7 Neurobiology and Cognitive Neuroscience of Substance Use Disorders

7.1 Overview of Substance Use Disorders

The purpose of this chapter is to provide an overview of what we know about the neurobiological mechanisms of substance use disorders (SUD) and their related neuropsychological underpinnings (reward-processing, conditioning, craving, impulse control, negative urgency, attentional bias, and emotion regulation) and to understand how individuals progress from early experimentation with drug or alcohol use, to craving, and then to impaired decision-making around drug use, compulsive use, and loss of control. When we speak about "drugs," we are talking about any of the following: cocaine, opiates, alcohol, nicotine, cannabis, and caffeine, since addictive behavior can develop towards any of these substances [1]. Conditioned learning plays a key role in the development of the disorder, and pleasure or relief provided by use drugs of abuse affects the brain chemistry to cause a vicious cycle (Box 7.1, Fig. 7.1).

Box 7.1 Terms Related to Conditioned Learning [2–4]

- Negative Reinforcement: the process by which removal of an aversive stimulus (or aversive state, in the case of addiction) increases the probability of a response.
- Positive Reinforcement: the process by which addition of pleasant or euphoric state increases probability of a response.
- Classical Conditioning: a type of learning that involves the acquisition of an automatic response elicited by a stimulus (i.e., dog salivates when food and bell ringing are paired together, then salivates even when food taken away in response to bell ringing). Learning strengthens the links between a stimulus and a response.
- Operant Conditioning: a type of learning through rewards and punishment that results in an association being made between a behavior and a consequence for that behavior. Learning strengthens the links between a behavior and a consequence.
- Reward: stimulus intended to encourage and increase a behavior or response.
- Punishment: stimulus intended to discourage and decrease a behavior or response.

The use of the drugs and the immediate neurochemical consequences "stamp in" the experience of taking the drug and solidify its future use [2, 3, 5–8]. The other known physiological effects of drugs on the brain, including tolerance and

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Fig. 7.1 This figure depicts the conditioning processes that cause and perpetuate substance use disorders. Red boxes – stage of addiction process. Blue circles – neurobiological/psychological consequences of and contributors to the addiction process (LTP long-term potentiation, LTD long-term depression)

withdrawal, play a major role in perpetuation of the disorder as well via the associated negative affect states. SUD involve several key neurotransmitter systems [dopamine (DA), norepinephrine, glutamate, opioids] and brain regions (striatum, prefrontal cortex, including anterior cingulate cortex and orbitofrontal cortex, amygdala, insula, cerebellum, visual cortex), as has been demonstrated through studies done in animals and humans, the latter mostly determined through neuroimaging studies [1, 5–11].

7.2 Core Brain Regions

The dopaminergic system, or the "mesolimbic dopamine system," refers to the network of neurons projecting from the midbrain ventral tegmental area (VTA) ("meso = mid-brain") to the ventral striatum [in which the nucleus accumbens (NAc) resides], as well as amygdala (both "limbic"), and is a key pathway in the "liking" process (dopaminergic projections from NAc to ventral tegmental area (VTA) are also important, but less discussed) [12–14]. The "nigrostriatal system" refers to the system of DA neurons projecting from the substantia nigra to the dorsal striatum (caudate and putamen), and this is involved in action initiation and drug-seeking behaviors. Habit formation and learning and conditioning occur via the effects of DA in both the mesolimbic and mesostriatal system, but the mesostriatal system is especially important in the movement-based aspects of habit (e.g., it is this system that is damaged in Parkinson's disease). The "mesocortical system" refers to the system of DA neurons projecting from the VTA to the prefrontal cortex (PFC) ("cortical") and is also involved in the "liking" process [15–17]. The PFC is broken down into many important brain areas including the anterior cingulate, orbitofrontal, dorsolateral, and ventromedial (abbreviated ACC, OFC, DLPFC, and vmPFC, respectively), all of which play important roles in decision-

