



Review

The SEEKING mind: Primal neuro-affective substrates for appetitive incentive states and their pathological dynamics in addictions and depression

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ABSTRACT

Appetitive motivation and incentive states are essential functions sustained by a common emotional brain process, the SEEKING disposition, which drives explorative and approach behaviors, sustains goal-directed activity, promotes anticipatory cognitions, and evokes feelings of positive excitement which control reward-learning. All such functions are orchestrated by the same “archetypal” neural processes, activated in ancient subcortical areas and transported to the forebrain by the mesolimbic dopamine (ML-DA) system. In mammals, the neurophysiology of the SEEKING urge is expressed by DA-promoted high-frequency oscillations, in the form of transient and synchronized gamma waves (>30 Hz) emerging in limbic forebrain and diffusing throughout basal ganglia-thalamocortical (BG-T-C) circuits. These patterns may be considered basic “SEEKING neurodynamic impulses” which represent the primary-process exploratory disposition getting integrated with information relative to the external and the internal environment.

Abnormal manifestation of SEEKING and its neural substrates are evident in clinical depression and addiction. Specifically, depression is characterized by reduced recruitment of SEEKING, while addictions reflect re-organizations of the SEEKING disposition around ultra-specific appetitive memories and compulsive activities.

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1. Introduction

It is generally accepted that all animals are evolutionarily endowed with at least two opposite basic motivational tendencies, namely approach and withdrawal, whose activation is accompanied by positive and negative affective states usually called 'rewards' and 'punishments' in behavioral neuroscience studies (Plutchik, 1980). Such opposite psychological-behavioral states have been conserved in all mammalian species, but perhaps even in very simple species like invertebrates (see Huber et al., 2011), allowing organisms to search for life-supporting events and to avoid harmful ones.

Although we know that there can be many distinct emotional processes aroused from unconditional brain systems in action (Panksepp, 1982, 1998, 2011a), those global categories called positive and negative affect are useful for distinguishing what have been philosophically discussed, since time immemorial, as the pains and pleasures of affective life.

Interestingly, approach and withdrawal tendencies are also expressed in vocal communicative patterns in many species, including crying and laughter in humans. Indeed, recent investigations of laboratory rats highlight two general categories of ultrasonic vocalizations, the ~50 kHz positive vocalizations, that appear in appetitive contexts and during positive social interactions, with properties that resemble childhood laughter (Panksepp, 2007), and the ~22 kHz vocalization, exhibited in aversive contexts and under social and environmental threats (for summaries, see Brudzynski, 2007, 2009; Burgdorf and Panksepp, 2006; Knutson et al., 2002; Panksepp et al., 2002).

The existence of basic approach systems, which contrast with functionally opposing withdrawal processes, has been postulated by many philosophers and scientists, and, in the "modern era", by Schneirla (1959), from a pre-neuroscientific behavioral-ethological perspective, and by Glickman and Schiff (1967), from a neuroscience perspective. Now, with the extraordinary progresses that has been achieved in the past half century of neuroscience, such opposite tendencies have been related to the interaction of multiple neural circuits localized in extended brain regions, from the lower brainstem to the forebrain (for summary, see Panksepp, 1998; Panksepp and Biven, 2011). Therefore, approach and withdrawal were eventually linked to the action of two types of brain networks that have traditionally been called the "Brain Reward System" and the "Brain Punishment System" by some (e.g., Moriyama et al., 1984), the "Behavioral Activation System" and the "Behavioral Inhibition System" by others (Gray, 1985), or, ultimately, "the Reward System" and the "Antireward/Stress System" (Koob, 2009). The basic subcortical neuroanatomy of such opposing bi-polar networks has been identified using intracranial electrical stimulation and drug microinjections procedures (Ikemoto, 2010; Panksepp, 1998) (Fig. 1). Abnormal functioning of these basic brain systems is now commonly seen to be involved in psychiatric disorders. For instance, depression and addiction have been related to altered balance between the Brain Reward system and the Brain Antireward/Stress system (Koob, 2009; Stone et al., 2008).

The discovery of incentive-based brain reward networks – mediating appetitive eagerness, approach and incentive reward – originated from the seminal experiments with electrical self-stimulation of the brain (ESSB) discovered by Jim Olds and Peter Miller in 1953. Indeed, it was shown that the stimulation of a complex of neural structures located in the lateral hypothalamic-medial forebrain bundle (LH-MFB) trajectory reinforces operant behaviors (such as lever press) and at the same time induces active exploration and approach (Glickman and Schiff, 1967) with a postulated unitary incentive property (Trowill et al., 1969). However, for historical reasons, the dominance of a cognitive-behavioristic view prevented a full discussion of the

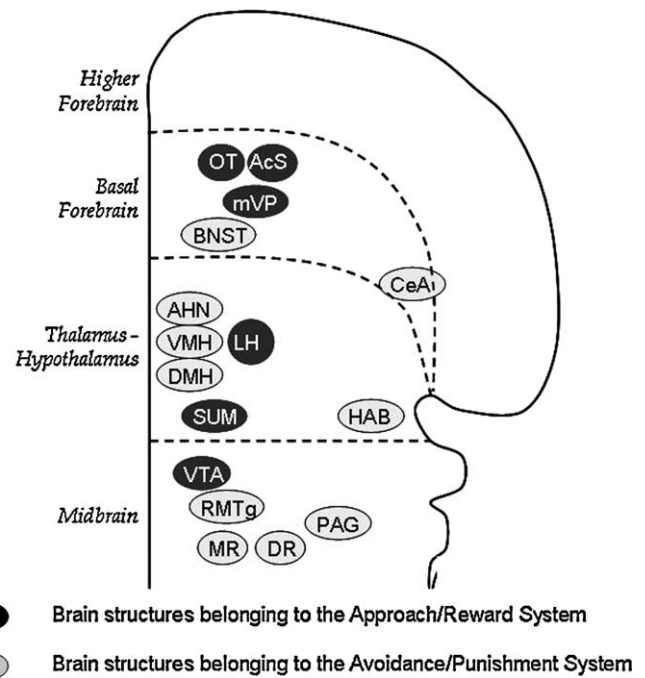


Fig. 1. The basic neuroanatomy of the Approach/Reward and Avoidance/Punishment systems. Schematic drawing shows a flat map of the rat brain adopted and modified from the one by Swanson (2004). Based on brain electrostimulation and drug microinjection studies, the figure indicates a set of subcortical structures promoting reward and appetitive behavioral arousal (black circles) and a set of structures promoting punishment signals and active escape or other negative emotional reactions (gray circles). Interestingly, the two neural networks are widely interconnected and exert a mutual inhibitory influence (Ikemoto, 2010; Panksepp, 1998). Abbreviations: AcS, nucleus accumbens shell; AHN, anterior hypothalamic nucleus; BNST, bed nucleus of the stria terminalis; CeA, central amygdala; DMH, dorsomedial hypothalamus; DR, dorsal raphe; HAB, habenula; LH, lateral hypothalamus; MR, medial raphe; mVP, medioventral pallidum; OT, olfactory tubercle; PAG, periaqueductal gray; RMTg, rostromedial tegmental nucleus; SUM, supramammillary nucleus; VMH, ventromedial hypothalamus; VTA, ventral tegmental area.

deeper evolutionary psychobiological and affective implication of such experimental findings. Some theories emphasized mainly the reinforcement- or reward-learning functions of this neural system (Everitt and Robbins, 2005; Fibiger, 1978; Schultz, 2001, 2010; Spanagel and Weiss, 1999; White and Milner, 1992; Wise, 1978, 2004), others its behavioral activation and appetitive functions (Berridge, 2004; Berridge and Robinson, 1998; Depue and Collins, 1999; Gray, 1985; Ikemoto, 2010; Salamone and Correa, 2002; Wise and Bozarth, 1987). Most of these formulations reflected a strictly third-person, observer-based conceptual perspectives (that is traditional in behavioral neuroscience), with no clear vision of the underlying affective states, aside from some kind of generalized "reward" effect.

Some time ago, an alternative, organism-centred view was formulated, namely the hypothesis that neural areas supporting ESSB, especially along the ML-DA trajectory, constituted a basic emotional brain circuit, that may be appropriately called the SEEKING/EXPECTANCY system, whose activation changes the individual's attitude towards the environment, promoting an energized appetitive disposition, which unconditionally promotes exploration and foraging for resources, and creates expectancy states that allow animals to anticipate the presence of future rewards (Alcaro et al., 2007; Ikemoto and Panksepp, 1999; Panksepp, 1998). This SEEKING disposition (for short) is characterized by (i) overt behavioral responses (exploration, seeking and approaching), (ii) by memory and cognitive effects ('reinforcement' of associative learning, activation of contextual memories and anticipatory pre-

dictions) and by (iii) specific kinds of positive affective feelings (a generalized incentive 'emotional' reward state, that does not reflect the pleasure of sensation, but rather the euphoria of appetitive eagerness).

