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Review

Affective neuroscientific and neuropsychoanalytic approaches to two intractable psychiatric problems: Why depression feels so bad and what addicts really want

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ABSTRACT

The affective foundations of depression and addictions are discussed from a cross-species – animal to human – perspective of translational psychiatric research. Depression is hypothesized to arise from an evolutionarily conserved mechanism to terminate protracted activation of separation-distress (PANIC/GRIEF) systems of the brain, a shutdown mechanism which may be in part mediated by down-regulation of dopamine based reward-SEEKING resources. This shutdown of the brain's core motivational machinery is organized by shifts in multiple peptide systems, particularly increased dynorphin (kappa opioids). Addictions are conceived to be primarily mediated by obsessive behaviors sustained by reward-SEEKING circuits in the case of psychostimulant abuse, and also powerful consummatory-PLEASURE responses in the case of opioid abuse, which in turn capture SEEKING circuits. Both forms of addiction, as well as others, eventually deplete reward-SEEKING resources, leading to a state of dysphoria which can only temporarily be reversed by drugs of abuse, thereby promoting a negative affect that sustains addictive cycles. In other words, the opponent affective process – the dysphoria of diminished SEEKING resources – that can be aroused by sustained over-arousal of separation-distress (PANIC/GRIEF) as well as direct pharmacological over-stimulation and depletion of SEEKING resources, may be a common denominator for the genesis of both depression and addiction. Envisioning the foundation of such psychiatric problems as being in imbalances of the basic mammalian emotional systems that engender prototype affective states may provide more robust translational research strategies, coordinated with, rather than simply focusing on, the underlying molecular dynamics. Emotional vocalizations might be one of the best ways to monitor the underlying affective dynamics in commonly used rodent models of psychiatric disorders.

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The affective neuroscience approach advocated by Panksepp (1998) makes two key assumptions which allow us to tackle important and difficult questions in psychology in novel and productive ways. These two assumptions are that, first, emotions evolved to *do* something specific in relation to biologically significant and

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life-challenging situations. They are not mere epiphenomena. And second, that the *felt* aspects of emotions – specific kinds of affect – serve a central purpose: namely to motivate the organism to promote its survival and reproductive success. We suggest here that a research strategy based on the dual-aspect monist position of affective neuroscience – to the effect that brain and mind concepts are merely two different perspectives on the same fundamental processes (Panksepp, 2005b; Solms and Turnbull, 2002) – can help cognitive neuroscience, biological psychiatry and related fields weave together the diverse yet still poorly integrated wealth of psychobiological findings that have emerged in recent decades, regarding healthy affective functioning – emotional well-being (Panksepp, in press) – and the specific derangements of psychopathology, including drug addictions (Panksepp, 2010) and depression (Panksepp and Watt, in press; Watt and Panksepp, 2009) that will be specifically discussed here. It can do so by revealing the biologically significant situations that the various basic emotion command systems of the brain are designed to manage, in relation to the specific emotional feelings that they were evolutionarily designed to generate (Panksepp, 1991, 2005a).

We have argued elsewhere (Panksepp, 2010; Solms and Panksepp, 2010) that neuroscience approaches which marginalize felt subjective experiences can lead us down blind alleys. Here we take two cardinal examples – two very commonplace and yet still puzzling clinical conditions, depression and addiction – to illustrate how knowledge of the basic emotion command systems that mediate these conditions provide a more comprehensive and parsimonious understanding of them. Too much of modern behavioral neuroscience has tried to leap from brain molecules and similar mechanisms directly to the behavioral facts of addiction and depression without adequately considering conserved emotional mammalian brain systems in the middle. We believe that the basic emotion command systems now called SEEKING and PANIC (or GRIEF), to maintain clarity about primary-process emotional networks, underlie the pivotal dynamics of both depression and addiction (which often overlap clinically [Kendler et al., 2003]).

1. SEEKING and PLEASURE

As has been extensively reviewed elsewhere (see, for example, Alcaro et al., 2007; Ikemoto and Panksepp, 1999; Panksepp, 1998; Berridge, 2003; Ikemoto, 2007, 2010), the SEEKING system is regulated by a number of neurochemistries, centrally by dopamine, but also by acetylcholine, GABA, glutamate, serotonin, opioids, orexin, and multiple other peptides. Panksepp (1981, 1982) was the first to fully conceptualize that artificial stimulation of this motivational system does not generate pleasurable feelings and blissful satiation in mammals – as the *consummation* of a need might be expected to – but rather impels the animal to excitedly *seek more of the stimulation* (in other words, rewarding brain stimulation along the MFB actually increases the *appetitive* drive that leads us to rewards, rather than the sensory-consummatory pleasure that indicates that valuable resources have been obtained by the body). This and subsequent research led Panksepp and his students to conceptualize the mesolimbic DA trajectory – normally termed a 'reward' system – as a SEEKING/EXPECTANCY system (Panksepp, 1982, 1998; capitals in the original). Berridge and Robinson (1998) subsequently drew a similar distinction between 'wanting' and 'liking'.

