

The role of brain emotional systems in addictions: a neuro-evolutionary perspective and new 'self-report' animal model

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ABSTRACT

The evolutionary significance of neurochemical events in the brain has received minimal attention in the field of addiction research. Likewise, the general failure of neuroscientists to postulate how basic brain circuits might mediate emotional urges has retarded the development of scientific perspectives that could inform new inquiries into the underlying dynamics and treatment of addictions. In this paper, we revisit the argument that prototypically abused substances activate or alter specific emotional brain systems that were evolutionarily designed to signal potential increments or decrements in fitness. We then discuss two distinct emotional systems (reward seeking and separation distress) which may track different types of potential changes in fitness. Based on this evolutionarily inspired approach, we illustrate how a mammalian model of emotion (i.e. rodent ultrasonic vocalizations) may enable scientists to predict drug-related phenomena such as abuse potential, anatomical location of mediating neural substrates, and the psychological impact of withdrawal. We conclude by discussing some therapeutic and social implications of examining drug addiction processes with multiple emotional brain systems in mind.

KEYWORDS Addiction, appetitive motivation, emotion, evolution, seeking, social behavior, ultrasonic vocalizations.

INTRODUCTION

In comparison to cultural, environmental, biological and pathological accounts, evolutionary explanations for addiction have received relatively scant elaboration (Nesse & Berridge 1997). The hypothesis that addictive compounds must act on evolutionarily conserved brain substrates is supported by the simple fact that other mammals readily exhibit compulsive self-administration of the same drugs as humans (Wise 1998). The subcortical neural systems that modulate these compulsions appear to be anatomically, chemically and perhaps emotionally/motivationally conserved across mammalian species (Butler & Hodos 1996; Panksepp & Panksepp 2000). Obviously, these systems were pre-

served because they serve some critical purpose other than promoting the vigorous intake of highly purified chemical compounds recently developed by humans.

An evolutionary perspective raises novel questions about these brain systems. For instance, what functions do these systems normally subserve in mammals and, in the case of addiction, how can drug ingestion divert or even commandeer the normal functioning of these systems? Answers to these questions may bring us closer to potential remedies for some of the deleterious effects of drug addiction. In this paper we will argue that, in part, the neural substrates that are deranged by addiction normally track anticipated increases or decreases in fitness, or by animals' automatic affective responses that help pass on their genes to future generations.

At one level, of course, all evolved brain systems promote fitness either directly or indirectly. For instance, reflexes (e.g. withdrawal) allow an animal to rapidly and unthinkingly avoid stimuli that threaten physical harm (e.g. sudden loud sounds that activate startle). However, emotional feelings may establish a common fitness metric across different stimuli within a given brain, and so are more flexible. While reflexes are rigid and limited in connecting only one type of sensory stimulation with one type of behavioral output, emotional systems confer flexibility in both the interpretation of inputs and the generation of outputs. In addition, reflexes are by definition nonreflective and happen unconditionally in response to stimuli, while emotional systems are proactive (i.e. experience expectant) and can anticipate fitness-relevant stimuli. Indeed, current advances in neuroscience have revealed a variety of genetically ingrained emotional systems in subcortical regions of the brain that guide and channel the arousal and activities of higher brain systems (Panksepp 1998a).

SOME EVOLUTIONARY THESES CONCERNING ADDICTIVE URGES

Before delving into the intricacies of how drugs of abuse may affect such systems, we first lay out a conceptual path from fitness concerns to emotional changes to addictive behaviors, taking into consideration the interplay between different levels of analysis, from proximal to distal. To set the stage, let us first begin with a number of theses, some of which may seem surprising to those who do not approach the study of addiction from a neuroevolutionary theoretical viewpoint.

1. Emotional feelings signal potential increases or decreases in fitness

Although animals are obviously not consciously computing their fitness, they are aware of their feelings at some level and respond accordingly, as evidenced by their behavior. For instance, life-enhancing stimuli evoke positive feelings which promote and sustain approach behaviors, while life-threatening stimuli evoke negative feelings which encourage avoidance behaviors (Young 1959). Presumably, there are sets of brain processes that allow animals to distinguish various opportunities and threats (i.e. first-order emotional 'fitness incrementer' and 'fitness decrementer' mechanisms) from events that have no bearing on a given individual's fitness. As harbingers of potential changes in fitness, these emotional brain mechanisms might function to prioritize sensory inputs and mobilize motor outputs accordingly.

