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The Intersection between Neurobiological and Psychological Theories of Substance Use Disorders

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Why do people engage in substance use? This may seem like an easy question. Most people can think of reasons for having a drink at the end of a long day, waking up with some coffee, or taking a painkiller for a pulled muscle. A more difficult question, though, is why some people *abuse* substances. Substance use disorders (SUD) rank among the most widespread and costly illnesses nationwide. In 2011, 6.5% of the population was dependent on alcohol or had problems related to alcohol use, and more than 2.5% of the population met clinical criteria for dependence or abuse of an illicit substance. This particular problem also accrues over $600 billion per year in costs related to crime, diminished work productivity, and healthcare (National Institute of Drug Abuse 2012). Although there are certainly many factors that contribute to the transition from simply using a substance to a chronic, recurrent pattern of use that leads to impairment in various life domains, core neurobiological and psychological processes are continually implicated in the development and maintenance of SUD.

Most consistently, SUD are characterized by marked dysfunction in reward-seeking behavior (American Psychiatric Association 2013). A defining feature of SUD is the excessive pursuit and use of a substance that is disproportionate to the hedonic (i.e., pleasurable) impact derived from it. However, basic human and animal neuroscience literature indicates that reward is not a unitary construct, but instead multifaceted. Reward is believed to be comprised 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, Robinson, and Aldridge 2009). Importantly, this line of research demonstrates that these components of reward may vary across individuals and drive the transition from use to SUD within an individual.

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Given that reward-related abnormalities are omnipresent in SUD, it is important to understand the impact abnormalities in reward processing have on these clinical phenomena. The goal of this chapter is to summarize and synthesize the findings in reward processing and SUD. First, we provide a brief overview of the basic neuroscience literature on reward. Next, we review the specific neural abnormalities that have been identified, to date, within SUD. Finally, we integrate the basic neurobiological patterns with important psychological theories, specifically self-medication and distress tolerance. An integrative focus on abnormal neurobiological and psychological functioning may help to clarify the nature of deficits across SUD and better predict the onset of and recovery from these issues.

The Neurobiology of Reward

Not only has significant progress been made in parsing the psychological components of reward, but also in identifying the underlying neural mechanisms associated with each component. Broadly speaking, reward processes are represented in the brain by a complex network involving many subcortical structures such as the nucleus accumbens, ventral tegmentum, ventral pallidum, amygdala, and mesolimbic dopamine projections, as well as cortical structures, including the orbitofrontal cortex (OFC), anterior cingulate (ACC), and insula. Evidence from animal studies (i.e., preclinical) and human studies suggests that interactive components in this circuitry link processes involved in reward-related functioning, such as cognition, emotion, and goal-directed behavior (Everitt et al. 2008; Haber and Knutson 2010).

Though there is inherent complexity in the interrelationships of specific brain regions within this reward circuitry, certain structures have been principally associated with distinct reward processes of "liking," "wanting," and learning, respectively (Berridge, Robinson, and Aldridge 2009). It is important to note that "liking" and "wanting" are not the same as subjective 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 subjective feelings of liking (e.g., enjoyment) or wanting (e.g., desire), but these reward-related processes may also occur implicitly without the associated subjectivity (Berridge 2006). Simply put, an individual with a SUD may report that s/he subjectively 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.

"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 subjective pleasure, "liking" is a process that represents an implicit or objective reaction to hedonic

stimuli that is not dependent on a conscious feeling of pleasure. "Liking" reactions can be elicited by a variety of conditioned and unconditioned stimuli ranging from tastes (e.g., sweet) to drug-mediated rewards, money, and sex (Beaver et al. 2006).

Much of the initial research used to identify and define "liking" comes from conditioning studies with animals. Using objective measures, such as facial reactions to conditioned sweet tastes, Berridge and colleagues identified a number of hedonic hotspots in the ventral pallidum and the shell of the nucleus accumbens 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 and Robinson 2003). Activation of these hotspots closely relates to increases in "liking" reactions, such as affective reactions in rats elicited by oral infusions of sucrose, whereas damage to these regions corresponds to a "disliking" reaction (e.g., gaping, prevomiting reaction to bitter *and* sweet tastes; Peciña 2008). In humans, the core neural components of "liking," or the experience of pleasure, include the ventral pallidum and the ventral striatum, specifically the shell regions of the nucleus accumbens (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, including GABA-receptor feedback and mesolimbic outputs to certain locations in the NAc shell and the ventral pallidum, also modulate "liking" (Berridge and Robinson 2003).