The SEEKING system motivates animals to engage with the world – to eagerly forage, curiously explore, and optimistically expect – in short, to turn to the outside world for attaining pleasurable experiences. The SEEKING system, while tonically active, is particularly stimulated internally by medial hypothalamic 'need detector' mechanisms, and externally by enticing opportunities in the world. And when it is activated, it impels the animal to engage with the real objects that satisfy our inner needs (thus matching needs with opportunities). We therefore suggest that healthy activity of the SEEKING system (e.g., optimal tonic levels of DA and appropriate phasic responses of the system to the presence or possibility of rewards), leads to a feeling of engagement, expectancy and agency, all of which are intrinsically positive. Conversely, the down-regulation of this system can be associated with feelings of emptiness, 'deadness', and lack of hope and interest. Such a perspective provides a contrasting view to the abundant "psychology-free" language that has been used to discuss this key brain emotional system in much of behavioral neuroscience.

As has also been reviewed extensively elsewhere (Panksepp, 1998), a PLEASURE (sensory reward) system, with mu opioids as a key neurotransmitter, is thought to mediate the hedonic, consummatory aspects of numerous rewards, including sex and food (Kelley and Berridge, 2002; Peciña et al., 2006). Thus, pleasurable experiences are generated via PLEASURE (and other) systems, which utilize the SEEKING system for their hedonic ends, but consummatory pleasures are not mediated primarily by DA. A specific kind of pleasure arises with social contact and strong attachment bonds, which is also thought to be mediated by opioids, as well as other neuropeptides (Insel and Young, 2001; Panksepp, 1998). Through the action of this system, being close to significant others leads to feelings of comfort, security, and pleasure.

These very ancient brain molecules, which are thought to have evolved in the brain initially for their analgesic and other strictly homeostatic properties, additionally came to serve *social* properties. Levels of these peptides signaled to the organism whether the organism was socially connected or not, with social pain (separation distress) signaling low levels of these critical opioids (Panksepp, 1998). This latter affective mechanism – which Panksepp calls the PANIC–GRIEF system – is especially highly developed in mammals, which are exquisitely social animals. It is also present in birds. This system has its epicenter in a neuronal network that courses between the anterior cingulate gyrus, various basal forebrain and diencephalic nuclei, and the dorsal periaqueductal grey. When social attachment bonds are broken through separation or loss, these brain mechanisms make the sufferer "feel bad" in a particular way. This special type of social pain is traditionally termed 'separation distress', and is most readily identified in animal models by distress vocalizations (Panksepp, 1998).

Bowlby (1980) classically described this behavioral phenotype as 'protest' behavior. The biological value of this type of pain is that it motivates the sufferer to seek reunion with the lost object, to draw the attention of the caregiver who may be looking for the lost infant, and to avoid prolonged separation in general. However, if reunion fails to materialize, then a second mechanism kicks in, which shuts down the distress and causes the lost individual to *give up*, preserving one's energy and staying in one place to maximize the chance of being found and surviving. This 'giving up' has been termed the 'despair' phase of social loss (Bowlby, 1980; Panksepp et al., 1991). *This sequence from protest to despair provides a powerful animal model for human clinical depressions*. The details of the neurochemistries and dynamics of this process have been extensively reviewed elsewhere (Watt and Panksepp, 2009). Separation distress as a prototypic mammalian affective state may of course also give rise to important cognitive (tertiary-process) extensions in humans that probably do not exist in animals, such as guilt, shame, and feelings of desertion, rejection, or abandonment, all of which require complex cognitive processing interacting with this prototype emotional state.

2. The affective neuroscience model of depression

Given these starting points, we think it is tremendously productive to consider *why depression feels bad*. This fundamental problem curiously has not been addressed in psychiatry, at least not in an

explicit fashion. One must unfortunately conclude from this that what depression *feels* like does not matter much in contemporary psychiatric science; instead, what appears to matter most to contemporary behavioral neuroscience researchers are the physical *correlates* and *causes* of depressive behaviors in preclinical animal models. Psychiatric research has in recent decades focused on a number of neuromodulatory systems whose activities correlate with, or appear to facilitate depression, including (but not limited to) possible down-regulation of norepinephrine and serotonin systems, overactivity in the cholinergic system, dysregulation of basic stress cascades, perhaps in part due to elevated inflammatory signaling, decreased mu opioid and oxytocin signaling, decreased neurotrophin signaling, and down-regulated dopaminergic signaling, perhaps associated with increased kappa opioids (dynorphin) (see, for example, Schildkraut, 1965; Harro and Oreland, 2001; McEwen, 2007; Knoll and Carlezon, 2010).

