Review

Reward loss and addiction: Opportunities for cross-pollination

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Abstract

Paradigms used to study the response to and consequences of exposure to reward loss have been underutilized in approaches to the psychobiology of substance use disorders. We propose here that bringing these two areas into contact will help expanding our understanding of both reward loss and addictive behavior, hence opening up opportunities for cross-pollination. This review focuses on two lines of research that point to parallels. First, several neurochemical systems involved in addiction are also involved in the modulation of the behavioral effects of reward loss, including opioid, GABA, and dopamine receptors. Second, there are extensive overlaps in the brain circuitry underlying both reward loss and addiction. Common components of this system include, at least, the amygdala, ventral and dorsal striatum, and various prefrontal cortex regions. Four emerging avenues of research that benefit from emphasis on the common ground between reward loss and addiction are reviewed, namely, the neural circuitry involved in reward devaluation, the influence of genetic and reward history on the behavioral vulnerability and resilience, the role of competing natural rewards, and emotional self-medication. An understanding of the role of reward loss in addiction will point to a deeper understanding of the initiation and maintenance of substance use disorders.

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Contents

1. Reward loss and addiction: psychobiological parallels
2. Effects of drug of abuse on reward loss
   2.1. Reward loss and opioids
   2.2. Reward loss, conflict, and GABA anxiotytics
   2.3. Reward loss and the dopamine reward signal
   2.4. Other receptors: cholinergic and cannabinoid receptors
3. Neural commonalities between reward loss and addiction
   3.1. Anterior cingulate cortex (ACC)
   3.2. Orbitofrontal cortex (OFC)
   3.3. Medial prefrontal cortex (mPFC)
   3.4. Insular cortex (IC)
   3.5. Striatum
   3.6. Lateral habenula (LHb)
   3.7. Amygdala
4. Emergent topics
   4.1. Circuitry for reward devaluation and implications for SUDs
   4.2. Genetic vulnerability to reward loss and addiction
   4.3. Role of competing natural rewards
   4.4. Reward loss and emotional self-medication
5. Concluding remarks
Acknowledgements
References

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Drug addiction is one of the most pressing and complex current social issues. The latest National Survey on Drug Use and Health (Center for Behavioral Health Statistics and Quality, 2015) estimated that during 2014, around 21.5 million people in the United States exhibited a substance use disorder (SUD), with symptoms including sustained excessive consumption, loss of use control, tolerance, craving, withdrawal, and relapse (American Psychiatric Association, 2013). As a result, the identification of psychobiological factors underlying SUDs is a major challenge for current research. A rich set of behavioral processes and experimental procedures have been suggested and used as a way to better understand the psychobiology of drug addiction, and as a strategy to improve prevention and treatment (Ahmed, 2012). The present review highlights the psychobiological mechanisms and potential applications of reward loss paradigms, an underutilized but promising research area for the comprehensive study of some of the learning, motivational, and emotional factors that contribute to the initiation and maintenance of addictive behavior. Reward loss refers to situations in which an expected appetitive reinforcer (expected on the basis of prevailing signals) is not presented or is reduced in magnitude or quality. Although reward loss does not involve the delivery of aversive stimuli, it instigates behavioral and neurophysiological responses similar to those induced by the presentation or anticipation of aversive events (Amiel, 1992; Papini and Dudley, 1997; Papini et al., 2006).

Current research places a special emphasis on understanding the transition from initial drug use to compulsive drug seeking and taking (e.g., Everitt and Robbins, 2016; Kelley and Berridge, 2002; Robinson and Berridge, 2000). Research suggests that the onset, development, and establishment of compulsive drug seeking and taking are mediated by a complex set of underlying psychobiological systems (Goldstein and Volkow, 2011). The interaction of such systems controls, among others, (1) learning and motivational processes dependent on dopaminergic neurons of the mesocorticolimbic brain circuitry (Volkow and Morales, 2015; Gipson and Kalivas, 2016), (2) cognitive deficits related to dysfunctional top-down cortical control of behavior (Robbins et al., 2008), and (3) reward processing and emotional dysregulation (Egli et al., 2012; Koob, 2013; Koob and Le Moal, 2001; Koob and Volkow, 2010; Sinha, 2008).

Stressful life events are also relevant to understand the initiation and development of addictive behavior (Gorden, 2002; Hayaki et al., 2005; Keyes et al., 2011). Individuals suffering from addictive disorders have problems to cope with and adjust to unexpected environmental events and uncertainty (Brewers et al., 2015; Ersche et al., 2016). These events involve not only aversive stimulation, but also negative changes in the relative value of appetitive stimulation (that is, the complete or partial loss of reward). Indeed, the most stressful events suggested by relative value of appetitive stimulation (that is, the complete or partial loss of reward). According to this notion, organisms make decisions and adjust their behavior toward one incentive as a function of their experience with different rewards. For instance, the emotional impact of rejection by a romantic partner can be best understood in the context of the value of the rewards (e.g., romantic, social, support) received before the separation (Sharr and Hazan, 2008). The loss of reward derived from a romantic breakup triggers a variety of behavioral, physiological, affective, and cognitive changes that are dependent on brain areas involved in reward processing, emotion, and addiction (Fisher et al., 2010). In fact, that life events inducing negative emotions are related to both drug addiction and reward loss has been separately, but consistently supported by an increasing amount of clinical and experimental research (Hassanbeigi et al., 2013; Konopka et al., 2013; Waldrop et al., 2007).

Flaherty (1996) suggested that the adaptive significance of reward loss must be viewed in terms of reward relativity. According to this notion, organisms make decisions and adjust their behavior toward one incentive as a function of their experience with different rewards. For instance, the emotional impact of rejection by a romantic partner can be best understood in the context of the value of the rewards (e.g., romantic, social, support) received before the separation (Sharr and Hazan, 2008). The loss of reward derived from a romantic breakup triggers a variety of behavioral, physiological, affective, and cognitive changes that are dependent on brain areas involved in reward processing, emotion, and addiction (Fisher et al., 2010). In fact, that life events inducing negative emotions are related to both drug addiction and reward loss has been separately, but consistently supported by an increasing amount of clinical and experimental research (Hassanbeigi et al., 2013; Konopka et al., 2013; Papini et al., 2015; Spanagel et al., 2014). This review intends to bring focus to the reciprocal benefits that stem out of bringing together two areas of research that have proceeded largely independently: reward loss and drug addiction. Opportunities for cross-pollination of these research areas will be discussed in the following sections in relation to two points: (1) the psychobiological parallels between reward loss and addiction, centered on the effects of some drugs of abuse on reward loss paradigms and on the common components of the neural circuitry underlying reward loss and addiction, and (2) recent advances in reward loss research related to four items, namely, a hypothesis of the neural circuitry underlying reward devaluation, genetic vulnerability for addiction and reward history, drugs and competing natural rewards, and emotional self-medication based on drugs with addictive potential.

