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Review

Behavioral functions of the mesolimbic dopaminergic system: An affective neuroethological perspective

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ABSTRACT

The mesolimbic dopaminergic (ML-DA) system has been recognized for its central role in motivated behaviors, various types of reward, and, more recently, in cognitive processes. Functional theories have emphasized DA's involvement in the orchestration of goal-directed behaviors and in the promotion and reinforcement of learning. The affective neuroethological perspective presented here views the ML-DA system in terms of its ability to activate an instinctual emotional appetitive state (SEEKING) evolved to induce organisms to search for all varieties of life-supporting stimuli and to avoid harms. A description of the anatomical framework in which the ML system is embedded is followed by the argument that the SEEKING disposition emerges through functional integration of ventral basal ganglia (BG) into thalamocortical activities. Filtering cortical and limbic input that spreads into BG, DA transmission promotes the "release" of neural activity patterns that induce active SEEKING behaviors when expressed at the motor level. Reverberation of these patterns constitutes a neurodynamic process for the inclusion of cognitive and perceptual representations within the extended networks of the SEEKING urge. In this way, the SEEKING disposition influences attention, incentive salience, associative learning, and anticipatory predictions. In our view, the rewarding properties of drugs of abuse are, in part, caused by the activation of the SEEKING disposition, ranging from appetitive drive to persistent craving depending on the intensity of the affect. The implications of such a view for understanding addiction are considered, with particular emphasis on factors predisposing individuals to develop compulsive drug seeking behaviors.

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Abbreviations: ARAS, ascending reticular activating system; BG, basal ganglia; CPP, conditioned place preference; DA, dopamine; ESSB, lectric self-stimulation of the brain; FAPs, Fixed Action Patterns; GABA, gamma aminobutyric acid; MFB, medial forebrain bundle; ML, mesolimbic; ML-DA system, mesolimbic dopamine system; NS-DA system, nigrostriatal dopamine system; NE, norepinephrine; Nacc, nucleus accumbens; pFC, prefrontal cortex; TD, temporal difference models; VP, ventral pallidum; VTA, ventral tegmental area

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Contents

1. Introduction

1.1. *The mesolimbic dopamine (ML-DA) system*

The ML-DA system (Fig. 1) has received considerable attention due to its involvement in a range of psychological processes and neuropsychiatric diseases. In fact, after the development of a DA theory of schizophrenia (Carlsson, 1974, 1978; Snyder, 1972; Meltzer and Stahl, 1976), additional ML-DA hypotheses have been proposed to explain addiction (Wise and Bozarth, 1981, 1987; Koob, 1992), attention deficit hyperactivity disorder (ADHD) (Oades, 1987; Levy, 1991; Russell, 2000), and depression (Willner, 1983a,b; Dailly et al., 2004) as well as global behavioral activation (Gray, 1995) ranging from response persistence to behavioral compulsions (Salamone and Correa, 2002; Everitt and Robbins, 2005).

Localized electrical brain stimulation studies (Olds and Milner, 1954; Heath, 1964; Olds, 1977; Wauquier and Rolls, 1976) have implicated the ML-DA in positive rewarding states (Wise, 1978, 1981; Wise and Rompre, 1989) as well as in appetitive motivated behaviors (Panksepp, 1971, 1981a, 1982, 1986, 1998; Blackburn et al., 1987, 1989; Berridge and Robinson, 1998; Ikemoto and Panksepp, 1999). Since DA is also released in response to aversive stimuli and stress (Abercrombie et al., 1989; Puglisi-Allegra et al., 1991; Rouge-Pont et al., 1993; Pruessner et al., 2004), it appears to promote generalized behavioral arousal under both positive as well as negative emotional conditions, perhaps in terms best conceptualized as the seeking of safety (Ikemoto and Panksepp, 1999). Moreover, the ML-DA system has recently been recognized for its role in the determination of personality traits, including "novelty" or "sensation" seeking (Bardo et al., 1996; Zuckerman, 1990), "extraversion" (Depue and Collins, 1999), and "impulsivity" (Cardinal et al., 2004).

Current interpretations of ML-DA functions diverge with respect to emphasis on unconditioned or behavioral priming effects (motivational theories) versus conditioned effects (learning theories). The "psychomotor activation" hypothesis (Wise and Bozarth, 1987), the "behavioral activation system" hypothesis (Gray, 1995), the "behavioral facilitation" hypothesis (Depue and Collins, 1999), the "SEEKING system hypothesis" (Panksepp, 1981a,b, 1998; Ikemoto and Panksepp, 1999), the "wanting" hypothesis (Berridge and Robinson, 1998), and the "effort-regulation" hypothesis (Salamone and Correa, 2002; Salamone et al., 2003) all acknowledge a motivational interpretation of ML-DA functioning. They share a common perspective based on the classic distinction between appetitive and consummatory phases of motivated behaviors (Sherrington, 1906; Craig, 1918), and with relatively minor differences, consider