While dopamine traditionally has been linked to sensory pleasure, research indicates that this neurotransmitter is not adequate for initiating a "liking" response (Berridge and Robinson 1998). For example, activation of dopamine in the NAc through amphetamine microinjection does not change the "liking" response, but does increase the motivational component of a reward (Wyvell and Berridge 2000). As such, the primary role of dopamine has been linked to incentive salience, learning, and other reward-related functions (Berridge 2006).

"Wanting": The motivation salience of rewards

Although "liking" and "wanting" may seem tightly coupled, these processes are neurobiologically and psychologically separable. "Wanting" refers specifically to incentive salience that motivates approach toward rewards rather than simply activation of the aforementioned neural mechanisms associated with a "liking" response. It is often mediated by the reward stimulus itself, and does not require elaborate cognitive expectations. As such, "wanting" is distinct from subjective 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 learned stimuli (e.g., conditioned stimuli). Research on the neural systems responsible for "wanting" uses 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 them (Berridge and 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 firing is diminished when predicted rewards do not occur (Schultz 2007). Thus, it is hypothesized that one function of dopamine is to connect incentive salience 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 seeking response to sucrose without impacting the experience of pleasure for sucrose (Wassum et al. 2009), once again highlighting a distinction between "liking" and "wanting." In addition, 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.

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 associative value of reward may be separated from its motivational value, depending on the learning processes. At a simplified level, learning involves building knowledge about a specific relationship, 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 and gambling tasks in humans) rely more heavily on cortical structures, including OFC, insular cortex, and prefrontal cortex, but also include interactions with subcortical regions.

One function of the OFC is quick associative learning (e.g., stimulus–reinforcement) and the alternation of these associations 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 change in the environment (e.g., object reversal and go/no-go tasks; see Rolls 2000 for review). Additionally, this region plays a role in attaching affective valence to stimuli through its relationship with the amygdala (London et al. 2000) and evaluating stimulus characteristics through connections with regions believed to underlie memory functions (e.g., dorsolateral prefrontal cortex; Perlstein, Elbert, and Stenger 2002).

The insular cortex is believed to play an important role in the anticipation or expectancy of reward (Balleine and Dickinson 2000), whereas the ACC encodes

previous reward outcomes (Kennerley, Behrens, and Wallis 2011). Additionally, 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 prefrontal cortex and dorsolateral prefrontal cortex (Bechara, Tranel, and Damasio 2000). These neural regions that represent different learning processes serve to associate cues with their context, and with particular responses such as "wanting" a reward or engaging in action to consume the reward. Thus, reward-related learning may bridge the stages of hedonic "liking" (pleasure) with motivational learning.

Even though there is some evidence of partially separable neural substrates across these three core reward processes, it is important to note that each of these psychological components of reward are connected and function together as a coordinated network integrating emotional, motivational, and learning processes. The multifaceted nature of the reward circuitry is important for adaptive functioning, and understanding dysfunctions within this circuit can provide a clearer understanding of the neurobiology of SUD.

Reward Dysfunction in Substance Use Disorders

While different types of substance have different pharmacological and pharmacokinetic properties, their habit-forming, or abuse-related, effects involve a common denominator: a dysfunction in reward circuitry. Increasingly, evidence demonstrates that substance abuse "hijacks" the neural circuitry of reward (Berridge and Robinson 2003). Essentially, substances work in the brain by tapping into this network and interfering with the way components normally send, receive, and process information. Accordingly, studies suggest that structural and functional changes *within* this network, as well as impaired communication *between* brain regions in this network, contribute significantly to the pathogenesis of SUD. More specifically, a number of preclinical and clinical studies support the hypothesis that the primary neural substrates of persistent substance use are linked to "wanting" (salience detection) and learning (associative memory), processes affected by mesolimbic dopamine and the prefrontal cortex (Hyman, Malenka, and Nestler 2006; Tiffany 1990). While the various substances impact multiple neural regions and neurotransmitters (e.g., serotonin) (Kranz, Kasper, and Lanzenberger 2010), the mesolimbic DA system is activated by all major substances of abuse and is of central importance to all (Hommer, Bjork, and Gilman 2011).