### 1. Reward loss and addiction: psychobiological parallels

Reward loss involves the invalidation of anticipatory representations of positive beliefs and goals related to positive reinforcement (Miceli and Castelfranchi, 2015), resulting from a comparison between obtained and expected rewards (Flaherty, 1996). Reward loss is studied in the laboratory using an array of procedures that can be divided in two classes (see Table 1): Reward devaluation, in which the value of a reward is downshifted from a previous higher appetitive value to a lower, nonzero value; and reward omission, in which there is a complete withdrawal of the reward (Papini et al., 2006; Papini et al., 2015). Examples of reward devaluation procedures are consummatory successive negative contrast and instrumental successive negative contrast (Flaherty, 1996). In these tasks, behavior (whether consummatory or instrumental) is rewarded with a large reward for a number of preshift sessions and then the magnitude or quality of the reward is downshifted. This unexpected reward downshift causes either consummatory suppression or instrumental avoidance of the goal. These effects are transient. Examples of reward omission are appetitive extinction paradigms (Norris et al., 2009). In these tasks, either consummatory or instrumental, the downshift is from reward to nonreward, a change that causes the behavior to decrease to very low levels. Reward loss has been widely shown to induce an emotional response described in terms of an aversive internal state usually referred to as frustration (Amiel, 1992; Papini and Dudley, 1997), disappointment (Flaherty, 1996; Miceli and Castelfranchi, 2015), anxiety (Gray, 1987), or, more recently, psychological pain (Papini et al., 2015). This emotional state is accompanied by a set of responses that include aggressive behavior, escape responses, behavioral inhibition, release of stress hormones, and depression-related symptoms (Huston et al., 2013; Papini and Dudley, 1997). In particular, there is extensive research showing a close relationship between

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Experimental procedures involving reward loss: definitions and descriptions.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reward</td>
<td>Procedure</td>
</tr>
<tr>
<td>Devaluation</td>
<td>Consummatory successive negative contrast</td>
</tr>
<tr>
<td>Devaluation</td>
<td>Instrumental successive negative contrast</td>
</tr>
<tr>
<td>Omission</td>
<td>Consummatory extinction</td>
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<tr>
<td>Omission</td>
<td>Instrumental extinction</td>
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</tbody>
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reward loss and negative emotion. Both reward devaluation and omission are followed by activation of the hypothalamic-pituitary-adrenal (HPA) axis (Coe et al., 1983; Cooer et al., 1971; Davis et al., 1976; Flaherty et al., 1985; Kawasaki and Iwasaki, 1997; Mitchell and Flaherty, 1998; Pecoraro et al., 2009). Additionally, the effects of reward loss are modulated by both early and late sources of negative emotion, including exposure to the random neonatal stress procedure (Ruetti et al., 2010), early handling (Cuency et al., 2014), maternal separation (Matthews et al., 1996), social isolation during adolescence and/or adulthood (Shanab and Ralph, 1979), physical restraint (Ortega et al., 2013b), open field exposure (Justel et al., 2014), and peripheral pain (Ortega et al., 2011a), among others.

Negative emotional states also affect drug addiction. Increased activity of the HPA axis facilitates drug self-administration (Piazza et al., 1991) and individual stressor reactivity is persistently disrupted by chronic drug self-administration (Mantsch et al., 2007). Emotion induced by stimuli such as foot shocks, forced swimming, or immobilization facilitates drug self-administration and reinstatement of drug seeking behavior after a drug-free period (Ahmed and Koob, 1997; Anisman and Weller, 1974; Fullgrabe et al., 2007; Goeders and Guerin, 1994; Nash and Maickel, 1985; Piazza and Le Moal, 1998; Shaham et al., 2000). Social situations such as isolation, interaction, aggression, and defeat increase drug self-administration (Alexander et al., 1981; Caldwell and Riccio, 2010; Marks-Kaufman and Lewis, 1984). Chronic stress is also a key vulnerability factor in the development and relapse of addiction (Brady and Sinha, 2005; Sinha, 2008). Overall, interactions between the stress response and reward brain systems have been proposed as the neurobiological basis for increases in the acute use and chronic abuse of drugs induced by negative emotional states (Yap and Miczek, 2008), and both become dysregulated in addicted organisms (Edwards and Koob, 2010; Egli et al., 2012; Koob and Le Moal, 2001; Sspanegel et al., 2014). Similar interventions also affect and are affected by reward-loss, including restraint stress and physical pain (Jiménez-García et al., 2016; Mustaca and Papini, 2005; Ortega et al., 2011a; Ortega et al., 2013b), HPA axis activation (Pecoraro et al., 2009), postdevaluation administration of memory enhancers like corticosterone and d-cycloserine (Bentesola et al., 2006; Norris et al., 2011; Ruetti et al., 2009), dopamine release in the nucleus accumbens (Genn et al., 2004a), amygdala lesions (Kawasaki et al., 2015, submitted), dorsomedial striatum lesions (Torres et al., 2016), anterior cingulate cortex lesions (Ortega et al., 2011b), and insular cortex lesions (Lin et al., 2009), among others. As discussed below, this neurobehavioral overlap suggests a bidirectional communication between reward loss and addiction that can help us understand, for example, how a reward loss experience can increase the individual’s vulnerability to develop an SUD and why addictions can make a person more reactive to an experience of loss.

2. Effects of drug of abuse on reward loss

Behavior induced by reward loss has been extensively characterized from a pharmacological perspective (Flaherty, 1996; Papini et al., 2015). Most studies have used reward devaluation, rather than omission (appetitive extinction), but there is an emerging literature that focuses on the emotional underpinnings of appetitive extinction (Mustaca et al., 2009; Papini et al., 2015). Most of the studies cited in the review that follows include appropriate controls to discard alternative explanations of drug effects in terms of actions on the processing of the absolute value of the reward, nonspecific drug effects, and sensory-motor interference (see below). Therefore, we argue that such drugs draw their addictive potential in part from their efficacy at reducing negative emotions associated to reward loss, such as frustration, disappointment, and grief. As a result, these studies can help identify with greater precision the functions of various neurochemical systems involved in reward loss and SUDs.

2.1. Reward loss and opioids

A role of opioid receptors on reward devaluation is suggested by studies administering opioid agonists and antagonists. Rowan and Flaherty (1987) reported that the effects of reward devaluation were diminished by morphine and also that this effect of morphine was abolished by naloxone, an opiate antagonist. Naloxone was also found to increase behavioral suppression induced by the downshift of a sucrose solution (Daniel et al., 2009; Pellegrini et al., 2005). Morphine and naloxone are nonselective opioid receptor agonist and antagonist, respectively, although they have greater affinity for mu receptors (Papini and Ortega, 2011). Further research based on the administration of selective opioid-receptor agonists and antagonists has shown that opioid receptors play specific roles in different stages of the reward devaluation experience, as proposed by Amsel’s (1992) frustration theory and Flaherty’s (1996) multistage model. Both theories suggest that the initial reaction to the loss is regulated by different underlying mechanisms relative to the response ensuing after some experience with the devalued reward. Consistent with these views, the selective delta opioid-receptor agonist DPDPE [δ-Penicillamine2-δ-Penicillamine5-enkephalin] and the antagonist naltrexone reduced and enhanced, respectively, the consummatory suppression induced by reward devaluation (Pellegrini et al., 2005; Wood et al., 2005). Interestingly, these effects were observed when these drugs were administered before the first downshift session, but not when they were administered before the second downshift session. By contrast, the kappa opioid-receptor agonist U50,488H reduced the impact of a second reward devaluation, but had no effect when administered before the first downshift (Wood et al., 2008). Importantly, none of these drugs affected consummatory behavior in unshifted controls, thus suggesting a specific action of opioids on psychological pain derived from the loss of an expected reward, rather than on the response to the current reward.

A role of opioid receptors on reward omission has also been reported. Morphine has a dose-dependent (biphasic) effect on responding during the extinction of a lever press response (Molinengo, 1964), whereas endorphins delayed appetitive extinction from an instrumental task (Le Moal et al., 1979). Conversely, naloxone facilitated food and sexual appetitive extinction, interfered with escape from a context previously associated to appetitive extinction, and accelerated extinction from ethanol-induced conditioned place preference (Cunningham et al., 1998; Holloway, 2012; Norris et al., 2009).

Overall, the research reviewed above on both reward devaluation and omission tests suggests that opioid receptors modulate the intensity and time course of the response to an episode involving reward loss (Papini, 2009; Papini et al., 2015). The role of opioids as a source of SUDs can hardly be overemphasized.