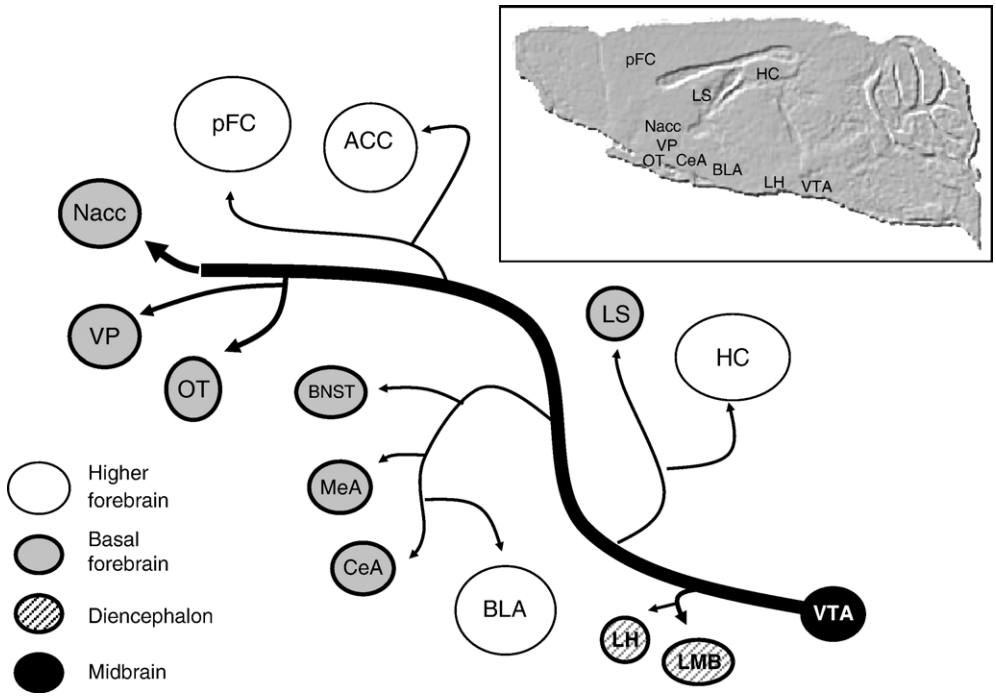

Fig. 1 – The ML-DA system. The figure shows a schematic representation of the main forebrain areas reached by the mesolimbic DA system (Swanson, 1982; German and Manaye, 1993; Haber and Fudge, 1997). According to anatomical and evolutionistic criteria (Swanson, 2000), the structures innervated by ML-DA have been divided in diencephalic, basal forebrain and higher forebrain areas. *Midbrain:* VTA = ventral tegmental area. *Diencephalon:* LH = lateral hypothalamus, LMB = lateral mammillary body. *Basal forebrain*: Nacc = nucleus accumbens, VP = ventral pallidum, OT = olfactory tubercle, CeA = central nucleus of amygdala, MeA = medial nucleus of the amygdala, BNST = bed nucleus of stria terminalis, LS = lateral septum. *Higher forebrain*: pFC = prefrontal cortex, ACG = anterior cingulated cortex, BLA = basolateral amygdala, HC = hippocampal complex.

the DA system as a fundamental drive for the expression of appetitive-approach behaviors.

The "reinforcement" (Fibiger, 1978; White and Milner, 1992; Everitt and Robbins, 2005) and the "reward" hypotheses (Wise, 1978; Wise and Rompre, 1989; Schultz, 1997, 1998, 2001; Spanagel and Weiss, 1999; Di Chiara, 2002; Wise, 2004), on the other hand, have largely focused on DA as a learning mediator. While motivational theories are interested in the proactive actions of DA transmission on future behaviors, learning theories tend to consider retroactive effects on strengthened associations among past events. Although modern incentive motivation concepts view rewards as promoters of motivational arousal and increased behavioral readiness (Bolles, 1972; Bindra, 1974; Toates, 1986; Berridge and Robinson, 1998), learning theories consider that the "most important role of DA in incentive motivation is historical; it is the stamping-in of stimulus–reward association that has established incentive motivational value for previously neutral stimuli" (Wise, 2004).

Multiple attempts to integrate motivational and learning perspectives of ML-DA transmission have been pursued (e.g., Berridge, 2004; Toates, 2004; Koob, 2004), but a coherent evolutionary-ethological view of how brain DA promotes certain types of unconditional psychobehavioral tendencies is typically missing in most formulations. Therefore, a comprehensive hypothesis integrating new findings with earlier literature on rewarding electric brain stimulation has yet to emerge. In our opinion, such needed integration may be achieved by postulating a role of ML-DA in modifying primary-process emotional behaviors[1] and internal affective states (Panksepp, 1998, 2005).[2] In fact, emotions and affects have repercussions both on the way animals act in the world and learn through experience. As extensively described in previous works (Panksepp, 1981a,b, 1998; Ikemoto and Panksepp, 1999), ML-DA promotes the emergence of the *SEEKING emotional disposition*,[3] which we envision as an affective urge

[1] An emotional behavior is a flexible and coherent adaptive response to biologically relevant stimuli. It has an instinctual and inherited basis but is different from other instincts because of its plastic nature and its strong subjective-affective aspects. All the emotional behaviors are constituted by a wide array of behavioral and autonomic responses coordinated as an emotional operating system (or emotional command system) constituted of specific neural circuits within the brain (Panksepp, 1998).

