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Allostatic View of Motivation: Implications for Psychopathology

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Motivation as a concept has many definitions. Donald Hebb (1949) argued that motivation is "stimulation that arouses activity of a particular kind" (p. 172), and C. P. Richter (1927) argued that "spontaneous activity arises from certain underlying physiological origins," and such "internal" drives are reflected in the amount of general activity (p. 307). Dalbir Bindra (1976) defined motivational function as a "rough label for the relatively persisting states that make an animal initiate and maintain actions leading to particular outcomes or goals" (p. 363), and a more behavioristic view is that incentive motivation is "given the properties of energizing behavior (along with other motivational factors) and of being proportional to the amount and quality of the reinforcer" (Bartoshuk, 1979, p. 695).

All of these definitions point to certain common characteristics of our concept of motivation. It is a state that varies with arousal and guides behavior in relationship to changes in the environment. The environment can be external (incentives) or internal (central motive states or drives), and such motivation or motivational states are not constant and vary over time. The concept of motivation was linked inextricably with hedonic, affective, or emotional states in the context

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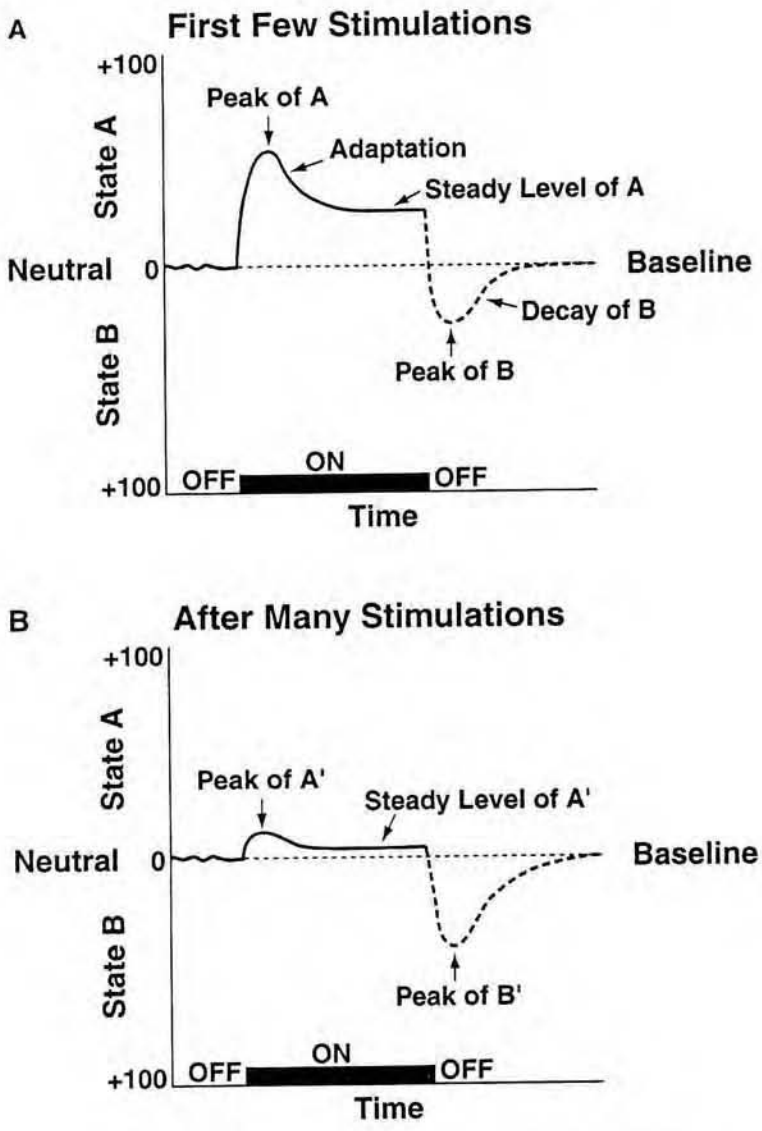

Figure 1. (A) The standard pattern of affective dynamics produced by a relatively novel unconditioned stimulus. (B) The standard pattern of affective dynamics produced by a familiar, frequently repeated unconditioned stimulus. (From Solomon, 1980. Copyright © 1980 by the American Psychological Association. Reprinted with permission.)

of temporal dynamics by Solomon's opponent-process theory of motivation. Solomon and Corbit (1974) postulated that hedonic, affective, or emotional states, once initiated, are automatically modulated by the central nervous system with mechanisms that reduce the intensity of hedonic feelings. Termed the "opponent-process" theory of motivation, Solomon argued that there is affective or hedonic habituation (or tolerance) and affective or hedonic withdrawal (abstinence). He defined two processes: the *a-process* and the *b-process*. The *a-process* could consist of either positive or negative hedonic responses. It occurs shortly after presentation of a stimulus, correlates closely with the stimulus intensity, quality, and duration of the reinforcer, and shows tolerance. In contrast, the *b-process* appears after the *a-process* has terminated and is sluggish in onset, slow to build up to an asymptote, slow to decay, and gets larger with repeated exposure. Thus, the affective dynamics of opponent-process theory generate new motives and new opportunities for reinforcing and energizing behavior (Solomon, 1980; Figure 1).