2.2. Reward loss, conflict, and GABA anxiolytics

Most drugs with anxiolytic effects modulate GABA\(_A\) receptors (gamma aminobutyric acid type-A receptors) and can support addictive behavior (Lader, 1994; Tan et al., 2011). These drugs also show consistent effects on reward loss. Administration of benzodiazepine anxiolytics, which enhance GABAergic transmission by binding to a specific site in the GABA\(_A\) receptor, diminishes the impact of reward devaluation on consummatory behavior, a consistent effect that has been shown to be unrelated to the appetite-stimulant effects of these drugs (Flaherty et al., 1986; Flaherty and Rowan, 1988; Mitchell et al., 2004). Interestingly, the ameliorating effect of benzodiazepine anxiolytics on reward devaluation is observed when drugs are administered before the second incentive downshift session, but not when administered before the first downshift session, suggesting that the attenuating action of benzodiazepines on reward loss requires some experience with the devalued reward (Flaherty et al., 1996; Flaherty et al., 1986; Liao and Chuang, 2003; Ortega et al., 2014a). Accordingly, when rats had access to the devalued reward for 20 min in the first postshift session (instead of
the usual 5 min), the benzodiazepine chlordiazepoxide had no effect during minutes 1–5, but it attenuated the suppressive effects of reward devaluation during minutes 6–10—the downshift effect dissipated during minutes 11–20 in saline and chlordiazepoxide groups (Flaherty et al., 1986). Additional studies support this hypothesis and exclude alternative explanations based on differences between the first and the second downshift experience in terms of dose/response functions, memory traces, or retention intervals (Flaherty et al., 1986, 1990). Whereas benzodiazepines require some experience with the devalued reward to have an effect, the barbiturate sodium amobarbital, which binds to a different site of the GABA<sub>A</sub> receptor than that of benzodiazepines, reduces the effects of reward devaluation regardless of prior reward downshift experience, that is, when administered before either the first or the second downshift session (Flaherty et al., 1982). Similar attenuating effects of GABA<sub>A</sub>-ergic anxiolytics have been observed in reward devaluation tasks based on massed-trial and instrumental situations, in which there is no clear-cut distinction between initial and subsequent reward devaluation trials in terms of pharmacological selectivity (Flaherty and Checke, 1982; Flaherty and Driscoll, 1980; Morales et al., 1992; Phelps et al., 2015; Rosen et al., 1967; Torres et al., 1996). For example, Morales et al. (1992) trained rats in a one-way avoidance task in which a downshift from 30 s to 1 s in the safety compartment deteriorated avoidance behavior relative to an unshifted control always given 1 s in safety. The benzodiazepine diazepam eliminated this contrast effect in a dose-dependent manner.

Although benzodiazepines also seem to attenuate the emotional response induced by reward omission, inconsistent results have also been reported in extinction tasks (see Ruettli and Justel, 2010). For example, chlordiazepoxide increased lever press responding (for food or electrical brain self-stimulation) and running behavior (for food) when administered during extinction sessions (Feldon and Gray, 1981; Gandelman and Trowill, 1968; Heise et al., 1970). However, Beck and Loh (1990) found that chronic administration of the benzodiazepine diazepam decreased the rate of instrumental responding and increased competing responses during the extinction in the radial arm task. Similar results were reported during extinction of lever pressing (Leslie et al., 2005, 2012; Williams et al., 1990). Similar inconsistencies were found in consummatory tasks. Benzodiazepines (e.g., diazepam, chlordiazepoxide, lorazepam) increased resistance to extinction when rats were first trained with water as the reward and then exposed to an empty sipper tube in an instrumental extinction task (Bialik et al., 1982; Soubrie et al., 1978); however, diazepam accelerated consummatory extinction after a transition from 32% sucrose to water (Justel et al., 2011). The source for this discrepancy between instrumental and consummatory effects is unclear.

Ethanol results in similar anxiolytic effects to those of benzodiazepines and also modulates GABA<sub>A</sub>-ergic function (Tan et al., 2011). Consistently, the effects of ethanol on reward loss are similar to those previously described for benzodiazepine anxiolytics. Ethanol diminished the behavioral suppression induced by reward devaluation when administered before the second devaluation session, but had no effect when administered before the first one (Becker and Flaherty, 1982), and had an effect after several downshift events (Kamenetzky et al., 2008). It should be noted that chlordiazepoxide also has a reducing effect on reward devaluation during the initial session after several downshift cycles (Flaherty et al., 1996). Ethanol had an additive effect when simultaneously administered with chlordiazepoxide using ineffective individual doses (Becker and Flaherty, 1983). Like diazepam, ethanol also facilitated consummatory extinction after a transition from 32% sucrose to water (Kamenetzky et al., 2009b).

The surprising effect of postrtrial chlordiazepoxide administration on reward devaluation deserves special mention. As noted above, presession administration of chlordiazepoxide before the first downshift session has no effect on reward devaluation. However, postrtrial administration appears to disrupt memory consolidation processes for learning about the new, devalued reward (Ortega et al., 2014a; Glueck et al., 2015). As a result, the suppressive effects of reward devaluation on consummatory behavior were lengthened. Interestingly, postrtrial administration of chlordiazepoxide did not affect the performance of unshifted controls, had no effect when its administration was delayed for 3 h after the session, was ineffective when animals had completely recovered from the downshift event, and did not support a conditioned taste aversion. Thus, the effect of postrsession chlordiazepoxide administration on reward devaluation is selectively related to an emotionally significant reward devaluation event.

GABA<sub>A</sub>-ergic transmission is a key component of brain processes that contribute to reduce the negative effects of loss-induced negative emotions. Their activation after some experience with the loss event has taken place suggests that these receptors may be critically involved in the resolution of approach-avoidance conflicts (Flaherty, 1996). After some experience with the devalued conditions, situational cues and signals might become ambivalent, promoting both approach and avoidance of the same goal. Anxiolytics may bias the conflict in favor of approach by reducing negative emotions instigating goal avoidance (Flaherty, 1996; Gray and McNaughton, 2000).

2.3. Reward loss and the dopamine reward signal

Although several experiments failed to demonstrate an action of dopaminergic drugs on reward devaluation (Flaherty, 1996; Torres et al., 1996), more recent reports suggest that studying the role of dopamine receptors in reward loss is a promising research line. First, Barr and Phillips (2002) showed that withdrawal from o-amphetamine delayed recovery from reward downshift in a consummatory task, a result interpreted as indicative of increased emotionality in withdrawn animals. Second, Nikiforuk and Popik (2009) trained rats in a progressive ratio schedule of reinforcement in which the value of the last completed response ratio (break point) was used as the dependent variable. When the initial reward, 32% sucrose, was replaced by 4% sucrose, vehicle-treated animals showed a decrease in the break point, whereas animals treated with cocaine, a dopamine reuptake inhibitor, showed little or no decrease in the break point. However, the fact that cocaine also increased responding for unshifted controls suggests a general effect of the drug on reward processing, rather than a specific action on the impact of the reward devaluation. Third, Phelps et al. (2015) trained rats to make a nose-poke response to a light cue to obtain four pellets; the reward was devalued to one pellet in repeated cycles. The indirect dopamine agonist amphetamine attenuated the reward devaluation effect, reducing response latency and increasing premature responses, whereas the D1/D2 dopamine receptor antagonist alpha-flupenthixol had the opposite effect. Although these results were interpreted as indicative of the involvement of dopamine receptors in the drive to respond for a reward, the lack of appropriate nondevalued controls makes it difficult to discard alternative explanations, including reward processing, attention, and motor control.