Certainly there are good reasons for pursuing these lines of inquiry, including the antidepressant actions of selective serotonin reuptake inhibitors (SSRIs), which initially suggested a possible dysregulation in serotonin systems as etiologic in depression (although recent evidence suggests that downstream effects on neural growth factors and other processes may better account for their modest antidepressant actions [see Berton and Nestler, 2006 for review]). Additionally, the fundamental participation of a dysregulated HPA axis in depression (McEwen, 2004) and the abundant evidence suggesting fundamental linkages between early life stress and depressive vulnerability (Heim et al., 2004) can lead us in a more productive direction, away from the early monocular focus on serotonin and norepinephrine in depression research. Serotonin, after all, is an all-purpose modulator of moods and emotions, not only of depressive ones (Berger et al., 2009). It is probably for this reason that SSRIs are used to treat not only depression but also a host of other forms of emotion dysregulation, such as panic attacks and obsessive–compulsive disorder. However, the failure of SSRIs and selective norepinephrine reuptake inhibitors (SNRIs) to immediately or directly affect the primary affective modulator systems may be a cardinal reason why they are either not effective at all, or minimally effective, in so many cases of depression (Warden et al., 2007).

In terms of understanding the causes and basic mechanisms of depression, the field is still largely in the preliminary stages. Fundamental issues remain to be considered. We think it will be productive to shift our focus to the *clinical phenomenology* of depression. Depression is characterized above all else by a complex of *feelings*, centrally featuring low self-esteem, loss of motivation, low energy, a basic hopelessness, and loss of capacity to experience pleasure in relation to virtually every type of reward. We suggest that a point of departure for making parsimonious sense of this complex of feelings is indicated by an exclusion criterion offered in the DSM IV definition of major depression:

"The symptoms are not better accounted for by bereavement".

This differential diagnostic criterion arises from a psychiatric tradition that emerged at the turn of the last century (based on more than 2000 years of folk psychology and medical thinking) that recognized a deep continuity between the symptomatology of grief and that of depression (for an excellent review of this history, see Horwitz and Wakefield, 2007). Freud (1917) drew the connection clearly for several generations of psychoanalysts and psychiatrists by considering melancholia (depression) as a pathological descendent of mourning. Notably, Freud said that in mourning the external world is impoverished, while in depression the ego is impoverished. However, with the revolution in biological treatments for depression, this distinction has been progressively overlooked (Horwitz and Wakefield, 2007), and we believe that our attention should be refocused on the deep relation between depression and the actual brain mechanisms by which feelings of social loss are encoded, since the "despair" phase of separation is the normal affective state that most closely resembles clinical depression (Harris, 1989).

Indeed, supporting the long-standing psychoanalytic correlation of depression with loss, it is well established today that early separation experiences do indeed predispose to depression (Heim and Nemeroff, 1999; Pryce et al., 2005), possibly through epigenetic changes in classic stress cascades that McEwen and colleagues (e.g., McEwen, 2007) have identified, and possibly also via other 'pro-inflammatory' mechanisms (Hennessy et al., 2001). We also know that a first depressive episode is most commonly triggered by social loss (with a large literature extending from Bowlby, 1980 to Watt and Panksepp, 2009).

So why does depression feel bad? It feels bad, in terms of our basic hypothesis (fully developed by Watt and Panksepp, 2009, which can be consulted for a fuller review of relevant literature), because the protest phase of the separation response (PANIC–GRIEF) feels bad for the reasons already described, as does the despair phase characterized by shutdown of the SEEKING system. In other words, it seems reasonable to hypothesize that the core brain basis of depression revolves around the process by which separation distress is normally shut down (possibly by primary effects of kappa-opioids on VTA output, with this process intimately hinged to protracted stress cascades [Shirayama et al., 2004; Nestler and Carlezon, 2006; Land et al., 2008; Knoll and Carlezon, 2010]). Such basic effects on the SEEKING system lead animals and humans to fundamentally 'give up' in relation to all kinds of potential biological goals. Given the range of experimental effects of kappa agonists (see, for example, Bals-Kubik et al., 1989; Bruchas et al., 2010; Bruijnzeel, 2009; Greenwald et al., 1997; King et al., 1999; Margolis et al., 2003; Todtenkopf et al., 2004), we hypothesize that in this condition, the organism is in a quasi-analgesic state (a form of numbness), lowered SEEKING energy, and impaired hedonic tone in the worst cases which are the hallmark features of depression. This state may be induced by actual loss, or may be arrived at via different pathways (e.g., Parkinson's disease or other conditions), but they all culminate in the same constellation of neurodynamics and hence the same subjective experience.

The question remains as to why some people respond to loss with healthy grieving and others succumb to depression. This of course is a fundamentally unresolved problem for the field, but a partial answer may rest in the extent to which a current loss (including loss of social status as opposed to classic 'object' loss) recapitulates or resonates with unresolved early losses, or may be particularly penetrating and hurtful, underlining in some basic way the individual's helplessness and powerlessness. Potent examples of this category of loss obviously include early maternal losses for young children and infants, losses of one's own children as a young parent, and losses late in life of a deeply beloved partner. These are intrinsically profound losses, where separation distress is particularly protracted and intense, and where a sense of comfort and repair of the loss is especially hard to achieve (at times, impossible). These kinds of losses are almost universally depressogenic, at least mildly, for almost everyone including the most resilient individuals. On the other hand, in those lacking 'emotional resilience' (perhaps simply another way of talking about vulnerability to stress and depression), even minimal losses and a wide variety of stresses can be potently depressogenic. Given the human capacity for *symbolic* losses and separations, some cases of depression may not be associated with any overt, observable loss at all. Thus, one could argue that each instance of depression reflects an intersection between the degree of vulnerability on a 'resilience vector' and the degree of severity on a 'stressor vector'.