2. As a fitness-enhancing heuristic, animals strive to maximize pleasant feelings and minimize unpleasant feelings

Combining this statement with the above statement and applying the transitive property, this translates into 'animals will attempt to increase exposure to stimuli that potentially maximize fitness and decrease exposure to stimuli that potentially minimize fitness'. However, the mediating role of emotional feelings cannot be omitted from this equation. Emotional feelings act as the common hedonic metric along which everything, from apples to oranges to cocaine, can be compared. In the vernacular, this means that animals will pursue activities that promote pleasurable feelings and desist from activities that instigate aversive feelings and distress. The implication is that, if these mediating affective brain mechanisms can be triggered powerfully by stimuli that have nothing to do with fitness, animals may begin to behave as if those stimuli are more important than naturally fitness-enhancing activities such as feeding, drinking, copulating and sleeping. Nowhere is this more apparent than in the concrete example of animals who will forgo food and water to repeatedly press a bar for brain stimulation of medial forebrain areas until the point of exhaustion and, finally, death (Olds 1977).

3. If pharmacological challenges can act upon and alter emotional systems, other hedonic processes dependent on these systems (including but not limited to social relations) may suffer

Whereas 'natural' opportunities and threats stimulate emotional systems within certain physiological parameters, the efficacy of drugs to stimulate these systems is limited only by the ingenuity of biochemists who design such substances (Shulgin & Shulgin 1991). Thus, many drugs of abuse have the potential to stimulate emotional brain systems in a super-physiological manner. When emotional systems are challenged repeatedly and excessively in particular environments various obsessions and compulsions can emerge which begin to govern lives. In some cases, intensified urges emerge from neuroadaptive alterations that the presence of the drug wreaks on emotional brain systems (Berridge & Robinson 1998; White & Kalivas 1998) and in others, through aversive opponent-process counter-regulatory processes initiated by the absence of the drug (Kreek & Koob 1998). Either type of change can probably sustain motivation for drug ingestion since affective homeostasis now depends on the presence of exogenous neuroactive substances in the system. When individuals reach such neuropsychological impasses, they have become 'addicted', a process that has the classic characteristics of a regulatory disorder or a brain 'disease' (Leshner 1997).

4. Because mammals depend on kin for survival, social stimuli serve as especially powerful mammalian emotion-elicitors

The inability of young mammals to survive and thrive without parental contact has been documented richly (Harlow & Harlow 1962). In addition to subserving homeostatic housekeeping duties, emotional brain systems of mammals probably channel much of an organism's energy into keeping friends near and foes at bay. This can be seen clearly in socio-emotional behaviors that occur throughout the mammalian life-span, for example in the case of 'distress vocalizations' shown by most infant mammals which encourage social proximity and, thus, survival (Panksepp 1982, 1998a; Panksepp *et al.* 1998).

5. If adequate social bonds fail to develop, an individual may show an altered future tendency to engage emotional brain systems through other (e.g. pharmacological) means

Social bonding not only provides infant mammals with the nutrients and warmth they require to survive, but also probably has long-term effects on the functioning of an individual's emotional circuitry. For instance, emerging evidence suggests that rats (Jones *et al.* 1990) and monkeys (Higley *et al.* 1991) isolated early in life show greater sensitivity to psychostimulants and alcohol later in life, due possibly to their increased background anxiety. Conversely, in rats, early social stimulation can reduce adult stress vulnerability (Francis & Meaney 1999), which may confer protection against the development of addictions later in life. Although investigators have only begun to elucidate the neural mechanisms underlying these effects, this postulate underscores the idea that affective brain systems regulate and are regulated by the social milieu during development (Panksepp 2001). Together, these propositions indicate that an evolutionarily inspired investigation of emotional brain systems (Panksepp 1998a; Panksepp *et al.* 1998) can help us to understand how drugs become addictive, and hopefully how one can intervene in such processes. Along with other investigators (Wise 1998), we suspect that drugs of abuse 'trick' animals by causing them to associate changes in these fitness-tracking systems with arbitrary drug-related stimuli rather than species-specific fitness relevant stimuli, and thus reorient emotional brain system towards drug-seeking.

In the remainder of this paper, we highlight two of the various emotional brain systems that may play a role in drug addiction, and provide an account of how a specific mammalian model of emotional processes, namely the study of the emotionally expressive ultrasonic vocaliza-

tions of rats may help investigators to map the abuse potential of various substances. This strategy may also help us clarify how drugs functionally modify the very systems they act upon, perhaps to facilitate the 'switch processes' that govern transitions to addiction.