Reward omission paradigms also seem to respond to dopaminergic drugs of abuse. First, Barker and Rebec (2016) reported that repeated cocaine administration resulted in a more negative slope for latencies to respond and a steeper slope for lever presses across days of training, when compared to controls in a reward omission task. Second, Herling et al. (1979) reported that cocaine and o-amphetamine administration in monkeys increased response rates during an operant appetitive extinction task. Third, cocaine and heroin administration prior to extinction of a Pavlovian learning task disrupted extinction performance from an overexpectation procedure (i.e., response decrement after compounding stimuli trained separately and pairing them with the same reward magnitude), but not from simple acquisition (Lucantoni et al., 2015). Finally, acute cocaine administration enhanced extinction responding when brain stimulation of dopaminergic pathways was used as reward in adult rats prenatally stressed (Gao et al., 2011). In the prenatal stress procedure, dams were periodically subject to physical restraint and exposed to a bright light.
2.4. Other receptors: cholinergic and cannabinoid receptors

The brain cholinergic system has been scarcely explored in reward-loss studies and the little available information shows inconsistent results. For example, the cholinergic agonist nicotine and the antagonist scopolamine were without effects when administered prior the first or second postshift session of a reward devaluation task (Flaherty, 1996; Genn et al., 2004b). With respect to reward omission, scopolamine increased resistance to extinction in a number of instrumental situations, including lever pressing for sucrose (McCoy, 1972) or water (Morley and Russin, 1978), but not for food (Olds, 1970). By contrast, administration of acetylcholinesterase inhibitors resulted in faster extinction after training in several tasks, such as fixed-ratio schedules (Glazer, 1972) and discrimination training (Whitehouse, 1966), and increased errors in a serial problem-solving task (Banks and Russell, 1967). Similarly, nicotine increased response rates during extinction of a lever pressing response associated to either visual stimulation or a 4% sucrose solution (Barret and Bevins, 2013).

Type-1 cannabinoid (CB1) receptor agonists can significantly influence the behavioral reaction to reward devaluation. Genn et al. (2004b) found that low doses of CP-55,940 abolished consummatory suppression induced by downshifting a sucrose solution. Similarly, the CB1 receptor agonist WIN 55-212,2, administered into the basolateral amygdala, prevented the enhancing effect of a negative event (elevated platform test inducing open-space anxiety) on instrumental reward devaluation, without affecting the reaction to the reward devaluation itself (Ramot and Akirav, 2012). Reward omission phenomena have also been manipulated by cannabinoid agents, although mixed results have been reported. On the one hand, delta-9-tetrahydrocannabinol (THC) administration can facilitate instrumental extinction (Gonzalez et al., 1971), increase aggression induced by morphine withdrawal (Boshka et al., 1966), and abolish resistance to extinction induced by partial reinforcement training (Drewnowski and Gray, 1975). On the other hand, the CB1 antagonist rimonabant disrupted extinction learning in an aversive, but not in an appetitive Barnes maze conditioning task, suggesting that cannabinoid receptor agonists are less critical for the extinction of this appetitively motivated behavior (Harloe et al., 2008).

The research reviewed in this section constitutes the first step to identify commonalities between reward loss and addiction in pharmacological terms. There is no question that many drugs with abuse potential (e.g., morphine, benzodiazepines, ethanol, psychostimulants, nicotine, cannabis) affect performance in a variety of reward-loss situations. Our hypothesis is that these modular drug effects of the negative emotions induced by events involving reward loss are one causal factor in the early development and later maintenance of addictive behavior. One possible avenue to pursue this connection would be to shift from drug administration to drug self-administration, especially under procedures mimicking drug intake in humans. We return to this issue in a later section on emotional self-medication.

3. Neural commonalities between reward loss and addiction

The reviewed evidence on the effects of addictive drugs on reward devaluation and omission, and their underlying neurochemical mechanisms suggest parallels between reward loss and addiction at the level of neural circuitry. This section describes research on the role of several brain areas that have been shown independently to modulate reward loss and drug abuse, including the mesocorticolimbic brain circuitry and extended amygdala, typically highlighted in addiction and emotion research (Gipson and Kalivas, 2016; Koob, 2013; Koob and Volkow, 2010, 2016; Lu and Richardson, 2014; Sinha, 2008; Volkow and Morales, 2015).

3.1. Anterior cingulate cortex (ACC)

Kalivas and Volkow (2005) suggested two main functions for the ACC in SUDs. First, this area would be involved in the robust motivation induced by stimuli predicting drugs of abuse, compared to stimuli predicting natural rewards. Second, the ACC would be related to difficulties in the cognitive control of drug seeking. This cognitive deficit is particularly obvious in anxiety situations. For instance, Sinha et al. (2005) found that recovery of personal memories related to a negative situation was accompanied by ACC hypoactivation and striatum hyperactivation during craving in cocaine addicts, compared to controls. Based on these and additional findings, Sinha and Li (2007) suggested that dysfunction of the ACC, among other brain structures, is involved in negative emotional states induced by exposure to drug-associated stimuli, increasing the probability of relapse.

Several studies suggest that the ACC is also involved in the control of behaviors induced by reward loss. Lesions of the ACC eliminated the effects of reward devaluation in an instrumental task (Gurwitz et al., 1970), retarded recovery from a consummatory reward devaluation manipulation (Ortega et al., 2011b), and resulted in impaired appetitive extinction from acquisition in a Pavlovian task (Griffin and Berry, 2004). A role of the ACC on reward loss is further suggested by reduced pCREB expression and c-Fos activation of this area following consummatory reward devaluation (Glucek et al., 2015; Pecoraro and Dallman, 2005). pCREB (phosphorylated cyclic adenosine monophosphate responsive element-binding protein) is a marker of synaptic plasticity, whereas c-Fos (a gene-transcription factor) is a marker of neuronal activity. This evidence is particularly relevant in this context, given the significant role played by CREB in the development of drug addiction (Nestler, 2004).

3.2. Orbitofrontal cortex (OFC)

The OFC is also related to deficits in the inhibitory/executive control of drug seeking behavior, the processing of stimuli with negative emotional value, and the assignment of relative motivational value to stimuli predicting drug availability (Volkow and Baler, 2014). In particular, it has been proposed that its brain location and circuitry makes the OFC a key candidate for the integration of information about the value of future outcomes in choice situations (Schoenbaum et al., 2006). According to this view, abnormal functioning of the OFC has been related to loss of control and compulsive drug taking (Volkow and Fowler, 2000). Moreover, a role of the OFC in the interaction between drug addiction and negative emotion is suggested by the finding that its inactivation attenuates the reinstatement of cocaine self-administration induced by exposure to foot shocks, but not by priming injections of cocaine (Capriles et al., 2003).

Two studies suggest a role of the OFC on reward loss. First, Pecoraro and Dallman (2005) reported increased c-Fos activation in the OFC of rats exposed to reward downshift test. Second, Ortega et al. (2013a) reported that OFC lesions reduced the behavioral suppression observed during the initial response to reward devaluation (without affecting the behavior of unshifted controls) and also eliminated the enhancement of lever pressing observed during partial reinforcement acquisition training in autoshaping (relative to continuous reinforcement training). These results were interpreted as a lesion-induced deficit in a nonassociative factor (e.g., drive) tied to reward loss. A role of the OFC in reward omission has also been suggested by recent work showing impaired appetitive extinction after functional inactivation of the OFC in rats (Panayi and Killcross, 2014), and on the observation of complex patterns of brain activation and deactivation during instrumental extinction in humans (Finger et al., 2008).

3.3. Medial prefrontal cortex (mPFC)

Several possible disruptions on psychobiological processes have been associated with mPFC function under addiction states. For instance, Goldstein and Volkow (2011) suggested that the mPFC is involved in disrupted delay gratification, enhanced stress reactivity, enhanced drug-stimuli seeking, and decreased motivation for other.
stimuli, all common impairments in SUDs. Interestingly, Baratta et al. (2015) found that the optogenetic inhibition of mPFC neurons in the infralimbic area mediated the effect of escapable shocks on the extinction of cocaine seeking behavior, compared to animals that experienced inescapable shocks. Additionally, studies indicate that stress hormones target mPFC neurons to produce the neuroendocrine and behavioral changes associated with drug dependence (Lu and Richardson, 2014).