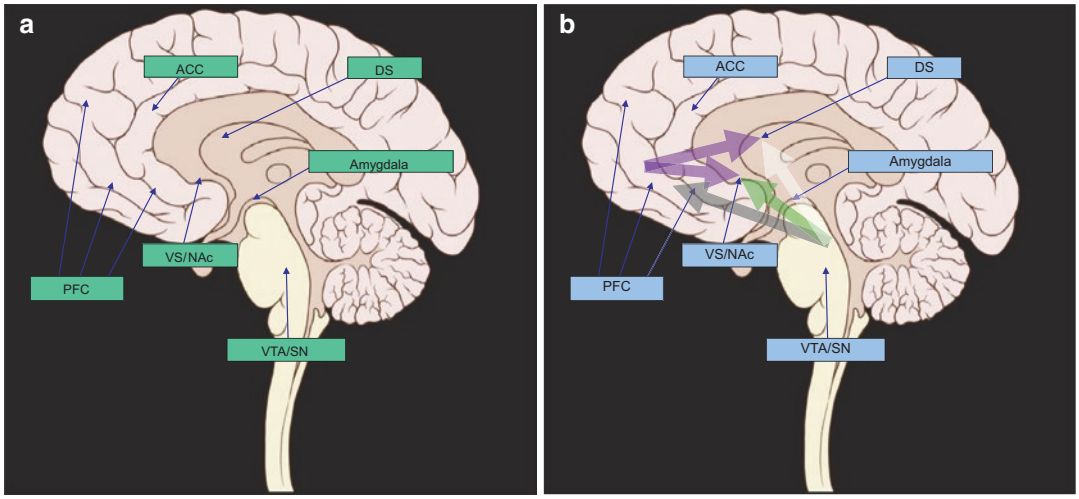

Fig. 7.2 (**a**) This figure shows the approximate locations of several important brain regions which are involved in the initiation, development, and perpetuation of substance use disorders and includes brain regions involved in reward, stress response, and executive control. ACC anterior cingulate cortex, PFC prefrontal cortex; includes anterior cingulate, orbitofrontal, dorsolateral, and ventromedial (ACC, OFC, DLPFC, VMPFC, respectively), DS dorsal striatum, includes caudate and putamen, VS/NAc ventral striatum and nucleus accumbens; nucleus accumbens resides in the ventral striatum, VTA/SN ventral tegmental area and substantia nigra. (**b**) This figure depicts the three key dopaminergic pathways. Mesolimbic system – network of dopamine (DA) neurons projecting from VTA to the VS, where the NAc resides; key pathway in "liking" process (green). Nigrostriatal system – network of DA neurons projecting from the SN to the DS; involved in action-initiation and drug-seeking behaviors (white). Mesocortical system – network of DA neurons projecting from the VTA to the PFC; also involved in the "liking" process (black). Frontostriatal circuits – network of projections from PFC into the VS and DS; works with cue-related DA release to drive drug-seeking behavior (purple)

making, cue processing, and action initiation (Fig. 7.2a, b). For example, DLPFC is involved in working memory (the ability to hold information in memory in order to perform a task) and impulse control, whereas vmPFC and ACC are more directly linked with limbic centers and sensory areas and respond to drug-related sensory cues [10, 11, 18]. Lateral OFC is involved in decision-making, whereas medial OFC tends to be more cue-reactive and immediately responsive to reward [10, 11, 18]. Other important brain areas in reward involve the insula, which is a relay that processes bodily sensations like gustatory and gut-related pleasure and links higher-order decision-making regions [19]. Opioid, glutamate, and GABA receptors exist throughout the brain, including the VTA and NAc, where their actions play key roles at many of the stages of the addiction process. For example, neurons projecting from cortex to the striatum release glutamate into dorsal striatum, which importantly affects the power of a drug-related cue to affect attention and behavior around drug-seeking and use [20, 21].

7.3 Reward

Drugs and pleasurable experience cause release of DA into the NAc and other brain regions (e.g., basolateral amygdala) [5, 22, 23], otherwise known as "reward" or "liking" [13, 14]. The mesolimbic DA system plays a key role in this process, as does the mesocortical system. The more rewarding the drug is evaluated to be, and the greater the self-reported pleasantness, the greater the release of extracellular DA in the NAc [1, 5, 7, 22, 23]. Pharmacological blockade of DA receptors and lesions of the mesolimbic dopaminergic system reduce the reward value of drugs of abuse [24–27]. A tendency towards reward sensitivity is mediated in part by a hypersensitive DA system [28, 29]. The dopaminergic

projections that link VTA to NAc and VTA to PFC are crucial pathways of the reward system. DA neurons in the VTA form strong reciprocal connections with regions such as the NAc, lateral hypothalamus, and PFC [30]. The striatum (dorsal striatum and NAc) serves a very important role in the reward pathway by serving as the main integration site for dopaminergic inputs from the VT and glutamatergic inputs from the PFC, amygdala, hippocampus, and thalamus [30].