To avoid misunderstanding, we will state our hypotheses as simply and unambiguously as possible. (1) The constellation of feelings that we call 'depression' *mean* something. They mean that the

Table 1
Neurobiological factors forming an interactive depressive matrix.

Depressive factor	Driven by	Producing	Behavioral and symptomatic correlates
Increased CRF, hypercortisolemia, cholecystokinin and reduced BDNF	Multifactorial limbic influences on paraventricular nucleus promoting activation of HPA stress axis.	Increased dynorphin, decreased 5-HT, reduced neuroplasticity/HC atrophy. Intensification of separation distress. Disrupted ventral HC feedback on core affective regions.	Dysphoria, sleep and appetite loss. Reduced short-term memory, and other cognitive deficits.
Increased acetylcholine	Reduction of social and other rewards, declining opioid tone, and any other social punishment.	Facilitation of separation distress circuitry and other negative emotions. Effects on other core variables.	Negative affect and excess attention to negativistic perceptions and thoughts.
Decreased mu opioids and oxytocin	Separation distress, other stressors, including physical illness and pain.	Disinhibition/release of stress cascades; decreased 5-HT and DA; overdriven NE. Promotion of pro-inflammatory cytokine generation.	Anhedonia and sadness, reduced positive affect and reduced sense of connection. Suicidality.
Increased dynorphin in accumbens/VTA	Stress cascades.	Down regulation of VTA and mesolimbic DA system.	Anhedonia, dysphoria, loss of motivation.
Increased pro-inflammatory cytokines	Acute but probably not chronic stress, acute reduction of opioids.	Promotion of stress cascades, decreased serotonergic and increased glutamatergic tone. Impairment of HPA axis negative feeback.	Fatigue, malaise and appetitive losses. Increased cognitive disruption. Anhedonia.
Reduced serotonergic drive/vulnerability	Stress, increased corticosteroids, cytokines, decreased mu opioids.	Lowered dopaminergic and increased noradrenergic drive. Less functional segregation among brain systems.	Poor affective regulation. Impulsivity. Obsessive thought, suicidality.
Diminished catecholaminergic (DA and NE) tone	Constitutional vulnerability, stress and poor reward availability.	Reduced "signal-to-noise" processing in all sensory-perceptual and motor/executive systems.	Fatigue, diminished psychic "energy": appetitive sluggishness, dysphoria. Impaired coordination of cognitive and emotional information processing.

animal has given up normal pursuits and rewards and has behaviorally shutdown. (2) 'Despair' normally follows (and shuts down) 'protest', also known as 'separation distress'. (3) Separation distress is mediated in part by glutamatergic drive (see Normansell and Panksepp, this issue), and soothed by mu opioid and oxytocin mechanisms, but during the period of active protest, all behavioral indicators, especially the hyperactive agitation, suggest that this emotion has aroused DA-mediated SEEKING urges (i.e., attempts at reunion). (4) Despair is mediated, in part, by kappa opioid mechanisms, which shut down SEEKING through accumbens feedback on VTA. (5) This sequence is activated in normal bereavement (a feeling of loss, which, despite protest, is not followed by reunion). Pathological (excessive, unwarranted or maladaptive) engagement of this mechanism is called depression.

From this set of basic hypotheses, new avenues for treatment could emerge from an understanding of what can prevent, reverse or relieve this shutdown. Because the separation distress system is regulated by the hormonal and neuropeptide releases that precede childbirth and facilitate maternal care (e.g., opioids, oxytocin, and prolactin), and we have known for a long time that the same opioids that regulate the brain's separation/attachment responses have powerful anti-depressant properties (Bodkin et al., 1995), these neurochemistries should continue to be explored, with the addictive risks of opiates being taken into account. The fact that this is a very modest risk in the case of buprenorphine, since it is a mixed agonist–antagonist, that loses opioid activation properties at higher doses, makes it a potentially strong candidate agent for rapid treatment of depression, although a properly blinded trial has never been done, because of the association of the drug with addiction (Bodkin et al., 1995).

Fully understanding the contribution of different components of the distress/despair shutdown cascade may also help us understand the neural substrates of the various depressive subtypes. For example, dynorphin-facilitated shutdown of dopamine-driven appetitive systems (when an individual 'gives up' in despair) may form an independent etiological mechanism in a subset of cases where the loss of motivation features most prominently; a sensitized HPA axis (with amygdala sensitization) might correlate with depression with anxiety; and so on. We think this line of research (Mague et al., 2003; Knoll and Carlezon, 2010) is a particularly productive one for developing new biological treatments. Indeed, buprenorphine is currently the only approved available medicine (for opiate addiction detoxification) that has such desirable kappa-antagonist properties. Moreover, understanding the basic mechanisms of depression gives us a framework for identifying the unquestionably highly polymorphic genetic and environmental factors that predispose individuals to depression, as well as the basis of efficacy for non-pharmacological interventions such as psychotherapy and exercise, both of which promote positive feelings, psychotherapy perhaps in large part because of the creation of a supportive-empathic social environment. Table 1, derived from the summary by Watt and Panksepp (2009) underlines what we currently understand about the matrix of biological factors implicated in depression, and also outlines how interactive these factors may be. This in turn suggests a much more pluralistic concept of the fundamental neurobiology of depression than is suggested by the 'single factor' theories that have dominated the field of psychiatry since the first work on depression.

