 2007). For example, during food deprivation, administration of mu-opioid antagonists (e.g., naloxone) into the basolateral amygdala blunts the taste-reactivity response in rats to sucrose without impacting palatability and lever pressing (i.e., measures of pleasure) for sucrose (Wassum et al., 2009). Furthermore, inhibition of glutamatergic projections from the basolateral amygdala to the NAc reduces motivated response for sucrose (Stuber et al., 2011). Together, these findings suggest that along with DA, opioid, and glutamatergic activity in the basolateral amygdala is important for motivated behavior.

Unlike the simple guessing/gambling tasks described above in relation to 'liking' in which reward delivery is random, tasks in which reward cues elicit motivated approach behavior are relevant to 'wanting.' Here, reward attainment is dependent on effective behavioral performance, such as quickly responding to a cued target stimulus (Knutson et al., 2000). Predictive cues that signal potential reward elicit a centroparietal P3 (Goldstein et al., 2006) that covaries with BOLD signal response in the NAc (Pfabigan et al., 2014). Following this cue-P3, a centrally-maximal slow wave termed the contingent negative variation develops in anticipation of responding to the upcoming target stimulus, reflecting coordinated activity across a network spanning the NAc, thalamus, and supplementary motor area (Plichta et al., 2013).

2.3. Learning: the association between previous rewards and predicting future rewards

Though the processes of 'wanting' and predicting reward are related, the differential neural structures implicated in these processes indicate that the associative value of a reward may be separated from its motivational value, depending on the learning processes. At a simplified level, learning involves: building knowledge about specific relationships between cues, behaviors, and reward outcomes; understanding the associative causation between stimuli; and elaborating on those associations. Neural substrates for building associations (e.g., assessed during instrumental or Pavlovian conditioning in animals and often through conditioning, probabilistic learning, and gambling tasks in humans) rely more heavily on cortical structures, including orbitofrontal, ACC, and prefrontal cortex, but also include interactions with subcortical regions.

One function of the OFC is quick associative (e.g., stimulus–reinforcement) learning and the alteration of associations of this type when the contingencies change (Rolls, 2000). For example, primates with lesions to the OFC show impairment in tasks that require learning about which stimuli are rewarding or not and in altering their behavior when the contingencies in the environment change (e.g., object reversal and go/no-go tasks; see Rolls, 2000 for review). Additionally, this brain region plays a role in attaching affective valence to stimuli through its relationship with the amygdala (London et al., 2000) and evaluating stimulus characteristics though connections with regions believed to subserve memory functions (e.g., dorsolateral PFC; Perlstein et al., 2002). The ACC, meanwhile, is critically involved in demanding learning tasks and is important for encoding previous reward outcomes (Kennerley et al., 2011). A specific brain potential response that has been localized to the ACC is the error-related negativity (ERN), an electrocortical response posited to reflect dopamine-system activation at times when participants make errors in cognitive tasks (Frank et al.,

[2] The FN was initially identified in studies on error detection and reinforcement learning (Miltner et al., 1997), was later studied within simple gambling/guessing tasks (Gehring & Willoughby, 2002), and has recently been reconceptualized as the reward positivity, or RewP (Holroyd et al., 2008; Proudfit, in press). The role of laboratory task is mentioned here as a way to highlight the principle that an ERP component is defined not only by its timing and scalp distribution, but also by the specific event that gave rise to the neural activity. ERPs are not necessarily interchangeable across tasks (Kappenman & Luck, 2014); the 'FN' elicited by reward delivery on a simple guessing task may be dissociable from the 'FN' elicited by feedback on a speeded response task (i.e., monetary incentive delay) or on a probabilistic learning task—and each may by differentially impacted by SUD/MDD. Consideration of the event that elicits neural activity is crucial for linking any psychophysiological measure specifically to reward 'liking', 'wanting', learning, or some combination thereof.

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2005; Holroyd & Coles, 2002). In addition to indexing online recognition of errors in performance, the magnitude of the ERN predicts the degree to which an individual can learn from errors, thus making it a useful indicator of reward learning and context updating capacity. Lastly, the value of reward, and ultimately decision-making based on those values in an effort to promote goal-directed behavior, is processed in the anterior ventromedial PFC and dorsolateral PFC (Bechara et al., 2000). In sum, these anterior brain regions represent different learning processes and serve to associate cues with their context, and with particular responses such as 'liking' a reward, 'wanting' a reward, or engaging in action to consume the reward.

Even though there is some evidence of partially separable neural circuits for these three core reward processes, it is important to note that these differing psychological components of reward are connected and function together as a coordinated network integrating emotional, motivational, and learning processes. The multifaceted nature of the neural circuitry for reward is important for adaptive functioning, and dysfunction is implicated in many psychopathologies. However, there is also utility in considering a more nuanced examination of this circuit, one that can provide a clearer understanding of overlapping neural mechanisms that both independently and comorbidly contribute to various psychopathologies (e.g., SUD and MDD).

3. Reward dysfunction in substance use disorders

SUDs are defined by uncontrollable and compulsive seeking and use of drugs/alcohol, which persists in spite of negative health and social consequences. Different types of substances have different pharmacological and pharmacokinetic properties; however, their habit-forming effects involve a common denominator, namely, a dysfunction in reward circuitry. Increasingly, evidence demonstrates that substance abuse "hijacks" the neural circuitry of reward (Berridge & Robinson, 2003). More specifically, a number of preclinical and clinical studies support the hypothesis that the primary neural substrates for persistent substance use are linked to 'wanting' (salience detection) and learning (associative memory) processes affected by mesolimbic dopamine and the prefrontal cortex (Motzkin et al., 2014; Hyman, 2005; Tiffany, 1990). While the various substances impact multiple neural regions and neurotransmitters, the mesolimbic DA system is activated by all major substances of abuse and is of central importance to all (Hommer et al., 2011).