From a neurobehavioral perspective it was hypothesized that in brain motivational systems the initial acute effect of an emotional stimulus or a drug is opposed or counteracted by homeostatic changes in brain systems. Certain systems in the brain were hypothesized to suppress or reduce all departures from hedonic neutrality (Solomon & Corbit, 1974). This affect control system was conceptualized as a single negative feedback, or opponent, loop that opposes the stimulus-aroused affective state (Solomon & Corbit, 1974; Siegel, 1975; Poulos & Cappell, 1991). In this opponent-process theory, tolerance and dependence are inextricably linked (Solomon & Corbit, 1974), and affective states—pleasant or aversive—were hypothesized to be automatically opposed by centrally mediated mechanisms that reduce the intensity of these affective states. In the context of drug dependence, Solomon argued that the first few self-administrations of an opiate drug produce a pattern of motivational changes similar to that observed in Figure 1A. The onset of the drug effect produces euphoria that is the *a-process*, and this is followed by a decline in intensity. Then, after the drug wears off, the *b-process* state emerges as an aversive craving state (Figure 2).

More recently, opponent-process theory has been expanded into the domains of the neurocircuitry and neurobiology of drug addiction from a physiological perspective. An allostatic model of the brain

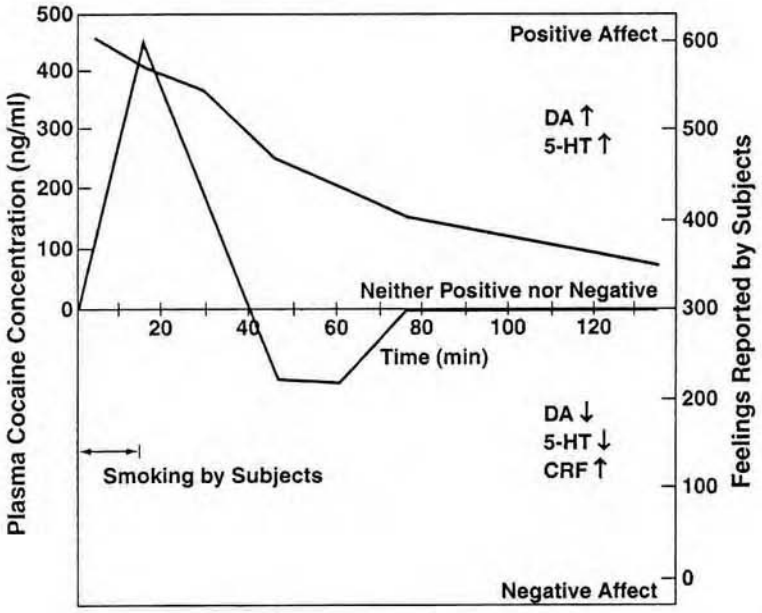

Figure 2. Demonstration of the opponent-process theory *b-process* state emerging as an aversive craving state. Dysphoric feelings followed the initial euphoria in experimental subjects who smoked cocaine paste, even though the concentration of cocaine in the plasma of the blood remained relatively high. The dysphoria is characterized by anxiety, depression, fatigue, and a desire for more cocaine. The peak feelings for the subjects were probably reached shortly before the peak plasma concentration, but the first psychological measurements were made later than the plasma assay. Hence, the temporal sequence of the peaks shown cannot be regarded as definitive. (Adapted from Van Dyke & Byck, 1982. Copyright © 1982 by Scientific American, Inc. All rights reserved. Printed with permission.)

motivational systems has been proposed to explain the persistent changes in motivation that are associated with vulnerability to relapse in addiction, and this model may generalize to other psychopathology associated with dysregulated motivational systems. In this framework, addiction is conceptualized as a cycle of spiraling dysregulation of brain reward systems that progressively increases resulting in the compulsive use of drugs. Counteradaptive processes such as opponent-process that are part of the normal homeostatic limitation of reward function fail to return within the normal homeostatic range and are hypothesized to form an allostatic state. This