NEURAL SUBSTRATES OF ADDICTION

In the above arguments we implied that either potential increments in fitness or removal of decrements in fitness should generate positive feelings. However, these two types of evolutionarily salient possibilities might generate quite different types of positive feelings. Specifically, the prospect of new opportunities might generate an excited state of anticipatory eagerness, while removal of an imminent threat might promote a state of calm security and serenity. A dimensional model describing these states has been derived from studies of human self-reported affect and mood, and could potentially provide a functional bridge across animal and human literatures (see Fig. 1) (Watson & Tellegen 1985; Feldman-Barrett & Russell 1999).

Thus, in the remainder of this paper, we will discuss two related emotional brain mechanisms that probably lie at the heart of some of the most prototypical forms of drug addiction (e.g. to psychostimulants and opioids).

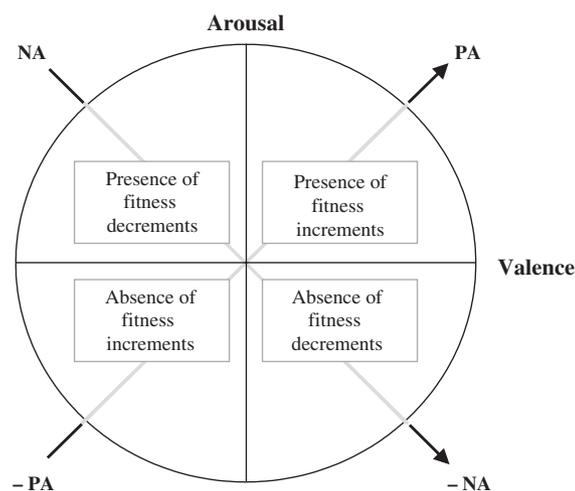


Figure 1 Mapping of fitness concerns to an affective circumplex. Potential increases in fitness create a vector moving up and to the right, which generates positive feelings (i.e. PA: positive affect) involving high arousal, while removal of potential decrements in fitness creates a vector moving down and to the right, which generates positive feelings involving low arousal. Potential decreases in fitness create a vector moving up and to the left, which generates negative feelings (i.e. NA: negative affect) involving high arousal, while removal of potential increments in fitness creates a corresponding vector moving down and to the right, which may generate different negative feelings involving low arousal

Specifically, dopamine systems may most powerfully modulate the urge to seek out life-sustaining resources and new opportunities, while opioids may play a more prominent role in modulating the pleasure we obtain from consuming those resources (Panksepp 1998a). Other emotional circuits probably also play a role in other types of addiction, including tranquilizers such as benzodiazepines and barbiturates that can markedly attenuate aversive internal states (e.g. fear) which signal potential decrements in fitness, but we will not consider those issues here.

EMOTIONAL BRAIN SYSTEMS ASSESSING INCREMENTS IN FITNESS

According to the theses stated above, some brain systems must inform an animal of potential increments in fitness. We would postulate that these systems generate phenomenology that takes the form of highly aroused positive feelings. The addictive cycle typically starts with the voluntary consumption of an artificial agent. Gradually, an overwhelming compulsive urge to consume the agent emerges, which probably involves activation of this fitness-incrementing system. Some individuals are more or less vulnerable than others because of the strengths or weaknesses of their genetic endowment (Miller *et al.* 1997), and others because of the environments in which they live (Westermeyer 1999). Although drugs can produce an enormous number of physical and psychological changes in the brain, we do not yet know what governs this transition from casual, non-compulsive drug use to sustained addictive urges. However, we do know that all forms of drug intake acquisition are slower in animals with weaker or partial damage to ascending dopamine (DA) systems, especially the mesolimbic/mesocortical systems that project from the ventral tegmental area (VTA) to the ventral striatum or nucleus accumbens (NAcc) and prefrontal cortex (Ikemoto & Panksepp 1999).

Although theorists originally conceptualized these systems as modulating the positive hedonic qualities of natural rewards (Wise & Rompre 1989), more recently there has been a growing consensus that these underlying 'reward' or 'reinforcement' systems also mediate specific adaptive behavioral sequences related to appetitive engagements with the world (Berridge & Robinson 1998; Kelley 1998; Schultz 1998; Ikemoto & Panksepp 1999). Emerging evidence suggests that ascending mesolimbic dopamine systems were designed to arouse foraging and reward-seeking on the motor side (the expectancy/seeking system of Panksepp 1982, 1998a; Ikemoto & Panksepp 1999), and increased sensitivity to reward-associated stimuli on the sensory/perceptual side (the

'incentive salience' or 'wanting' system of Robinson & Berridge 1993). These tendencies are bolstered by concomitant positive feelings associated with high appetitive arousal.