3.1. Dysfunctional 'wanting': incentive-sensitization theory

In general, it is proposed that individuals with substance abuse have altered incentive saliency in relation to reward (e.g., 'wanting'; Volkow et al., 2004a, 2004b). This enhanced saliency is initiated by the higher intrinsic reward properties of drugs, which is largely regulated by mesolimbic DA. Robinson and Berridge's (1993) incentive-sensitization theory posits that the repeated use of substances initiates a cycle whereby perceptual stimuli (e.g., environmental cues, money, paraphernalia, etc.) associated with the substance acquire incentive value, and as the stimuli-substance associations increase in strength the valuation attached to such stimuli increases, thus making the substance even more wanted. These high reward values lead to a recalibration of reward thresholds, which result in decreased sensitivity to naturally occurring stimuli (e.g., sex and food; Zijlstra et al., 2009). As a result of hyperactivity in the reward circuit, motivation and memory circuits are also over-activated and decision-making capabilities associated with the frontal cortex are inhibited. Furthermore, long-term exposure to drugs is theorized to cause permanent changes in the substance–reward circuit, including the ventral tegmental area, basal forebrain (amygdala), dopaminergic connections between the ventral tegmental area and basal forebrain, and OFC (Koob & Le Moal, 2001; Moeller et al., 2013; Volkow et al., 2004a, 2004b).

Of note, these brain systems that are affected, or essentially sensitized to the rewarding properties of substances, do not mediate the pleasurable effects (i.e., 'liking') of drugs but, as noted above, instead mediate the psychological processes of 'wanting' and associative learning (Berridge, 1996). That substances of abuse can promote drug-taking behavior in the absence of any subjective hedonic effects (Fischman & Foltin, 1992) appears inconsistent with the notion that the positive reinforcing effects of substances can be equated with their hedonic impact. Findings from preclinical research studies support this idea, indicating that manipulations of dopamine neurotransmission exert effects on approach behavior ('wanting') without changing basic hedonic reactions ('liking'). For example, there is preclinical evidence from work with mice suggesting that chronically elevated DA facilitates 'wanting' and learning in an incentive motivation task involving sweet-taste reward, but does not alter the 'liking' reactions (hedonic responses) to such rewards. More specifically, Peciña et al. (2003) found that hyperdopaminergic DA mice required fewer trials to learn incentive associations and paused less frequently in a runway test, but failed to show higher orofacial 'liking' reactions during an affective taste reactivity test. Research in humans similarly shows a unique pattern of dissociation between 'liking' and 'wanting.' For example, an alcohol prime (but not a juice prime) increases alcohol 'wanting' in heavy and light social-drinkers as measured by increased alcohol consumption; however, priming does not increase alcohol 'liking' as measured by taste ratings (Hobbs et al., 2005). In other work with cocaine addicts (Lambert et al., 2006), both exposure to stimulant treatment (for symptoms of attention deficit and hyperactivity disorder) and regular use of cigarettes were found to predict the highest degree of 'wanting' for cocaine (self-report of 'always wanted more') and the lowest degree of 'liking' (self-reported global positive effects from cocaine).

Converging clinical evidence highlights the importance of mesolimbic-mediated salience detection, or 'wanting', in the maintenance of SUD. Increases in DA have been reported in amphetamine users, with this increase being associated with subjective reports of the reinforcing properties of the substance (Drevets et al., 2001). Along with these studies, increases in striatal DA induced by stimulant drugs have been associated with the perceived experience of wanting the substance (e.g., self-reported desire for more drug and feelings of being high; Volkow et al., 2004a, 2004b). Additionally, positron emission tomography (PET) studies have reported acute DA metabolic changes during the administration of substance and long-term brain changes in DA activity with continued use of substances. PET studies also have consistently demonstrated a reduction in availability of D2 receptors in the striatum, which is inversely associated with DA levels in the midbrain, in SUD subjects (cocaine, methamphetamine, heroin, and alcohol) compared to controls (Volkow et al., 2004a, 2004b).

In addition to imaging methods, electrophysiological research in humans emphasizes a specific deficit in salience detection in SUD. Studies have largely focused on the P3, an ERP related to dopamine production and the evaluation of motivationally salient information (Polich, 2007). With relation to SUD, an enhanced P3 to alcohol cues has been found between alcoholics and non-alcoholics, between non-alcoholic relatives of alcoholics and relatives of controls, as well as between non-alcoholic offspring of alcoholic fathers and offspring of controls (Iacono et al., 2008). Similar increases in P3 amplitude have also been reported in smokers while viewing smoking cues (Warren & McDonough, 1999), in methadone-maintained participants when viewing opiate-related pictures (Lubman et al., 2007), and in cocaine users when viewing drug cues (Dunning et al., 2011) (see Ceballos et al., 2009 for review). However, a number of studies have reported reduced P3 amplitude and longer P3 latency in individuals with SUDs when completing cognitive challenge tasks that do not involve substance-related cues compared to individuals with no history of SUD (Bauer, 2001; Iwanami et al. 1994, 1998; see Sokhadze et al., 2008, for review). Across studies, a pattern emerges whereby individuals with SUD display enhanced P3 in response to cues depicting a particular drug of choice,

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but reduced P3 in response to cognitively demanding, non-substance related information. Considering the abundant evidence for reduced P3 in standard tasks as an endophenotype marker for externalizing proneness (Hicks et al., 2007) or trait disinhibition (Yancey et al., 2013), enhanced P3 reactivity to substance-related stimuli in addicts, who depending on sample selection are not necessarily characterized by trait externalizing, could reflect a possible neural prioritization of incentivized stimuli, yielding inefficient processing of information in other contexts.