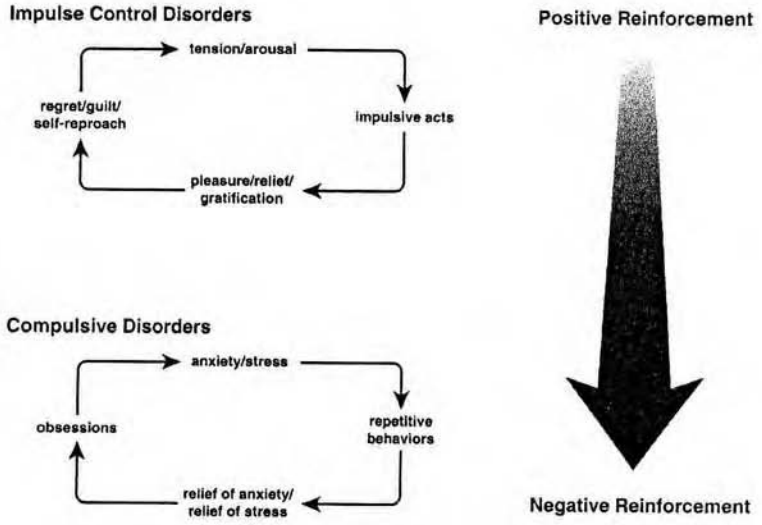

Figure 3. Diagram showing stages of impulse control disorder and compulsive disorder cycles related to the sources of reinforcement. In impulse control disorders an increasing tension and arousal occurs before the impulsive act, with pleasure, gratification or relief during the act. Following the act there may or may not be regret or guilt. In compulsive disorders, there are recurrent and persistent thoughts (obsessions) that cause marked anxiety and stress followed by repetitive behaviors (compulsions) that are aimed at preventing or reducing distress (American Psychiatric Association, 1994). Positive reinforcement (pleasure/gratification) is more closely associated with impulse control disorders. Negative reinforcement (relief of anxiety or relief of stress) is more closely associated with compulsive disorders.

allostatic state is further hypothesized to be reflected in a chronic deviation of reward set point that is fueled not only by dysregulation of reward circuits per se but by recruitment of brain and hormonal stress responses.

Drug addiction has been conceptualized as a chronic relapsing disorder characterized by compulsive drug-taking behavior with impairment in social and occupational functioning. From a psychiatric perspective, drug addiction has aspects of both impulse control disorders and compulsive disorders (Figure 3). Impulse control disorders are characterized by an increasing sense of tension or arousal before committing an impulsive act; pleasure, gratification, or relief at the time of committing the act; and following the act there may or may not be regret, self-reproach, or guilt (American Psychiatric

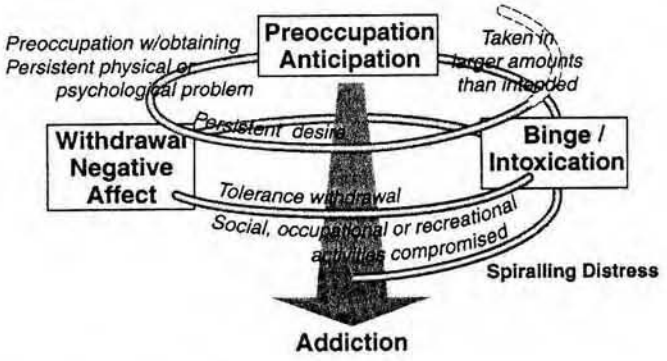

Figure 4. Diagram describing the spiraling distress-addiction cycle from a psychiatric perspective, including the three major components of the addiction cycle (preoccupation/anticipation, binge/intoxication, and withdrawal/negative affect) with the different criteria for substance dependence from the *Diagnostic and Statistical Manual of Mental Disorders* incorporated. (From Koob & Le Moal, 1997. Copyright © 1997 by the American Association of the Advancement of Science. Reprinted with permission.)

Association, 1994). In contrast, compulsive disorders are characterized by anxiety and stress before committing a compulsive repetitive behavior, and relief from the stress by performing the compulsive behavior. As an individual moves from an impulsive disorder to a compulsive disorder there is a shift from positive reinforcement driving the motivated behavior to negative reinforcement driving the motivated behavior. Drug addiction has been conceptualized as a disorder that progresses from impulsivity to compulsivity in a collapsed cycle of addiction comprised of three stages: preoccupation/anticipation, binge/intoxication, and withdrawal/negative affect (Figure 4). Different theoretical perspectives ranging from experimental psychology, social psychology, and neurobiology can be superimposed on these three stages that are conceptualized as feeding into each other, becoming more intense, and ultimately leading to the pathological state known as addiction (Koob & Le Moal, 1997).