Current evidence suggests that the emotional brain system involving the VTA/NAcc pathway is most active during initiation and establishment of drug intake behavior (Wise *et al.* 1995; Ranaldi *et al.* 1999). Interestingly, rapid withdrawal from agents which most directly modulate this dopaminergic circuitry (e.g. psychostimulants such as cocaine and amphetamine) precipitates the hedonic opposite of excitement and reward-seeking behavior, namely a negative feeling state characterized by low arousal, apathy and lethargy. This observation reinforces the notion that in an attempt to compensate for supra-physiological levels of stimulation, brain processes can become unstable, fluctuating from one end of a particular hedonic continuum to the other. This dynamic underscores the fact that a given emotional system can probably indicate both increases and decreases of fitness depending on whether it has been over- or under-aroused from some homeostatic norm. Thus, our ascription of fitness 'increment' and 'decrement' roles primarily highlights what we deem to be the most likely evolutionary message when drugs directly influence a given system.

EMOTIONAL BRAIN SYSTEMS ASSESSING ABSENCE OF DECREMENTS IN FITNESS

Positive feelings can also be generated by the perception of security against potential decrements in fitness. However, these types of positive feelings may differ phenomenologically from those associated with potential increments in fitness; for example, they may be more likely to involve lower levels of arousal. For most mammals, these calming and positive feelings of security can be evoked both by the presence of a loved one or an abundance of natural resources. In line with this analogy, our past analysis of opioid systems in social processes was premised on the possibility that this system plays an important role in the development of social dependencies and attachments (Panksepp *et al.* 1980).

Opiate addiction involves three major criteria which have striking parallels to the process of forming social attachments: (1) development of an initial hedonically based attraction or liking response; (2) the gradual diminution of the active liking as one develops 'tolerance' or habituates to the drug, which sets up; and (3) the possibility of an affectively compelling withdrawal response when the drug is rapidly withdrawn (Panksepp *et al.* 1980). These parallels led us to ask whether opiate drugs

and opioid peptides are uniquely efficacious in reducing separation distress (Panksepp *et al.* 1978; Vilberg *et al.* 1984). Indeed, all opioids that stimulate mu receptors powerfully reduce indices of separation distress at very low, non-sedating doses in animal models (Panksepp *et al.* 1980). The urge to consume these compounds can also be modulated by social processes, and social processes can additionally modulate opioid dynamics in the brain (Wongwitdecha & Marsden 1996). Interestingly, these effects appear to be stronger among kin than non-kin (D'Amato 1998).

In short, the satisfactions to be derived from affiliative social bonds appear to be regulated, in part, by the same brain opioid systems that also mediate addiction to narcotics such as morphine and heroin (Keverne *et al.* 1989; Panksepp 1998a). This evidence raises the possibility that narcotic addiction operates partially through brain mechanisms which ensured mammalian social bonding over the course of evolution. This reasoning might help to explain why certain personality types are especially powerfully drawn to opioid abuse. For instance, we would anticipate that individuals who experience especially intense social distress and insecurities would be especially vulnerable to opiate abuse, and this prediction has been affirmed by some clinical research (Calsyn *et al.* 1988). Indeed, the same dynamic may help explain why opiate addictions are especially prevalent among the socially disenfranchised.

Since the emergence of the social reward hypothesis, increasing evidence has demonstrated that opioids play an important role in the elaboration of rewarding aspects of other social interactions such as sexual stimulation (Argiolas 1999) and play (Panksepp *et al.* 1985), as well in the consumption of nonsocial rewards such as tasty food (Berridge 1996). Unfortunately, the precise manner in which emotional brain mechanisms actually represent these rewarding aspects of stimuli remains largely unstudied. Such a hedonic representation might result from opioids operating in distinct circuits or in very widespread brain areas (Panksepp & Bishop 1981). There may also be substantial overlap between the opioid circuitry representing social and nonsocial rewards at low levels of the neuroaxis such as the peri-aqueductal gray (PAG), where a remarkable number of emotional brain systems converge (Panksepp 1998b). Although these opioid-modulated systems have received less experimental attention than the dopamine-modulated circuitry mentioned earlier, opponent processes precipitated by rapid withdrawal from opiates confirm our speculation that these systems confer distinct types of positive emotional phenomenology. Typically, opiate withdrawal involves highly arousing negative states (e.g. anxiety, irritability) which are the opposite of feelings of calmness and security that opioids produce, and these withdrawal effects are appar-

ently quite different from the low-arousal but negative feelings of anhedonia induced by 'crashes' which typically follow psychostimulant binges.