Furthermore, there is some evidence that this increased engagement in salience detection and reward processing decreases during withdrawal. Bauer (2001) demonstrated that continued abstinence from heroin, cocaine, and alcohol was associated with a trend toward normalization of the P3 (c.f., Bauer, 1997 in cocaine-dependent patients). Additionally, delta-frequency EEG activity, known to be associated with reward-processing and salience detection (Knyazev, 2012), reduced proportionally as the number of days in withdrawal from crack-cocaine increased (e.g., withdrawal was measured in crack-cocaine dependent patients from day 1 to 68; Alper et al., 1990; see also Prichep et al., 1996; Roemer et al., 1995). Broadly speaking, these electrophysiological patterns suggest that substance cues acquire enhanced motivational salience compared to non-substance-related cues, but that these associations may diminish once the substance–stimulus reward associations are degraded. Thus, in addition to neuroimaging methods, the P3 and other EEG referents may represent important biological indicators for a dysfunction in the RDoC Approach Motivation (i.e., 'wanting') domain within SUD.

Dopamine-system abnormalities (either directly measured or through electrophysiological proxies) are central to understanding reward-related dysfunction in SUDs, but in many ways this specific dysfunction is insufficient to explain the pattern of abnormal processing that occurs in addicted individuals. Enhanced approach motivation toward substances in the form of increased salience detection is an important factor in the development of SUD; however, the interaction of this process with reinforcement-based learning is essential for building habit-forming tendencies. In fact, as discussed in the next section, many reported DA findings occur in the context of functional and structural changes in the frontal cortex. For example, evidence exists that observed deficits in striatal DA are associated with lower metabolic activity in the PFC (e.g., ACC and OFC). Thus, in addition to the central role of 'wanting'-based circuitry, available evidence points to an important role for cortical, learning-based brain regions within the reward circuit, such as the PFC, in substance addictions.

3.2. Dysfunctional learning: disruption in the brain's memory and control systems

One of the most consistent findings in individuals with SUD is abnormal activation in the PFC (Goldstein et al., 2007; Volkow et al., 2003). Several recent structural imaging studies report reduced morphological volume in the (pre)frontal lobe in various forms of drug addiction, such as cocaine and heroin dependence and alcohol-dependent individuals (Goldstein, & Volkow, 2002; Jernigan et al., 1991; Liu et al., 1998). Functional imaging studies also consistently show increased activation in the amygdala, OFC, and ACC among cocaine and heroin addicts when exposed to drug cues (London et al., 2000; Volkow & Fowler, 2000). This dysfunction in areas of prefrontal cortex, along with evidence for connectivity deficits between these areas and limbic-subcortical structures (e.g., ventral striatum, amygdala) (Ma et al., 2010; Motzkin et al., 2014), may give rise to multiple deficits common in SUD, from altered learning to behavioral control.

Animal studies demonstrate that rats with lesions to the ACC and PFC display continued responses to cocaine, even when the cocaine-associated cue is no longer present (Weissenborn et al., 1997). Relatedly, substance-dependent humans display a lack of adaptive associative learning between stimulus and outcome, as evidenced by reward-dependent perseverative response patterns even in the absence of a previously presented reward cue (Wilson et al., 2004). This failure to update learned associations also may be related to the preponderance of evidence linking SUD to risky decision-making (Bechara, 2003; Bechara & Damasio, 2002; De Bellis et al., 2013).

Several patterns of altered executive-function-mediated decision-making have been observed in SUD. Specifically, deficits in learning-based reward circuitry are related to impulsive choice and higher delay discounting (of future rewards relative to immediate ones), especially under experimental conditions entailing presentation of drug-related cues or drug-deprivation (Coffey et al., 2003; Giordano et al., 2002). For example, Bechara et al. (2002) reported a larger skin conductance response to monetary reward and in anticipation of outcomes that yield a large reward in a subset of substance dependent individuals. Elsewhere, Franken et al. (2007) found that cocaine dependent patients had decreased ERN amplitudes compared to a control group. Another study by Easdon et al. (2005) reported that acute administration of alcohol to healthy volunteers in low and moderate doses decreased ERN amplitude.

The combination of hyperactive 'wanting' and dysfunctional learning suggests that reward-related cues, such as drug cues, are not only particularly salient, but persist in activating reward circuitry without proper opposition from prefrontal regions. Since the interaction between 'wanting' and learning circuits is bidirectional, the activation of these reward-related processes serves to further strengthen the saliency or conditioned strengths of drug cues. That is, SUD may be initiated and maintained through a process by which especially salient stimuli grab hold of attentional resources, attain motivational priority, and trigger changes in memory and control circuits of the brain.

4. Reward dysfunction in major depression

MDD is marked by persistent, debilitating low mood in conjunction with other characteristic cognitive and physical symptoms. Many of the commonly observed symptoms in MDD entail disturbances in functions regulated by reward circuitry, including disruptions in appetite, sleep, energy level, and pleasure, suggesting that reward dysfunction plays a fundamental role in the pathophysiology of MDD (Nestler et al., 2002; Nestler & Carlezon, 2006; Russo & Nestler, 2013). Of note, the primary diagnostic criterion of anhedonia is defined as diminished interest or pleasure in normally enjoyable activities, a symptom which could reflect impairment in perceived wanting, liking, or both. A primary goal in translating findings from the neuroscience of reward, therefore, is to more clearly delineate the nature and scope of reward dysfunction in MDD.

4.1. Diminished 'liking': blunted reactivity to reward delivery

To date, the most consistent finding of reward dysfunction in MDD is blunted reactivity to monetary reward outcomes in the striatum, including the bilateral putamen, caudate, and NAc (Forbes et al., 2009; Knutson et al., 2008; Moses-Kolko et al., 2011; Pizzagalli et al., 2009; Steele et al., 2007). Similar indications of striatal hypoactivation have also been observed in response to other types of pleasurable stimuli, including happy faces (Keedwell et al., 2005), pleasant words (Epistein et al., 2006), and the taste of chocolate (McCabe et al., 2009), suggesting that MDD is characterized by a generalized deficit in striatal reactivity that spans both primary and secondary rewards.