Opioids are also released to reward in the NAc and VTA with consumption of a rewarding substance, mediate "liking," and play a key role in the subjective experience of pleasure [13, 14, 27]. Some posit that endogenous opioids, rather than DA, play the most important role in mediating the reward component of drug and alcohol use [17]. For example, the μ opioid blockers naloxone and naltrexone reduce the pleasure experienced with alcohol consumption [27]; however, DA antagonists reduce cocaine-enhanced brain-stimulation reward in rats [31]. Opioid peptide release in the VTA plays a key role in modulating the quantity and quality of DA release into the ventral striatum [32].

7.4 Conditioning: Positive Reinforcement

As drug use progresses, repeated drug use causes the drug use behavior to become linked with the stimuli and events that preceded and accompany drug use, such as the drug-using environment [1, 33], or visual, auditory, or olfactory drug cues. Habits develop as a result of the DA-mediated conditioning and positive reinforcement from drugs' euphoric effects [15, 34]. Higher levels of reward lead to more powerful learning and conditioning processes at the neurobiological level, which contributes to greater future motivation to obtain a reward upon exposure to familiar reward-related cues (Fig. 7.1).

Conditioning requires long-term potentiation (LTP) and long-term depression (LTD), which is a phenomenon of neural plasticity known to underlie the learning, consolidation, and refinement of both adaptive and maladaptive behaviors [34–36]. There is a huge diversity of cellular plasticity mechanisms [34]. Those include Hebbian-type plasticity, (includes LTP and LTD), as well as homeostatic sync scaling and metaplasticity (modifications that maintain synaptic strength within a functional range) [34, 37, 38]. DA is a key player in reward-related learning, and dopamine agonists induce reward learning (explaining why Parkinson's patients who get L-Dopa, a dopamine precursor, can develop behavioral addictions) [39, 40], and D1 receptors may be key for this process [17, 26]. Glutamate, via its effects on N-methyl-D-aspartate (NMDA) receptors, is the other key player; blockade of NMDA receptors, which blocks LTP and LTD [34, 37], also prevents many behavioral adaptations normally associated with drug reinforcement, such as conditioned-place preference, behavioral sensitization, and self-administration [17, 34]. Sensitization (a process in which repeated administration of drugs causes increased motor and/or behavioral responses to their stimulant and rewarding effects that also parallels LTP and is seen as a marker of conditioning in animal models) is also mediated by the interacting effects of glutamate and DA in mesolimbic and mesocortical circuits [17, 34].

7.5 Motivation: Positive Reinforcement

After conditioning has occurred, motivation to obtain a rewarding substance ("wanting"), often associated with craving, increases in the context of exposure to environments or cues associated with previous experiences of pleasantness and euphoria [13, 14, 41]. Greater sensitivity to cues, as is demonstrated in hundreds of imaging and self-report studies in humans, is related to greater craving and then greater seeking [13, 14, 19, 28, 41, 42]. Incentive-sensitization theory posits repeated intake results in an increased incentive salience for drugs of abuse, which also contributes to loss of control (Fig. 7.1) [13, 14, 41].

Motivation to obtain a rewarding substance is mediated by DA release into the dorsal striatum in response to drug cues [16, 34], with increased

release of DA into the striatum in response to drug cues associated with greater drug-seeking [15, 16, 34]). Furthermore, glutamate release into dorsal and ventral striatum from projections from the PFC into the dorsal and ventral striatum "frontostriatal circuits" (Fig. 7.2b) (specifically their binding to AMPA receptors [15]) works in concert with cue-related DA release to drive further drug-seeking behavior [16, 17, 34]. Opioids, via their effects in the NAc, VTA, and extended amygdala, also likely play a role in motivation, with several studies showing that naltrexone blocks the brain's response to alcohol cues and craving for future use, mediating relapse prevention [27]. These exert their effects through binding in the striatum, VTA, and extended amygdala.

A significant amount of our understanding of the neurobiology of motivation is due in large part to animal studies in which animals are trained to engage in a behavior to procure a substance and then trained that the substance is no longer available (extinguished), so drug-seeking behaviors disappear. Then, the behavior (as measured through self-administration, a return to environments where drugs were previously used as a conditioned place preference, or working hard on a task that previously produced a drug) is "reinstated" by presentation of numerous amounts of possible cues including drug cue (something that reminds the person of prior use, such as a context, a visual cue, a sound, a smell), stress (which we will discuss below more in the negative reinforcement section), and the drug itself (e.g., re-experiencing the cocaine use feeling will trigger intense drug use seeking and a binge). These reinstatement paradigms model these types of triggered relapse [9].