Dysfunctional "wanting": Incentive-sensitization theory

In general, it is proposed that individuals with substance abuse have altered saliency values related to reward (e.g., "wanting") (Volkow et al. 2004b). This enhanced saliency is initiated by the higher intrinsic reward properties of drugs, again largely regulated by mesolimbic DA. Robinson and Berridge's (1993) incentive-sensitization

theory posits that the repeated use of substances initiates a cycle whereby any stimuli associated with the substance acquires incentive value, and as the stimuli–substance associations increase in frequency the value 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 (via the frontal cortex) are inhibited. Furthermore, long-term exposure to drugs causes 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 and Le Moal 2001; Volkow, Fowler, and Wang 2004a).

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). For example, there is preclinical evidence in mice that suggests chronically elevated DA facilitates "wanting" and learning in an incentive motivation task for a sweet reward, but elevated DA did not alter the "liking" reactions to the hedonic impact of those sweet tastes. More specifically, Peciña and colleagues (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.

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

In addition to imaging methods, electrophysiological research in humans emphasizes a specific deficit in salience detection in SUD. Studies have focused on the P300, an event-related potential (ERP) related to dopamine production and the allocation of attentional resources to salient or task-related stimuli (Polich 2007). With relation to SUD, an enhanced P300 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 P300 amplitude

have also been reported in smokers while viewing smoking cues (Warren and 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). Furthermore, there is some evidence that this increased attention toward salience detection and reward processing decreases during withdrawal; as such, reductions in delta electroencephalography rhythms, a signature of reward-processing and salience detection, has been reported in crack-cocaine users during the substance withdrawal period (Alper et al. 1990). In general, an enhanced P300 to substance-related cues may provide an important biological marker of crucial psychological mechanisms relevant to addiction. Specifically, these electrophysiological patterns suggest that during addiction, substance cues capture attentional resources and acquire enhanced motivational salience compared to non-substance-related cues, but that these associations may diminish once the substance–stimulus reward associations are degraded.

The incentive-sensitization theory and the concomitant neural abnormalities (i.e., "wanting"-based neural processes) are central to understanding SUD. It suggests that the repeated administration of a substance increases its reinforcing properties, progressively gains control of the reward and motivational circuitry, and over time commands control of behavior. However, reward-related dysfunction associated with "wanting" does not occur in isolation. In fact, many of the DA findings associated with "wanting" are moderated by functional and structural changes in the frontal cortex. For example, the deficits in striatal DA are associated with lower metabolic activity in the prefrontal cortex (PFC). Thus, in addition to the central role of "wanting"-based circuitry, studies emphasize the importance of cortical, learning-based, brain regions within the reward circuit, such as the PFC.

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). Several recent structural imaging studies report morphological volume loss in the (pre)frontal lobe in various forms of SUD, such as cocaine, alcohol, and heroin dependence (Goldstein and Volkow 2002; 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 and Fowler 2000). This dysfunction in areas of prefrontal cortex, along with its connection to limbic-related subcortical areas (e.g., ventral striatum, amygdala), 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, Robbins, and Everitt 1997). Relatedly, substance-dependent humans display a lack of adaptive associative learning between stimulus and outcome, such that dependent individuals show reward-dependent perseverative response patterns even in the absence of a previously presented reward cue (Wilson, Sayette, and Fiez 2004). This failure to update learned associations also may be related to the preponderance of evidence linking SUD to risky decision-making.

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 when experimental manipulations use drug stimuli or drug-deprivation (Coffey et al. 2003). Bechara and colleagues (Bechara and Damasio 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. Moreover, substance-dependent individuals display attenuated insula activation, which is associated with increased risk-taking (Paulus et al. 2003).