Converging evidence has also emerged from ERP studies utilizing simple guessing/gambling tasks with random reward delivery (Proudfit, in press): In two recent studies focusing on 'pure', unmedicated MDD samples, FN amplitude was blunted compared to controls (Foti et al., 2014; Liu et al., 2014). A blunting of FN amplitude has also been observed in relation to MDD symptomatology within non-clinical samples, including adults (Foti & Hajcak, 2009) and children (Bress et al., 2012, in press). Moreover, there is preliminary

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evidence that blunted FN amplitude may represent a neurobiological indicator of risk (Foti et al., 2011), in terms of its ability to prospectively predict first-episode MDD onset over and above other known risk factors (Bress et al., 2013).

In one multimodal neuroimaging study, blunted FN amplitude and striatal BOLD hypoactivation were both found to be driven specifically by a subgroup of MDD individuals who also reported impaired mood reactivity to positive events, a core feature of melancholic MDD (Foti et al., 2014). That is, MDD individuals with nonreactive mood—reflecting impairment in the perceived hedonic impact of positive events—exhibited profound reduction in FN amplitude and hypoactivation in the NAc; by contrast, MDD individuals who reported intact mood reactivity exhibited normal reward functioning that was indistinguishable from controls. These group differences in reward processing were linked specifically with the symptom of nonreactive mood and were not apparent for the full, *DSM*-defined categories of melancholic or atypical MDD. This pattern indicates how psychophysiological data of reward dysfunction can potentially be utilized to refine the anhedonic phenotype.

Through the lens of the componential model of reward, blunted FN amplitude and BOLD striatal activity to reward outcomes in MDD likely reflect primary impairments in 'liking'. Among individuals with MDD, blunted reactivity to monetary reward and to pleasant stimuli are associated with diminished consummatory pleasure, suggesting that these physiological response deficits signify reduced hedonic valuation of reward (Epstein et al., 2006; Forbes et al., 2009; Liu et al., 2014; Foti et al., 2014; Keedwell et al., 2005). Conversely, restoring striatal activity increases perceived liking: Deep brain stimulation of the NAc leads to clinical improvement in treatment-refractory MDD by eliciting increased self-reported pleasure and engagement in pleasurable activities (Bewernick et al., 2010; Schlaepfer et al., 2008).

Further, evidence from studies of neurotransmitter function suggest that deficient reward-related striatal activity in MDD may be partly accounted for by mu-opioid and endocannabinoid dysfunction. Animal data indicates that mu-opioid agonists reduce depressive behavior (Berrocoso et al., 2013; Berrocoso & Mico, 2009; Yang et al., 2011); in humans with MDD, mu-opioid transmission in the NAc and ventral pallidum is dysregulated (Kennedy et al., 2006), and genetic variation in mu-opioid activity moderates the effectiveness of antidepressant medication (Garriock et al., 2010). Relatedly, evidence from an animal model of MDD indicates that antidepressant treatment normalized endocannabinoid functioning (Hill et al., 2008), and in humans diagnosed with MDD, variation in endocannabinoid-related genes was found to be predictive of both striatal reactivity to happy faces and responsiveness to antidepressant treatment (Domschke et al., 2008). Insofar as mu-opioid and endocannabinoid activity within the NAc shell and ventral pallidum have been closely linked with the hedonic valuation of rewards (Berridge et al., 2009)—and both are identified as molecular measures of relevance to the RDoC construct of Initial Responsiveness to Reward Attainment—these findings highlight possible neuromodulatory mechanisms for impaired 'liking' in MDD.

4.2. Diminished learning: insensitivity to reward contingencies

In addition to evidence for deficient 'liking', other research indicates that reward learning is also impacted in MDD. A number of behavioral studies using probabilistic reinforcement tasks have demonstrated that MDD is associated with impaired reward learning, as evidenced by an inflexible response style that is not modulated by reward contingencies (Henriques & Davidson, 2000; Pizzagalli et al., 2008; Vrieze et al., 2013). Specifically, individuals with MDD fail to maintain a response bias toward more frequently rewarded stimuli in the absence of immediate reinforcement, indicating that the learned association is updated too quickly on trials where rewards are not delivered (Pizzagalli et al., 2008). This behavioral insensitivity to reward contingencies is correlated with anhedonia severity and is predictive of poor treatment outcome (Vrieze et al., 2013). In addition, impaired reward learning in MDD is associated with blunted activity within the NAc, as well as the dorsal and rostral ACC (Kumar et al., 2008). Building on these data, a recent study demonstrated that impaired behavioral accuracy in MDD during a reversal learning task was associated specifically with blunted NAc activity to unexpected reward outcomes, and not with punishment outcomes (Robinson et al., 2012). Unlike in SUD, impaired reward learning in MDD appears to be distinct from error-related brain activity, which remains intact. In contrast with SUD, recent evidence indicates that ERN amplitude is driven by comorbid anxiety rather than MDD per se (Bress et al., in press; Weinberg et al., 2012).

Impaired reward learning in MDD may be explained in part by diminished neural activation during reward anticipation. Studies have observed caudate hypoactivation during the anticipation of uncertain reward outcomes (Forbes et al., 2009; Olino et al., 2011; Smoski et al., 2009), as well as blunted left frontal activity as indicated by alpha EEG rhythms (Nelson et al., 2013; Shankman et al., 2007, 2013). Considered together with the evidence of blunted 'liking' discussed above, one possible explanation for these findings is a bidirectional link between hedonic devaluation and diminished learning in MDD. The devaluation of reward outcomes may blunt the anticipation of reward feedback and disrupt the maintenance of reward contingencies, which in turn may reinforce further hedonic devaluation.