Many lines of evidence indicate that "SEEKING" is a concept rooted in highly characteristic psycho-behavioral and neurobiological processes that drive organisms interacting with specific environmental goal objects, and that are usually active before the organism has formed detailed cognitive or perceptual representations of those objects. Due to its intrinsic positive affective value the activation of SEEKING is experienced by organisms as rewarding *per se*, leading to ESSB without the need for any traditional form of consummatory activity and explicit sensory rewards. Therefore, the SEEKING view grants organisms a mental life, specifically affective-emotional states created from complex, large-scale unconditioned neural dynamics that constitute the psycho-behavioral foundation for organismic existence (Alcaro et al., 2007; Ikemoto and Panksepp, 1999; Panksepp, 1981a).

In this paper, we integrate our traditional perspective with new empirical findings coming from neurochemical and electrophysiological studies and indicating that SEEKING is related to the emergence of transient high-frequency oscillatory patterns in the limbic forebrain of mammals, and that ML-DA transmission favours the expression and the diffusion of such rhythms. Moreover, since the knowledge of neural aspects of SEEKING may be relevant for psychiatry, we will discuss how depression and addiction may be characterized by an abnormal expression of SEEKING at both brain and behavioral level. In sum, we will focus on a description of the SEEKING disposition from the perspective of its psycho-behavioral features (Section 2), followed by an analysis of its neuroanatomical (Section 3.1), neurochemical (Section 3.2) and neurodynamic substrates (Section 3.3). We end (Section 4), with a discussion of the possible involvement of the SEEKING disposition in major depression and addiction.

2. Psycho-behavioral features

SEEKING, a large-scale integrated process elaborated throughout the MFB, engenders and organizes the organism's intrinsic motor-actions and related autonomic, sensory and cognitive processes, all of which constitute a critically important neuro-affective organismic state-control function. As shown by lesion studies, damage to the SEEKING system renders all animals amotivational, with no eagerness to do anything (Stellar and Stellar, 1985). Without nursing, such animals die. Clearly a massive system like this, which is essential for everything animals do, has an incredible number of sub-functions that are hard to tease apart. But there is every indication that these "parts" work in a coordinated fashion to generate a unified emotional drive, accompanied by an exploratory behavioral urge and energized-euphoric feelings. In our view, not only does this system mediate a positive euphoric feeling quite different from sensory pleasures, but also, with conditioning, the SEEKING system generates a vast array of anticipatory cognitions as well as reward-learning effects that underlie classical and operant conditioning. Independently from its various cognitive, behavioral, affective and learning manifestations, the SEEKING disposition should be considered a single emotional entity since it is based on characteristic neurobiological processes and it is aimed towards a single general-purpose intentional (an intention-in-action) goal. This goal is to SEEK and approach a specific source of stimulation, either perceptually processed or cognitively represented.

2.1. Unconditioned expressions of SEEKING

The SEEKING disposition is characterized by instinctual behavioral tendencies that help organisms to attend, move, explore and

approach goal-objects – via many actions such as locomotion, orientation, specific types of head and body movements, eye saccades, sniffing in olfactory creatures, and sensorial investigation of many non-aversive objects that are confronted during foraging. Through such coordinated behavioral patterns, synchronized with changing autonomic states, specific objects or features of the external environment, including salient non-reward events (Horvitz, 2000), are kept within the organism attentive focus and quickly acquire learned *secondary-reward*, or learned incentive value, that has been renamed "incentive salience" (Berridge and Robinson, 1998). However, it is by no means clear that this is due to any kind of change in the sensory-perceptual field itself; it could largely reflect a heightened attention and responsiveness to objects in the world, without and increases in sensory salience.

In laboratory animals, the emergence and energization of the SEEKING patterns has been observed after the following conditions:

- states of deprivation from limited access to resources that are essential for survival (such as food- or water-deprivation);
- novel environments or familiar environments containing novel objects;
- environments containing physical or social rewards as well as stimuli previously associated with such rewards;
- controllable mild stress: situations having moderately aversive effects that can be avoided using efficacious coping strategies;
- injections or intake of moderate dose of drugs of abuse (psychostimulants, opioids, alcohol, THC, nicotine) either peripherally or directly within-brain areas belonging to the SEEKING system;
- electrostimulation of brain areas innervated by the medial forebrain bundle (MFB).

The manifestation of the primary-process SEEKING emotional state, carried out by the ancient LH-MFB situated subcortical processes, give rise to characteristic energized-euphoric feelings of desire which accompany many animal and human appetitive activities, whether unconditional or conditional. Recent human data have demonstrated that the SEEKING brain circuitry, as predicted, is involved in the emergence of a characteristic appetitive affective state, which may be described as "enthusiastic positive excitement" or "euphoria" (Drevets et al., 2001; Volkow and Swanson, 2003) and that do not resemble any kind of sensory pleasure (Heath, 1996; Panksepp et al., 1985). Moreover, vivid descriptions of evoked eagerness feelings and desire come from stimulation of the MFB and nucleus accumbens in humans (Coenen et al., 2009; Schlaepfer et al., 2008; also see Coenen et al., 2011). However, the activation of brain substrates for SEEKING can, under the right conditions – e.g., when the individual is hungry – also promote the hedonic pleasures that accompany consummatory behaviors (Berridge and Kringelbach, 2008; Sharot et al., 2009), but this may be a direct effect of the energy-homeostatic "drive" systems of the brain (Dube et al., 2010; Panksepp, 1974).

The presence of a positive affective state associated with SEEKING has been demonstrated in animals not only through self-stimulation reward but also with the "condition place preference" (CPP) paradigms (Carr and White, 1986; Ikemoto, 2003; Trowill and Hynek, 1970). Recent investigations in rats have also shown that the positive affective state related to the SEEKING disposition is manifested spontaneously by 50-kHz ultrasonic vocalization, through which animals communicate their appetitive social desires (Burgdorf and Panksepp, 2006). Animals do not make these sounds when actually consuming rewards. In sum, although we can not know whether animals are self-aware of their internally experienced primary-process emotional states, such as SEEKING, empirical evidence indicates that such an emotional urge is accompanied by a characteristic affective tone that influences the way organisms perceive their environment (CPP). Moreover, it is

also evident that mammals are able to communicate such affective value when interacting with conspecifics.

It may be questioned if the positive euphoric feelings associated with SEEKING are expressed in aversive contexts or mild stressful conditions that also activate SEEKING-type behavioral patterns. In such cases, it is possible that SEEKING acts decreasing the intensity of negative affects related to aversive contexts in order to sustain anticipatory representations of “safety” and to promote active coping strategies. In any event, the SEEKING disposition projects organisms forward, persistently, in space and time. Through learning, SEEKING arousal also facilitates the elaboration of secondary-process anticipatory states and higher-order “forethoughts” or positive cognitive expectancies (Panksepp, 1981a; Wise, 2005). The empowerment of the anticipatory cognitive schemata may also be related to goal-oriented attentive processes (animals become less distractible), and SEEKING energizes activity, and, with the aid of norepinephrine, may increase concentration and effort to achieve one’s goals (Salamone et al., 2009).

2.2. SEEKING in learning

Although most studies have adopted a strictly mechanistic interpretation of molecular and cellular adaptive changes involved in the formation and consolidation of memories (Nestler, 2004; Huang et al., 2004; Centonze et al., 2001; Hyman and Malenka, 2001), abundant evidence indicates that reward-learning is sustained by the activation of a global appetitive state that we have called the SEEKING disposition.

We know that novel or unusual stimuli, which unconditionally activate sniffing and curiosity-exploratory behaviors (Clark and Trowill, 1971), can rapidly be associated with unconditioned stimuli in classical conditioning paradigms, and that overexposure without associated rewards tends to block conditioning (Rescorla and Wagner, 1972). This fact indicates that a preliminary activation of SEEKING by novelty facilitates associative learning, albeit it is empirically open whether it is essential for *all* types of associative learning. Moreover, spontaneous sniffing behaviors or 50-kHz vocalizations are exhibited by rats during fixed-interval delivery of rewards in conditioned learning (Burgdorf et al., 2000; Clark and Trowill, 1971; Panksepp, 1981a), and operant responses for rewarding brain stimulation and conventional rewards are typically preceded by some exploratory or investigative activity (Clark and Trowill, 1971; Ikemoto and Panksepp, 1994).

It is also relevant that conditioned stimuli can enhance instrumental responses also for unconditioned stimuli different from the ones with which the conditioned stimulus had previously been paired (Corbit and Balleine, 2005). Moreover, environments associated with food-rewards enhance the effects of amphetamine (a SEEKING facilitator) on locomotor activity, as do environments previously associated with amphetamine (Yetnikoff and Arvanitogiannis, 2005). In these two cases, the behavioral effects of environmental stimuli do not depend on direct stimulus–response associations, since these associations have never been previously temporally paired. Accordingly, we may conclude that a heightened exploratory–SEEKING urge has been internally associated with the environmental stimuli, and is potentiated whenever an animal is returned to similar environments.