Cocaine is a powerfully reinforcing psychostimulant with high addiction potential and provides a model with which to bridge the domains of motivation and psychopathology. Cocaine increases the

availability of monoamines at the synaptic level in the brain, and much is known about the neuropharmacological basis of its acute reinforcing effects. Early work suggested a primary role for the mesolimbic dopamine system that projects to the basal forebrain (Koob, 1992). More recent evidence suggests that both dopaminergic and serotonergic terminals within a basal forebrain macrostructure termed the extended amygdala (central nucleus of the amygdala, bed nucleus of the stria terminalis, and a transition area in the region of the shell of the nucleus accumbens) have a particularly important role in the acute rewarding effects of cocaine (Koob, Sanna, & Bloom, 1998). Significant evidence also exists to show that these systems can be dysregulated by prolonged self-administration of cocaine yielding an opponent-process-like change in the neurochemistry of the extended amygdala. Continuous self-administration of cocaine for 12 hours produces decreases in extracellular levels of dopamine and serotonin in the nucleus accumbens as measured by *in vivo* microdialysis (Figure 5). However, there are even more dramatic increases in extracellular levels of the brain stress neurotransmitter corticotropin-releasing factor (CRF) in the central nucleus of the amygdala during acute withdrawal (Figure 6). Both of these changes could be hypothesized to contribute to the brain neurochemical representation of the "opponent loop" conceptualized by Solomon (1980).

However, drug addiction, and cocaine addiction in particular, is considered a chronic relapsing disorder where subjects episodically administer the drug and become abstinent. What is unknown is what neurochemical/neurocircuitry changes occur that provide the motivational basis for vulnerability after the acute withdrawal during periods of abstinence and how such changes lead to escalation in drug intake over time. Animal models of escalation of drug intake have been established using prolonged access to drugs that are beginning to provide some insights into the neurobiological changes that may lead to vulnerability to escalation in drug intake and relapse.

Historically in animal models of cocaine self-administration the focus was restricted to stable behavior from day to day in order to reliably interpret within-subject designs aimed at exploring the pharmacological,and neuropharmacological basis for the acute reinforcing effects of cocaine. Typically, rats allowed access to fewer than 3 hours of cocaine per day, after acquisition of self-administration, establish highly stable levels of intake and patterns of responding

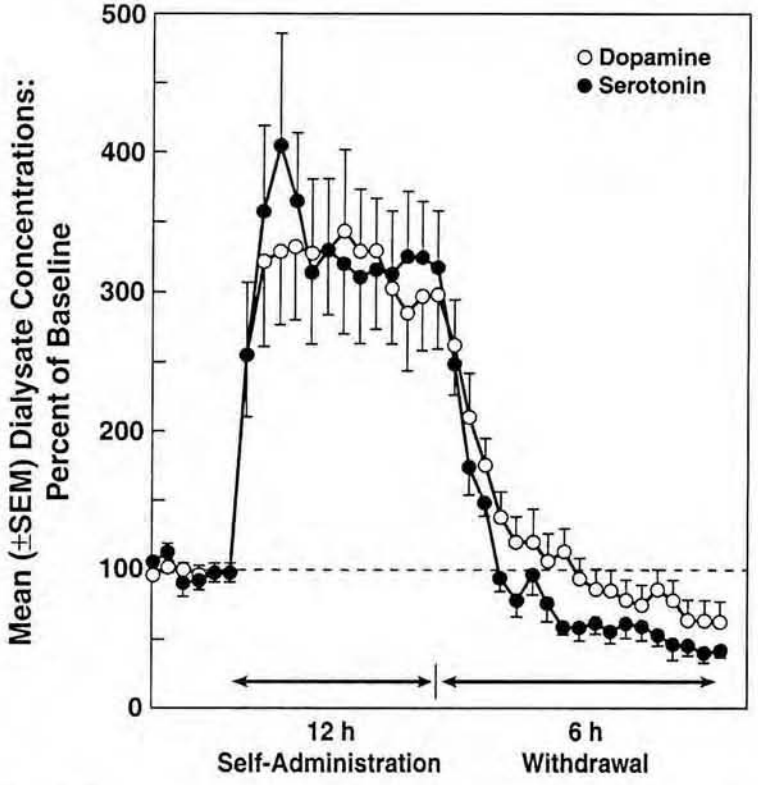

Figure 5. The profile of dialysate serotonin and dopamine concentrations and a corresponding representative reinforcer delivery record during a 12-hour extended-access cocaine self-administration session. The mean (± SEM) presession baseline dialysate concentrations of serotonin and dopamine were 0.98 ± 0.1 nM and 5.3 ± 0.5 nM, respectively ($n = 7$). (Adapted from Parsons et al., 1995. Printed with permission.)