In contrast with this robust evidence for impaired 'liking' and learning in MDD, there is evidence that, under some circumstances, active anticipation during the pursuit of reward may be unaffected in MDD—suggesting that 'wanting' remains intact. On the one hand, there is consistent evidence from resting state EEG measures that represent positive affect and approach behavior (i.e., 'wanting' in the absence of reward cues) indicating blunted left frontal activity in individuals with MDD (Davidson, 1992, 1998; Debener et al., 2000; Gotlib et al., 1998; Henriques & Davidson, 1990, 1991). Though it is possible that 'wanting' is impaired at rest, explicit instructions to actively pursue rewards appear to normalize 'wanting' but not 'liking' in MDD, suggesting that hedonic devaluation, but not the capacity for 'wanting', is central to MDD pathology. For example, in two studies using a monetary incentive delay task in which participants were instructed to earn rewards by quickly responding to a cued target stimulus and learning contingencies, the MDD groups exhibited robust NAc activation during target anticipation that was comparable to controls, as well as normal behavioral performance on the task (Knutson et al., 2008; Pizzagalli et al., 2009); NAc activity to reward outcomes, however, was blunted. A similar pattern has also been observed in remitted MDD, with frontostriatal hyperactivity during active reward anticipation and hypoactivity to reward outcomes (Dichter et al., 2012). A key methodological difference in these studies relative to others demonstrating reduced reward-cue reactivity is that anticipatory striatal activity was examined *in the service of approach behavior*—i.e., in a context where effective responding to the cued target stimulus was required to earn a reward—rather than under conditions of passively awaiting a random reward outcome, not calling for approach behavior. When individuals with MDD are explicitly instructed to pursue potential rewards, they are able to successfully recruit anticipatory reward-related neural activity that is consistent with 'wanting', even though 'liking' remains impaired. In other words, the *capacity* for 'wanting' may be unaffected in MDD, independent of other observed deficits in 'liking' and learning.

In sum, the extant literature indicates that MDD is primarily characterized by a combination of impaired 'liking' and learning. There is diminished hedonic impact of rewards, as indicated by blunted FN amplitude and NAc activation, and reward contingencies are not maintained, presumably owing to reduced NAc and ACC responsivity (Kumar et al., 2008). Separate from these two components of reward dysfunction, the capacity for active 'wanting' appears to be relatively intact in MDD, with robust striatal activation evident in the context of approach behavior in pursuit of reward.

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5. Synthesis of findings

5.1. A multidimensional, transdiagnostic perspective on reward dysfunction

A substantial body of evidence indicates that both MDD and SUD are associated with dysfunctional reward processing across multiple units of analysis. These two literatures have grown in parallel with one another, but with a focus on one disorder or the other and limited consideration of their co-occurrence, despite the fact that SUD and MDD are commonly observed together and reciprocally impact the course of one another. To draw this research closer in line with the clinical reality of complex comorbidity, a transdiagnostic perspective is warranted. While there are important methodological differences between these two literatures (e.g., the typical use of drug-related reward cues in SUD and monetary reward in MDD), we offer here a preliminary framework to inform future, integrative research by reframing these literatures with respect to the componential model of reward. Insofar as past research has focused largely on 'pure' cases of SUD or MDD (that is, considering these diagnoses in isolation), we focus on these two diagnostic categories as illustrative anchor points with characteristic profiles of reward dysfunction (Fig. 1). It will be important for future research, however, to expand upon this framework in order to establish other, likely more complex profiles of reward functioning not shown in Fig. 1; these other profiles may represent liability factors and contribute to the occurrence of SUD/MDD, as well as other mental health problems.

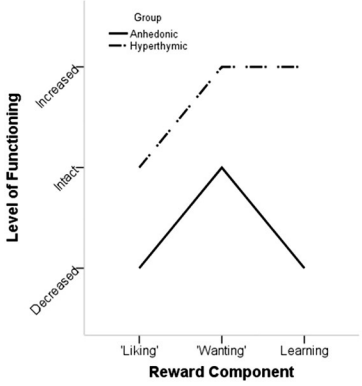
Based on the available evidence, we propose that relatively 'pure' cases of SUD and MDD represent two extreme forms of reward dysfunction, with distinct profiles: Primarily Hyperthymic and Primarily Anhedonic, respectively (Fig. 1). The Primarily Hyperthymic (i.e., 'pure' SUD) profile is associated with excessive 'wanting', as evidenced by increased activity throughout the mesolimbic dopamine reward circuit and an increased P3 to substance-related cues, as well as evidence for an increase in perceived desire for the substance; in the Primarily Anhedonic profile, 'wanting' appears to normalize during instructed reward pursuit, despite deficits in passive reward anticipation and baseline (i.e., resting state) approach motivation. On the other hand, the Primarily Anhedonic profile (i.e., 'pure' MDD) is characterized by impaired 'liking,' as evidenced by blunted striatal activity and a blunted FN to reward delivery, as well as a decrease in perceived pleasure; in the Primarily Hyperthymic profile, 'liking' is largely intact. More broadly, the Hyperthymic profile is associated with hyperactivity and the Anhedonic profile is associated with hypoactivity in reward circuitry, but these abnormalities appear to map onto distinct components of reward: enhanced incentive salience in the Hyperthymic, and reduced hedonic impact of rewards in the Anhedonic profile.

Reward learning, on the other hand, is impacted differently across the two profiles. Unlike the findings for 'liking' and 'wanting', abnormal learning appears to form a bipolar dimension that spans both profiles. The Primarily Hyperthymic profile is associated with hypersensitivity to reward contingencies, perseveration on stimuli which were rewarded previously, and a failure to update learned associations when presented with negative feedback (i.e., increased, but inefficient learning). The Primarily Anhedonic profile, conversely, is characterized by an insensitivity to reward contingencies and a failure to maintain learned reward associations over time when presented with negative feedback (i.e., the absence of reward). In other words, the Primarily Hyperthymic profile is associated with a learning style in which reward contingencies are not updated quickly enough, whereas the Primarily Anhedonic profile is associated with a learning style in which reward contingencies either decay or are overwritten too quickly when a reward is not delivered. Each of these deficits in the integration of reward feedback is associated with ACC dysfunction. In addition, perseverative reward learning in the Hyperthymic profile is associated with OFC dysfunction, and insensitive reward learning in the Anhedonic profile is associated with ventral striatal dysfunction.