Behavioral neuroscience studies have indeed demonstrated that the activation of SEEKING by external stimuli is a prerequisite for their effects as rewards in classical and operant conditioning paradigms (Alcaro et al., 2007). For us, the most fascinating aspect of reward is that it can strictly be a within-brain emotional–hedonic process, and not one that is critically dependent on external-sensory, peripheral bodily rewards. It is something that can be considered to be ‘intrapyschic’ – an evolved tool for living that allows animals to become engaged with a large variety of survival

pursuits. In our view, the activation of the SEEKING disposition favours attentive functions in the acquisition phase as well as the recollection of past events in the recovery phase of memory retrievals. Therefore, the SEEKING disposition is like some kind of “affective glue” binding together perceptual, motor, and cognitive representations into unified intentional sequences that may be recovered and further re-activated by memories of sensory rewards. In other words the mechanisms of “reinforcement” may be fundamentally affective in the brain.

2.3. SEEKING in evolution

The presence of an inbuilt within-brain SEEKING drive has been evident in the study of diverse animal classes, such as reptiles (Molina-Borja and Gómez-Soutullo, 1989), mammals (Panksepp, 1981a), birds (Fidler et al., 2007), fishes (Dubuc et al., 2008), and amphibians (Patton and Grobstein, 1998). Some preliminary findings have also indicated that invertebrates possess a rudimentary neural system responsible for exploration and SEEKING (Gray et al., 2005; Tinetti et al., 2007). Its widespread presence in the animal kingdom indicates that SEEKING is a fundamental emotional urge with very old evolutionary origin. Interestingly, however, the behavioral patterns through which SEEKING is expressed have remained substantially the same in all vertebrate species: forward locomotion, orienting movements and sniffing, or other equivalent sensorial investigative patterns, for instance antennae movements in crayfish (Alcaro et al., 2011).

One global function of such an appetitive disposition is to actively obtain information from the external environment, integrating it with basic drives reflected in various homeostatic–visceral detection systems, and to generate actions for obtaining resources, while avoiding potential dangers. Such fundamental emotional processes may have helped guide the evolution of many higher brain functions, from aspects of memory formation to higher cognitive activities. The expression of SEEKING within the cognitive domain may then eventually exert downward inhibitory influence over the activating power of external stimuli, constraining organismic appetitive activity to become intrinsically more focussed and habitual (i.e., when new learning is translated into habit-structures in the dorsal striatum) on the one hand, and more flexible on the other (i.e., through higher frontal executive functions facilitated by working-memory). However, those higher functions continued to be linked critically to earlier primary-process emotional functions, especially during early development, so that the lower psycho-behavioral and neurobiological processes of the ancestral SEEKING states preside over higher cognitive strategies of mature organisms (for a discussion of such nested hierarchies, see Northoff et al., 2011).

An important neuro-evolutionary aspect concerns the expression of SEEKING within the cortical–subcortical midline structures conceptualized as the “Core-Self” (Panksepp and Northoff, 2009), and the way the constituent organismic coherence integrating midline brain systems controls all basic emotional dispositions in accordance with internal visceral states and with past experiences. It is not possible here to deepen this complex argument. We just mention that SEEKING is an essential function of the Core-Self, conveying internal excitation into exploratory and approach patterns directed towards the external world (see Section 3), and then permitting the “externalization” (or “objectification”) of internal needs. However, although a profound functional similarity exists in the primary-process expression of SEEKING in all mammalian species, many differences emerge in the secondary- and tertiary-process manifestations, especially in remarkably well-cerebrated animals such as humans. Indeed, our sophisticated working-memory and complex self-reflective capacity, related to the growth of prefrontal lobes along with the capacity for sym-

bolic thinking, permit the channeling of SEEKING not only towards external objects of perception, but also towards internalized mental representations of subjective environments (promoting human creativity). Therefore, in humans, the SEEKING disposition may be organized around objects that are not directly perceivable to others and expressed through behavioral and cognitive activities that are much more complex than those found in other species. In such internalized SEEKING functions, only an attitude of empathic and attentive focus on the inner psychological world may help us understand the psychiatrically important vicissitudes of SEEKING urges that transpire in other people (especially those who are floridly psychotic), which becomes an essential component of psychotherapy.

3. Neurobiology of SEEKING

The neuro-architecture of the SEEKING system is highly conserved in evolution, with some general functional plans shared across all vertebrates, and perhaps invertebrates (see Huber et al., 2011). The simplicity of their nervous system makes invertebrates good candidates for studying the very basic neural architecture of SEEKING. For example, abundant progress in that direction has been done for worms *Caenorhabditis elegans* (Gray et al., 2005; Rankin et al., 2009), and for crayfish (Mellon, 2000; Sullivan and Beltz, 2005). In general, the invertebrate SEEKING system is characterized by close connections between neurons involved in sensory information processing, especially in the olfactory domain, and neurons involved in the promotion of motor patterns directed towards exploration and approach. Within such circuit, DA transmission seems to still act as an essential modulator capable of increasing appetitive drive and the incentive salience of external stimuli (Hills et al., 2004).

Also in mammals the SEEKING disposition is promoted by DA transmission within intermediary “associative” subcortical neural areas connecting sensory and motor processing. Most such areas are part of the “olfactory-limbic lobe”, where the affective value of external stimuli is translated into intentional behavioral patterns (Mogenson et al., 1980). As shown later, the ML-DA system of mammals connects midbrain and forebrain nuclei involved in the basic expression of the ancestral SEEKING urge with more recently evolved forebrain areas where internally generated drives are elaborated in accordance with perceptual, cognitive and visceral information. The ML-DA system is then a neurochemical bridge through which the very basic SEEKING patterns are transformed, via learning, into larger and more complex SEEKING neurodynamic patterns (Fig. 2).

3.1. Neuroanatomy

The discovery of ESSB by Olds and Milner (1954) represented the first step in the recognition of the neuroanatomy of SEEKING. ESSB studies led to the knowledge of several brain areas whose activation has rewarding effects, since animals tend to repeat operant behaviors (e.g. lever pressing) that promote a subtle but dynamic form of within-brain rewarding feelings. When stimulation parameters are adequately arranged, rats easily respond more than 100 times per minute, commonly responding more than they need to get all rewards, and maintaining such response rates for hours until the point of physical exhaustion (Olds, 1958). Rats involved in ESSB may neglect essential biological needs, starving to death or ignoring aversive shocks under special testing conditions (Routtenberg and Lindy, 1965; Valenstein and Beer, 1962).

The interpretation of ESSB has been controversial from the beginning. Initially it was assumed that electrical stimulation was inducing a kind of satisfaction “pleasure” typically associated