between daily sessions. To explore the possibility that differential access to intravenous cocaine self-administration in rats may produce different patterns of drug intake, rats were allowed access to intravenous self-administration of cocaine for 1 hour and 6 hours per day. With 1-hour access (short access) to cocaine per session via intravenous self-administration, drug intake remained low and stable, not changing from day to day as observed previously. In contrast, with 6-hour access (long access) to cocaine drug intake gradually escalated over days (Ahmed & Koob, 1998; Figure 7). In the escalation group,

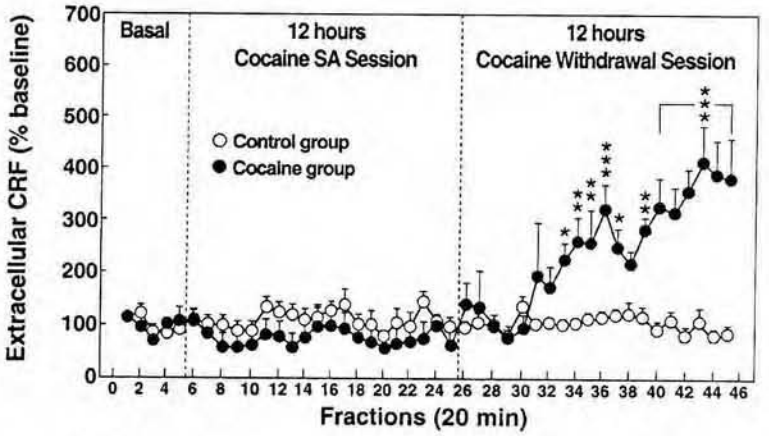

Figure 6. Mean (± SEM) dialysate CRF concentrations collected from the central nucleus of the amygdala of rats during baseline, a 12-hour cocaine self-administration session, and a subsequent 12-hour withdrawal period (Cocaine Group, $n = 5$). CRF levels in animals with the same history of cocaine self-administration training and drug exposure, but not given access to cocaine on the test day, are shown for comparison (Control Group, $n = 6$). The data are expressed as percentages of basal CRF concentrations. Dialysates were collected over 2-hour periods alternating with 1-hour nonsampling periods. During cocaine self-administration, dialysate CRF concentrations in the cocaine group were decreased by about 25% relative to control animals. In contrast, termination of access to cocaine resulted in a significant increase in CRF efflux, which began approximately 5 hours postcocaine and reached about 400% of presession baseline levels at the end of the withdrawal session. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; Simple Effects after overall mixed factorial ANOVA. (Adapted from Richter & Weiss, 1999. Copyright © 1999 by Wiley-Liss, Inc. Printed by permission of Wiley-Liss, Inc., a subsidiary of J. Wiley and Sons, Inc.)

there was an increased early intake as well as sustained intake over the session and an upward shift in the dose-effect function suggesting an increase in hedonic set point. When animals were allowed different doses of cocaine during self-administration the long access animals titrated cocaine effects as well as the short access rats, but the long access rats consistently self-administered almost twice as much cocaine at any dose tested, further suggesting an upward shift in the set point for cocaine reward in the escalated animals (Ahmed & Koob, 1998).

According to the hedonic allostasis hypothesis described above, tolerance to drug hedonic effects and increased motivation for these effects are inextricably linked to the same chronic perturbation in