In terms of general reward processes, as conceptualized traditionally (Sherrington 1906; Craig 1918), these fitness-tracking systems tend to operate in a symbiotic fashion, with dopamine-modulated systems regulating approach to rewards and opioid-modulated systems regulating reward consumption (Berridge 1996; Robinson & Berridge 1993). When the systems become deranged or disconnected, strange and seemingly maladaptive behaviors emerge. For instance, rats will self-stimulate dopaminergically modulated medial forebrain areas continually to the point of death (Olds 1977). From an evolutionary point of view these animals are spurred on, even in the face of the threat of imminent bodily collapse, by the psychological prospect of continually increasing fitness. From a phenomenological point of view, we would predict that these animals experience a subjective trajectory of ever-increasing excitement or 'high'. No consummatory reward ever transpires to culminate the cycle, and so reward intake negative-feedback systems do not have the opportunity to halt the activity of the appetitive systems. Thus, the animal becomes caught in a positive feedback loop of compulsive self-administration behavior that eventually leads to death—clearly an outcome that will not enhance that individual's fitness. But such a rarefied scenario involving laboratory rats may have important implications for human drug addiction. If ingestion of certain substances can disconnect appetitive and consummatory systems, the resulting behavior could have disastrous consequences for the ingester.

We have postulated that emotional brain processes mediate the link between fitness concerns and the beginning stages of addiction in mammals. This postulate implies that if we could devise a mammalian model that discriminates between different emotional processes, we could use that model to track and predict phenomena related to addiction. For example, such a model could be used to predict the abuse potential of various compounds, and to better map the neurochemical brain substrates that support the hedonic effects of those compounds.

AN ANIMAL MODEL OF EMOTION AND ITS IMPLICATIONS FOR DRUG ADDICTION

Indeed, we have argued that an unconditioned behavior noted historically by ethologists during rodent social interactions (Sales & Pye 1974)—ultrasonic vocalizations—may be used to model emotional states in rats. We first discovered that rats make abundant amounts of a

relatively high (~55 kHz) and short (< 0.5 s) type of ultrasonic vocalization (hereafter, 50 kHz USVs) during playful interactions both with conspecifics (Knutson *et al.* 1998) as well as familiar human experimenters (Panksepp & Burgdorf 1999; Panksepp & Burgdorf 2000). Other researchers had observed these vocalizations previously in the context of other types of rewarding social interactions such as proceptive behavior prior to sexual intercourse (Barfield *et al.* 1979). Further, we found that rats make 50 kHz USVs during presentation of cues which predict the upcoming delivery of non-social rewards such as food (Burgdorf *et al.* 2000). This evidence led us to postulate that these vocalizations could index a positive and aroused emotional state akin to the appetitive excitement typically associated with reward-seeking (Knutson *et al.* 1999), much like the state that we have hypothetically associated with the perception of potential increments in fitness.

Based on these findings, we predicted that rats would make these vocalizations in locales associated with the prior administration of psychostimulants or opiates. This hypothesis was supported in empirical tests, and 50 kHz USVs turned out to provide a more sensitive index of where the rats had received these compounds than traditional place preference measures (Knutson *et al.* 1999). In line with our argument that psychostimulants and opiates induce different positive emotional states, even though places associated with the administration of both amphetamine and morphine elicited 50 kHz USVs, acute administration of amphetamine only, but not morphine, increased 50 kHz USVs (Panksepp & Burgdorf 2000).

In line with the postulates mentioned earlier, we also hypothesized that forebrain dopamine activity would modulate the likelihood that rats would make 50 kHz USVs. Accordingly, we found that cues which signaled impending electrical stimulation of dopamine-rich brain areas (such as the VTA) did indeed evoke 50 kHz USVs (Burgdorf *et al.* 2000) (see Fig. 2). As summarized in that paper, similar vocalization patterns are also evoked by cues for 'natural' rewards (i.e. food, play, sex) as well as drugs of abuse. These findings suggest that 50-kHz USVs index anticipatory positive affect and reward-seeking behavior, and thus may model an affective component of drug craving in human addicts. Moreover, injection of dopamine agonists into the nucleus accumbens powerfully and dose-dependently evoked this vocalization, and this effect could not be accounted for by general increases in activity (Burgdorf *et al.* 2001a). Accordingly, other investigators have also documented that glutamate administration to the dopamine-modulated preoptic region of the hypothalamus (which plays a prominent role in the generation of sexual appetitive behavior) also unconditionally elicits 50 kHz USVs (Fu & Brudzynski 1994), and this effect is mediated by dopaminergic neu-