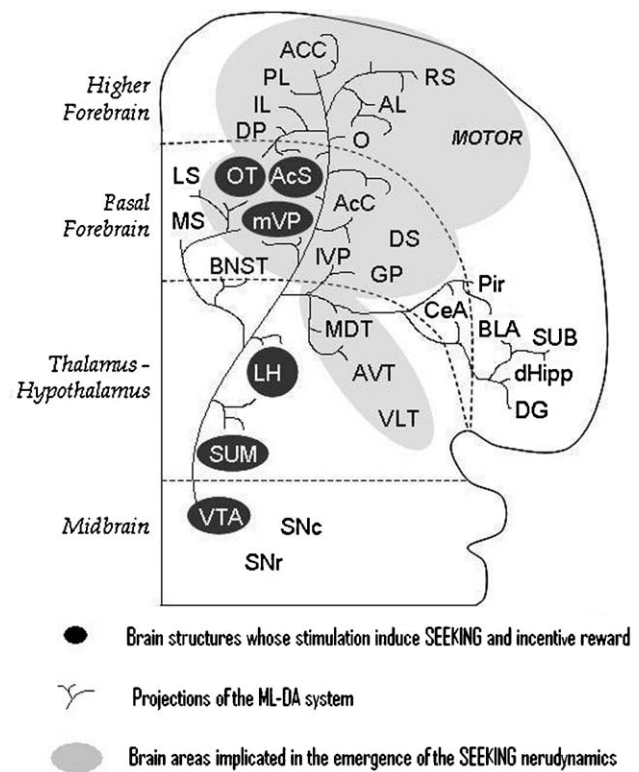


Fig. 2. The neuro-architecture of the SEEKING system. Schematic drawing shows a flat map of the rat brain adopted and modified from the one by Swanson (2004). This figure shows all principal brain areas and circuits directly involved in the promotion of the SEEKING emotional disposition. Black circles indicate neural structures whose electrical or chemical stimulation promote active exploration and approach as well as incentive reward (see Section 3.1). Such basic SEEKING network is widely innervated by ML-DA projections that originate in the VTA and diffuse to large portions of the anterior limbic brain (see Section 3.2). Gray zones indicate brain areas involved in the emergence and the diffusion of those neurodynamic patterns expressing the SEEKING drive (see Section 3.3). The figure then summarizes all neural components involved in the neuroanatomical, neurochemical and neurodynamic aspects of SEEKING. Abbreviations: ACC, anterior cingulate cortex; AcC, nucleus accumbens core; AcS, nucleus accumbens shell; AHN, anterior hypothalamic nucleus; AL, agranular insular cortex; AVT, anteroventral thalamus; BLA, basolateral amygdala; BNST, bed nucleus of the stria terminalis; CeA, central amygdala; DG, dentate gyrus; dHipp, dorsal hippocampus; DMH, dorsomedial hypothalamus; DP, dorsal peduncular cortex; DR, dorsal raphe; DS, dorsal striatum; GP, globus pallidus; HAB, habenula; IL, infralimbic cortex; LH, lateral hypothalamus; LS, lateral septum; IVP, lateral ventral pallidum; MDT, mediodorsal thalamus; MOTOR, motor cortex; MR, medial raphe; MS, medial septum, mVP, medioventral pallidum; O, orbital area; OT, olfactory tubercle; PAG, periaqueductal gray; Pir, piriform cortex; PL, prelimbic cortex; RMTg, rostromedial tegmental nucleus; RS, retrosplenial cortex; SNC, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; SUB, subiculum; SUM, supramammillary nucleus; VLT, ventrolateral thalamus; VMH, ventromedial hypothalamus; VTA, ventral tegmental area.

with human consummatory behaviors (Olds, 1956; Wise, 1978). However, it was also recognized that brain stimulation induced behavioral arousals, promoted abundant exploratory behaviors and approach if there were interesting things in the environment, and also, with time, to stable consummatory patterns, such as drinking, feeding, gnawing and predation (Gallistel, 1974; Glickman and Schiff, 1967; Panksepp, 1981a, 1982; Trowill et al., 1969; Valenstein et al., 1969). Therefore, it was suggested that ESSB fosters a general disposition to approach environmental stimuli, which may constitute the core of the incentive concept as used in psychology (Glickman and Schiff, 1967; Trowill et al., 1969). Gradually, it became widely accepted that the reward associated with ESSB experiments should have something to do with brain appetitive and incentive states rather than with sensory pleasure-rewards (Berridge and Robinson, 1998; Blackburn et al., 1987).

Along very similar lines, in our work, the function of the brain system activated in ESSB was conceived to be an emotional anticipatory EXPECTANCY sensory-motor process (Panksepp, 1981a, 1982, 1992, 1996), that we have later called SEEKING (Alcaro et al., 2007; Ikemoto and Panksepp, 1999; Panksepp, 1996, 1998; Panksepp and Moskal, 2008).

This not to say that all forms of ESSB reflect the same type of reward process; discrimination studies, using two sites along this system, suggested that there are, at the very least, two psychologically distinguishable self-stimulation related reward processes in the brain (Stutz et al., 1974), the septal sites, involved more in sexual pleasure, while LH–MFB trajectory sites were more involved in incentive motivation (Heath, 1996; Panksepp, 1981, 1985) and mediate the most effective substrate for robust and persistent self-stimulation at sites that unconditionally promote foraging (Olds and Olds, 1963; Olds and Peretz, 1960; Phillips and Mogenson, 1969; Routtenberg and Malsbury, 1969; Routtenberg and Sloan, 1972). Lesion studies demonstrated that no single structure is necessary to support ESSB and that reward is presumably processed by a network of multiple brain regions widely interconnected (Ikemoto, 2010; Ikemoto and Panksepp, 1994).

Subsequent experiments with intracranial drug self-administration procedures permitted more precise characterization of the LH–MFB brain regions involved in reward processes and appetitive functions, and an identification of neurochemistries quite directly involved in mediating reward (Ikemoto and Wise, 2004; Ikemoto, 2010). The set of structures promoting approach and euphoric appetitive eagerness are the ventral tegmental area (VTA), the lateral hypothalamus (LH), the supramammillary nucleus of the hypothalamus (SUM), the olfactory tubercle (OT), the VS/Nacc, and the mpFC (Fig. 1) (Panksepp, 1981; Wauquier and Rolls, 1976).

It has been supposed that such a vast and psychologically homogenous neural network (Stutz et al., 1974), that has been conceptualized very recently with a classic ‘behavioral approach’ concept (Ikemoto, 2010). We would suggest that this is insufficient to capture the overall integrative function of this system, and still recommend that SEEKING provides the complexity of dispositions that this system actually mediates. For instance, SEEKING refers not only to a variety of overt exploratory-foraging behaviors but also to an emotional disposition that possesses a subjectively experienced affective tone, and an intrinsic intentional structure that may be expressed at a non-motor cognitive level.

3.2. Neurochemistry: the ML-DA system

After the discovery of EBBS, when ascending dopamine systems were characterized (Ungerstedt, 1971) it rapidly became evident that the ML-DA system was an essential component for the behavioral activation and some of the rewarding effects of MFB stimulation (Wise, 2008; Wise and Rompre, 1989). Drug administration, microinjections and lesion studies, all confirmed that ML-DA transmission influence the rewarding properties of self-stimulation (Wise, 1996), although opioids had both interactive and independent rewarding effects. It has also been demonstrated that animals tend to self-administer compounds that increase DA levels in ML areas (see Alcaro et al., 2007 and Ikemoto, 2010 for reviews). In general, manipulations that stimulate DA transmission within the VS/Nacc, the ventral pallidum (VP), the OT and, partially, the prefrontal cortex (pFC), produced rewarding effects, as measured with either self-administration or conditioned place preference procedures, or simply the distinct behavioral activating effects of exploration, foraging and approach. Although intracranial self-administration studies have importantly revealed the role of many other neurochemicals different from DA in brain reward and approach functions (Ikemoto, 2010), the ML-DA system remains the

principal neurochemical that seem involved in the whole trajectory of the SEEKING system.

It has been empirically demonstrated that DA is released in two different modalities, called “tonic” and “phasic” DA transmission (Grace, 1991). Tonic transmission refers to a slow diffusion of small concentrations of DA in the extracellular space, outside the synaptic cleft, and it is related to regular firing of DA cells and to impulse independent release in terminal areas (Grace, 2000). On the contrary, phasic DA release follows bursting activity of VTA–DA neurons (Gonon, 1988; Goto et al., 2007), after which high levels of DA molecules are released into the synaptic cleft at up to millimolar concentration (Garris et al., 1994) and then rapidly removed via a re-uptake system (Floresco et al., 2003). Recent research has emphasized the role of phasic DA in the process of reward and appetitive arousal. Indeed, DA cell bursts and phasic DA release occur in presence of unpredicted salient, novel, and rewarding stimuli as well as neutral stimuli predicting future rewards (Horvitz, 2000; Schultz et al., 1997; Wightman and Robinson, 2002). Moreover, DA cell bursts are accompanied by orienting and approach movements directed towards specific cues (Bromberg-Martin and Hikosaka, 2009; Bromberg-Martin et al., 2010; Han et al., 1997). Also, ML cells fire and release DA during REM sleep (Lena et al., 2005), with complex participation in sleep–waking patterns (Monti and Monti, 2007).

From our perspective, phasic DA release may transiently activate SEEKING patterns in coincidence with specific cue- or context-dependent information, attributing to such information an incentive motivational, action-orienting effect. Despite the current popularity of a cognitive interpretation of VTA–DA activity in term of a “reward prediction-error signal” (Schultz and Dickinson, 2000), it is more likely that phasic DA release simply sparks off transient neural dynamics associated with SEEKING (see next paragraph). For example, in a recent experiment it was shown that phasic DA in VS/Nacc peaks just at the time of lever press for food reward and not in coincidence to predicting cues or reward delivery (Nakazato, 2005).

If phasic DA release may convey a transient SEEKING signal within-brain circuitries (Wightman and Robinson, 2002), tonic DA seems more related to the sustained activation of the SEEKING emotional state. Microdialysis studies indicated that tonic ML-DA concentrations increase during the exploration of novel stimuli (De Leonibus et al., 2006), during reward-SEEKING (Damsma et al., 1992; Malkesman et al., 2010) as well as during consummatory behaviors (Damsma et al., 1992; Sahr et al., 2008). Moreover, stressful situations increase tonic DA levels only in case of active coping, but not when animal give up searching for safe havens (Cabib and Puglisi-Allegra, 1996; Imperato et al., 1993; Mangiavacchi et al., 2001; Pruessner et al., 2004; Puglisi-Allegra et al., 1991; Ventura et al., 2002).