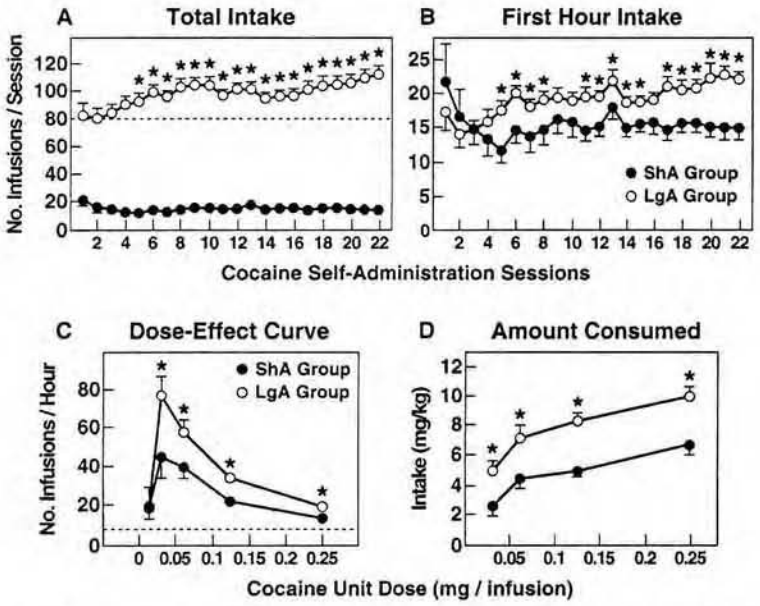

Figure 7. Effect of drug availability on cocaine intake (mean ± SEM). (A) In long access (LgA) rats ($n = 12$) but not in short access (ShA) rats ($n = 12$), mean total cocaine intake started to increase significantly from session 5 ($p < 0.05$; sessions 5 to 22 compared to session 1) and continued to increase thereafter ($p < 0.05$; session 5 compared to sessions 8–10, 12, 13, 17–22). (B) During the first hour, LgA rats self-administered more infusions than ShA rats during sessions 5–8, 11, 12, 14, 15, and 17–22 ($p < 0.05$). (C) Mean infusions (± SEM) per cocaine dose tested. LgA rats took significantly more infusions than ShA rats at doses of 31.25, 62.5, 125, and 250 µg/infusion ($p < 0.05$). * $p < 0.05$ (Student's t test after appropriate one-way and two-way analysis of variance). (From Ahmed & Koob, 1998. Copyright © 1998 by the American Association for the Advancement of Science. Reprinted with permission.)

brain reward homeostasis (or allostasis). To directly test this hypothesis, two groups of rats were differentially exposed to cocaine self-administration as described above (i.e., 1-hour short access and 6-hour long access groups). The animals first were prepared with bipolar electrodes in either the right or left posterior lateral hypothalamus. One week postsurgery they were trained to respond for electrical brain stimulation. Intracranial self-stimulation (ICSS) thresholds measured in µA were assessed according to a modified discrete-trial current-threshold procedure (Markou & Koob, 1993). During the *screening phase*, the 22 rats tested for self-administration were

allowed to self-administer cocaine during only 1 hour on a fixed-ratio 1 schedule after which two balanced groups with the same weight, cocaine intake and ICSS reward thresholds were formed. During the *escalation phase*, one group had access to cocaine self-administration for only 1 hour per day (short access or ShA rats) and the other group for 6 hours per day (long access or LgA rats). The remaining eight rats were exposed to the same experimental manipulations as the other rats, except that they were not exposed to cocaine. ICSS reward thresholds were measured in all rats two times a day, 3 hours and 17–22 hours after each daily self-administration session (ShA and LgA rats) or the control procedure (drug-naive rats). Each ICSS session lasted about 30 minutes.

Elevation in baseline ICSS thresholds temporally preceded and was highly correlated with escalation in cocaine intake (Ahmed, Kenny, Koob, & Markou, 2002). Further observation revealed that postsession elevations in ICSS reward thresholds failed to return to baseline levels before the onset of each subsequent self-administration session, thereby deviating more and more from control levels. The progressive elevation in reward thresholds was associated with a dramatic escalation in cocaine consumption in LgA rats as previously observed. Within 12 days, the first-hour cocaine intake in LgA rats rose to a level almost two times greater than that observed in ShA rats. Total intake in LgA rats also increased almost continually over the same period of time from 75.5 (± 13.9) to 125 (± 4.3) cocaine injections. The gradual elevation in ICSS reward thresholds associated with drug intake escalation did not result from a general inability to respond, as demonstrated by the lack of differences between groups in response latencies for ICSS (Ahmed et al., 2002). Finally, the rate of elevation in reward thresholds measured 1 hour before the daily access to cocaine (i.e., slope of elevation) was highly correlated ($r = 0.78$, $p < 0.01$) with the intensity of escalation in total cocaine intake. Finally, after escalation had occurred, an acute cocaine challenge failed to facilitate brain reward responsiveness to the same degree as before. These results show that the elevation in brain reward thresholds following prolonged access to cocaine failed to return to baseline levels between repeated, prolonged exposure to cocaine self-administration (i.e., residual hysteresis), thus creating a greater and greater elevation in baseline ICSS thresholds. These data provide compelling evidence for brain reward dysfunction in esca-

lated cocaine self-administration and strong support for the hedonic allostasis model of drug addiction.

Similar changes in self-administration of heroin and alcohol have been observed in animals with more prolonged access (Ahmed, Walker, & Koob, 2000) or a history of dependence (Roberts, Heyser, Cole, Griffin, & Koob, 2000). Ethanol-dependent rats will self-administer significantly more ethanol during acute withdrawal than rats in a nondependent state. In these studies, Wistar rats are trained using a sweet solution fadeout procedure to self-administer ethanol in a two-lever operant situation where one lever delivers 0.1 ml of 10% ethanol and the other lever delivers 0.1 ml of water. Nondependent animals typically self-administer doses of ethanol sufficient to produce blood ethanol levels averaging 25–30 mg% at the end of a 30-minute session, but rats made dependent on ethanol self-administer almost twice as much ethanol. With unlimited access to ethanol during a full 12 hours of withdrawal, animals will maintain blood ethanol levels above 100 mg% (Roberts, Cole, & Koob, 1996). When animals were subjected to repeated withdrawals and ethanol intake was charted over repeated abstinence, operant responding was enhanced by 30–100% for up to four–eight weeks postwithdrawal. These results suggest an allostatic-like increase in ethanol self-administration in animals with a history of dependence on ethanol that is not observed in animals maintained on limited access of 30 minutes per day.