[2] An affective state is the basic subjective feeling characteristic of primary-process homeostatic drives, emotions and the resulting sustained moods.

[3] In this paper we will continue to use the convention of capitalizing the SEEKING disposition indicating that a specific neurodynamic state is activated and the SEEKING system to help highlight that a functional neural system is being discussed. Please also note that capitalizations are used to (i) avoid part–whole confusions, (ii) to alert readers to the claim that these may be *necessary* brain systems for those types of emotional behaviors and feelings although by no means *sufficient* for all the emotional manifestations.

that characterizes all motivated behaviors. This view has been around as long as the more recent incentive salience and reinforcement-type theories but has been typically ignored by those committed to behaviorist learning paradigms.

1.2. *Functional anatomy of the mesencephalic DA projections*

In mammals, most DA-containing neurons are clustered within three major mesencephalic groups: A8 cells in the retrorubral field, A9 cells in the substantia nigra (SN) and A10 cells in the ventral tegmental area (VTA) (Dahlstrom and Fuxe, 1964; Ungerstedt, 1971; Lindvall and Bjorklund, 1974; Fallon and Moore, 1978; German et al., 1983; Arsenault et al., 1988; German and Manaye, 1993). Similar organizations of DA cell bodies have been demonstrated in reptiles (Smeets et al., 1987; Smeets, 1988; Gonzalez et al., 1994) and birds[4] (Smits et al., 1990; Durstewitz et al., 1999). In addition, less dense aggregations of DA neurons inhabit the supramammillary region of the hypothalamus, the dorsal raphe and the periaqueductal gray (Swanson, 1982; Gaspar et al., 1983). Morphological characteristics, anatomical locations, ascending projections and their associations with arousal functions have led many to assign DA neurons to the classical "reticular formation" (Moruzzi and Magoun, 1949; Schiebel and Scheibel, 1958; Leontovich and Zhukova, 1963). Placed within the context of the reticular activating system (Parvizi and Damasio, 2001), DA neurons are sensitive to various global states of organisms, and their ascending projections modulate brain arousal in accordance with those states (Geisler and Zahm, 2005).

The mesencephalic DA cell groups (A8, A9 and A10) lack clear anatomical boundaries, develop in parallel from common embryonic tissues (Olson and Seiger, 1972; Fallon and Moore, 1978; Hu et al., 2004), and partly overlap in their projection fields (Nauta et al., 1978). Their axons project largely to structures located in the anterior part of the forebrain and modulate the activity of cognitive–executive re-entrant circuits between the cortical mantle and the BG (Alexander et al., 1986; Kalivas et al., 1999) (Fig. 2). Such circuits are involved in the organization of practically all motivated behaviors, both highly flexible and more automatic. It is thought that BG–thalamocortical circuits produce adaptive behavioral flexibility, while their dysregulation underlies a whole plethora of neuropsychiatric diseases, from depression to obsessive-compulsive disorders, from addiction to Parkinson's, etc. (Swerdlow and Koob, 1987; Robbins, 1990; Deutch, 1993; Kropotov and Etlinger, 1999; Jentsch et al., 2000; Graybiel and Rauch, 2000; Joel, 2001; Groenewegen, 2003). Resembling a spiraling, functional organization (Zahm and Brog, 1992), a special type of "state" process, information flow appears to exist between different loops of such circuitries with feed-forward processing from limbic regions (especially medial frontal areas) to executive and motor circuits (Heimer and Van Hoesen, 2006). DA neurons thereby act as an intermediary of limbic-emotional and motivational action outflow (Haber et al., 2000; Joel and Weiner, 2000; Mogenson et al., 1980b).

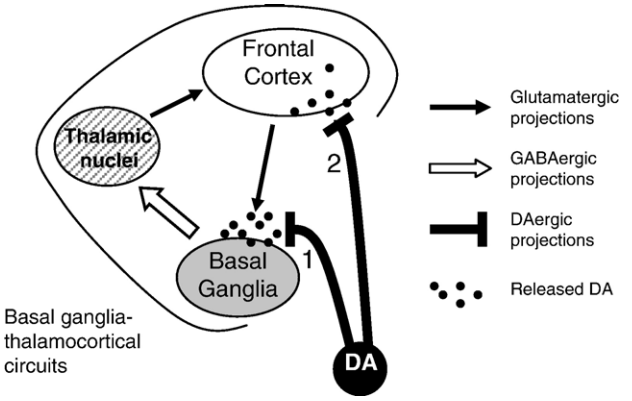

Fig. 2 – DA innervation of BG–thalamocortical circuits. All ascending mesencephalic DA projections innervate the BG rather widely, while only the ML-DA system projects to the frontal cortex. Although the DA transmission in frontal cortex has received an increasing interest, our paper is mainly focused on the role of DA release in BG. In particular, DA transmission in ventral and dorsal striatal areas (the input areas of BG) modulates the communication between glutamatergic projections arriving from frontal cortex and GABAergic neurons located inside the striatum. In such a way, DA regulates the diffusion of neural activity patterns within basal ganglia–thalamocortical circuits. The figure does not show the segregation of BG–thalamocortical circuits described by Alexander and coll. (1986), but the schematic representation can be applied to limbic, associative or motor loops of those circuits.