Based on the analysis of complex feedbacks between tonic and phasic DA transmission, we have advanced the hypothesis that tonic DA levels usually strengthen the internal motivational signal-to-noise ratio in neural networks, increasing the efficacy of phasic DA in promoting SEEKING signals (Alcaro et al., 2007). If tonic DA levels are low, phasic DA events are generally too weak in activating the SEEKING neurodynamics, and the organism tends to retire from an active engagement with the environment. To the contrary, excessive tonic DA levels strengthen the power of DA signals in such a way that SEEKING is repetitively expressed without any relation to specific environmental contexts or events. Only moderately high tonic DA levels are then sufficient to promote SEEKING patterns that are guided by sensorial and cognitive representations of the external environment. Incidentally, the control by DA of cognitive functions in prefrontal cortical areas has been found to follow an inverted-U-shaped profile, with too little or too much DA being detrimental for working-memory (Goldman-Rakic et al., 2000).

Due to the complexity of feedback regulators between tonic and phasic DA transmission, the expression of SEEKING is not only a factor of quantity (that is how much the disposition is active in ML circuits), but also a factor of organism–environment tuning. In our opinion, the experienced affective component is maximally active when SEEKING is open to the modulation of perceptual and cognitive representations of the external environment. In such cases, the emotion is behaviorally expressed in explorative and approach movements towards objects, and perceived as positive excitement. To the contrary, when the SEEKING neural dynamics reverberate in a closed way, they promote compulsive actions and positive exploratory–investigatory affects are substituted by a sense of urgency, which can become maladaptive, hence pathological.

A key issue for any hypothesis is to explain how DA transmission may promote the emergence of the designated behaviors at brain network levels – in this case, the SEEKING disposition. We know that ML-DA cell bodies originate in mesencephalic cell groups, mainly located in the A10/VTA, and their axons project largely to anterior forebrain structures, modulating the activity of re-entrant circuits extending between the basal forebrain/basal ganglia (BG) and the cortical mantle, called BG–thalamo–cortical (BG–T–C) circuits (Alexander et al., 1986; Kalivas et al., 1999; Ungerstedt, 1971). Although many studies have investigated the effects of DA release within terminal brain regions by focussing on molecular or cellular adaptations, and single-cell electrophysiological responses (e.g., Greengard, 2001; Nicola and Deadwyler, 2000), a clear understanding of behavioral and psychological functions of ML-DA transmission require large-scale network analyses of the brain that very few studies have conducted.

3.3. Neurodynamics

Wide scale electrophysiological neurodynamic studies will eventually be needed to envision a global system like SEEKING in action. Unfortunately, only modest progress has been made with such approaches. However, some recent studies have started exploring how DA modulates global–field dynamics and influences oscillatory patterns within projection areas. Although most were originally focused on the role of nigrostriatal DA transmission in Parkinsonian disease (Brown, 2003; Lee et al., 2004; Magill et al., 2004), some result may also be extended to the role of ML-DA transmission under normal behavioral conditions (Berke, 2009; Cohen et al., 2009; Pennartz et al., 2009). In sum, these findings demonstrated that DA modulates oscillatory patterns emerging in BG–T–C circuits and other regions of the anterior limbic brain. The most robust effect of DA release is a decrease in power and coherence of beta-frequency oscillations (~15 Hz) (Brown, 2003; Dejean et al., 2008; Hammond et al., 2007) and of cortical-derived low frequency oscillations (~1 Hz) in the entire BG–T–C network (Galati et al., 2010; Tseng et al., 2001). Interestingly, this desynchronization effect is related to the facilitation of movement initiation and/or execution (Cassidy et al., 2002; Courtemanche et al., 2003; Kuhn et al., 2004; Rivlin-Etzion et al., 2006; Sharott et al., 2005).

It has also been shown that DA promotes transient high-frequency oscillations in the gamma band (>30 Hz) (Berke, 2009; Brown, 2003; Demiralp et al., 2007; López-Azcárate et al., 2010). Interestingly, gamma rhythms are present in waking, REM sleep (Franken et al., 1994) and during spontaneous active behaviors (Maloney et al., 1997) and they seem to have an important function in temporal organization of cognitive, perceptual and motor functions (see Fries et al., 2007 for a review). Some authors suggested that gamma rhythms are involved in sensory awareness and consciousness (Engel and Singer, 2001; Tononi et al., 1998), while others in the emergence of intentional brain states (Freeman, 2003).

We actually ignore how gamma oscillatory waves are exactly generated in neural networks and how DA transmission may favour their expression. However, it has been shown that GABA inhibitory neural networks have an intrinsic capacity to generate high-frequency oscillations (Llinás, 2001; Steriade, 1996). More recent evidences also suggest that gamma synchronization is locally promoted by GABA fast-spiking neural activity either in cortical or in striatal areas (Cardin et al., 2009; Kopell and Ermentrout, 2004). Exciting fast-spiking interneurons (Bracci et al., 2002) and facilitating the emergence of their sequential activity patterns in inhibitory networks (Stewart and Plenz, 2006), DA may then promote transient synchrony in the gamma band which is locally generated and eventually communicated to distant areas.

Recent investigations focusing more specifically on DA transmission in the striatum, the principal input structure of BG, revealed that gamma rhythms are related to movement initiation in dorsal striatal areas (Masimore et al., 2005) and with decision-making and reward functions in VS/Nacc areas (Cohen et al., 2009; van der Meer and Redish, 2009). With a sophisticated combination of local field potentials, single-unit and behavioral analyses, it has been shown that ~80 Hz gamma oscillations in VS/Nacc are temporally related mostly to the emission of approach movements and also, to a minor extent, with reward delivery and consummatory behaviors (Kalenscher et al., 2010). Moreover, many single neurons phase-locked their discharge patterns to gamma waves. It was also demonstrated that gamma oscillations were specifically expressed when the animal was moving towards a potential reward site and not when it was moving in other directions. The authors suggested that gamma rhythmicity was not a function of just movements, but “of cognitive aspects of reward-seeking behavior” (Kalenscher et al., 2010, p. 1669). However, in our view, cognitive processes, are only one “slice of the pie”, and gamma oscillations may be more globally viewed as the overall emotional–motivational neurodynamics through which the SEEKING disposition is expressed, accompanied by a feeling of excitement/euphoria (not ‘pleasure’) that is evolutionarily designed to achieve a diversity of useful outcomes. We think that gamma rhythms in ventral BG are the “SEEKING wave packets”, binding together cognitive, perceptual, motor and affective visceral processes into single dynamic entity. Within such hypothesized SEEKING waves, perhaps related to bursts of sniffing which highlight anticipatory states in rodents (Panksepp, 1981, 1998), some specific neurodynamic sequences related to explorative and approach movements are somehow released in accordance with specific affective–sensorial and cognitive representations (Alcaro et al., 2007).

The VS/Nacc is currently accepted as a convergence node for diverse inputs coming from distinct limbic areas involved in different perceptual, cognitive and affective aspects of goal-directed activities. Indeed, together with the piriform cortex and the olfactory bulb, the VS/Nacc forms an olfactory network producing coherent 50–70 Hz oscillations (Berke, 2009), perhaps involved in sensorial aspects of SEEKING, and in the discrimination/recognition of a reward site (Kalenscher et al., 2010). On the other hand, together with the pFC, the Nacc forms a SEEKING motor network that oscillates at 70–100 Hz and generates patterns such as exploratory locomotor activity accompanied usually by sniffing (Berke, 2009). A third network is instead constituted by Nacc and hippocampus, characterized by the superimposition of theta and gamma rhythms and mainly involved in spatial navigation and decision-making about movement directions (Lansink et al., 2009; Tort et al., 2008). Therefore, sensorial/cue-information (from piriform cortex and amygdala), spatial/contextual information (from hippocampus), and internal-state information (from the anterior cingulate cortex and orbitofrontal cortex) converge in VS/Nacc (especially the Nacc shell) (Fig. 3): at this point of neural functioning, DA-promoted gamma rhythms may incorporate incoming

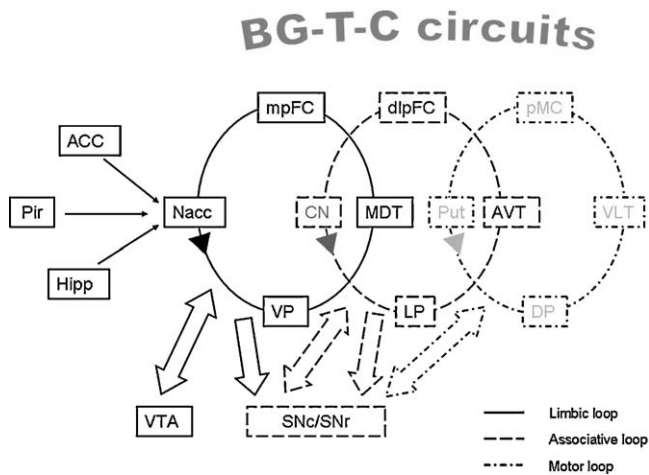


Fig. 3. Brain circuitries for the SEEKING wave packets. The presence of high-frequency gamma oscillations associated with active exploration, approach and goal-directed actions have been found in the Nacc and in limbic structures that project to the Nacc, such as the ACC, the Pir and the Hipp. From the Nacc, the SEEKING wave packets diffuse across BG-T-C circuits, passing through the limbic, the associative and the motor loop. Such ventromedial–dorsolateral gradient of diffusion is possible thanks to the interconnections between BG areas and the VTA/SN DA system that show a spiralling functional organization. Abbreviations: ACC, anterior cingulate cortex; AVT, anteroventral thalamus; BG-T-C, basal ganglia-thalamo-cortical; CN, caudate nucleus; dlpFC, dorsolateral prefrontal cortex; DP, dorsal pallidum; Hipp, hippocampus; LP, lateral pallidum; MDT, mediodorsal thalamus; mpFC, medial prefrontal cortex; Nacc, nucleus accumbens; Pir, piriform cortex; pMC, premotor cortex; Put, putamen; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; VLT, ventrolateral thalamus; VP, ventral pallidum; VTA, ventral tegmental area.

information within the SEEKING wave packets which already poses an intrinsic/instinctual affective-action and incipient intentional (intentions-in-action) structure.