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

Integrating neurobiological and psychological theories of substance abuse

There have been impressive advances in our understanding of the neural mechanisms related to both reward and SUD. Such advances particularly enhance our understanding of the underlying implicit factors driving addictive behavior, that is, "liking," "wanting," and learning (Berridge et al. 2009); however, it is necessary to integrate such findings with psychological theories of substance use in order to better understand the complex interplay between implicit mechanisms and the somewhat more explicit psychological factors that contribute to and maintain SUD. For example, research indicates that both somatic and emotional distress are important to the development and maintenance of SUD (Cheetham, Allen, Yucel, and Lubman 2010; Kreek and Koob 1998), highlighting the importance of an individual's subjective experience. As such, the following section will integrate two prominent psychological theories of addiction, self-medication (Khantzian 1985) and distress tolerance (Brown, Lejuez, Kahler, Strong, and Zvolensky 2005; Buckner, Keough, and Schmidt 2007) with the current understanding of underlying reward processees to aid in a more complete understanding of substance use.

Self-medication

One of the most widely held explanations for SUD is the self-medication hypothesis. The self-medication hypothesis suggests that the distressing psychological state associated with other mental health issues and stress is subdued by the psychotropic effects of substances and as a result increases the vulnerability for SUD (Khantzian 1985). In fact, a variety of substances have acute psychological side effects that are in opposition to the common symptoms of stress, anxiety, and depression. For example, cocaine use often results in increased positive mood, self-confidence and self-esteem, energy, and a decrease in fatigue (Dodgen and Shea 2000). Conversely, alcohol is often related to increases in relaxation and sedation (Dodgen and Shea 2000). In both examples, substances allow emotions to be removed from awareness and may be taken to avoid the distressing affect.

In support of the self-medication model, Johnston and O'Malley (1986) found that, in response to self-report questionnaires, 22% of US adolescents cited "To get away from my problems or troubles" as a reason for substance use. In a study by Suh et al. (2008), self-reported depressive emotion predicted a higher likelihood of preferring alcohol, which the authors suggest highlights the close association between the desire for change in affective state and alcohol use. Additionally, poor affect regulation, negative mood states such as depression, and poor coping skills have been identified as risk factors for SUD (Eftekhari, Turner, and Larimer 2004). Together, these data suggest that an attempt at self-medication is used to alleviate other distressing states.

As noted above, reward circuitry centers on many of the regions and connections disrupted in SUD, such as connections between the NAc, frontal cortex, and amygdala. Moreover, the effect most substances of abuse have on these regions is the inverse of what is associated with disorders such as depression, some forms of anxiety, and the exposure to chronic stress. For example, depression is associated with blunted striatal (i.e., NAc) activity and a reduction in dopamine and serotonin. Similarly, chronic stress has been linked to dysfunctions in the production and utilization of dopamine (Pani, Porcella, and Gessa 2000). Most substances of abuse, however, stimulate dopamine activity in limbic regions, affecting other neurotransmitter systems and enhancing the reinforcing properties of substances. Additionally, when psychostimulants and alcohol are used for a short amount of time, serotonin, another important component of the reward circuitry, increases its functioning capabilities. This supports the idea that those with psychological problems may try to self-medicate with these substances in order to reverse the effects of the blunted activity (Markou, Kosten, and Koob 1998). Finally, a substantial body of research indicates that nicotine compensates for some of the cognitive impairments (e.g., difficulty in learning processes) produced by psychological distress 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 and Gould 2008).

Essentially, it is possible that the psychologically distressed (e.g., anxious, depressed, stressed) brain seeks comfort and stimulation and other neural abnormalities are assuaged by the intake of substances. Unfortunately, though, self-medication not only potentially alters deficits associated with other psychological issues, but also activates ones associated with "wanting" (i.e., increased ventral tegmental area (VTA), amygdala, striatum activity) and other learning processes, so vulnerability to SUD may be increased.