Although DA cell groups form an anatomical continuum, the ML-DA system has been differentiated from the nigrostriatal (NS) DA system on the basis of anatomical and functional criteria (Bernheimer et al., 1973; Ungerstedt et al., 1974). The ML-DA system (Fig. 1), situated more medially in the brain, is more ancient in brain evolution than the more laterally situated NS-DA circuitry, and it has been more clearly implicated in the regulation of intentional, motivated movements, in flexible-emotive behaviors and in the process of "reward" than the laterally situated NS-DA fields (Papp and Bal, 1987; Wise and Bozarth, 1987; Blackburn et al., 1989; Berridge and Robinson, 1998; Ikemoto and Panksepp, 1999). The NS-DA system, in contrast, controls procedural aspects of movements and motivated behaviors as it reaches more dorsal areas of BG, where behavioral and cognitive habits are learned, stored and expressed (Hornykiewicz, 1979; Carli et al., 1985, 1989; Graybiel, 1997; Jog et al., 1999; Haber, 2003).

1.3. *How can DA affect behavioral and psychological processes?*

DA receptor activated molecular pathways have been partially unraveled (Greengard et al., 1999, 2001a), but the precise mechanisms by which DA influences behavioral and psychological phenomena remain unclear. As a modulator of neural activity, DA interacts with fast synaptic transmission (Green-

[4] Comparative studies in vertebrates have demonstrated the loss of some dopamine (and noradrenaline) cell groups in amniotes compared with anamniotes, especially in the hypothalamic periventricular region (Smeets and Gonzalez, 2000).

gard, 2001b) and thereby influences the way specific external information is processed within the brain (Mesulam, 1998). One hypothesis posits that DA regulatory function increases the signal-to-noise ratio and enhances the efficacy of neural networks in elaborating biologically significant signals (Rolls et al., 1984; DeFrance et al., 1985; Kiyatkin and Rebec, 1996; Nicola et al., 2000). Based on in vivo and in vitro single-cell studies, the signal-to-noise ratio hypothesis explains how behavioral and motivational arousal processes may be linked to specific cognitive or perceptual representations. However, for understanding how behavioral and psychological arousal is processed in the nervous system, large-scale energetic states of the brain, instead of electrical activity of single neurons, need to be considered (Steriade, 1996, 2000; Ciompi and Panksepp, 2004; Llinas et al., 2005; Freeman, 2005). DA modulates global-field dynamics, desynchronizes cortical-derived oscillatory rhythms and promotes high-frequency waves along the gamma band within BG–thalamocortical circuits (Brown and Marsden, 1998; Brown, 2003; Magill et al., 2004; Lee et al., 2004). In our view, these rhythms may be accompanied by the release of *neurodynamic instinctual sequences*, which are essential infrastructures for intentional behaviors.[5] Neurodynamic sequences are repetitive sequential activity patterns reverberating across specific areas and circuits of the brain. Recently, they have been called "avalanches" (Beggs and Plenz, 2003, 2004), and their influence on brain activity may be described with the concept of "dynamic attractors" (Freeman, 2000, 2001, 2003).

The sequential patterns favored by DA in ventral BG–thalamocortical circuits may relate to an instinctual drive to seek life-supportive aspects of the environment and to actively escape those aspects that could be destructive. These neurodynamic sequences are evolutionarily intrinsic, but epigenetically refined, procedural patterns associated with the expressions of exploring and approach behaviors (i.e., locomotion, sniffing, head movements, saccades). The reverberation of such sequential patterns within brain circuits changes the individual's attitude towards the environment, promoting the SEEKING disposition to dominate the motivational landscape of the organism (Panksepp, 1998). This establishes a variety of expectancy states that energize and coordinate the anticipation of life-supporting events with characteristic reward seeking behavioral tendencies (Panksepp, 1981a,b, 1986). In this way, primary-process "intentions in action" get transformed into learning and thought-related "intentions to act" (Panksepp, 2003).

[5] Intentions literally mean to tend to something. In their primary-process form, they are endogenously produced instinctual activities that naturally predispose generalized (initially objectless) action urges to evolve behaviorally towards more specific goal-directed responses. Here, we generally choose to use the concept of intentional behaviors instead of goal-directed behaviors because goal-directed behaviors presuppose the explicit representation of the goal. On the contrary, intentional behaviors are intrinsically driven by impulses of neural activity organizing a specific type of behavioral sequence even before specific objects come to be represented as the final goals. In summary, intentional behaviors are sustained initially by the unconditional tendency of basal forebrain/BG circuits to complete a neurodynamic sequence once it has been activated.

1.4. *Cardinal feature of the affective neuroethological perspective*

Our interpretation of the behavioral functions of the ML-DA system is based on a theoretical perspective we have called the *affective neuroethological view*. Such a perspective has characteristic features that diverge from current dominant theoretical models and that focus on a series of currently neglected elements.