Neuroanatomical studies have indicated the VS/Nacc as an important “boundary area” connecting the limbic brain (ACC, mpFC, hippocampus, amygdale) to dorsolateral motor structures (dorsolateral pFC, dorsolateral BG, motor cortex). For this reason, the VS/Nacc has been defined an “interface between limbic and motor system” where internal “motivation are translated into action” (Mogenson et al., 1980). From our perspective, this role may be due to the diffusion in BG-T-C circuits of the SEEKING neurodynamics formed in VS/Nacc and related limbic structures.

Interestingly, the interconnections between BG areas and the ML-DA system show a spiralling functional organization, with DA neurons acting as an intermediary of a ventromedial–dorsolateral gradient that goes from the limbic to the associative to the motor loop of such circuits (Haber et al., 2000; Joel and Weiner, 2000). Thus the dorsal striatum is ideally situated to generate behavioral habit structures, while no longer having robust reward attributes as does the ventral striatum. Therefore, DA transmission favours the emergence of the SEEKING wave packets in the limbic brain, but it may also promote passage of that in BG-T-C circuits, to limbic, associative and motor loops (Fig. 3). In such a way, limbic brain activation states are translated within the frontal cortex into higher-order intentional patterns aimed at exploring, seeking and approaching new environmental reward opportunities, or available for rapid utilization of learned cognitive and motor sequences that already have solidified goal-directed habit functions. Interestingly, recent studies have revealed that the DA projections to the VS/Nacc participate in various distinct sub-functions of the overall SEEKING urge: the medial part of DA projections directed to the Nacc shell subterritories are important for integrating novel reward opportunities, while the lateral portions directed to the Nacc core and dorsal striatum are more for the actual execution

of conditioned responses, and solidifying new behavior patterns into habitual modes of behavior, that may simply require properly directed approach behaviors (Ikemoto, 2010). In sum, this evidence suggests that the ventromedial shell parts of ML-DA system is more concerned with the unconditioned emotional aspects of SEEKING, when affective intensity is high, while the dorsolateral parts are more involved with the conditioned learned expression of SEEKING, when unconscious habits take over behavioral control.

4. The SEEKING disposition and psychiatric diseases

Within the affective neuroethological perspective we advocate here, most psychiatric disorders are emotional-affective diseases, with observable dysfunctional neural processes that express and modulate basic emotional drives. Psychiatric diseases may emerge from maladaptive communications and emerging imbalances between higher forebrain areas involved in complex representation of our interpersonal world and basic emotional operating system located in ancient subcortical regions, especially when lower affective processes prevail over gradually established higher cognitive function.

Experimental and clinical evidences suggest that the SEEKING brain system is differentially involved in various psychiatric diseases. For example, there is abundant evidence for abnormal ML-DA functioning in schizophrenia (Carlsson, 1978; Meltzer and Stahl, 1976; Snyder, 1972), addiction (Koob, 1992; Wise and Bozarth, 1987), attention deficit hyperactivity disorder (ADHD) (Levy, 1991; Oades, 1987), and depression (Nestler and Carlezon, 2006; Willner, 1983a,b). Recent neurophysiological studies have also revealed disturbed gamma oscillatory activity in the anterior forebrain in some of the above-mentioned diseases. For example, abnormal neural oscillations and synchrony in the gamma and beta range have been found in schizophrenic patients (Uhlhaas and Singer, 2010). Here, we will focus on the potential role of imbalanced SEEKING dispositions in two important and often related pathologies, depression and addiction, focusing on all the levels of analysis discussed above (also see the contribution by Zellner et al., 2011).

4.1. Depression

In the DSM-IV, two core symptoms characterizing Major Depressive Disorders are “anhedonia”, that is defined as a state of reduced interest for pleasurable activities, and “helplessness” or “hopelessness”, that are defined as a sense of impotence and of the inevitability of feeling one’s own despair. Such symptoms have been replicated in animal models. Some of them consist in placing animals under uncontrollable negative situations while depression is measured as a ‘giving up’ resulting in a failure to cope (helplessness) (Porsolt, 2000; Henn et al., 1985; Overmier and Seligman, 1967). In other models, depression is assessed as a reduced motivation to seek rewards (anhedonia), based on the disturbances animals show in responding for ESSB or for exploring new environments (Anisman and Matheson, 2005; Bevins and Besheer, 2005; Nestler and Carlezon, 2006; Overstreet, 1993; Willner et al., 1992; Zacharko and Anisman, 1991).

Although depression is a very complex disease, with many interacting etiologic factors, we would like to present a simplified model of such pathology based on the analysis of a single emotional factor. In our view, helplessness and anhedonia may be related to a deficiency in the SEEKING emotional disposition, that is normally aroused when animals search for sensory rewards as well as for more secure environmental conditions (“safety”). Under this simplified view, we look at depression as a state of reduced engagement with all aspects of the world, due to an endogenous hypo-functionality of the SEEKING network or to an inhibition of

its activity by other brain circuits, such as those involved in processing negative emotions (GRIEF/Separation–Distress, FEAR or RAGE) (Panksepp, 2011b; Panksepp and Watt, 2011; Watt and Panksepp, 2009). We are conscious that the “SEEKING deficiency” may be caused or exacerbated by specific cognitive evaluations, previous learning, homeostatic self-regulatory adaptations and many other processes not considered in this work. However, we think that independently from other underlying mechanisms, depression is a state generally characterized by reduced SEEKING at the behavioral, neurobiological and psychological levels.

In accord with our hypothesis, animal models of depression show reduced metabolic activity of the SEEKING network in appetitive aversive or resting-state conditions (for overview, see Harro et al., 2011; Kanarik et al., 2010). Indeed, Fos immunohistochemistry studies showed that depressed mice are characterized by marked reductions in neural activity stimulated by stress or novel environments in the VS/Nacc, the anterior piriform cortex (PiCx), the anterior and posterior cingulate gyri (ACC, PCC), the dorso-medial and dorsolateral pFC, the secondary motor cortex (Stone et al., 2006, 2007, 2008). In rats, chronic stress procedures that induce depression led to decreased Fos-immunoreactivity in the Nacc after sucrose injection (Grippio et al., 2004). Moreover, congenitally helpless rats present reduced metabolic activity in the ventral tegmental area (VTA), the ventral pallidum (VP), the dorsal basal ganglia (BG), the lateral and medial septal nuclei, and the cingulate and frontal cortex (Shumake and Gonzalez-Lima, 2003; Shumake et al., 2003). Finally, in a recent meta-analysis study, we have demonstrated that depressive animals show a resting-state metabolic hyperactivity in several subcortical brain structures that are known to exert an inhibition over the SEEKING network, such as the PAG, the MR and DR, and the Hab (Alcaro et al., 2010).

It has also been suggested that “anhedonia and amotivation, symptoms prominent in depressive patients, are mainly governed by DA neurotransmission in reward and motivation circuits” (Nader et al., 1997). Animal studies support the idea that a deficit in DA transmission, especially in the ML pathway, is responsible for both helplessness and anhedonia (Di Chiara et al., 1999; Dunlop and Nemeroff, 2007; Nestler and Carlezon, 2006). For example, chronic stress and other procedures that induce behavioral depression cause a parallel dysregulation of ML-DA transmission and DA receptor functionality (Cyr et al., 2001; Daftary et al., 2009; Friedman et al., 2007; Imperato et al., 1993; Nestler and Carlezon, 2006; Papp et al., 1994; Willner, 1983a,b; Yadid et al., 2001). Moreover, animals genetically vulnerable to depression show a deficit in ML-DA transmission, such as decreased extracellular DA levels in the Nacc (Dremencov et al., 2005; Zangen et al., 2001), decreased expression of DA transporter protein (DAT) in several ML regions (Jiao et al., 2003), and reduced metabolism in the VTA (Shumake et al., 2003). Finally, mutant mice lacking a protein that regulates the activity of D2 receptors (Par-4) showed predisposition to depressive behaviors (Park et al., 2005).