Evidence showing the involvement of the mPFC in reward devaluation is conflicting. Pecoraro et al. (2008) reported that mPFC lesions accelerated behavioral recovery after reward downshift; however, unshifted controls were absent in their study. By contrast, Ortega et al. (2013a) found no detectable effects of mPFC lesions on consummatory suppression induced by reward devaluation in an experiment that included unshifted controls. Molecular studies indicated enhanced pCREB expression in the prelimbic section of the mPFC (Gleave et al., 2015) and mPFC c-Fos activation following reward devaluation (Pecoraro and Dallman, 2005).

With respect to reward omission, facilitation of extinction from an appetitive Pavlovian task has been reported after inactivating the prelimbic section of the mPFC (Mendoza et al., 2015). Moreover, a set of studies showed that lesions of the prelimbic mPFC enhanced reinstatement and renewal of extinguished responding in an appetitive Pavlovian task (Rhodes and Killcross, 2004, 2007).

3.4. Insular cortex (IC)

Some psychobiological models have incorporated IC function in the circuitry underlying SUDs. A key function of the IC is the representation of interoceptive states of the body (Craig, 2002). For example, Paulus and Stein (2006) reported that individuals with a higher tendency toward anxiety also show increased IC activation when processing salient stimuli. This is consistent with the proposal that the IC is a key brain area modulating the disrupting nature of interoceptive cues on choice processes involved in drug use and relapse (Cisler et al., 2013; Naqvi and Bechara, 2009, 2010; Volkow and Baler, 2014). Consistent with this view, smokers with insular damage were able to stop smoking without experiencing craving or relapse, unlike smokers with damage in other brain regions (Naqvi et al., 2007). Similarly, inactivation of the granular IC disrupted the reinstatement of nicotine self-administration after extinction (Forget et al., 2010).

Several sources of evidence also suggest a role for the IC in reward loss. Behavioral suppression induced by reward devaluation is eliminated by IC lesions, which do not affect unshifted controls (Lin et al., 2009). This result can be interpreted as a failure for the reward devaluation procedure to induce an emotional response in IC lesioned animals. Consistent with this finding, Pecoraro and Dallman (2005) reported IC c-Fos activation following reward devaluation.

3.5. Striatum

Striatal function has been widely recognized as critical for reward processing and addiction (Everitt and Robbins, 2013), although the precise way in which striatal subcomponents contribute to addictive behavior remains elusive because of the complexity of this circuit. Briefly, the striatum can be divided into two main regions: the dorsal striatum (including the dorsomedial and dorsolateral divisions), and the ventral striatum or nucleus accumbens (NAc). As the major integration site of the circuit involving also areas of the prefrontal cortex and thalamic nuclei, the striatum receives inputs from brainstem sources such as the ventral tegmental area (VTA) and the substantia nigra, as well as from the hippocampus, amygdala, and raphe nuclei, among others. The outputs project mainly to brainstem nuclei and to the thalamus, which, in turn, projects back mainly to the prefrontal cortex (Lanciego et al., 2012). Extensive evidence suggests an involvement of the striatum in the acute and chronic effects of abuse drugs, as well as in the transition from initial drug use to compulsive drug seeking and taking (Yager et al., 2015). For example, the shell division of the NAc plays a key role in mediating the acute reinforcing effects of abuse drugs, whereas the influence of drug-associated conditioned stimuli on drug-seeking behavior seems to depend mainly on the core division of the NAc and on the dorsal striatum (Everitt and Robbins, 2013).

Striatal function is also related to reward loss, but in a complex way that requires more research to be fully understood. Increased pCREB expression in the dorsomedial striatum and c-Fos activation in the NAc were reported following reward devaluation (Gleave et al., 2015; Pecoraro and Dallman, 2005). There is also evidence of decreased dopamine efflux in the NAc of during reward devaluation (Genn et al., 2004a) and reward omission (Biedhoff et al., 2015). In addition, NAc lesions affected instrumental reward devaluation (Leszczuk and Flaherty, 2000) and disrupted enhanced responding after a surprising reward omission in rats (Judice-Daher and Bueno, 2013), but had no detectable effect on reward devaluation in the consummatory situation (Eagle et al., 1999; Leszczuk and Flaherty, 2000). Finally, lesions on the dorsomedial striatum did not affect consummatory reward devaluation or omission; however, such lesions eliminated the behavioral activation typical of partial reinforcement during acquisition of lever pressing in the autoshaping situation (Torres et al., 2016). The authors concluded that output from dorsomedial striatum neurons is important for enhanced motivation in reward–uncertain conditions.

3.6. Lateral habenula (LHb)

Extensive evidence suggests that the mesocorticollimbic brain system is crucial for the processing of rewards, including the encoding of reward-prediction errors characterizing reward loss. In this vein, dopamine neurons projecting from the VTA to the NAc are activated by unexpected rewards or reward-predicting stimuli, and inhibited by the omission of expected rewards (Ungless et al., 2010). This inhibition seems to depend on inputs coming from the LHb, as several electrophysiological studies suggest (e.g., Kimura et al., 2007). Furthermore, the LHb has been proposed as a detector of “worse-than-expected outcomes,” based on its key role in appetitive extinction (Friedman et al., 2010, 2011) and in decision-making under reward uncertainty conditions (Stopper and Floresco, 2014). Additional studies suggest that the LHb also regulates reactivity to inescapable shocks (Shumake and Gonzalez-Lima, 2003), anxiety responses (Pobbe and Zangrossi, 2008), depressive states (Sartorius et al., 2010), and, most importantly in the present context, addictive behavior, including drug seeking and taking, relapse, reinstatement, and extinction (Friedman et al., 2010; Haack et al., 2014; Lecca et al., 2014; Maroteaux and Mameli, 2012; Velasquez et al., 2014).

3.7. Amygdala

One of the key functions of the amygdala is the establishment of learned associations between events with motivational value, so that previously neutral stimuli can become signals (Everitt et al., 2003). This function has been suggested to be connected to the dysregulation of reward and stress responses underlying compulsive patterns of drug seeking and taking (Egli et al., 2012; Koob and Le Moal, 2001; Volkow and Baler, 2014).

The amygdala has also been linked to reward loss. Direct evidence is suggested by the reduction and elimination of consummatory reward devaluation effects after lesions of the centromedial and lateral amygdala, respectively (Becker et al., 1984). These lesions did not affect unshifted controls, but they were rather large and not very uniform in location. Still, the results were consistent with subsequent research based on more precise methods. For example, local infusion of the benzodiazepine diazepam into the central amygdala also attenuated consummatory reward devaluation (Liao and Chuang, 2003). Furthermore, c-Fos expression was enhanced in the lateral amygdala following the first reward devaluation event (Pecoraro and Dallman,
and pCREB expression was increased after the second devaluation event relative to the first one when basolateral and central nuclei were analyzed together (Glueck et al., 2015).

Consistent with these findings, reversible inactivation of the centromedial amygdala during the first reward downshift event reduced consummatory reward devaluation (Kawasaki et al., 2015). Importantly, this inactivation procedure did not affect anticipatory negative contrast, a procedure involving the same rewards, but arranged in a Pavlovian-like fashion that has proven insensitive to anxio-
lytics (Flaherty, 1996). In anticipatory negative contrast, licking for 4% sucrose is lower if this is followed immediately by access to 32% sucrose, rather than followed by access to 4% sucrose. Furthermore, in the same experiment, centromedial amygdala inactivation also increased locomotion in the central area of a well-lit open field, an effect suggesting reduced innate fear of an open space. Based on this pattern of results, Kawasaki et al. (2015) suggested that output from the centromedial amygdala tags the event as involving negative emotion. A follow up experiment involving excitotoxic lesions of the basolateral amygdala produced a different pattern of results (Kawasaki et al., submitted). In this case, basolateral lesions also eliminated reward devaluation, but in both the consummatory successive negative contrast and in the anticipatory negative contrast situations. The lesion also impaired appetitive extinction in autoshaping, but spared open field activity. The authors suggested that the basolateral amygdala is involved in reward comparisons, that is, the contrast between current and expected rewards. Basolateral lesions affected behavior in tasks involving transitions in re-
ward magnitude—reward devaluation and omission—but had no effect in a task known to induce negative emotion, but unrelated to reward comparisons—the open field task.