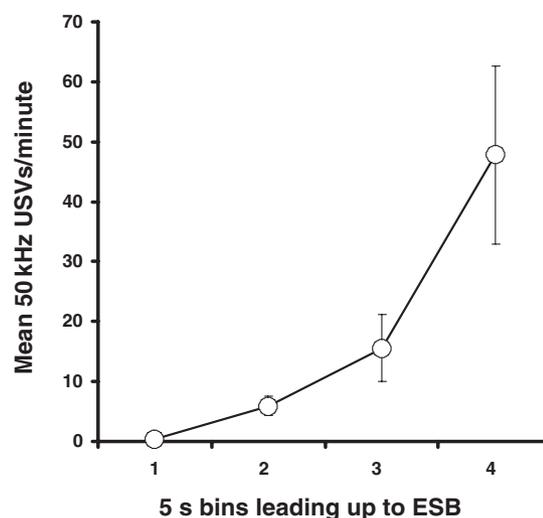


Figure 2 50 kHz USVs in 5 s bins leading up to rewarding electrical stimulation of the brain (ESB) of the lateral hypothalamus delivered on a fixed interval 20 s schedule (data abstracted from Burgdorf, Knutson & Panksepp 2000; please note that Fig. 1 of that paper is for the first day of testing, and the data for this figure are previously unpublished data from the 4th day of testing)

rotransmission (Wintink & Brudzynski 2001). Taken together, this evidence suggests that the 50 kHz USV may be used as an index for the abuse potential of various compounds in rats, as well as a means of mapping brain circuitry which generates emotional states involving high arousal and positive valence.

Fifty kHz USVs can be distinguished from a longer (>0.5 s) and lower-frequency (~22 kHz) type of ultrasonic vocalization (hereafter, 22 kHz USVs). Rats readily make 22 kHz USVs in the context of aversive social interactions such as defeat during fighting (Thomas *et al.* 1983), in the presence of predators (Blanchard *et al.* 1991) and during presentation of cues which signal non-social punishments such as footshock (Tonoue *et al.* 1986). These vocalizations may derive ontogenetically from early 40 kHz distress calls that infant rats make during social separation (Blumberg & Alberts 1991). According to the postulates outlined earlier, this evidence indicated to us that 22 kHz USVs might model an aroused but negative emotional state in rats, much like the state related to the perception of impending decrements in fitness (Miczek *et al.* 1995).

In line with this reasoning, we observed that rats make increased 22 kHz USVs in locales where they had previously received aversive compounds such as naltrexone or lithium chloride (Burgdorf *et al.* 2001b). Indeed, the brain circuits in which electrical stimulation unconditionally elicits these 22 kHz USVs in anaesthetized rats include areas rich in mu opiate receptors such as the periaqueductal gray (Yajima *et al.* 1980; Depaulis *et al.* 1992). Finally, other investigators have reported that

withdrawal from opiates potently increases spontaneous 22 kHz USVs in rats (Vivian & Miczek 1991). Thus, 22 kHz USVs seem to play a complementary role to 50 kHz USVs in rats, providing a model of highly aroused but negative emotional states which may track potential fitness decrements.

Although this research is at an early stage, rat ultrasonic vocalizations may provide an especially powerful model for analyzing how emotional brain systems change during transitions to addiction. For instance, we would predict that as an animal becomes addicted to a drug to the point where it supersedes other rewards in perceived value, investigators might observe a sudden elevation in 50 kHz USV production during presentation of cues that predict drug availability. Additionally, a close analysis of the underlying emotional circuits that modulate these vocalizations may provide a view as to where and how in the brain drug cravings are intensified. We would predict that drug-cue-evoked 50 kHz USVs might also index prior sensitization to drugs of abuse, a phenomenon which has been especially well-studied in the case of psychostimulants (Kalivas 1995; Berridge & Robinson 1998).

These findings also affirm our hypotheses that certain drug addictions and social interactions utilize some of the same neural circuits. In the case of mammals, certain aspects of drug addiction may be mediated by brain systems that were designed in evolution to help facilitate social interaction. Since rats' ultrasonic vocalizations emerge spontaneously and are relatively stereotyped, they may provide a remarkably easily studied index of internal affective states. Indeed, from a certain vantage, such vocalizations may be deemed to be emotional 'self-reports' even though we would not ascribe any communicative 'intentionality' to them. Accordingly, we assume provisionally that the intensity of certain emotional states is encoded in the frequency and intensity of rats' vocal output. Because vocalizations require little energy to produce and serve the function of communicating affective states to other members of social networks (e.g. in order to coordinate social activities), they may provide especially sensitive 'readouts' of the status of brain emotional circuits which are relevant to drug addiction. Tracking the precise manner in which addictive compounds can commandeer these circuits promises to write an exciting chapter in an evolutionarily informed psychopharmacology of drug abuse.