Although the main antidepressant drugs act at the level of the serotonergic and noradrenergic systems, adaptations at the levels of the ML-DA system seem to constitute the final pathway mediating their therapeutic effects. Indeed, various efficacious antidepressant therapies induce functional re-organization of the ML system, increasing DA transmission in the Nacc (Ichikawa and Meltzer, 1995; Keck et al., 2002; Pallis et al., 2001; Ventura et al., 2002; Zangen and Hyodo, 2002), and the functionality of D2-like receptors (Gershon et al., 2007; Spyraki and Fibiger, 1981). Acute administration of psychostimulants (cocaine and amphetamine) enhances synaptic DA transmission and reduces depressive states in animals, increasing the attempts to cope with stress and the motivation for brain stimulation reward (Alcaro et al., 2002; Steru et al., 1985; Wise, 1996). On the other hand, withdrawal from chronic psychostimulant exposure depletes brain DA, which pro-

motes depressive states (Barr and Markou, 2005; Kitanaka et al., 2008; Paterson and Markou, 2007).

It has also been shown that DA agonists or other drugs that favours DA transmission may have antidepressant effects (Anisman et al., 1979a; Basso et al., 2005; Fu et al., 2006; Willner, 1997; Yamada et al., 2004), while DA antagonistic drugs have depressive-inducing effects (Anisman et al., 1979b; Cheeta et al., 1994; Wise, 1978). Finally, recent studies showed that complex molecular adaptations involving CREB activity in the Nacc (see Nestler and Carlezon, 2006 for a review) and the release of dynorphin along the meso-accumbens pathway promote depressive behaviors in rodents (Mu et al., 2011).

We close this section by revisiting the neurodynamic issues addressed earlier. Although relevant data is currently modest, indirect evidence suggests that depression is characterized by reduced anterior forebrain gamma oscillatory waves, that we have previously defined as the “SEEKING wave packets”. For example, parkinsonian patients suffer from depression and are characterized by absence of gamma waves in BG-T-C circuits (Brown, 2003). Moreover, transcranial magnetic stimulation treatment, a modestly effective antidepressant therapy, increases gamma oscillations in pFC (Barr et al., 2009). Finally, high-frequency (<100 Hz) deep brain stimulation (DBS) of ACC (Cg25) and the Nacc shell region has substantial antidepressant effects (Bewernick et al., 2010; Mayberg et al., 2005; Schlaepfer et al., 2008) and increases gamma oscillatory activity in the orbitofrontal cortex (OFC), the medial prefrontal cortex (mPFC) and mediodorsal thalamus (MD) (McCracken and Grace, 2009). We would take these preliminary results to suggest the hypothesis that depression may be related to reduced emergence and diffusion of the SEEKING wave packets into other brain regions, especially frontal and dorsal striatal regions, while effective antidepressant therapies may help restoring their normal expression in brain circuits. In this respect it may be interesting to see how the SEEKING wave packets synchronize with key unconditional indices of arousal of this system, including VTA–DA neuron bursting, investigatory sniffing bouts, and 50 kHz ultrasonics, which are controlled by mesolimbic dopamine and can be used to monitor the positive hedonic status of animals (Burgdorf et al., 2007; Panksepp, 1981, 2010a; Rossi and Panksepp, 1992, also see Burgdorf et al., 2011).

4.2. Addiction

Many current behavioral neuroscience studies consider drug addiction as a “pathological usurpation of the mechanism of reward-related learning” (Hyman, 2005). Consequently, addiction is at times treated pharmacologically or psychologically, in order to extinguish dysfunctional memories (Kaplan et al., 2011). However, such a view often fails to consider the role played by emotional-affective processes in learning, and the critical importance of shifting affective states in the genesis of addictions (see Zellner et al., 2011). Indeed, we may be wise to consider that very often compulsive drug seeking may represent for addicts a most efficacious way to counteract the dominance of negative affective states (Koob and Le Moal, 2001). For instance in opiate addiction, excessive feelings of depressive psychological pain arise from separation to distress circuits (Panksepp, 1981b). Together with humans self-report analyses, animal behavioral studies show that addiction is characterized by depression, anxiety and other negative affects, which become evident during withdrawal periods whether from drugs or other addictive habits (Koob and Le Moal, 2008; Panksepp et al., 2002).

Although such negative symptoms have been generally related to neural adaptations following chronic drug exposure, where compulsive addictive cycles have been established (Koob, 2009), several lines of evidence indicate that some neural and psychological anomalies may be present in susceptible individuals before the

initiation of drug assumption, predisposing individuals to develop drug abuse as well as other forms of compulsions such as gambling and obsessive sexuality (Campbell et al., 2009; Khantzian, 2003; Koob and Volkow, 2010; Le Moal, 2009). For example, a hyper-excitability of the brain stress system may be observed not only in drug addicts but also in predisposed individuals (Panksepp, 2010b; Sinha, 2008), which may promote dopaminergic drive (Daftary et al., 2009). Therefore, we hypothesize, along with related work (Kassel, 2010), that drug addiction further strengthens an emotional liability already present before initiating chronic use. But what, beside feelings of social isolation and excessive stress, may such a liability reflect?

In accord with the focus of this review, we will propose that addicts are generally characterized by an abnormal expression of SEEKING. If depression is characterized by a general reduction of SEEKING urges, addiction may be described as a re-organization of such a weakened emotional disposition around specific and often dangerous environmentally driven activities. In our affective neuroethological view, addiction is the result of an “emotional shrinkage”, due to an ever increasing, and eventually exclusive recruitment of the SEEKING emotional disposition by memories of addictive rewards and desires to alleviate the dysphoria arising from drug withdrawal (Koob, 2009; Panksepp, 2010b). In some forms of addiction, especially in the first stages, the normal emotional aspects of SEEKING are still active, but come to be strictly circumscribed to specific contexts and activities. In other forms, especially in the later stages, the natural emotional attitude to SEEK various rewards is largely overwhelmed by the establishment of compulsive habits that have largely lost direct positive value and are repeated exclusively to calm an increased sense of psychological pain, anxiety and tension.

It is difficult to trace back all the psycho-behavioral and neurobiological features characterizing addiction through all the intervening stages, from initial predisposition to compulsive use and relapse episodes. In order to give a synthetic picture, we will focus mainly on those features that characterize addiction vulnerability, without considering the enormous amount of data about the effects of chronic drug exposure in the brain. In such a way, the results may be extended also to those forms of addiction that are not based on drug abuse, such as pathological gambling, compulsive shopping, binge eating, hypersexuality, and internet addiction.

Interestingly, animal models have revealed that addiction vulnerability is characterized by signs of increased responsiveness (sensitization) of the SEEKING disposition to certain environmental stimuli. For example, compared to controls, animals predisposed to develop addiction show higher locomotion, and exploration in novel environments, and they also demonstrate higher preference for novel environments (Dellu et al., 1996; Piazza et al., 1989; Rouge-Pont et al., 1993). These patterns suggest that vulnerable individuals may be characterized as “novelty seekers” or “sensation seekers” (Bardo et al., 1996), with enhanced activation of the SEEKING disposition to all unusual stimuli.

The increased responsiveness of the SEEKING system to novelty may be responsible for an increased conditioning power of environmental stimuli. Indeed, recent studies have indicated that animals predisposed to addiction show higher tendency to SEEK and approach cues previously associated with reward instead of the reward itself (Flagel et al., 2010). In turn, the higher responsiveness of the SEEKING disposition to conditioned stimuli may increase the secondary-reward value (incentive salience) of drug-associated cues and lead to the establishment of compulsive habits after some experience of drug intake. As underlined by the “incentive sensitization hypothesis”, addiction is indeed sustained by an increased attractive power of certain environmental stimuli and behavioral activities (Robinson and Berridge, 1993).

The hyper-excitability of the SEEKING disposition in addiction has been demonstrated also at the neurochemical level. Increased DA release after novelty, drugs and drug-related cues has also been shown in animals vulnerable to addiction (Bradberry et al., 1991; Hooks et al., 1992; Piazza and Le Moal, 1996; Robinson and Berridge, 2000; Rouge-Pont et al., 1993; Zocchi et al., 1998). Moreover, rats selected for high responsiveness to psychostimulants and novelty present increased firing and bursting activity of the ML-DA system in basal conditions (Marinelli and White, 2000). Such “endogenous sensitization” has been explained by increased efficacy of synaptic signals connecting descending glutamatergic inputs to the VTA (Marinelli and White, 2000; Melis et al., 2009). However, doubts about the endogenous sensitization hypothesis has come from experiments showing that vulnerable rats have a slower resting-state rate of DA release and uptake in Nacc compared with normal rats (Chefer et al., 2003). Therefore, in such animals, increasing firing and bursting of DA neurons correlates with less rapid and robust ML-DA transmission in resting-state conditions, and the addictive cycles may further weaken the resting-state affective tone of the system, leading to the vicious cycle discussed by Koob (2009) and Khantzian (2003). Incidentally, the increased activity of DA neurons may be attributed to a deficiency in DA transmission, since DA blocks the spreading of top-down glutamatergic inputs and brakes the diffusion of cortical synchronized activity in BG and midbrain DA nuclei (Tseng et al., 2005; Wichmann and DeLong, 2003).