We suggest, in harmony with the psychoanalytic perspective that emphasizes a dynamic relation between the various components of the mind, that relations between these factors play important roles not only in depression but also in 'co-morbid' conditions such as addiction, panic disorder and obsessive–compulsive disorder (which seems to revolve more around PANIC/GRIEF networks than FEAR/anxiety) (Panksepp, 2006). As we have suggested elsewhere (Watt and Panksepp, 2009; Solms and Panksepp, 2010), sustained activation of the PANIC system can lead to shutdown, down-regulation or dysregulation of the SEEKING system, which we suggest are key components of depression, addiction and OCD respectively. Specifically in relation to depression, the down-regulation of the mesolimbic/mesocortical DA system may be associated with increased dynorphin signaling. Similarly, dysregulation of the PLEASURE and/or SEEKING systems can predispose to some forms of addiction. While our perspective allows for the magnification of 'incentive-salience' pursuant to the use of drugs of abuse (Berridge and Robinson, 1998; Volkow and Li, 2004; Volkow et al., 2007), we suggest that a primary deficit or dysregulation in one or both of the above emotional systems that we implicate in depression is a more fundamental problem in addiction.

3. The affective neuroscience model of addiction

Interestingly, Freud (1898) called masturbation a "primal addiction," that may serve as a substitute for mature sexual relations. We suggest that this perhaps surprising parallel highlights the central phenomenon of addiction – namely that substance abuse is a rewarding activity that generates positive affects (and reduces negative ones; for full discussion of this 'opponent process', see Khantzian, 2003; Koob and Le Moal, 2001) although it does not sustain reproductive fitness. More specifically, substance abuse employs brain mechanisms that generate specific kinds of positive affects, and not necessarily just ones that reflect pleasurable consummatory activities (such as those arising from feeding, copulation or other social activities [Avena et al., 2008; Panksepp, 1982]), and thus motivate animals to perform the work that is necessary to achieve them.

The difficulty is that drugs of abuse allow appetitive reward and consummatory reward systems to be stimulated artificially, generating positive affect without the natural effortful and competent behavior patterns that typically mediate the acquisition of rewards. In substance abuse, users progressively choose these artificial rewards over natural ones. The motivation to perform the effortful work to achieve biologically useful goals in an indifferent and even hostile world is thereby substituted by mere self-administration of pleasure-producing (or unpleasure-reducing) substances. Thus affective considerations are of critical importance in understanding the various forms of drug abuse, which often operate through unique affective processes as well as typically shared ones, such as mesolimbic dopamine activity (Koob and Le Moal, 2001; Wise, 1998; Robinson and Berridge, 2000, 2003). Here we will focus largely on psychostimulant and opioid addictions. We will argue that stimulant abuse operates much more through appetitive reward mechanisms while opiate abuse has a greater impact on consummatory reward affects. In addition, practically all drugs of addiction operate in part through dopamine appetitive arousal (Wise, 1998). And all drugs of abuse, including nicotine and alcohol, when withdrawn after prolonged administration, produce a profound reduction in brain dopamine appetitive affect (Epping-Jordan et al., 1998; Schulteis et al., 1995).

Drug addictions are clearly manifested in ways that could easily promote derangements of reproductive fitness, because generating positive feelings that are not derived from external consummatory objects will commonly promote demise (starvation, for example) and species extinction (no offspring). It is a sad but incontrovertible fact that our biological needs cannot be met narcissistically, by mere *feeling* of reward versus *actual achievement* of reward. Biological needs represent a true *lack* in the organism that can only be rectified by a specific object in the outside world. From a psychodynamic point of view, substance abuse, like compulsive masturbation, therefore represents a failure to negotiate the transition from helplessness to competence in the social world and social mastery – the arena of all the competitions that we simply must enter in order to survive and reproduce. If we can trace the mechanism by which we normally traverse this transition, we will have identified a pivotal locus of the derangement of normal developmental processes that underlie addiction.

It seems unlikely that evolution would have left this important task to moral persuasion (education or learning) alone. There must be some intrinsic mechanism that motivates us to forego empty pleasures in favor of the more difficult and risky business of engagement with the real world. In psychostimulant addiction, we believe that the critical mechanism is 'captivation' of the SEEKING system, which mediates appetitive processes more than consummatory ones. If the biology of reward entailed a unitary brain mechanism, as some still seem to claim for the mesocortical–mesolimbic dopamine (DA) 'reward system' (Haber and Knutson, 2009; Rolls, 2005), then it is difficult to imagine why animals would ever bother with effort and risk, and not just go straight for the reward. We argue that this is because the mesocortical–mesolimbic DA system is not a simple sensory pleasure 'reward' system at all – despite the fact that almost all drugs of abuse (like all forms of appetitive behavior) do indeed massively increase DA activity in this system.