The generalizability of this model to other mammalian species remains to be evaluated, but preliminary primate data suggests that they also show specific types of vocalizations when anticipating rewards (Weerts *et al.* 1998). While we might predict that most mammalian species (including humans) express affect, their species-specific displays need not be vocal. The extent to which social contexts modulate the expression of these affective

displays also deserves further exploration, but we have observed both 50 and 22 kHz vocalizations in non-social situations to index putative affective responses (Vivian & Miczek 1991; Knutson *et al.* 1999; Burgdorf *et al.* 2000).

ISSUES REGARDING THE ASSESSMENT OF HUMAN EMOTION

Although the study of emotion has traditionally received more research support in the human realm, the increased cognitive sophistication of humans relative to rats poses certain problems for scientists who would hope to utilize emotional indices to predict addiction-related phenomena. Some literature on samples of drug addicts indicates that emotional self-report does not necessarily predict self-administration behavior. For instance, addicts will self-administer very low doses of addictive compounds (e.g. cocaine and morphine) from dilute experimental sources that they claim generate no feelings at all (Fischman & Foltin 1992; Lamb *et al.* 1991). But we would argue, along with others, that emotional brain mechanisms do not have to pass the threshold of conscious reflection in order to influence behavior (LeDoux 2000). In fact, highly reflective organisms that always think before acting would probably not have a high probability of representing their genes in future generations. There are also many emotional indices in humans besides verbal self-report which are less subject to voluntary control, and researchers have only begun to explore whether these measures might predict addiction-related phenomena such as self-administration or relapse. Examples include non-verbal behaviors such as facial and vocal expression (Scherer 1986; Ekman 1993), as well as psychophysiological indices such as skin conductance and emotion-potentiated startle (Stritzke *et al.* 1995).

Even if the activity of emotional brain circuits can guide behavior in the absence of conscious awareness, we would still posit that more intense activation of these systems provides the necessary conditions or 'seeds' for self-reported emotional experience in humans. Once an experience becomes intense enough to pass a certain threshold of awareness, it may then become available to reflection and verbal self-report. Many different criteria might determine the levels of such thresholds of awareness, especially with respect to pharmacological challenges. Factors related to familiarity with the compound in question may play a role. For example, with weak sources of psychoactive cannabinoids, inexperienced users often report no clear psychological effects, and only gradually do they become attentive of the 'high' that is produced by the drug (Weil & Zinberg 1986). Also the novelty of the environment in which the drug is admin-

istered (e.g. an experimental laboratory) may consume attentional capacities which might otherwise be directed towards assessing internal states. Finally, the very effects of drug addiction might compromise the link between emotional mechanisms and reflective capacity, or addiction may draw recruits who have impaired reflective capacity to begin with (Iacono *et al.* 1999). Fortunately, all of these issues can and hopefully will be assessed empirically in the near future.

THERAPEUTIC IMPLICATIONS

In addition to pointing towards novel research avenues to explore, a theoretical approach based on the evolutionary function of emotional brain systems has implications for the treatment of addictions. For instance, accumulating evidence suggests that drug administration does not only activate emotional brain systems, but also may alter them in long-lasting ways. The bulk of current research has focused on dopaminergic forebrain circuitry. The neural changes that drug use can instigate in dopaminergic systems include decreases in dopamine cell size (Sklair-Tavron *et al.* 1996), a chronic increase in the sensitivity of the postsynaptic dopamine receptors known as 'sensitization' (Kalivas 1995; Berridge & Robinson 1998) and various changes in the sensitivity of presynaptic dopamine receptor sites (Self & Nestler 1995; Self 1998). Alterations in intracellular first, second and third messenger cascades observed in postsynaptic neurons represent especially provocative targets for therapeutic interventions (Self & Nestler 1995; Self 1998).

Although no one would claim that we are close to developing a pharmacological cure for drug addiction, the abundance of emerging molecular data is generating unprecedented optimism that such interventions shall one day enter the realm of possibility. Candidates range from endogenously produced dopamine antagonists as well as partial agonists (Kreek 1996; Romach *et al.* 1999) to externally provoked immunization against dopamine agonism (Mets *et al.* 1998). However, according to evolutionary considerations outlined previously, agents which directly antagonize dopamine should have antihedonic effects (Brauer & de Wit 1996), so we may expect difficulties with such targeted pharmacological regimens in terms of ensuring compliance from patients.