Neuropharmacological studies have shown that enhanced ethanol self-administration during acute withdrawal and protracted abstinence can be dose-dependently reduced by intracerebroventricular pretreatment with a γ-aminobutyric acid (GABA) agonist (Roberts et al., 1996) and a competitive CRF antagonist (Valdez et al., 2002). Identical doses and administration of these neuropharmacological agents to nondependent rats has no effect on self-administration of ethanol. These results suggest, during the development of dependence, not only a change in function of neurotransmitters associated with the acute reinforcing effects of ethanol (GABA) but also recruitment of a key element of the brain stress systems (CRF).

Acute withdrawal from drugs of abuse produces opponent-process-like changes in reward neurotransmitters in specific elements of reward circuitry associated with the extended amygdala as well as recruitment of brain stress systems that motivationally oppose the hedonic effects of drugs of abuse. Such changes in these brain

systems associated with the development of motivational aspects of withdrawal are hypothesized to be a major source of potential allostatic changes that drive and maintain addiction. In this context, *allostasis* is defined as the process of achieving stability through change; *allostatic state* is a state of chronic deviation of the regulatory system from its normal (homeostatic) operating level; and *allostatic load* is the cost to the brain and body of the deviation, accumulating over time, and reflecting in many cases pathological states and accumulation of damage. More specifically, allostasis from the drug addiction perspective is the process of maintaining apparent reward function stability by changes in reward and stress system neurocircuitry. Decreases in the function of dopamine, serotonin, and opioid peptides are hypothesized to contribute to a shift in reward set point as well as recruitment of brain stress systems such as CRF (Figure 8). All of these changes are hypothesized to be focused on a dysregulation of function within the neurocircuitry of the basal forebrain macrostructure of the extended amygdala.

The present formulation is an extension of Solomon's opponent-process to an allostatic framework with a hypothesized neurobiologic mechanism (Figure 8). The initial experience of a drug with no prior drug history shows a positive hedonic response *(a-process)* and a negative hedonic response *(b-process)*, each represented respectively by increased and decreased functional activity of reward transmitters. The *b-process* is hypothesized to involve modest recruitment of brain stress neurotransmitter function. However, insufficient time between re-administering the drug to retain the *a-process* and limit the *b-process* leads to a transition to an allostatic reward state as has been observed in escalation of cocaine intake and ethanol intake in animal models. Under conditions of an allostatic reward state the *b-process* never returns to the original homeostatic level before drug taking begins again, thus creating a greater and greater allostatic state in the brain reward systems, and by extrapolation a transition to addiction. The counteradaptive opponent-process does not balance the activational process *(a-process)* but in fact shows a residual hysteresis. The results with cocaine escalation and brain reward thresholds provide empirical evidence for this hypothesis. This residual hysteresis can be hypothesized to involve not only decreases in reward neurotransmission such as dopamine, GABA and opioid peptides, but also recruitment of brain stress systems such as corticotropin-releasing fac-