The distinction we draw here is similar to that drawn by Berridge and Robinson (1998), whose research findings eventually led them to draw an analogous (but as we shall see, not identical) distinction between the mammalian brain mechanisms for 'wanting' and 'liking', with 'wanting' being just one step removed from SEEKING. (A full history of the diversity of views in this theoretical hornet's nest is summarized in Alcaro et al. (2007) and Panksepp and Moskal (2008).) In contrast, it is ever increasingly clear that the feelings of satisfaction for many of the specific rewards of the natural world are mediated by endogenous opioids – and range from social rewards (Panksepp, 1981) to more discrete items such a tasty food, which one has to ingest (Avena et al., 2008). The distinction between the brain's appetitive and consummatory 'reward' mechanisms helps to make sense of the fact that addicts do not generally find their psychostimulant (e.g., amphetamine and cocaine) substance-induced DA surges to be pleasurable; at times they do not even *like* the objects of their addictive *wants* (Bolla et al., 1998; Kassel, 2010). In contrast, practically all studies of opioid abuse indicate that addicts obtain pleasurable, relaxing feelings directly from the drugs they begin to gradually crave, which gradually recruits the SEEKING reward aspects of appetitive cravings. This recruitment of the SEEKING system is indicated by the finding that opioids can maintain self-administration at low doses that produce only very mild psychological effects (Lamb et al., 1991).

Most recent addiction research into the 'wanting' aspect of the brain's "reward" mechanisms has, however, not been interpreted within Panksepp's framework, as summarized above. Rather than emphasizing the active, agentic nature of the organism which is motivated internally to explore, forage, and expect, the concept of "wanting' is linked more to the attractive power of sensory-perceptual processes – to 'incentive salience' (Robinson and Berridge, 2003). In this latter model, DA activity is said to *predict* which objects are likely to produce pleasurable experiences (incentive), and thereby to motivate the animal to selectively attend to such objects (salience). Addiction researchers who follow this view (e.g., Volkow et al., 2007) accordingly argue that drug-induced DA surges make addicts over-incentivize the drugs that generate such surges – and associated environmental cues – making them excessively important (inappropriately salient).

We suggest that integrating incentive salience into a larger SEEKING perspective helps to disentangle several processes that appear to be conflated in the basic incentive salience model. Drug-induced surges in salience attribution should incentivize the addict to pay extra attention to the *pleasure-generating* things they come across while high, not to the DA promoter that induced the high itself, and to "want" those things more in the future. This does predict the observed reinstatement of addictive behaviors, presumably by amplification of a craving process, in humans and animals exposed to the paraphernalia and other cues of drug consumption (Volkow and Li, 2004). However, this is not the only thing that happens, and we suggest that looking at substance abuse within the framework of the natural history of the pleasure SEEKING timeline sheds light on the problem.

We would argue that the incentive salience mechanism (in which the mesolimbic–mesocortical DA system does indeed play a key role) is actually a higher-order process in the cascade of appetitive eagerness. In the natural course of events, animals have to (1) be driven to seek the objects of its biological needs in the outside world, surely an invigorating appetitive-action activity, before they can (2) experience the pleasurable rewards that such

objects generate, which in turn enables animals to (3) learn from such experiences – i.e., associate specific objects with the pleasurable relief of each biological need. Only then can animals have any basis for predicting appropriate pleasures from the sight or smell of specific objects (i.e., attribute incentive salience). In short, incentive-salience relies on past learning, while SEEKING is an intrinsic emotional-affective system that allows learning to occur.

Why, then, is this simple and primary DA-activated process so heavily implicated in addiction? After all, SEEKING is the step in the putative process that leads the animal *away* from narcissistic self-soothing (from Freud's 'masturbation'); why then do substances of abuse *increase* activation of this DA mechanism? Does this not reveal a contradiction in the parallel between masturbation and addiction (self-soothing)?

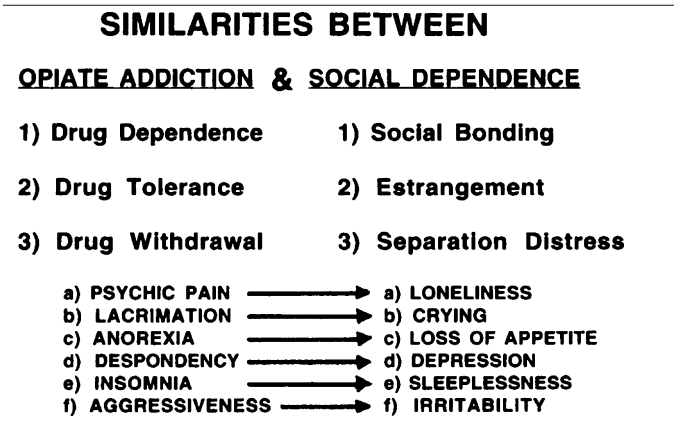
It certainly would be a contradiction if it were not for the important finding (made in relation to cocaine addiction in the 1980s, and in subsequent studies in relation to methamphetamine, alcohol and heroin, too) that D2 receptors are consistently *decreased* in addicts, even long after the resolution of acute withdrawal effects (Volkow and Li, 2004). Recent research has also shown that relatively decreased D2 receptors *precede* the development of an addiction – that it may in fact be an important biological marker of addictive vulnerability (Volkow et al., 2007). From an affective neuroscience point of view, this condition would be the opponent-process of the appetitive-SEEKING reward that temporary (i.e., artificial pharmacological) arousal of dopamine systems promotes (Johnson, 2008; Khantzian, 2003; Koob and Le Moal, 2001).