This picture is complicated by experiments with analogous amygdala manipulations, but involving reward devaluation or omission in instrumen-
tial conditioning situations. For example, the effects of instrumental reward devaluations were enhanced by lesions of the central nucleus, but reduced by lesions of the basolateral nucleus (Salinas et al., 1996). As reviewed above, both lesions eliminated the effects of re-
ward devaluation on consummatory behavior (Kawasaki et al., 2015, submitted). Regarding reward omission, basolateral amygdala lesions or inactivation increased resistance to extinction from conditioning tasks using appetitive reinforcers (Burns et al., 1999; McLaughlin and Floresco, 2007), whereas they had reduced resistance to extinction after appetitive Pavlovian training (Kawasaki et al., submitted). The enhancing effect of surprising reward omissions on instrumental lever pressing was also impaired by large amygdala lesions that included the central and basolateral nuclei (Tavares et al., 2014).

4. Emergent topics

4.1. Circuitry for reward devaluation and implications for SUDs

The preceding review makes it clear that the psychobiology of re-
ward loss intersects with drug addiction in terms of neurotransmitters, neuromodulators, and neurocircuitry. Some of the most salient parallels involve: (1) the effects of drugs with addictive potential on reward loss (e.g., opioids, GABAergic anxio-
lytics, dopaminergic drugs); (2) the role of NAc neurons as reward value markers in both reward loss and drug seeking and taking, and its regulation by input from the LHb via the VTA; (3) the functions of the amygdala in reward comparisons (basolateral nucleus) and in tagging reward loss and drug withdrawal with aversive value (central nucleus); (4) the possible antagonistic functions of the ACC and IC in reward expectancy, affecting reward de-
valuation and extending to drug anticipation triggered by exterceptive or interoceptive cues; (5) the disruption of top-down cognitive control in drug addiction via dysfunction in various areas of the prefrontal cortex that also affect reward loss; and (6) the role of the dorsal striatum as a possible output component connected to reward uncertainty and habitual drug seeking and taking.

This intersection between reward loss and drug addiction brings to the table “the usual suspects” in terms of neurotransmitters and brain areas. It is still useful to consider the brain circuitry underlying one in-
stance of reward loss as a way of drawing attention to potential func-
tions that may otherwise be ignored. There is little surprise in the common elements between reward loss and drug addiction, including reward expectancies and the negative emotion that ensue when such expectancies are violated. But reward loss can only have an impact on be-
havior when devaluations or omissions occur in the context of a reactivated reward memory. This function, called here reward compari-
sion, is not typically invoked to understand the neurobiology of addiction (but see Grigson, 2008) or of fear conditioning, the more typical model for negative emotion (e.g., Toyote et al., 2015). The effects of reward loss on behavior are complex and to some extent depend upon the compo-
ents of the situation (e.g., whether instrumental or consummatory). We believe that at this point in the development of research, there is enough information about the effects of neural manipulations on con-
summatory successive negative contrast (see Table 1) that it would be worth organizing the information in terms of a neural circuit. Fig. 1 pre-

tends this circuit as a testable hypothesis that contains some key ele-
ments, and produces an output that modulates licking. Two functions nec-

essary for a significant response to reward devaluation are dis-
guished: reward comparison and negative emotion. The proposed reward comparison mechanism centers on the BLA (Kawasaki et al., submitted), a nucleus that receives information about the current re-
ward (4% sucrose) via the PbN-thalamus pathway and also from the reactivated memory of the expected reward (32% sucrose) via the PbN-thalamus–IC pathway. Electrophysiological recordings show that BLA neurons respond to taste stimuli (Fontanini et al., 2009), probably by receiving inputs from the PbN and/or gustatory thalamus (Bielavska and Roldan, 1996). Anatomical connections between the IC and the BLA have been widely recognized (e.g., Yamamoto et al., 1984). Thus, it is hypothesized here that lesions of the PbN (Grigson et al., 1994), gustatory thalamus (Reilly and Trifunovic, 2003), and IC (Lin et al., 2009) eliminate the effects of consummatory devaluations by disrupting the reward comparison mechanism (see Reilly and Trifunovic, 2003). Without the comparison, consummatory behavior simply adjusts to the current reward level (absolute reward value) without producing a contrast effect (relative reward value). The task of the BLA comparator is hypothesized to be to produce an output that carries information about the significance of the current- vs.-expected discrepancy.

Significant discrepancies would activate the negative emotion circuit. In this circuit, output from the BLA comparator activates the CeA direct-
ly or via intercalated cell masses (Paré et al., 2004) and the CeA provides the main source of behavioral suppression during reward devaluation
Fig. 1. Common elements of the neural circuitry underlying reward devaluation in consummatory successive negative contrast. This figure is intended to highlight the major components and it is not meant to provide an exhaustive outline of the circuit. Two levels are distinguished. The input/output level can be described as the taste/licking modal action pattern. The telencephalic level modulates the functioning of the taste/licking modal action pattern and it includes two major components: reward comparison and negative emotion. Reward comparison is suggested to be the function of the BLA, which receives information about the current reward (e.g., 4% sucrose) from the PbN-thalamus pathway and also retrieves a memory of the expected reward (e.g., 32% sucrose) assumed to be stored in the IC. If the output from the BLA involves a significant negative prediction error (i.e., the current reward is less valued than the expected reward), then the CeA is engaged to inhibit the taste/licking modal action pattern. In turn, activity in the CeA is assumed to be regulated by a loop involving the NAc, dorsal striatum, LHb, and VTA, and also by a BLA-ACC connection with an inhibitory influence on the CeA. The only output included in the figure is provided by the CeA. ACC: anterior cingulate cortex. BLA: basolateral amygdala. CeA: central amygdala. IC: insular cortex. LHb: lateral habenula. NAc: nucleus accumbens. NST: nucleus of the solitary tract. PbN: parabrachial nucleus. PFC: prefrontal cortex. VTA: ventral tegmental area.

We are also hypothesizing that an additional modulatory influence on CeA neurons involves the pathway connecting the NAc with the dorsal striatum and the LHb, which inhibits activity in the VTA. Such inhibition of VTA dopaminergic neurons may influence some unidentified area in the prefrontal cortex responsible for activating CeA output. There is evidence of a connection between the dorsal striatum and the LHb in primates (Saleem et al., 2002), but there is yet no evidence that the LHb provides a key signal for reward devaluation in the consummatory contrast situation, as it seems to do other tasks involving negative prediction error (Kimura et al., 2007; Stopper and Floresco, 2014). Thus, the net output from the CeA may be the result of excitatory afferents from the BLA and prefrontal cortex, and inhibitory afferents from the ACC. The consummatory successive negative contrast effect (see Table 1) would require that, at least initially, activation of the CeA dominates over the inhibitory cortical influences. However, with increased devaluation experience, inhibitory influences may play a key role in the recovery process. Interestingly, ACC lesions do not affect the level of consummatory suppression during the first reward devaluation session, but retard recovery from reward downshift in subsequent sessions (Ortega et al., 2011b). Output from the CeA represented in Fig. 1 is assumed to be a major (though not the only) influence ultimately inhibiting licking responses during consummatory reward devaluation.

4.2. Genetic vulnerability to reward loss and addiction

Potential factors underlying the transition from initial drug use to compulsive drug seeking and taking vary from the genetic to the social (Anthony et al., 1994). Individual differences in aspects related to reward dysregulation are a promising research field to understand the development and probability of relapse in drug addiction (Piazza and Le Moal, 1996). Similarly, several sources confirm the presence of individual differences that have unlocked the genetic correlates of behaviors induced by reward loss.