As implied by our distinction between dopamine- and opioid-modulated fitness tracking systems, additional therapeutic targets for antiaddictive drugs may be found among other systems that reduce feelings associated with decrements in fitness. A large number of agents have been discovered that modulate emotions such as separation distress which signal potential fitness decrements (Panksepp *et al.* 1988; Panksepp 1993). Relevant thera-

peutic compounds might include oxytocin agonists, prolactin agonists, nicotinic cholinergic agonists and alpha-1 noradrenergic agonists (e.g. clonidine)—all of which have been found to robustly and specifically modulate separation-distress in animal models (Panksepp 1998a; Panksepp *et al.* 1998). These agents may provide relief from the distress that arises from opioid withdrawal either alone or in combination. Indeed, clonidine has already served such a role in clinical practice (Gold 1993), an effect that is concordant with the relevant animal data (Rossi *et al.* 1983). Along similar lines, oxytocin has been found to reduce the development of tolerance to opioids (Sarnyai & Kovacs 1994), raising the possibility that oxytocin served the evolutionary function of sustaining the efficacy of opioid reward in young animals. Thus, oxytocin may help forestall the rapid habituation to social reward commonly associated with adolescence, and thus promote and prolong bonding processes necessary for infant survival.

We believe that the present focus on emotional brain systems may clarify a number of drug-related phenomenological issues. First, people may take different drugs in the service of inducing distinct affective experiences, and even though different drugs may eventually lead to addictive self-administration behaviors, they may do so by initially acting on quite different emotional brain systems. Secondly, even over the course of addiction to the same drug, a number of different emotional brain systems may come into play during self-administration, maintenance and withdrawal. Thirdly, phenomenological constructs that are often considered to be unitary in the drug literature (e.g. 'craving') may be profitably deconstructed and operationalized using a multiple emotion systems approach (Stritzke *et al.* 1996). As most investigators now realize, such possibilities imply that no one 'magic bullet' pharmacotherapy will address all types or stages of drug addiction. All habit forming compounds probably do not affect the same emotional brain systems, and thus should not induce the same kinds of hedonic experiences.

SOCIAL IMPLICATIONS

If drug administration can have a lasting impact on emotional brain systems, it will be interesting to observe how these alterations may affect the social tendencies of mammals over the course of development, and to what extent social variables can modulate addictive tendencies. For instance, at present there has been an increasing tendency to treat early childhood impulse control problems with psychostimulants. To some extent, such 'disorders' may index the build-up of playful energies in the nervous system (Panksepp 1998a), which become especially highly manifested if the frontal lobes are slow

to mature (Castellanos *et al.* 1996). Furthermore, psychostimulants are remarkably effective in reducing playful tendencies in animals (Beatty *et al.* 1982), which may provide one reason that such potentially addictive drugs can reduce attention deficit/hyperactivity disorder (ADHD) symptoms. These early experiences with psychostimulants may account partially for the higher incidence of drug abuse later in life of ADHD individuals. The critical scientific issue may not be how much drugs such individuals consume, but how much they desire, and how addictive, in a broad sense, their life-styles have become. There is evidence that chronic administration of psychostimulants may change the personality of animals (Nocjar & Panksepp 2002) These observations highlight a need for targeted preclinical research investigating the long-term effects of psychostimulants on the developing brain (particularly the frontal lobes) and behavior.

The idea that both drug addiction and social processes may enlist common emotional brain systems raises many questions about how social dynamics might play an important role in both facilitating and discouraging drug addiction. For instance, to what extent are adolescents drawn to drugs because of changing social dynamics over the course of development? To what extent can we ameliorate such urges by providing more supportive social structures in which the basic urges for a rich social life can be fulfilled? Might pharmacological curiosities such as 'placebo effects' reflect ways in which our emotional brain systems respond to socially supportive circumstances? Might a deep sense of spirituality, which is an effective mode of drug rehabilitation characteristic of 12-Step programs, also operate through basic emotional circuits of the brain? In this context it is noteworthy that individual differences in spirituality, like other emotional tendencies, do have genetic components (Waller *et al.* 1990). These are questions that investigators have barely started to address in empirically viable ways. We hope that some of the ideas we have outlined will stimulate conceptual linkages and empirical research that may yield credible answers to these questions. We also hope the evolutionary approaches which fully respect the deep emotional and motivational homologies which exist across species will become an increasingly influential way to think about both human and animal nature (Panksepp & Panksepp 2000).

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