Beyond the two profiles described here, a primary advantage of the proposed framework is that it portends the possibility of dimensional approach to classification. Each component reward process may be conceptualized as a transdiagnostic dimension of impairment, such that individual cases may be classified by a combination of (a) the nature of impairment across components ('liking', 'wanting', learning, or some combination thereof) and (b) the severity of impairment within each component (degree and pervasiveness of the impairment). Though 'pure' cases of either SUD or MDD dominate neuroscience research on reward-related abnormalities, they are clinically rare, and the Primarily Hyperthymic and Primarily Anhedonic profiles presented in Fig. 1 may only apply to a small subsample of patients. As recommended by RDoC, other profiles may be derived empirically by examining clinically heterogeneous samples, including cases of comorbid SUD/MDD, subthreshold SUD/MDD, and SUD/MDD co-occurring with other psychiatric diagnoses. It is expected that these cases will yield other, more mixed profiles of reward dysfunction (e.g., abnormalities across all three components). Teasing apart characteristic profiles of reward dysfunction in this way may yield a more parsimonious account of complex psychiatric illness than is feasible with the current nosology.

5.2. Reward dysfunction as a liability for SUD and MDD

RDoC offers a pathway for integrating information across genetic, physiological, behavioral, and self-report indices (Cuthbert & Insel, 2013), an approach which is well-suited to spur the identification of endophenotypes. The psychophysiological indicators of reward processing discussed here are highly promising candidates insofar as they may be used to bridge the gap between genetic risk and clinical



Profile of Dysfunction	'Liking' Random reward delivery	'Wanting' Integrating unexpected outcomes	Learning Reward cues, associated stimuli
Primarily Anhedonic	• *Behavior*: reduced self-reported pleasure • *Neural*: blunted activity in dorsal/ventral striatum; blunted feedback negativity	*Normalized under explicit task instructions*	• *Behavior*: insensitivity to previously rewarded stimuli; failure to maintain learned associations • *Neural*: blunted activity in ventral striatum and dorsal/rostral ACC
Primarily Hyperthymic	*Unaffected*	• *Behavior*: increased self-reported desire • *Neural*: increased activity in striatum, VTA, amygdala, OFC; increased P3 to substance cues	• *Behavior*: perseveration on previously rewarded stimuli; failure to update learned associations • *Neural*: reduced volume and blunted activity in OFC and ACC

Fig. 1. Left: Candidate profiles of dysfunction across component reward processes within 'pure' cases of MDD and SUD. The 'Primarily Anhedonic' profile reflects abnormalities observed in relatively pure cases of major depressive disorder; the 'Primarily Hyperthymic' profiles reflects abnormalities observed in relatively pure cases of substance use disorders. Right: Behavioral and neural indices of abnormalities within each reward component.

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phenomena in SUD/MDD. While the research to date is too limited to definitively designate specific forms of reward dysfunction as endophenotypes, reward dysfunction appears to be highly relevant to the onset and course of both SUD and MDD. As discussed below, there is emerging evidence that certain forms of reward dysfunction are present in vulnerable individuals prior to the onset of overt SUD/MDD symptoms and persist after symptom recovery, potentially reflecting neurophysiological liabilities for future illness.

With regard to SUDs, there is strong evidence that the development of these disorders and their associated reward dysfunction emerges from a common heritable factor, known as externalizing (Iacono, Malone & McGue, 2008; Krueger et al. 2002). Externalizing encompasses a range of problematic behaviors and traits (Finn et al., 2009; Krueger et al., 2007; Krueger & Markon, 2006; Krueger et al., 2001; Gorenstein & Newman, 1980) and, as a latent construct, it enables investigators to study dysfunctional processes associated with diverse disinhibitory psychopathologies, including SUD, that share a common genetic liability. Externalizing confers a substantial trait-like risk for SUDs (Vaidyanathan et al., 2011, 2012); individuals high on externalizing start using substances earlier in life, display higher rates of more severe substance use, and have higher rates of relapse.

While many types of dysfunction contribute to the development and maintenance of externalizing psychopathology, reward dysfunction—particularly in the 'wanting' and learning components—consistently emerges as a key risk factor. Notably, there is substantial evidence for a reduced amplitude of P3 brain response in standard oddball paradigms among individuals high in externalizing (Iacono et al., 2003), an effect which has been reported in community, undergraduate, incarcerated, and patient samples diagnosed with externalizing psychopathology (e.g., substance use disorders, aggressive disorders) (Bauer et al. 1994a b; Bernat et al., 2007; Costa et al., 2000; Gao & Raine, 2009; Iacono et al., 2002; Kim et al., 2001; McGue & Iacono, 2005; O'Connor et al., 1994; Patrick et al., 2006; Polich, 2007; Venables et al., 2011). Moreover, recent research suggests this reduction in P3 amplitude specifically reflects diminished salience detection and hypersensitivity to motivational (i.e., reward-related) cues (Baskin-Sommers et al., 2014). Relatedly, studies using fMRI and PET have found that neural regions related to reward 'wanting' and learning are dysfunctional in individuals high on trait externalizing (Buckholtz et al., 2010a, 2010b). With regard to course of illness, a reduced P3 amplitude predicts relapse in offspring of alcoholic fathers, even before these offspring have had their first drink (Carlson et al., 2002). Elsewhere, Sinha and Li (2007) reported that increased reward salience, as indicated by medial PFC activation toward drug cues, was associated with a shorter time to relapse and a greater amount of substance used, but self-reported "craving" was not (see also Grüsser et al., 2004). Though not all individuals who have SUDs are high on trait externalizing, those that are may represent a particularly severe and stable subgroup of SUD that are characterized by early developmental reward dysfunction.