These findings are currently being interpreted to mean that individuals with blunted capacity to attribute 'incentive salience' gradually come to learn that only substances that can produce massive surges of D2-mediated activity are salient. But a better interpretation might be that individuals with blunted SEEKING capacities come to learn (especially if not otherwise helped by parents, educators and the like) that substances which produce massive surges of D2-mediated activity enable them to *gain access to pleasurable experiences and objects in the outside world* that would otherwise be relatively inaccessible to them. The internal object of the addiction would then not just be the stimulant substance itself and associated amplification of external cues – as incentive salience theory suggests – but rather the possibility (or expectation, or even hope) of gaining social, sexual and other biologically useful rewards – possibilities that the substance artificially evokes. This alternative explanation of the link between reduced D2 receptivity and addiction has important clinical implications; so we believe it deserves careful consideration in future research.

As we have already noted, the PLEASURE-LUST or 'liking' aspect of the reward process is primarily mediated by opioids (acting on mu and delta receptors in the basal forebrain region in particular; see Panksepp, 1998; Berridge and Robinson, 1998; Kelley and Berridge, 2002; Kelley, 1999) (although DA also plays a role). The hedonic, analgesic and social-soothing properties of opioids (Panksepp, 1981; Keverne et al., 1989) are difficult to separate entirely, especially when considered from the lived viewpoint of what a substance abuser is trying to achieve. A diagnostic differentiation of this kind would certainly be clinically important, as indeed is the more basic distinction we have already drawn between those who are seeking DA stimulation and those who are seeking opioid-mediated euphoria or relief (cf. 'uppers' versus 'downers'). But now we must consider the opioid systems as a whole in relation to the formulation of addiction that we are considering here.

It is easy to see the link between an opiate-induced hedonic fog and the narcissistic delights of masturbation. We have likewise already provided an answer to the question as to why animals take the trouble to transcend masturbatory pleasures, so to speak, and engage instead with the outside world in pursuit of pleasure and relief from pain. The answer is found in the fact that a primary SEEKING instinct exists, alongside various PLEASURE-LUST instincts. This implies that masturbatory pleasure, while satisfying the second of these, leaves the first of them (the object-seeking instinct) dampened for a while but in the final accounting unsatisfied. All at once, this insight also throws the pivotal role of the PANIC–GRIEF instinct into sharp relief.

Table 2
Summary of the major similarities between the dynamics of opioid dependence and key features of social attachments.



From Panksepp (1998).

As already mentioned, this system evolved in order to foster social bonds, with clear adaptive advantages, attaching mothers (and to a lesser extent, fathers) to their genetic offspring, the offspring to their major sources of survival care, and genetically related conspecifics more broadly to each other (Panksepp, 1981, 1998). The price we have to pay for this evolutionary advantage, though, is the pain of social loss: separation distress (PANIC) and sadness (GRIEF). In addition to the pleasures of closeness, the avoidance of such pain also keeps us together. Neurochemically speaking, we cling to our mothers and lovers in order to keep our mu-opioid receptor activity contentedly high, and to prevent them from dropping distressingly low. Dopamine mediated SEEKING also participates in the pursuit of social-bonding, but perhaps only to the extent of organisms finding suitable partners (Curtis and Wang, 2005).

Now, it is of the utmost importance to note that the 'attachment' processes initiated by this instinctual system *have most of the hallmarks of addiction*. This allows one to construct a strong bridge between the dynamics of addiction, especially the anhedonic withdrawal processes, and depression (Panksepp and Watt, in press). Consider for a moment the similarities between substance addiction/withdrawal and social attachment/loss (Panksepp, 1981; and see Table 2, from Panksepp, 1998). Given these analogies, it is not surprising that opiates were historically the first line of treatment for depression (for summary, see Tenore, 2008), but are problematic for treatment because they are so addictive!