Distress tolerance

Coinciding with the self-medication model, increased focus has been placed on the role of distress tolerance (DT) in the development and maintenance of SUD. DT has been defined as both the perceived ability to tolerate unpleasant states (Leyro, Zvolensky, and Berstein 2010; McHugh and Otto 2011) as well as the ability to persist in goal-directed activity when experiencing psychological distress (Brown et al. 2002). In the case of SUD, it is hypothesized that low DT is associated with an amplification of both somatic (e.g. withdrawal symptoms) and emotional distress leading to increased use of avoidance-based coping (Zvolensky and Otto 2007). Put simply, individuals with this particular propensity for difficulties in tolerating distress may be at increased risk for experiencing negative emotional states as well as somatic stressors, such as withdrawal symptoms or pain, as intolerable, making them more likely to engage in avoidance-based coping behaviors such as self-medication to quell their distress.

In support of this theory, a number of studies have noted a link between low DT and increased levels of substance use including alcohol, cannabis, and cocaine (Buckner et al. 2007; O'Cleirigh, Ironson, and Smits 2007). Additionally, there is considerable evidence to suggest that individuals with low DT are more likely to specifically endorse coping motives as a contributing factor for their use (DeMartini and Carey 2011; Johnson et al. 2010; Zvolensky et al. 2004). Finally, low DT is also associated with a shorter time to relapse following periods of abstinence (Brandon et al. 2003; Brown et al. 2002; Daughters et al. 2005a; Zvolensky et al. 2001). This decreased latency suggests that low DT may be associated with an increased sensitivity to the range of emotional and physical withdrawal symptoms that emerge during a quit attempt. Indeed, low DT is also associated with higher rates of dropout from substance abuse treatment (Daughters et al. 2005b).

Despite the abundance of evidence implicating DT in the addictive process, studies investigating neurobiological mechanisms of DT are only recently beginning to emerge, with much of this line of research limited to animal models. Further research is needed, as greater clarification of the neural correlates of low DT will aid in the understanding of why some brains may be predisposed to SUD. Though speculative, Trafton and Gifford (2011) suggest that DT is a product of reward-driven behavior such that individual variability in this construct can be explained by differences in core-processes underlying "wanting" (i.e., incentive salience) and

learning. Specifically, the learned ability to adapt reward-seeking behavior based on availability of reward opportunities in the environment and the ability to inhibit immediate responding may be compromised in individuals with low DT. Essentially, DT may play an important role in both the hyperactive "wanting" and dysfunctional learning associated with development of SUD.

As previously described in this chapter, reward salience relies on dopamine neurons projecting into the NAc and OFC, such that rate of firing of these neurons dictates whether or not an individual should engage in a habitual (or addictive) behavior to gain immediate relief (Abler et al. 2006; Di Chiara 2002; Roesch and Olson 2004). In the case of substance use, individuals with low DT may be particularly prone to overvalue the reward or relief associated with use contributing to increased addictive behavior. Interestingly, evidence suggests that a number of factors can influence the reward value of indulging immediate impulses to obtain relief. For instance, Tice and colleagues (2001) noted that individuals who tend to eat for coping motives suspended this behavior when manipulated to believe that eating following a negative mood induction would not produce the expected relief, while Magen and Gross (2007) manipulated the value of reward through expectancy and noted that persistence at distressing tasks increased when participants were specifically told that they were engaging in a test of willpower rather than performance.

With regard to associations between low DT and dysfunctional learning, Trafton and Gifford (2011) suggest that reward-seeking behavior may represent a complex interplay between reward availability and a subpopulation of inhibitory medium spiny neurons (MSN) in the NAc that inhibit reward-seeking when they fire (Taha and Fields 2006). Therefore, those with low DT may not simply have a faulty "on" switch that prompts reward approach due to the aforementioned increases in dopamine firing, but also a faulty "off" switch such that reward-seeking is not properly inhibited based on the environmental availability of reward. This would suggest a particular vulnerability to aspects of dysfunctional learning in SUD such as perseverative drug-seeking responses even after the drug reward is removed (Wilson, Sayette, and Fiez 2004).