Within MDD, anhedonia has been proposed as a candidate endophenotype (Hasler et al., 2004). Specifically, it is thought that life stressors alter reward functioning, which then confers vulnerability to future MDD (Pizzagalli, 2014). Consistent with this model, developmental research has linked reward dysfunction to familial history of MDD and early life stress. A reduced FN has been observed among offspring of mothers with a history of MDD but not anxiety, even prior to the offspring's first depressive episode (Kujawa et al., 2014). This risk is moderated by early parenting style, particularly low authoritative parenting among mothers with a history of MDD (Kujawa et al., in press). Other research has observed a reduced FN following a negative mood induction (Foti & Hajcak, 2010), an effect which is more pronounced among individuals with a family history of MDD, who may be more susceptible to mood-related reward dysfunction (Foti et al., 2011). Relatedly, a blunted FN amplitude uniquely predicts first-episode MDD onset, over and above other known risk factors (Bress et al., 2013). Complementing findings from fMRI studies have shown reduced reward-related striatal activity in never-depressed offspring of mothers with past MDD (Gotlib et al., 2010; Monk et al., 2008; Sharp et al., 2014). This reward dysfunction may be trait-like and independent of symptom improvement: remitted MDD is characterized by blunted NAc reactivity to pleasant stimuli—despite normal perceived pleasure and wanting (McCabe et al., 2009)—and blunted frontostriatal reactivity to monetary reward (Dichter et al., 2012).

6. Understanding the comorbidity between SUD and MDD

Rates of lifetime comorbidity between MDD and SUD are high (Kendler et al., 2003; Vaidyanathan et al., 2012; Watson et al., 2005). One possible explanation for these high rates may relate to dysfunction in reward circuitry. While dissociable deficits in reward 'liking,' 'wanting,' and learning are associated with SUD and MDD, changes *within* the reward system associated with one disorder may actually increase risk for alteration in additional reward-related processes. Though very little work has directly examined the proposal that the high rates of comorbidity between SUD and MDD can be explained by reciprocal changes in the reward system, here we outline two possibilities, one where SUD-related dysfunction may lead to alterations associated with MDD and the other where MDD leads to alterations associated with SUD.

SUDs are associated with neural adaptations that occur in response to and withdrawal from substances. In both animal and human models, acute and chronic responses to substances lead to a reduction in brain dopamine and alterations to a number of brain regions (e.g., ventral cingulate gyrus, involved in mood regulation; prefrontal cortex, involved in executive functioning; ventral striatum, involved in reward processing; thalamus, involved in arousal; Gouzoulis-Mayfrank et al., 1999; Iyo et al., 1997; Sapolsky, 2003; Volkow et al., 2001a, 2001b). In addition to the neuronal changes in response to substance administration, changes in the brain's reward circuitry and in the amygdala have been implicated in inducing the negative emotional symptoms that often occur during early phases of withdrawal (Philibin et al., 2011). A common effect of withdrawal is reduced dopamine output in the NAc, with studies reporting a 25% to 64% reduction in dopamine levels during withdrawal from various substances (Watkins et al., 2000). These substance-induced adaptations, particularly associated with degradation of dopamine and neuronal integrity in the frontal cortex and striatum, overlap with the MDD-related decreased sensitivity to salient events (i.e., deficit in 'liking' mediated by the striatum), insensitivity to previously reward stimuli (i.e., learning deficit mediated by ACC), mood regulation, and regulation of arousal (Koob & Le Moal, 1997; Krishnan & Nestler, 2008; Saal et al., 2003; Volkow et al., 1997, 2003). Given the overlap between neurobiological changes due to SUD and those present in MDD, it is possible that a key to understanding the comorbidity between these two disorders is identifying the presence of SUD prior to the onset of MDD.

Apart from the risk associated with the onset of MDD as a result of neuroadaptations related to SUD, the most widely held explanation for SUD–MDD comorbidity is the self-medication hypothesis. The self-medication hypothesis suggests that the distressful psychological state associated with MDD is subdued by the psychotropic effects of substances and as a result increases the vulnerability for SUD (see Childress et al., 1994; Dodgen & Shea, 2000; Eftekhari et al., 2004; Johnston & O'Malley, 1986; Khantzian, 1985; Suh et al., 2008). As noted above, reward circuitry centers on many of the regions and connections disrupted in MDD, such as connections between the NAc, frontal cortex, and amygdala. However, the effect most substances of abuse have on these regions is the inverse of what is associated with MDD. For example, most substances of abuse stimulate dopamine activity in limbic regions, affecting other neurotransmitter systems and enhancing the reinforcing properties substance, supporting the idea that those with MDD may try to self-medicate with substances in order to reverse the effects of the blunted dopamine activity (Markou et al., 1998). Research

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also indicates that nicotine compensates for some of the cognitive impairments produced by MDD (i.e., failure to maintain learned associations) by activating receptors for the neurotransmitter acetylcholine, which is present throughout the mesolimbic pathway, and exciting different kinds of "interneurons" in the prefrontal cortex (Couey et al., 2007; Kenney & Gould, 2008). Essentially, the depressed brain seeks comfort and stimulation and depressed regions are invigorated by the intake of substances, suggesting that self-medication may assuage the effects of MDD by increasing activity within brain regions hypoactive in MDD. Unfortunately, self-medication not only alters deficits associated with MDD, but also activates ones associated with 'wanting' (i.e., increased VTA, amygdala, striatum activity) and other learning processes, thus, increasing vulnerability to SUD.

Without a doubt SUD and MDD are interrelated at a neurobiological level, and exposure to the physiological and psychological consequences of SUD and MDD leads to alterations of brain chemistry and connectivity. While some adaptations are reversible, others are not, leading to sustained differences in where neural pathways actually grow in the brain, concentration of specific neurotransmitters, and overall brain functioning. Ultimately, by understanding what the brain is going through during SUD and/or MDD, precise prevention and treatment programs can be developed and identified.