(1) Energy. Modern brain research often fails to account for the energetic and dynamic aspects of neural, behavioral and mental activities. We should ask why animals perceive the world as they do and are spontaneously active in globally energetic ways. How can cognitive computations arise in the brain without the support of global dynamic states that channel an organism's needs via large-scale brain network functions? Where do such global states arise, and how do they interact with informational processes?

New neurodynamic approaches that grant organisms intrinsic behavioral urges are needed to make sense of why organisms do what they do (Panksepp, 1998; Kandel, 1999; Freeman, 2000, 2003; Solms and Turnbull, 2002; Ciompi and Panksepp, 2004). It is time to introduce such concepts into the discussion of brain DA functions since mesencephalic DA and ascending reticular activating system (ARAS) are fundamental energetic sources for many types of neural activity[6] (Moruzzi and Magoun, 1949; Lindsley et al., 1949, 1950; Jones, 2003). In particular, behavioral activating properties of DA may depend on its capacity to influence global field dynamics in the forebrain, as reflected in DA facilitation of the emergence of fast-wave oscillatory rhythms in BG and cortical areas (Brown and Marsden, 1998; Levy et al., 2000; Tseng et al., 2001; Brown, 2003; Magill et al., 2004; Sharott et al., 2005).

(2) Internal procedural sequences. Behavior is not limited to learning and associative processes; neuro-behavioral instinctual processes, shaped by evolution, are essential for almost all aspects of goal-directed learning. Neurocognitive behaviorism denies (or at least ignores) an organism's intrinsic behavioral identity and thus neglects certain inborn adaptive capacities as fundamental determinants of learning (Lorenz, 1965). In addition to neural plasticity and top–down hierarchical brain processes, we must harness ethological traditions in order to better understand intrinsic capacities of organisms

[6] The ARAS represents an endogenous system for regulating brain activity and responding to environmental stimuli and it includes interconnected neural nuclei in the brainstem, the diencephalon and the basal forebrain. The ARAS has also been called the "isodendridic core" of the brain, consisting in a "neural continuum with overlapping dendritic fields stretching from spinal cord to telencephalon" (Geisler and Zahm, 2005, p. 287). As the main source of the basic sleep–wake cycle, it promotes waking arousal as well as behavioral inhibition (Jones, 2003). Placed within the context of the reticular activating system (Parvizi and Damasio, 2001), DA neurons are sensitive to various global states of the organism and their ascending projections modulate brain arousal in accordance with those states. Moreover, since most areas innervated by DA projections send feedback to DA neurons via direct and indirect pathways, the ascending DA systems form re-entrant loops with the reticular formation.

and thereby emphasize the importance to evolutionary constraints on learning (Tinbergen, 1951; Lorenz, 1965; Burkhardt, 2005). In vertebrates, such constraints emerge substantially from the influences that subcortical brain structures exert over neocortical functions (MacLean, 1990; Panksepp, 1998).

In particular, basal forebrain and BG are involved in the expression of sequential, species-specific movements, such as instinctive and unlearned sequential grooming movements in rodents (Cromwell and Berridge, 1996), which are the Fixed Action Patterns (FAPs) of ethologists[7] (Lorenz, 1950; Tinbergen, 1951; MacLean, 1990). Moreover, the BG influence learning, especially when different sequences of actions are linked into a single functional unit (Knowlton et al., 1996; Graybiel, 1998; Jog et al., 1999; Packard and Knowlton, 2002; Bayley et al., 2005). Basal forebrain areas, including BG, extended amygdala, septum and nucleus of Meynert (Heimer and Van Hoesen, 2006), represent the deep, subcortical parts of the cerebral hemispheres (Swanson, 2000), and they are essential foundations for higher information processing regions of neocortex to operate. Housing abundant GABA inhibitory neurons, they form reciprocal networks and send inhibitory outputs to thalamic, hypothalamic and midbrain nuclei (Kitai, 1981; Berardelli et al., 1998; Kropotov and Etlinger, 1999). Situated between the cortex, the diencephalon and the brainstem, the basal forebrain is viewed as largely inhibitory with tonical suppression of behavioral actions (Swanson, 2000). Nevertheless, when something perturbs its intrinsic equilibrium, particular sequences of activity are released. Therefore, basal forebrain nuclei have been considered "doors that, when unlocked, may release into action large functions outside them" (Llinas, 2002).

(3) *Emotions*. Dorsal BG areas control habitual behaviors, whereas other basal forebrain nuclei (ventral BG, extended amygdala, and septum) are involved in emotional behaviors (Koob, 1999; Swanson, 2000; Alheid, 2003; Heimer and Van Hoesen, 2006). Emotions comprise sequences of FAPs that characterize their expressive and communicative aspects (Darwin, 1872; MacLean, 1990; Llinas, 2002), but one main characteristic of emotion is to regulate the organism's behavioral repertoire in flexible ways. Behavioral plasticity arises when each emotional operating system orchestrates a wide range of potential responses in accordance with environmental conditions (Panksepp, 1998). When an emotion is activated, the organism's attention is focused largely on a particular set of stimuli, memories and responses. For example, an animal does not eat while experiencing intense fear; food is transiently excluded from its interests. Diffusion of basal forebrain/BG characteristic patterns communicates an emotional disposition within the brain. Such patterns represent the basic action tendencies characteristic of various primary-process emotions, whose neural representations influence the activity of many different brain regions and help match perceptual and cognitive representations into a global action tendency. In such a way, basal forebrain changes intentional states and orients behavior in specific directions.