First, rats exhibit distinct profiles of recovery from an experience of reward devaluation. S. Papini et al. (2014) conducted an extensive secondary analysis of such profiles using latent-growth mixture modeling and identified three distinct recovery trajectories. The majority of rats (83% of 262 animals) exhibited the usual response suppression followed by recovery to control levels of consummatory behavior. A second group (6%) showed either little or no evidence of consummatory suppression after reward downshift. However, some animals (11%) exhibited similar suppression to the first subgroup during the initial experience with reward devaluation, but subsequently expressed little evidence of recovery from the suppressive effects of reward downshift. Interestingly, the typical and no recovery profiles did not differ in performance during the initial reaction to the reward devaluation, but in their rate of recovery. These results are consistent with previous studies showing that opioid blockade with naloxone affected animals that exhibited slow recovery from reward devaluation, but not those exhibiting fast recovery, in groups matched by their initial response to the devaluation (Pellegrini et al., 2005). Thus, the initial response to reward downshift does not predict the speed of recovery from that event.

Second, individual differences in the initial reaction to and in the recovery from reward devaluation respond to selective breeding protocols (Torres and Sabariego, 2014). For example, Flaherty et al. (1994) selectively bred Sprague-Dawley rats showing large vs. small initial reaction to reward devaluation over seven generations. This selective breeding gave rise to two lines with extreme divergence in reactivity to reward...
downshift, although, unfortunately, random mating controls were not included in this study. Similarly, Ortega et al. (2014b) selectively bred Long-Evans rats based on differences in recovery rate from reward devaluation (fast vs. slow recovery). They found that the degree of behavioral suppression induced by reward downshift was reduced in the fast-recovery line after five generations, relative to a random breeding control line. By contrast, the slow-recovery line did not differ from random controls. Although the results derived from selective breeding based on reward devaluation reactivity appear promising, whether this selection protocol affects the proneness to take and abuse drugs awaits further investigation.

Extensive evidence shows that strains of rats selectively bred for differences in fear, anxiety, and emotional reactivity often also differ in situations involving reward loss. This includes evidence from Maudsley reactive vs. nonreactive rats (Rowan and Flaherty, 1991), initially selected for their degree of defecation in a novel open-field situation; Syracuse high- vs. low-avoidance rats (Flaherty and Rowan, 1989), initially selected for performance in an active avoidance task; Lewis vs. Fischer rats (Brewer et al., 2016; Freet et al., 2006), inbred strains differing in terms of many traits; and spontaneously hypertensive vs. Wistar-Kyoto rats (Bentosela and Mustaca, 2005), two divergent strains derived from the same stock. In all these cases, the more “emotional” strain exhibits increased response to reward downshift, although in no case were they evolved on the basis of this trait, with one exception: the Maudsley reactive rats actually showed smaller reaction to reward loss than the nonreactive rats (Rowan and Flaherty, 1991). Additional tests indicated that these animals were still showing the difference in emotionality in the open field as expected. Thus, the reason for these surprising results remains unknown.

Some of these strains also differ in drug intake and other behavioral traits related to vulnerability to addiction. For example, Lewis rats acquire self-administration of a number of abuse drugs, including cocaine and heroin, more rapidly and at higher rates compared with Fischer rats (Picetti et al., 2012). Importantly, this divergent pattern of cocaine self-administration correlates with differences in gene expression for endogenous neuromodulatory systems, such as opioid peptides and receptors, in specific brain regions, such as the dorsal striatum, linked to reward loss and uncertainty (Torres et al., 2016; Valenza et al., 2016; Wood et al., 2005; Wood et al., 2008).

The extensive and systematic characterization of the Roman high-avoidance (RHA) and low-avoidance (RLA) strains is of special importance in the present context because they have been studied in terms of both reward loss and drug addiction. Although initially selected for their good (RHA) vs. poor (RLA) two-way active avoidance performance in the 1960s, Roman rats consistently differ in situations involving drug taking (and related behavioral traits) and reward loss. For example, RHA rats show higher proneness to voluntarily self-administration of alcohol in comparison to RLA rats (Manzo et al., 2012). Similarly, only the RHA strain show behavioral sensitization in response to the repeated administration of cocaine, amphetamine, and morphine (Giorgi et al., 2007). These differences may be due to strain-dependent divergence in mesolimbic dopaminergic pathways (Tournier et al., 2013).

This picture changes when RHA and RLA rats are subject to reward loss. In this case, RLA rats have been shown to be consistently more reactive than the RHA rats when exposed to reward devaluation situations, including instrumental (appetitive and aversive) and consummatory tasks (Cuena et al., 2012; Cuena et al., 2015; Gómez et al., 2009b; Rosas et al., 2007; Sabariego et al., 2013; Torres et al., 2005). For example, downshifts from 12 to 2 pellets in the runway (Rosas et al., 2007), from 22 to 4% sucrose in the consummatory situation (Gómez et al., 2009b), and from 30 s to 1 s in safety in one-way avoidance contrast (Torres et al., 2005) have a stronger effect on behavior in RLA rats than in RHA rats. RLA rats also show faster extinction after continuous reinforcement than after partial reinforcement, an effect that is absent in RHA rats, which tend to exhibit slow extinction of instrumental behavior (Gómez et al., 2009a; Gómez et al., 2008). Finally, the most relevant evidence supporting a connection between addiction and reward loss derives from studies showing that only the more reactive RLA strain increases ethanol consumption in response to reward omission (Manzo et al., 2014).

In terms of the application of reward loss research to the study of the genetic basis of drug addiction, two interesting results are worth highlighting. First, individual differences in recovery from reward devaluation are associated to differential sensitivity of opioid and GABAergic receptors (Freet et al., 2006; Ortega et al., 2014b; Pellegrini et al., 2005), suggesting a common neurochemical background underlying addictive behavior and the response to reward loss. Second, microarray research with the Roman strains suggests that individual differences in response to reward devaluation are related to differences in brain expression of genes related to drug abuse and emotion, including TAAR2, PRL, CAMKK2, CRHBP, and HOMER3, among others (Sabariego et al., 2011, 2013). These results make these genes targets for future research on the interplay between reward loss and addiction.

One implication derived from the studies reviewed above, mostly centered on selectively bred strains, is that the same genes control the expression of mechanisms underlying reward loss and addiction (pleiotropic gene effects). This conclusion, however, must be taken with caution for several reasons. For example, strains selected for their response in reward loss situations were not studied in terms of addictive behavior (Flaherty et al., 1994; Ortega et al., 2014a, 2014b); vice versa, as far as the authors know, none of the strains selected on the basis of addictive behavior have been tested in reward loss situations. The Roman strains, which are well characterized in terms of both reward loss and addiction, were originally selected for their response in active avoidance learning and have subsequently been subjected to extensive inbreeding, which poses problems of its own. Inbreeding (i.e., pairing of male and female siblings) may lead to the random fixation of alleles other than those initially affected by selective breeding. Thus, an apparent correlation of phenotypes may be the result of different genes, rather than the result of the pleiotropic effects of the same genes (Crabbe et al., 1990). Support for a common genetic basis between two phenotypes would require comparisons among several inbred strains. These concerns would be minimized, although not completely eliminated, in comparisons between outbred strains specifically selected for vulnerability to reward loss or addiction. In outbred strains (i.e., pairings of nonsibling males and females), behavioral divergence is assumed to be the result of pleiotropic gene effects, with the genetic background remaining stable. However, such an assumption requires relatively large animal samples to minimize random gene fixations, a requisite rarely fulfilled in selective breeding studies with mammals.