A final process that may contribute to individual variability in levels of DT is the ability to inhibit an ingrained, habit-like, response; a process largely governed by the prefrontal cortex as well as associated brain regions including the ACC, ventral prefrontal, right inferior partial, and right dorsolateral prefrontal cortex (Chambers et al. 2009; Garavan et al. 2002). As Trafton and Gifford (2011) hypothesize, behaviors associated with low DT such as substance use may result from deficits in the inhibitory functioning of these regions. For individuals with low DT, these habitual behaviors, such as engaging in self-medication as a means of coping with negative affect, cannot be inhibited even in instances where the long-term contingency would favor longer toleration of distress. This is consistent with the findings related to dysfunctional learning in substance users, where previous studies indicate deficits to brain regions associated with executive functioning and behavioral inhibition (Goldstein et al. 2007; Goldstein and Volkow 2002; Liu et al. 1998), as well as studies suggesting greater impulsivity and poorer delayed discounting (Coffey et al. 2003).

Taken together, this line of research suggests that not only does the psychologically distressed brain seek out comfort but also that differences in DT may predispose certain individuals to engage in substance use. That is, those with low DT may overvalue the reward or relief afforded by substances and demonstrate increased difficulty in disengaging from reward-seeking behavior as well as inhibiting habitual use in the face of psychological or physical distress.

Conclusions

Increased understanding of the neurobiological and psychological processes involved in reward-functioning have greatly enhanced our understanding of how individuals can make the shift from occasional substance use (e.g. a glass of wine with dinner, use of opiate pain medication following dental surgery) to patterns of abuse and dependence. Indeed, SUD are no longer viewed as simply a moral failing or weakness on the part of the sufferer, but rather a complex interplay between neurobiological and psychological factors that influences the way in which a given individual processes information in the environment and seeks out reward.

In the current chapter, we have explored advances in reward processing and its relationship to SUD. As described, development of such disorders may represent the "hijacking" of neural circuitry related to reward, most prominently in the domains of "wanting" and learning (Berridge and Robinson 2003). This "hijacking" model supports the notion of a feed-forward cycle whereby substance use over time not only alters incentive salience (i.e., "wanting") and predictive associations related to the value of the reward (i.e., learning) but also promotes structural changes further perpetuating processing deficits in these areas. Importantly, the majority of these changes in reward circuitry and processing occur outside of an individual's awareness such that his/her subjective experience (i.e., no longer experiencing use as pleasurable or expressing a desire to stop using) may be in complete contrast to the neurological mechanisms of "liking" and "wanting," thereby potentially sabotaging his/her intentions to discontinue use. This discrepancy highlights the need to consider neurobiological processes, in conjunction with psychological theories of substance use, to enhance understanding of the interplay between implicit activation of reward circuitry and an individual's subjective experiences of psychological contributors to drug use such as depression, anxiety, and distress more broadly (Cheetham, Allen, Yucel, and Lubman 2010; Kreek and Koob 1998).

Although there have been great gains related to our understanding of the pathogenesis of SUD, further research is needed to fully understand the neurobiological and psychological deficits associated with problematic use. For instance, evidence suggests a distinction between the underlying processes of "wanting" and learning; however, there is also considerable overlap and interplay between these two constructs necessitating further study to determine how they are specifically parsed within the brain (Berridge et al. 2009). Additionally, future research should continue to explore how psychological theories of substance use relate to underlying

mechanisms of reward circuitry. For example, because limited longitudinal research has been done that integrates neurobiology and psychology, little is known about the directionality of dysfunction in the reward system and self-medication tendencies: does pre-existing reward dysfunction increase the likelihood of using substances to reduce psychological distress, or does the use of substance with a premorbid psychopathology impact reward processes resulting in dysfunction? Similarly, investigation into the neurobiological underpinnings of DT is only in its infancy, with most findings limited to animal populations or theoretical supposition from existing studies of reward circuitry (Trafton and Gifford 2011). Improved understanding of both neurobiological and psychological contributors to SUD, as well as the interplay of these processes, will not only enhance our understanding of the onset and maintenance of such disorders, but also aid in the development of targeted interventions to better address problematic substance use.

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