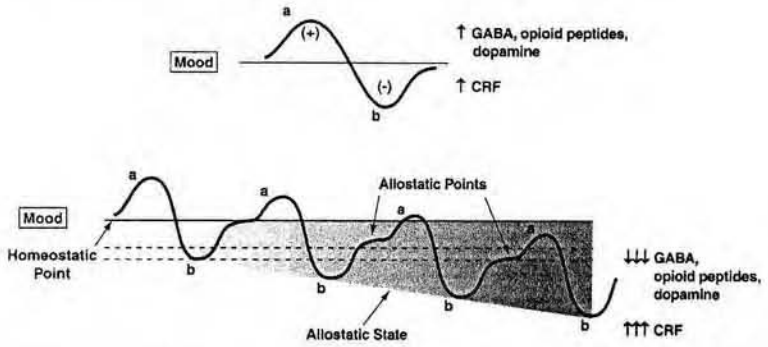

Figure 8. Diagram illustrating an extension of Solomon and Corbit's (1974) opponent-process model of motivation to outline the conceptual framework of the allostatic hypothesis. Both panels represent the affective response to the presentation of a drug. (Top) This diagram represents the initial experience of a drug with no prior drug history. The *a-process* represents a positive hedonic or positive mood state, and the *b-process* represents the negative hedonic or negative mood state. The affective stimulus (state) has been argued to be a sum of both an *a-process* and a *b-process*. An individual who experiences a positive hedonic mood state from a drug of abuse with sufficient time between re-administering the drug is hypothesized to retain the *a-process*. In other words, an appropriate counteradaptive opponent-process *(b-process)* that balances the activational process *(a-process)* does not lead to an allostatic state. (Bottom) The changes in the affective stimulus (state) in an individual with repeated frequent drug use that may represent a transition to an allostatic state in the brain reward systems and, by extrapolation, a transition to addiction. Note that the apparent *b-process* never returns to the original homeostatic level before drug taking is reinitiated, thus creating a greater and greater allostatic state in the brain reward system. In other words, the counteradaptive opponent-process *(b-process)* does not balance the activational process *(a-process)* but in fact shows a residual hysteresis. While these changes are exaggerated and condensed over time in the present conceptualization, the hypothesis here is that even during postdetoxification, a period of "protracted abstinence," the reward system is still bearing allostatic changes. In the nondependent state, reward experiences are normal, and the brain stress systems are not greatly engaged. During the transition to the state known as addiction, the brain reward system is in a major underactivated state while the brain stress system is highly activated. Small arrows refer to increased or decreased functional activity of the neurotransmitters. DA, dopamine; CRF, corticotropin-releasing factor; GABA, γ-aminobutyric acid. The following definitions apply: *allostasis*, the process of achieving stability through change; *allostatic state*, a state of chronic deviation of the regulatory system from its normal (homeostatic) operating level; *allostatic load*, the cost to the brain and body of the deviation, accumulating over time, and reflecting in many cases pathological states and accumulation of damage. (Modified from Koob & Le Moal, 2001. Copyright © 2001 by American College of Neuropsychopharmacology. Printed with permission.)

tor (Figure 8). Finally, these neurochemical/neurocircuitry changes observed during acute withdrawal may persist in some form even during postdetoxification defining a state termed "protracted abstinence."

An allostatic view of motivation provides an interesting framework for the development of psychopathology in a variety of domains. Allostasis originally was formulated as a hypothesis to explain the physiological basis for changes in patterns of human morbidity and mortality associated with modern life (Sterling & Eyer, 1988). High blood pressure and other pathology was linked to social disruption by a brain-body interaction. Using the arousal/stress continuum as their physiological framework, Sterling and Eyer argued that homeostasis was not adequate to explain such brain-body interactions, and the concept of allostasis has several unique characteristics that lends itself to more explanatory power. These characteristics include a continuous reevaluation of the organism's need and continuous readjustments to new set points, depending on demand. Allostasis can anticipate altered need and the system can make adjustments in advance. Allostatic systems also were hypothesized to use past experience to anticipate demand (Sterling & Eyer, 1988).

Extended to the domains of stress and the hypothalamic pituitary axis by McEwen (1998; 2000) and anxiety disorders and central CRF by Schulkin, McEwen, and Gold (1994) the concept of allostatic load was introduced, which is the price the body pays to adapt to adverse psychosocial or physical situations (McEwen, 2000). Allostatic load represents either external demands, such as too much stress, or internal demands, such as inefficient operation of the stress hormone response system. Similar connections have been made between allostatic changes in brain stress systems and posttraumatic stress disorder and anxiety disorders (Lindy & Wilson, 2001; Schulkin et al., 1994). A positive feedback interaction between glucocorticoids and CRF in the extended amygdala was hypothesized by Schulkin and colleagues (1994) as a substrate for specific symptoms of depressed patients such as expectation of adversity or negative outcomes. They argued that the loss of predictability and loss of perceived control leads to perpetual anticipation, is mediated by CRF in the amygdala, is modulated by glucocorticoids, and as such represents a neurobiological basis for the allostatic load and pathological arousal associated with melancholic depression. This early extension of the concept

of allostasis clearly anticipated some of the observations associated with reward deficits in animal models of drug dependence.

Others similarly have argued that since depression is an established outcome of stress (and indeed, an ongoing depressive episode itself can constitute a chronic stress) that depression also fits an allostatic model (Carroll, 2002). The neuroendocrinology of human depression closely resembles that of chronic stress in the laboratory, including increased hypothalamic pituitary axis activity, reduced glucocorticoid feedback, and dysregulated diurnal rhythms or cortisol (Checkley, 1996). Reflecting back to the concept of allostatic load, there is a strong relationship between the number of depressive symptoms exhibited by subjects, and premature mortality and depression are associated with many cardiovascular risk factors (Carroll, 2002). In addition, one can reasonably see how both developmental and genetic domains can modify allostatic load that may determine vulnerability to pathology (McEwen, 2000). The challenge for future research will be to explore how the neurochemical/neurocircuitry changes associated with drug addiction, including the dysregulation of brain stress systems, extend to other mood disorders and motivational disorders that fall in the impulsive/compulsive disorder domain.

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