From this perspective, it is inadequate to try to explain motivations, intentions and emotions simply from top–down cognitive or representational perspectives. Intentions-in-action, as intrinsic impulses to act, may best be viewed as neural dynamic sequences, which, once activated, constitute internal procedural drives[8] (Llinas, 2002). In our model, such neurodynamic sequences emerge from within basal forebrain and BG areas (Knowlton et al., 1996; Graybiel, 1998), and associated medial diencephalic and mesencephalic circuits, with parallel roles in learning and expression of motor habits and emotions (MacLean, 1990; Graybiel, 1997; Jog et al., 1999).

(4) *Affective feelings*. Neuronal activity is not limited to the production of computational representations of the world; it also helps organize a large variety of states, among which the emotions and associated affects have been ignored for perhaps too long (Panksepp, 1998, 2005). Removing affectivity from neuroscience may lead to a profound misunderstanding of intrinsic brain organization and functioning and hinder scientific understanding of how brains truly operate. A recently re-introduced James-Lange type view of emotions considers affective feeling to be produced by "somatic marker" representations of body changes (Damasio, 1996; Damasio et al., 2000). However, the nature of feelings should also incorporate the intrinsic intentionality of many instinctual behaviors; emotions are not only a consequence of "what happened" (Damasio, 1999), but also "what is happening", "what is going to happen" and "what may happen". Such processes are not uniquely human characteristics; an affective core underlying subjectivity appears to have emerged early in vertebrate brain evolution (Panksepp, 1981a,b, 1998, 2005), derived from brain systems that regulate the inner states of the organisms (MacLean, 1990; Damasio, 1999; Craig, 2003; Thompson and Swanson, 2003; Schulkin et al., 2003; Berntson et al., 2003; Porges, 2003; Sewards and Sewards, 2003; Alheid, 2003; Denton, 2006). The core affective substrate of every emotional feeling seems to be generated and, in part, informs hierarchically related neural networks that include, most prominently, the periaqueductal gray, the hypothalamus and the extended amygdala (Panksepp, 1998). Indeed, accumulating evidence for some kind of primary-process psychological experiences arising from such primitive subcortical circuits is becoming substantial (Panksepp, 2005; Merker, 2007). In our view, the core affective states are communicated to higher brain levels through the emergence of specific neurodynamic sequences, so that the cognitive–evaluative aspects of emotion can be elaborated in a coordinated fashion by various forebrain areas, especially orbitofrontal and medial frontal regions.

[7] In rodents, for example, the BG control instinctive and unlearned sequential grooming movements (Cromwell and Berridge, 1996). The homologues of BG in birds produce highly stereotyped behaviors, such as those used in song learning (Brainard, 2004; Kao et al., 2005), while the striatum in reptiles is involved in regulation of social behaviors (Greenberg, 2003). In primates and other mammals, BG control movements and cognitive executive processes (DeLong, 1990; Graybiel, 1995; Gerfen and Wilson, 1996), especially in initiation and expression of its automatic procedural component (Graybiel, 1998; Jog et al., 1999).

[8] As better described in Section 4, internal procedural drives are sequential neural activity patterns spreading within neural circuits and exerting a strong influence on brain activity. They push neural activity to evolve along specific directions, in accordance with the sequence specified by the pattern.

2. Empirical studies

2.1. *Electrical self-stimulation of the brain (ESSB)*

The discovery of ESSB by Olds and Milner (1954) represented a major breakthrough in understanding the neurobiological bases of reward. Electrical stimulation of various brain sites in association with specific behaviors increased the probability that animals would repeat those behaviors. These studies led to the recognition of reward areas in the brain (Olds et al., 1971; Wise, 1996, 2005; Chau et al., 2004) with the medial forebrain bundle (MFB) being a primary neural pathway interconnecting many relevant brain regions (see Wise, 2002 for a review). Olds (1977) extensively analyzed the pervasive neuronal learning during appetitive conditioning that occurred along the trans-hypothalamic self-stimulation continuum (for review, see Figure 8.3 in Panksepp, 1998). Furthermore, it was demonstrated that with fixed-interval stimulation of this substrate, animals would exhibit spontaneous conditioning characteristics of fixed-interval instrumental behavior (Clark and Trowill, 1971; Burgdorf et al., 2000).