So, *attachment is a primary form of addiction*, or perhaps more accurately, addiction is a deranged form of attachment. Anyone who has fallen in love knows the truth of this statement. Being in love with someone is almost indistinguishable from being addicted to them. This, surely, then, is the major biological endophenotype that is high jacked by opioid abuse. But where does this leave Freud's claim regarding masturbation? We presume that, pleasurable sensations notwithstanding, what distinguishes masturbation from actual copulation is not an absence of object-seeking but a *frustration* of object-seeking. One masturbates for *lack* of an object (whatever the reason for that lack might be). This is why mas-

turbation is considered inferior to copulation, not only by society, but also by the masturbator. Masturbation is ultimately an empty source of pleasure, in a very literal sense. Masturbation involves satisfaction of the PLEASURE-LUST instinct despite frustration of object-seeking, which implies empty (objectless) pleasure; pleasure without attachment, or worse: substitutive pleasure in the absence of a specific longed-for object (i.e., object of affection). This formulation fits perfectly with the understanding of addiction outlined above. Addiction, like masturbation, is a substitute and replacement not only for general mastery of the object world, but specifically for *the attainment of a secure love object*. In other words, what the masturbator really wants is not his or her hand, but rather an actual lover (for which one's own hand is a sorry substitute); by the same token, what the addict really wants is not a drug, but rather an actual reason to feel safe and warm and cared about (for which the drug is a sorry substitute). Freud's initial insight now can be explored with the deeper and more detailed insights (and potentially powerful new therapeutic tools) provided by modern affective neuroscience approaches to the underlying mechanisms around which the problem of addiction revolves; that we have the capacity to do this now makes it all the more imperative that we do not lose sight of this forest for the trees (Maté, 2008).

The direct implications for better translational studies is that the emotional-affective mechanisms envisioned to underlie both depressions and drug-addictions can now be envisioned in animal models, and rather directly monitored with the new armamentarium of emotional vocalizations that animals exhibit during shifting affective states, as discussed elsewhere (Brudzynski, 2007; Burgdorf et al., 2001a,b, 2007; Knutson et al., 2002; Panksepp et al., 2002; Panksepp et al., 2003).

To avoid misunderstanding, we will summarize our argument regarding addiction as succinctly as possible. All addictions are driven by (1) a primary appetitive process called SEEKING, plus (2) with some agents, like opioids, a primary consummatory hedonic process we can call primary-process PLEASURE – which rewards the SEEKING activity and thereby allows learning to occur – plus (3) a primary social process called attachment, which is mediated by the PANIC–GRIEF system. Once an attachment is established, reunion with the object of attachment is the specific pleasure that the addict seeks. Our argument is that addiction researchers who apply 'incentive salience' theory conflate (1) and (2), and they over-emphasize this aspect of addiction without recognizing the importance of (3), which in our view is the big-ticket item. It is the big-ticket item for the simple reason that the real object of processes (1) and (2) – what they really 'want' – is (3). Many addiction researchers today seem to think that what the addict wants is a drug (DA mediated); we by contrast think that what the addict really wants is to (i) arouse appetitive SEEKING euphoria (especially in the case of psychostimulants), withdrawal of which also produces an opponent process that is dysphoric in a way resembling lost-attachments, which highlights (ii) that opioid addicts specifically seek to restore lost attachments (mu opioid mediated), feelings of dysphoria that are partly mediated by the psychological pain of social-loss (PANIC/GRIEF) as well as eventual underactivity of the SEEKING urge (the "despair" of depression). The SEEKING followed by PLEASURE learning-processes that many other researchers prioritize are typically in the service of this particular type of 'wanting'. In other words: addicts, like chronic masturbators, are not simply looking for just *any* sensory reward; the substance abuse is also a self-soothing substitute for the attachment experience that addicts really want. As Freud wrote in 1898:

> "[The success of a treatment for addiction] will only be an apparent one, so long as the physician contents himself with withdrawing the narcotic substance from his patients, without troubling about the source from which their imperative need for it springs . . . [W]henever normal sexual life can no longer be established, we can count with certainty on the patient's relapse". (Freud, 1898, p. 276)

This conclusion still rings true more than a century after it was first reached. We would only add "social attachment" – primal mother–infant bonding – to Freud's use of the term "sexual life", since Freud implicitly included almost all other rewarding aspects of loving interaction under his broad use of the word "sexual".

Recent animal research has indicated that maternal CARE urges reduce the brain's tendency to find cocaine attractive (e.g., Ferris et al., 2005). Likewise, social dominance tends to reduce addictive urges, perhaps because such animals have stronger intrinsic emotional resources (Morgan et al., 2002). The substitutive attachment aspects of addiction probably go a long way to explaining why 12-step programs are among the most effective methods to break addictive cycles. They return participants into an emotionally engaged and ultimately satisfying social network, which is so patently lacking in the lives of many addicts. For those who seek new pharmacological therapies for addiction, we might suggest that they evaluate the paradoxical prediction (by current standards) that the opioid receptor agonist–antagonist buprenorphine, besides quelling the strong urge to consume opioids, partly by alleviating narcotic withdrawal symptoms, may be efficacious in reducing amphetamine and cocaine addictions. Low doses of a relatively non-addictive opioid receptor agonist/antagonist such as buprenorphine may help diminish the elevated psychic-pain of depressive affect during drug withdrawal – helping re-establish affective homeostasis – that addicts are ultimately seeking, and provide support while developing healthier social connections.

Conflicts of interest

No author reports any conflict of interest.

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