4.3. Role of competing natural rewards

An additional application of reward loss to drug addiction research was suggested by Grigson (1997, 2008). According to her view, a key component of drug addiction is the devaluation of natural incentives. Individuals suffering from an SUD tend to care less for their health, their job, and even their children. To model this effect, animals are exposed to natural rewards (e.g., sweet substances like saccharin) followed by drug administration. For instance, Grigson and Hajnal (2007) gave rats a single saccharin-morphine Pavlovian pairing and later tested the response to the saccharin alone. They found reduced saccharin intake and a blunting of dopamine levels in the NAc, as well as reduced NAc dopamine levels in response to morphine. Such suppressive effects on the consumption of various gustatory stimuli were found after pairings with a variety of drugs with addictive potential, including cocaine, amphetamine, ethanol, benzodiazepine anxiolytics, nicotine, and opioids (Grigson, 2008). There also individual differences in the suppressive effects of these pairings. For example, after saccharine-heroin pairings, some animals exhibited a pronounced reduction in saccharin intake, whereas other showed a milder effect; “high suppressors” also showed several additional behaviors related to addiction compared to “low
suppressors,” including reinstatement of heroin seeking after exposure to mild shock and a higher braking point in a progressive ratio test (Jenney et al., 2016). These results suggest that the incentive value of a natural reward (e.g., saccharin’s sweetness) can be reduced by a single pairing with morphine or heroin. The suppression of saccharin intake after saccharine-drug pairings is reminiscent of the anticipatory negative contrast effect described above. In this case, for example, intake of a weak saccharin solution is suppressed when it signals access to 32% sucrose, relative to a saccharin-saccharin pairing. Thus, consumption of a less sweet current reward is reduced by an expectation of a sweeter reward (Flaherty, 1996). However, the availability of some rewards can also reduce drug intake. For example, access to physical exercise reduces cocaine self-administration (Smith et al., 2016) and housing in an enriched environment reduces nicotine self-administration (Gomez et al., 2015). These data show that, as in reward loss, comparison among rewards and incentive relativity play a key role in the onset, persistence, and relapse of addictive behavior.

4.4. Reward loss and emotional self-medication

The ability of abuse drugs to diminish or relieve aversive emotional states induced by psychopathological conditions and drug withdrawal has been proposed as a precipitant factor for addiction. We will refer to this approach as the emotional self-medication (ESM) hypothesis, a hypothesis initially suggested by clinical evidence (Khantzian, 1985, 2013) and lately attracting experimental attention (Torres and Papini, 2016). Despite wide evidence showing that animals also consume drugs to alleviate a variety of negative emotional states, including drug withdrawal (Koob, 2013), most of these studies lack appropriate controls to test the self-medication hypothesis. Such lacking controls include: (1) Establishing that emotional activation is actually present during the episode of substance consumption; (2) Demonstrating that increased consumption is selective for substances that reduce negative emotions; (3) Showing that increased substance consumption is restricted to periods of increased emotional activation; and (4) Providing independent evidence that the consumed substance effectively reduces emotional activation (Manzo et al., 2015a, 2015b; Torres and Papini, 2016). In addition to these control issues, there is yet insufficient data exploring the breath of situations that induce ESM and the spectrum of substances that support ESM.

Several studies suggest that drug taking following reward loss can be considered a type of ESM. An initial study reported that reward devaluation induced approach to stimuli that were previously associated with systemic ethanol administration (Kamenetzky et al., 2009a). However, ESM requires direct consumption, rather than simply approaching a signal previously paired with the substance. Several experiments have used a procedure involving an induction task based on a reward loss paradigm (see Table 1) followed each day by a two-bottle preference test in which anxiolytics were diluted in water to simulate typical aspects of human drug taking, which usually involves voluntary and oral consumption. Manzo et al. (2015a) observed that preference for ethanol and the anxiolytic chlordiazepoxide was enhanced subsequently to a reward devaluation experience, relative to unshifted controls and to groups given access only to water. In the same line, Manzo et al. (2014) reported that preference for ethanol following reward omission was higher in the more emotionally reactive RLA-I rats than in the less reactive RHA-I rats. Additional research on reward loss and emotional self-medication reveals an interesting interaction between genetic and experiential factors based on a comparison of partial reinforcement vs. continuous reinforcement on drug intake. Partial reinforcement has been proposed as an effective treatment for developing resistance/resilience to reward loss, given its attenuating effects over the behavioral consequences of reward devaluation and omission (Pellegrini et al., 2004). Following this rationale, Manzo et al. (2015b) conducted an experiment in which emotionally reactive RLA-I rats were exposed to instrumental extinction sessions after partial vs. continuous reinforcement acquisition training. Each session was followed by free access to ethanol vs. water in the home cage. The results indicated that rats exposed to partial reinforcement showed lower preference for ethanol consumption after reward omission than those exposed to continuous reinforcement. Thus, exposure to reward uncertainty via partial reinforcement training counteracted a genetic predisposition for emotional self-medication after decades of selective breeding. This result can open up future research on behavioral interventions that could effectively protect against drug abuse and misuse (Manzo et al., 2015b).

5. Concluding remarks

Current research trends on the psychobiology of addiction have focused on a wide set of behavioral processes and related experimental procedures. However, in comparative terms, there has been a lack of attention to the role of reward loss in drug addiction. The present review makes it clear that there are extensive behavioral, neurochemical, and neurobiological parallels between the response to reward loss and the development and maintenance of drug addiction. Such parallels suggest avenues for cross-pollination between two lines of research that have proceeded relatively independently. An understanding of the psychobiology of drug addiction can be enhanced by incorporating existing findings and animal models from reward loss research. Furthermore, reward loss research suggests new avenues of scientific inquiry that are likely to shed light in our understanding of the transition from initial drug use to a compulsive set of drug seeking and taking habits. This is suggested by the reviewed research on the interaction between genetic vulnerability and reward history, the competing effects of natural rewards for the development and maintenance of drug seeking and taking, and the growing awareness of the role of emotional self-medication in drug addiction.

One area in which research on reward loss and addiction would seem to conflict with each other is in the role of habits. Habits are usually characterized as sequential behavior that occurs independently of outcome expectations and seem to be performed automatically. Under some conditions (e.g., extended training), the postraining devaluation of an outcome such as food may not disrupt instrumental responding established by that outcome (Adams, 1982). Such habitual behavior is an important component of well-established addictive behaviors (e.g., Everitt and Robbins, 2016), but, of course, it rounds counter to reward-loss effects, which critically depend on the violation of outcome expectations (e.g., Papini et al., 2015). Consistent with this view, a devaluation protocol consisting of pairing self-administration infusions of cocaine with LiCl (a toxin leading to gastrointestinal sickness) reduced responding established by cocaine reinforcement when devaluation occurred after short training sessions, but not when devaluation occurred after extended sessions of cocaine training (Leong et al., 2016). Although the transition from outcome-driven to outcome-independent behavior is usually presented as a sequential process dependent, for example, upon the amount of training (Packard and McGaugh, 1996), the process might be more complex than this view suggests. Habitual responding does not imply that outcome expectancies are no longer available, but may instead reflect the structure of the situation. Unpublished research suggests that animals that behave habitually when facing a single response option may show outcome-driven performance if confronted with a choice in which one option has been devalued from a large to a small reward, whereas the other option has been consistently paired with the small reward (Conrad and Papini, 2016). Under such conditions, rats show about the same responding to both options when each of them is presented in isolation, but shift away from the devalued option when given a simultaneous choice. Thus, the choice scenario may force outcome expectancies to re-take control of behavior even after extended training. Whether a similar approach could be useful in the treatment of well-established SUDs remains to be explored.
Drug addiction is one of the most complex and costly social problems, so the tools, both conceptual and empirical, derived from the study of reward loss can help to ameliorate human suffering. Because of significant parallels in the overlap of learning and motivational processes, reward devaluation and omission phenomena can provide significant inroads in the prevention and treatment of SUDs.

Conflict of interest

None.

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