It was also observed that electric stimulations of the MFB not only reinforce instrumental actions, but they also arouse a variety of consummatory behaviors such as drinking, feeding, gnawing and predation (Glickman and Schiff, 1967; Valenstein et al., 1969, 1970; Panksepp, 1971, 1981a,b). Such stimulations also induced generalized arousal, leading to exploratory behaviors not strictly related to any biological needs (Gallistel, 1974; Panksepp, 1981a,b). Thus, it was suggested that ESSB fosters a general incentive-based disposition to approach environmental stimuli (Glickman and Schiff, 1967; Trowill et al., 1969; Panksepp, 1981a,b). With the characterization of brain DA circuitry (Ungerstedt, 1971), it was further recognized that the ML-DA system is an important ascending and activating component of the MFB involved in the learning as well as in the motivational effects of electric brain stimulation (see Wise and Rompre, 1989 for a review). Moreover, increasing DA levels into the Nacc with psychostimulants enhances the rewarding properties of self-stimulation itself (Wise, 1996). The ML-DA system is now generally considered a key circuitry involved in promoting aroused states concerned with appetitive motivations, attention to rewards and behavioral persistence and, by some, the avoidance of punishment—namely the seeking of safety (Ikemoto and Panksepp, 1999).

2.2. *Psychomotor activating effects of DA drugs across vertebrates and invertebrates*

Drugs that enhance DA functions mediate the emergence of unconditional, behaviorally aroused states in many species. Facilitators of DA release, such as cocaine or amphetamine, and agonists of DA receptors promote waking and behavioral activation in all mammals (Randrup and Munkvad, 1972; Wise and Bozarth, 1987; Trampus et al., 1991; Nishino et al., 1998; Wisor et al., 2001). Rats and mice increase locomotor activity in response to such drugs and, if high doses are used, they show stereotypical behaviors (Wise and Bozarth, 1987). In contrast, decreased DA receptor stimulation is associated with hypoactivity and catalepsy (Fog, 1972; Johnels, 1982; Monti et al., 1990). Similarly to mammals, injection of cocaine increases locomotion in birds (Levens and Akins, 2001) and DA promotes locomotor and behavioral activity in amphibians (Matsunaga et al., 2004; Endepols et al., 2004).

DA induces hyperactivity and exploration also in adult fruit flies (McClung and Hirsh, 1998; Pendleton et al., 2002; Lima and Miesenbock, 2005; Kume et al., 2005) and other invertebrate species (Torres and Horowitz, 1998; Sawin et al., 2000; Hills et al., 2004), suggesting a remarkable evolutionary conservation of function. However, pro-DA drugs may also reduce locomotor activity in invertebrates, perhaps acting peripherally (Martinez et al., 1988; Pavlova, 2001; Panksepp and Huber, 2004; Chase et al., 2004; Jorgensen, 2004). Although effects of DA on invertebrate locomotion are not uniform, the rewarding properties for pro-DA drugs seem to be conserved across invertebrates (Bellen, 1998; Wolf, 1999; Kusayama and Watanabe, 2000; Bainton et al., 2000; Brembs et al., 2002; Panksepp and Huber, 2004; Reyes et al., 2005).

2.3. *Microinjections and lesion studies*

Starting with the work of Ungerstedt et al. (1974), pharmacological and lesion studies of areas with ML system cell bodies (VTA) and projections have clarified the behavioral functions of the DA transmission in mammals. Microinjections of DA drugs into the Nacc increase locomotor activity and exploratory behaviors (Jackson et al., 1975; Pijnenburg et al., 1976; Carr and White, 1987; Swanson et al., 1997; Schildein et al., 1998), conditioned approach responses (Taylor and Robbins, 1986; Kelley and Delfs, 1991; Burns et al., 1993; Wolterink et al., 1993; Parkinson et al., 1999; Wyvell and Berridge, 2000) and anticipatory sexual behaviors (Everitt et al., 1989; Everitt, 1990). DA enhancing microinjections are also associated with rewarding properties. Animals readily self-administer DA agonists or drugs that directly increase DA transmission in the Nacc (Hoebel et al., 1983; Phillips et al., 1994; Carlezon et al., 1995; Ikemoto et al., 1997a,b). In the conditioned place preference (CPP) paradigm, animals spend more time in environments associated with Nacc injections of psychostimulants and DA agonists (Carr and White, 1986; White et al., 1991; Liao et al., 1998). Experimental modulation of DA transmission in ventral pallidum (VP) and olfactory tubercle has similar, often even more intense, effects than in the Nacc (Ikemoto, 2003; Ikemoto et al., 2005). In fact, microinjections of various DA drugs in the VP elicit locomotion and reward-related behaviors (Gong et al., 1996, 1999; Fletcher et al., 1998) whereas VP lesions reduce responses to natural and artificial rewards (Hiroi and White, 1993; Gong et al., 1997). Microinjections of GABA-A receptor antagonists (e.g., picrotoxin, bicuculline) into the VTA increase locomotion by disinhibiting DA neurons (Arnt and Scheel-Kruger, 1979; Mogenson et al., 1980b; Stinus et al., 1982), and rodents will learn to self-administer GABA-A receptor antagonists (David et al., 1997; Ikemoto et al., 1997a) or NMDA agonist (Ikemoto, 2004) into the VTA.