In accordance with findings of Chefer and collaborators, low basal levels of ML-DA have been found in individuals vulnerable to addiction or with a history of chronic drug use (Gardner, 1999; George et al., 1995; Misra and Pandey, 2003; Nestler, 1993; Parsons et al., 1991; Weiss et al., 1992). This deficiency would predispose towards anxiety and depression, isolating individuals from their social and other rewarding environments, thereby preventing them from regulating their internal appetitive eagerness states through diverse open relationships with the external world. Therefore, the “self-medication hypothesis” (Markou et al., 1998; Khantzian, 2003) and the “reward deficiency hypothesis” (Comings and Blum, 2000) have interpreted addiction as attempts of self-regulating an endogenous hypoactive ML-DA system, which may be a key activator of the SEEKING disposition within forebrain.

An essential issue in addiction research is to integrate the evidence of an endogenous hypoactive ML-DA/SEEKING system with experimental results showing its enhanced responsiveness to some stimuli such as novelty, conditioned cue and drugs of abuse. In this context, addiction vulnerability may be expressed by a substantial shift in the way ML-DA activity is regulated. Specifically, we think that an endogenous deficiency of the ML-DA system is compensated, during development (adolescence), by increased excitatory drives coming from pFC and other higher forebrain structures. The hyper-excitability of the ML-DA system to glutamatergic input descending onto the VTA would cause increased DA release after environmental stimuli which are usually processed by higher forebrain structures, such as novelty and conditioned cues, predisposing individuals to be highly responsive to exogenous stimuli. In such a way, the bottom-up tonic activation of SEEKING by internal homeostatic drives, yielding endogenous arousal, may give way to exogenous top-down activation of the system by cortical areas involved in processing external cues.

In our view, such a predisposition is present during the initial stages of addiction, but is further exacerbated after chronic drug use, by the acquisition of specific contextual memories that stimulate the SEEKING circuit. How does all this relate to the aforementioned neurodynamic considerations discussed earlier? Obviously, it would be extremely relevant to know how addictions are expressed in term of the underlying network neurodynamics. Unfortunately, direct measures of oscillatory patterns in the brain of addicts are sparse, and they have almost exclusively

investigated in terms of the effects of chronic drug intake on brain activity. Interestingly, opioid and nicotine dependence are expressed by increases in functional synchronization of cortically derived rhythms (Domino, 2003; Fingelkurts et al., 2007). Moreover, stimulus-evoked cravings were accompanied by increased beta oscillatory waves in frontal regions of both cigarette smokers (Knott et al., 2008) and cocaine users (Reid et al., 2003), indicating intense cortical activation by such stimuli.

However, among the most important findings are those concerning the therapeutic effects of DBS. It has been recognized that DBS of Nacc may be efficacious in the treatment of depression (Schlaepfer et al., 2008), obsessive–compulsive disorders (Sturm et al., 2003) and alcohol addiction (Heinze et al., 2009) and that DBS of the Nacc shell attenuates cocaine priming-induced reinstatement of drug seeking in rats (Vassoler et al., 2008). Since DBS in the Nacc promotes gamma oscillations in different limbic areas (McCracken and Grace, 2009), we suspect that its therapeutic and protective effects depend on the facilitation of internal-generated SEEKING affects which contrast with exogenous cue evoked activations coming from higher forebrain areas. Thus, by establishing a healthier affective tone in the SEEKING system, the person may more easily free themselves from the bondage of conditioned external amplifiers of addictive urges.

4.3. Direct measures of affective states in depression and addiction animal models

We have discussed some of the SEEKING-linked neural underpinnings of depression and addictions, which is synergistic with various current behavioral models of addiction, but which have commonly ignored one key underlying issue – the affective feelings that accompany these psychiatric problems, especially in pre-clinical animal models that are increasingly used to ferret out the underlying neural mechanisms. This neglect is in line with most other current pre-clinical models of psychiatric disorders (Hyman, 2007; for a critique, see Panksepp, 2010a). We would simply indicate that we might do better if we more consistently included direct measures of affective changes in our pre-clinical research (e.g., Burgdorf et al., 2001a,b; Panksepp et al., 2002).

Although this has not been a common perspective in the study of animal models, it can finally be achieved, not only by monitoring the ‘reward’ and ‘punishment’ thresholds of brain emotional systems (Panksepp, 1998, 2005), but also direct vocal indicators of positive and negative affective states. For instance, in rats, 55 kHz ultrasonics index arousal of the SEEKING system (Burgdorf and Panksepp, 2006; Burgdorf et al., 2007), and 22 kHz ultrasonics index the arousal of discrete negative affective network of the brain (Brudzynski, 2007). It is increasingly clear that we can use these measures to estimate addictive liability (Knutson et al., 2002; Panksepp et al., 2002), as well as depressive tendencies (Panksepp, 2010a, and see Burgdorf et al., 2011). Further, we should be able to model disorders such as depression by direct stimulation of PANIC/GRIEF systems of the brain (Panksepp and Watt, 2011), and treat depression by stimulating the SEEKING system (see Coenen et al., 2011).

5. Conclusion: SEEKING and the emotional view of appetitive urges

Despite the continued need for rigorous behavioral and neurobiological analyses, a psychobiological perspective is also essential for realistic scientific confrontation with the problem of the intrinsic intentionality and coherence of brain emotional networks that evolution built into organisms (Panksepp, 1998). The primary-process emotional system perspective, preserve us from the allure of ruthless reductionism that the more pure behavioral neuro-

science approaches often embrace, and from endless equivocations about whether animals experience anything, since empirical evidences for an affective view of animal brains is next to definitive (Panksepp, 1998, 2005, 2011a; Panksepp and Biven, 2011).

SEEKING is fundamentally a fully integrated psychobiological concept, that gives equal attention to the psychological and the behavioral features as well as to the underlying brain mechanisms that mediate the natural urges of animals to engage adaptively with their environment. The unity and the force of SEEKING concept are due to its intrinsic intentionality. SEEKING is neither exclusively related to behavioral outputs (e.g. approach) nor to specific environmental cues. It expresses the organism’s attitude to move towards configurations emerging in its psychological–perceptual fields, both when actual objects are present in the external environment or, at least in humans, simply represented at the mental level. Therefore, the intrinsic intentionality of SEEKING is not well developed in purely objective cognitive–behavioristic perspectives. For that reason, we advocate more specific attention to the affective feeling qualities of positive anticipatory excitement and euphoria, which may represent the manifestation of the intrinsic intentionality that characterize the SEEKING disposition at the subjective level.

Although the use of psychological concepts such as emotions and feelings has continued to be banished during the rise of cognitive-behaviorism in behavioral neuroscience, new neurophenomenological and neuro-affective interpretations of past data suggest that such concepts have robust correspondences to brain functions (Panksepp, 1998; Panksepp and Biven, 2011; Panksepp and Northoff, 2009; Tononi and Edelman, 1998; Varela, 1999). This suggests new and unique conversations of how mammalian brains are functionally organized. Thus, in this paper, we proposed that SEEKING urges in mammals are related to characteristic neural oscillatory patterns promoted by DA in the anterior limbic forebrain, what we have called “SEEKING wave packets”. Such neurodynamic patterns express a primary-process emotional disposition that is rich with appetitive and incentive reward properties.

If we ignore the relevant intentional-experiential psychological aspects of animal emotional arousals we cannot have satisfactory pre-clinical models and hence deep neuroscientific explanations of psychiatric disorders. Here we highlighted depression and addictions as key examples of how to envision the underlying causal processes while not ignoring the psychological states of either animals or humans. Specifically, depression is characterized by a markedly weakened SEEKING disposition, perhaps most commonly initiated by sustained separation–distress (Panksepp and Watt, 2011). Addictions reflect profound re-organizations of the SEEKING urge around drug use related memories and associated compulsive habits, sustained by specific types of endogenous appetitive-affective dynamics.

We have no desire to deny or criticize the relevance or utility of other cognitive, behavioral or motivational interpretation of such diseases. However, we think that an affective neuroethological perspective adds coherence to interpretations of depression and addiction at all the relevant levels of analysis: the psycho-behavioral, the neuroanatomical, the neurochemical and the neurodynamic.

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