7. Future directions & conclusions

Drawing from the already substantial basic science literature on reward, clarifying the nature of reward-related symptoms in SUD and MDD represents a great opportunity for translational neuroscience. In the short term, it is expected that a multidimensional approach to assessing reward dysfunction will help to account for variability within the existing diagnostic categories of MDD and SUD (i.e., differentiate individuals with the same diagnosis who have distinct profiles of reward dysfunction), as well as identify mechanistic pathways for some instances of comorbid MDD/SUD. In the long term, it is expected that the existing categories of SUD, MDD, and other disorders will themselves be restructured as profiles of reward dysfunction within a dimensional classification system—profiles that (a) may be objectively quantified using psychophysiological measures and (b) will parsimoniously account for complex forms of illness in a way that the current nosology does not.

While we have outlined a preliminary model of multidimensional reward dysfunction across SUD and MDD, the supporting evidence remains incomplete. In fully implementing the RDoC approach, future studies may test this model directly by considering three key factors: selection of sample, task, and unit of analysis. First, it will be critical to examine how these psychophysiological indicators of reward dysfunction map onto clinical phenomena in potentially novel ways, regardless of existing diagnostic boundaries. For example, future studies should recruit individuals seeking mental health treatment at an outpatient clinic—without any diagnostic exclusion criteria—thereby allowing for a mixture of symptomatology related to MDD and SUD, as well as other co-occurring illnesses. With a clinically mixed sample, relatively large sample sizes will likely be required to achieve adequate statistical power for mapping individual differences in reward functioning. A more targeted sample, meanwhile, raises the question of what the relevant inclusion criteria should be. One viable approach would be to select subjects based on a dimensional trait related specifically to MDD and SUD (e.g., anhedonia and externalizing, respectively), rather than diagnostic category. Alternatively, subjects could be selected based on a measure tapping the underlying reward dysfunction (e.g., scale measuring reward sensitivity). This could be used to work 'outward' toward the relevant clinical phenotype, although it assumes that the biobehavioral dimension is well-characterized across multiple units of analysis.

Second, task selection is an important factor in the RDoC framework. Not only should the tasks reliably reflect the process of interest, but they should also be robust enough to capture individual and should relate to other processes as predicted (Lilienfeld, 2014). An important aspect of the RDoC framework is the assumed correlation and connection among different domains and units of analysis—a structure which requires empirical validation. This may be achieved by shifting away from single laboratory paradigms of 'reward' and instead incorporating a battery of tasks designed to target a set of processes. For example, studies could examine patterns of abnormal neural activity across: (a) a simple guessing task designed to target 'liking', (b) a speeded response task designed to target 'wanting', and (c) a probabilistic reinforcement task designed to target reward learning, all within a single sample. Two studies in healthy samples indicate that there exist modest interrelationships across tasks: Effective reward learning is moderately associated with striatal reactivity in a speeded response task (Santesso et al., 2008) and with FN amplitude on a simple guessing task (Bress & Hajcak, 2013).

Finally, the RDoC framework calls for integrating units of analysis in order to build profiles of processes across individuals, in which a multimodal psychophysiological approach will be valuable. ERP studies may effectively shed light on the time course of aberrant reward processing in order to parse distinct sources of neural activity that map onto the hedonic impact, processing, and anticipation of reward cues. Neuroimaging studies, meanwhile, will be important for clarifying the relative contribution of specific cortical and subcortical structures to each dimension of reward functioning. Further, for any given biological indicator of reward functioning, it is critical identify those symptom measures to which it relates and those to which it does not, information which is necessary to in order to set the boundaries of the relevant construct. That is, for a psychophysiological measure to capture 'liking' per se, it ought to relate more closely to self-reported pleasure than to desire or effective learning, and vice versa.

As these gaps in our understanding of reward processing are addressed, new pharmacotherapies and behavioral treatments may be developed to effectively treat SUD and MDD by targeting specific forms of reward dysfunction. Though research to date on such interventions in SUD is somewhat mixed, there is some promising evidence (Volkow et al., 2004): neural functioning related to 'wanting' can be normalized through drugs that block the ability of substances to increase DA cell firing, as well as strategies that interfere with conditioned responses to substance cues (Volkow et al., 2004). With regard to MDD, antidepressant treatment outcome has been associated with increased NAc activation and frontostriatal connectivity during the effortful up-regulation of positive emotions, suggesting that normalization of 'liking' may play a role in successful treatement (Heller et al., 2013). Further, for patients with treatment-resistant MDD, direct stimulation of the NAc using depth electrodes also appears to be an effective intervention and yields immediate improvement in reported anhedonia (Bewernick et al., 2010; Schlaepfer et al., 2008).

Beyond the potential for developing such targeted treatments for SUD or MDD, a coordinated treatment approach may ultimately be more fruitful. Studies of the efficacy of antidepressant medications in the treatment of substance-dependent patients with comorbid MDD have found that medications do reduce depression levels (Nunes & Levin, 2004; Torrens et al., 2005). There is also some evidence that antidepressants are more successful in reducing SUD in depressed substance abusers than non-depressed substance abusers (Markou et al., 1998). However, in terms of behavioral therapies, Carroll's (2004) review on the efficacy of cognitive-behavioral therapy and contingency management in the treatment of patients with co-occurring substance use and mood disorders concluded that although there is good evidence that these interventions decrease substance use, there is less evidence that they also lead to improvements in mood disorders. The influence of comorbid SUD and MDD on treatment outcomes appears to be complex and more research is needed. However, a better understanding of the reward circuitry altered by SUD and MDD will help form a heuristic basis in the search for genetic, molecular, pharmacological, and cognitive-behavioral therapies. In sum, an integrative focus on

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abnormal reward functioning across SUD and MDD may yield improved prediction of the onset, better recognition of the factors contributing to the maintenance, and more effective remediation of these disorders.

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