

Affective neuroscientific and neuropsychanalytic approaches to two intractable psychiatric problems: Why depression feels so bad and what addicts really want  
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1. Il lavoro presenta inizialmente due presupposti fondamentali dell' -affective neuroscience-  
**il primo: le emozioni si sono evolute in relazione al fare**  
**il secondo: le emozioni vengono “sentite” (parte affettiva delle emozioni) per motivare** l' organismo alla sopravvivenza e riproduzione. La loro (degli autori) strategia di ricerca parte da un approccio “dual-aspect monist position” delle neuroscienze affettive.

*...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*

2. Gli autori in questo articolo prendono in considerazione due patologie, **depressione a addiction** per illustrare i sistemi di comando basali ad entrambi.

*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.*

3. Il seeking system and il panic /grief system, sistemi emozionali di base, sottendono le dinamiche fondamentali di entrambe le situazioni cliniche

*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)*

4. The Seeking System era stato descritto da Panksepp in un primo momento come un sistema emozionale di base che spinge l'animale non solo verso comportamenti consumatori, ma verso la ricerca attiva della stimolazione

*but rather impels the animal to excitedly seek more of the stimulation.*

5. Al pari di un sistema emozionale che spinge l'animale ad essere attivo stimolato sia da fonti interne (cervello mediale) che da fonti esterne

*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*

6. Può quindi essere considerato un sistema di apertura al mondo e la sua chiusura comporta sentimenti di perdita di interesse e di speranza,

*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*

7. Oltre che far parte di un sistema Da di stimolazione, l'essere mediato da oppioidi, come da altri peptidi simili, induce a pensare ad un suo interessamento nel sistema dell'attaccamento e quindi un suo coinvolgimento nel separation distress

*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 Through the action of this system, being close to significant others leads to feelings of comfort, security, and pleasure.*

*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 –*

8. Quando i legami sociali sono interrotti è questo circuito basale che genera nel malato il feel bad (separation distress)

*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*

9. La sequenza che va dalla protesta fino alla disperazione può essere presa come modello della depressione umana, tenendo conto dei processi terziari in questa presenti che non ritroviamo negli animali

*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.*

## **10. Quindi perchè la depressione fa stare così male?**

*Firstly : Given these starting points, we think it is tremendously productive to consider why depression feels bad....*

*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)*

#### 11. la proposta centrale degli autori è di rifocalizzare l'attenzione sulla fenomenologia

*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.*

#### 12. Ma anche di riconsiderare la distinzione freudiana fra melancolia e depressione

*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.... 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. 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...We also know that a first depressive episode is most commonly triggered by social loss .*

#### 13. Quindi perchè la depressione fa stare così male? Questa la loro ipotesi

*So why does depression feel bad? It feels bad, in terms of our basic hypothesis ... 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 (...).*

*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 ..., 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.*

#### 14. Rimane aperta la domanda fondamentale della psicoanalisi e della psicopatologia in generale sul perché si reagisce diversamente alla perdita e quindi quale correlazione fra depressione e lutto.

Detto attraverso le parole degli autori:

*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.*

**15. Qui attraverso i nostri esempi clinici**, potremmo aggiungere come la psicoanalisi copre questa soggettività e resignifica il lutto alla luce della propria storia personale. In altre parole se il processo è identico, ciò che è variabile sono i contenuti individuali. Questo potrebbe anche essere un modo di guardare alla fenomenologia, come una manifestazione soggettivante la propria storia. Ma è questo un argomento che meriterebbe da solo un intero dibattito. Intanto proponiamo la sintesi degli autori dell'articolo in cui la descrizione del processo ha già in sé il fenomeno e l'evoluzione del fenomeno. Potremmo dire che il corteo sintomatologico del lutto o della depressione segue sempre questa sequenza, anche se non è un meccanismo a cascata? In 5 punti la loro ipotesi:

- 1) *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*

**16. Su questo punto molte domande possono essere poste:** Ritroviamo questa sequenza o parte di questa sequenza nelle nostre descrizioni cliniche? O ancora quale correlazione fra "sintomi" di depressione o vissuti "sentimenti" depressivi in altre altre patologie (ad esempio addiction, panico , ocd, ecc.)

*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)*

17. **E veniamo alle addiction**, è collocata nello stesso sistema di funzionamento del circuito del panico, in cui il meccanismo di funzionamento del seeking system è di tipo disregolativo:

*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.*

18. **Tesi central dell'addiction è la loro capacità di generare affetti positivi non necessariamente finalizzati alla generatività**

*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 ...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.*

19. Questo permette di accendere artificialmente il sistema di premiazione in maniera efficace al di là dell'ostilità del mondo. Tutte le dipendenze sono sostenute da un unico meccanismo dopaminergico

*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...*

*We will argue that stimulant abuse operates much more through appetitive reward mechanisms while opiate abuse has a greater impact on consummatory reward affects*

20. Le condotte di dipendenza possono essere spiegate attraverso l'esercizio della soddisfazione di bisogni biologici che necessitano dell'oggetto per essere soddisfatte e non possono esserlo nell'esercizio del narcisismo

*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...*

**21. Questa transizione può rappresentare un punto cardine nella comprensione delle addiction?**

*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.*

*In psychostimulant addiction, we believe that the critical mechanism is ‘captivation’ of the SEEKING system, which mediates appetitive processes more than consummatory ones...*

22. La dinamica delle addiction è letta da alcuni ricercatori all'interno del sistema di salienza e non del seeking, le sostanze con la loro capacità di appagare il “wanting” creano un' inappropriata salienza

*...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 make addicts over-incentivize the drugs that generate such surges – and associated environmental cues – making them excessively important (inappropriately salient).*

23. Gli autori dibattono in merito all'apprendimento di ciò che incentiva la salienza, mentre il seeking come sistema intrinseco precede la salienza stessa

*In short, incentive-salience relies on past learning, while SEEKING is an intrinsic emotional-affective system that allows learning to occur.*

24. Segue il parallelo con la masturbazione come concepita da Freud

*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)?*

25. Il punto centrale dell'articolo riguarda la stimolazione dei recettori D2, numericamente diminuiti nelle condotte tossicomaniache:

*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...*

*... 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.*

26. Dopo aver ripreso il parallelo con la masturbazione, ritornano alla stimolazione degli oppioidi e all'attaccamento: punto di unione dei processi depressivi e delle condotte additive

*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***

27. per riunificarle poi nella condotta masturbatoria come fonte vuota di piacere, al pari della condotta additiva vuota di piacere (objectless)

*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)*

## **28. attaccamento dentro alla teoria sessuale?**

*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".*