Neuroimaging studies in humans also support many of these theories, with hundreds of trials now showing brain activation in regions, such as the dorsal and ventral striatum, PFC, amygdala, insula, and visual cortex to drug cues, being linked to craving, development, and persistence of the disorder [1, 10, 27, 32–37, 39–46]. These drug-cue-related neuroimaging findings relate directly to studies showing cognitive biases (approach, attentional, and affective [28]) to drug cues in SUD and their ability to affect drug-seeking behavior. With repeated use, drug cues become more and more powerful in their ability to divert attention of the brain and motivational systems towards them, leading both consciously and unconsciously to craving and use of a drug [1, 47].

The chronicity of conditioning effects from substances are evident in both animal and human studies, as evidenced by relapse and the ability of drug-related cues to trigger engagement in compulsive drug-seeking behavior in long-term abstinent individuals with SUD [48]. That being said, there is good news here, too. Extinction processes, either through nutritional support, therapy, or simple abstinence, can train the brain to not respond to the cues so it becomes second nature over time. In fact, abstinence results in brain growth, and brain volume can begin to normalize even after 1 month of sobriety [10]. Ask anyone in recovery from SUD who will tell you that the more time sober reduces craving and leads to an increased ease resisting temptation to use [10].

7.6 Tolerance: Downregulation of Dopamine and Opioid System

As use progresses, the individual will experience less pleasure from the food ("liking") but will simultaneously experience an increased desire ("wanting") for the food, driving further reward seeking and consumption [13, 14, 28, 41]. Recall "tolerance" is the experience that individuals with SUD face where the more they use the drug, the more they need to achieve the same rewarding effect. Downregulation of DA and opioid systems mediates this effect, with studies showing progressively less release of DA and opioids to the drug of abuse [49], and reductions in presynaptic DA synthesis capacity, and DA receptor density [which could be types 1, 2, or 3 receptors (D1, D2, D3)] in the striatum [5, 22, 23, 28, 50–52]. These changes are also associated with a reduction in the subjective pleasure experienced with use of the drug and trouble experiencing reward from normal activities [15, 16, 34, 53],

which also may increase motivation to continue using and may contribute to loss of control in a desperate attempt to experience pleasure again (Fig. 7.1) [15, 16, 34].

7.7 Withdrawal and Hyperkatifeia

Withdrawal is induced by sudden cessation of chronic drug use and is usually characterized by signs and symptoms that are subjectively opposite to the acute positively perceived effects of the drug [6–8]. Hyperkatifeia is defined as an increase in intensity of the constellation of negative emotional or motivational signs and symptoms of withdrawal from drugs of abuse [6–8]. Excessive use of any substance of abuse leads to brain changes, such that upon substance cessation, the individual begins to enter into a state of intense dysphoria, associated with irritability, emotional and physical pain, malaise, sleep disturbances, anxiety, hypohedonia and elevated craving for drug use, as well as various other physical symptoms [2]. Withdrawal occurs in the early days of drug cessation; but also "protracted withdrawal," which is associated with dysphoria lasting for weeks to months and heightened vulnerability to craving and relapse, especially under stress for example, can mimic the withdrawal state [6–8, 46].

The withdrawal state is mediated by changes in several neurotransmitters and neural systems including brain glucocorticoid, corticotrophin-releasing factor, and noradrenergic activity in the limbic and emotional regions such as the extended amygdala and locus coeruleus [2, 6–8, 45]. Opioids also play an important role in these experiences and associated behaviors via their actions in the VTA, NAc, and extended amygdala [2]. Other neurotransmitter systems, including dynorphin, vasopressin, hypocretin, and substance P, and neuroimmune systems are also recruited by excessive alcohol consumption and drug use, producing aversive or stress-like states, also contributing to hyperkatifeia [6–8].

7.8 Conditioning and Motivation: Negative Reinforcement

The learned behavior to engage in an action to relieve physical or psychological discomfort is referred to as negative reinforcement [2]. Alcohol and other substances can initially dampen stress-related brain function and reduce emotional discomfort, which can contribute to learning to continue to use the drug to relieve negative affect (Fig. 7.1) [7, 8]. Neuroadaptations subsequently lead to the need for escalating doses to have the same relieving effect, and then repeated withdrawals lead to even more emotional discomfort when the drug wears off [6–8].

Because stress and negative affect states are so similar to the experience of withdrawal, drug-seeking is triggered by stress, depression, or anxiety, for example [3]. Emotional dysregulation, inefficient utilization of emotion regulation strategies, and a tendency towards dysphoric affect states have been noted as predictors for SUD that can make recovery more challenging [46, 54]. Although hyperkatifeia is most likely to manifest during the withdrawal/negative affect stage, it can also infiltrate other stages of the addiction cycle to promote or facilitate craving, a more rapid progression to loss of control and relapse [6–8].

It is believed by many experts that the negative reinforcement conditioning is as equally important as the positive in the development of addiction. For example, one study found that positive reinforcement that was associated with alcohol consumption did not differ as a function of the presence of alcohol dependence, but negative reinforcement behavior that was associated with alcohol consumption became stronger as alcohol dependence developed [6–8, 55]. However, like we see with positive reinforcement, extinction processes can also occur, making stress and negative affect less likely to trigger drug-seeking the more time someone has been sober [10].

7.9 Impulsivity and Executive Function Deficits

Lastly, but not least importantly, overuse of substances both causes and contributes to and results from impaired global impulse control, which can make it impossible to stay with a commitment to not use in the face of a strong craving, for example [1, 10, 28, 29, 34, 56–58]. In addition to driving reward-seeking behavior, frontostriatal circuits are also involved in processes of impulse control and inhibition of habitual responses [59], with DLPFC, dorsal ACC, parietal cortex and lateral OFC playing important roles [10, 17]. The hippocampus (and related learning and memory systems) also plays a role in cognitive, inhibitory control mechanisms and decision-making [60].

Deficiencies in functioning in these circuits and behavioral domains have been demonstrated time and again in numerous animal studies and in humans in many neuroimaging and neuropsychological testing studies in SUD models [10, 46, 61]. In humans, this commonly manifests in fMRI studies as reduced activation in circuits (PFC) involved in cognitive control during tasks requiring these brain functions [10, 11]. Moreover, as mentioned above, positron emission topography (PET) imaging studies show lower striatal D2 receptor availability in people with SUD, which is also believed to underlie some of the deficits in impulse control [16, 22, 23, 51, 52]. The DA system is well understood to play an important role in inhibitory control [28, 29], as well as in the ability to delay rewards [57, 58], whereas increased receptor availability may be protective against development of addictive behavior [28, 62]. It appears that D2 receptor availability might have a direct impact on prefrontal function, as demonstrated in studies showing that low D2 receptor density is associated with reduced prefrontal perfusion in cocaine use disorders [22, 63]. Additionally, studies show that an intensive exercise regimen reduces impulsivity and increases D2 and D3 receptor density (45), further supporting the importance of D2 receptor density in impulse control.

The combination of impaired impulse control and strong negative reinforcement conditioning is also posited to underlie the negative urgency trait (as discussed in Chap. 6), a trait which is also strongly associated with SUD [7, 8].

7.10 Benefits of Understanding the Neurobiology

Our rapid advancement in understanding the brain chemistry of SUD in the last several decades has significantly impacted and improved our ability to treat them over the last several years. For example, by understanding that SUDs are chronic, relapsing disorders, driven by long-standing brain changes, we now treat people with relapse prevention treatments, including medication, in some cases for years, instead of only using medications for days to reduce withdrawal, as we had done in the past. We also now know that preventing exposure to the substance of abuse reduces conditioned learning and enhances extinction, which may explain why abstinence is so important for some people and for some substances. Behavioral and pharmacologic interventions to target negative affect, impulsivity, cue reactivity, DA receptor density, and neuroinflammation are of growing interest to researchers and clinicians because of our deepening understanding of the underlying neuroscience. Furthermore, it has led to a reduction in stigma regarding addiction, with a greater appreciation that addiction is a disease just like cancer or diabetes, and not a fault in someone's willpower, nor a sign of character flaw or weakness. If similar circuitry drives food seeking, as the growing literature indicates, similar benefits might be observed to take place in the binge eating disorder, food addiction, and obesity treatment fields.

7.11 Conclusion

In conclusion, neurobiological processes exacerbated by conditioned learning play a role in the manifestation of SUD. These concepts provide insight to improve the treatment of SUD and disordered eating.

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