Experimentally enhanced DA function increases behavioral activity, whereas lesions of the ML-DA system reduce or eliminate exploratory and appetitive-approach behaviors (Koob et al., 1978; Fink and Smith, 1980; Robbins and Everitt, 1982; Evenden and Carli, 1985; Taghzouti et al., 1985; Robbins et al., 1989; Pierce et al., 1990; Pfaus and Phillips, 1991; Jones

and Robbins, 1992; Liu et al., 1998). Pharmacological reduction of Nacc DA transmission inhibits seeking-approach behaviors in response to reward-associated cues (Blackburn et al., 1992; Di Ciano et al., 2001; Parkinson et al., 2002; Wakabayashi et al., 2004). Interestingly, ML-DA depletion or inhibition disrupts active-avoidance behaviors (Jackson et al., 1977; Koob et al., 1984; McCullough et al., 1993), suggesting that ML-DA also participates in the seeking of safety (Ikemoto and Panksepp, 1999).

The functions of DA projections to the pFC are less clear. On one hand, intra-medial pFC injections of amphetamine produce moderate increases in open-field activity (Carr and White, 1987; Kelley et al., 1989) and DA transmission in the pFC is involved in the reinstatement of cocaine seeking behaviors in rats (McFarland and Kalivas, 2001; Park et al., 2002; McFarland et al., 2004; Sun and Rebec, 2005). On the other hand, microinjections of DA agonists in the pFC decrease spontaneous, novelty- and psychostimulants-induced locomotor activity (Radcliffe and Erwin, 1996; Broersen et al., 1999; Lacroix et al., 2000; Beyer and Steketee, 2000). A significant negative correlation also exists between mesocortical DA transmission and locomotor activity (Hedou et al., 1999). Consistent with these findings, pFC DA lesions produce hyperactivity (Tassin et al., 1978) and have anti-depressive effects[9] (Espejo and Minano, 1999; Ventura et al., 2002). Additional dilemmas exist concerning the role of mesocortical DA transmission in mediation of reward. Whereas rats self-administer cocaine directly into pFC and cocaine injected in the medial pFC induces CPP (Hemby et al., 1990), amphetamine in the medial pFC is not self-administrated (Goeders et al., 1986) nor does it induce CPP (Carr and White, 1986; Schildein et al., 1998). It has also been shown that lesion of mesocortical projections does not reduce reward learning (Isaac et al., 1989; Hemby et al., 1992; Shippenberg et al., 1993; Burns et al., 1993) or self-administration of intravenous cocaine (Martin-Iverson et al., 1986; Schenk et al., 1991; McGregor et al., 1996).

In contrast to the role of DA in ventral BG and prefrontal areas, ML-DA transmission within the amygdala (in basolateral as well as in medial and central nuclei) has been implicated in the expression and learning of fear (Pezze and Feldon, 2004). For example, inhibition of DA transmission within the amygdala reduces fear-potentiated startle (Greba and Kokkinidis, 2000), the retrieval of conditioned-fear associations (Nader and LeDoux, 1999) and has a general anxiolytic effect (de la Mora et al., 2005). On the other hand, rats self-administer D-amphetamine directly in the central nucleus of the amygdala (Chevrette et al., 2002), while DA transmission in the basolateral amygdala contributes to the establishment and reinstatement of instrumental and associative reward learning (Zarrindast et al., 2003; Andrzejewski et al., 2005; Alleweireldt et al., 2006). In summary, both positive and negative emotional behavioral dispositions appear to be stimulated by DA in the amygdala. However, since DA elicits active but not passive avoidance behaviors, it may be argued that central amygdaloid DA is still involved in promoting energized "approach towards safety" (Ikemoto and Panksepp, 1999). We would argue that in the absence of negative incentive stimuli, the ML-DA system largely promotes positive affective states and that only in the presence of various concurrent negative emotional states or stimuli might it contribute to aversive feelings. However, we do not know whether this contribution is to directly facilitate aversive feelings or, alternatively, perhaps to dampen those feelings, even though not to the point of affective neutrality. Much more work is needed on such aversion related affective issues.

2.4. *The Nacc core/shell distinction*

The Nacc consists of two anatomical and functional subdivisions, the shell and core (Zahm and Brog, 1992; Heimer et al., 1997; Zahm, 1999; Kelley, 1999; Di Chiara, 2002; Ikemoto et al., 2005). DA projections to the shell are more sensitive to a great variety of stimuli, including drugs of abuse (Pontieri et al., 1995), restraint and pharmacological stress (Deutch and Cameron, 1992; Horger et al., 1995; Kalivas and Duffy, 1995; King et al., 1997), food (Bassareo and Di Chiara, 1999) and novel stimuli or environments (Rebec et al., 1997; Rebec, 1998; Barrot et al., 2000). Moreover, microinjections of DA drugs into the medial shell, but not the core, support instrumental behaviors and CPP (Carlezon and Wise, 1996; Ikemoto et al., 1997a,b; Chevrette et al., 2002; Sellings and Clarke, 2003). It is generally accepted that the shell is involved in mediating the rewarding effects of psychostimulants (Parkinson et al., 1999; Rodd-Henricks et al., 2002; Ito et al., 2004), but there is less agreement concerning the psychomotor activating effects of these drugs. For example, the behavioral activating property has been attributed to an action of psychostimulants in the core (Weiner et al., 1996; West et al., 1999; Boye et al., 2001; Sellings and Clarke, 2003), in the shell (Heidbreder and Feldon, 1998; Parkinson et al., 1999; Ito et al., 2004) and in both structures (Pierce and Kalivas, 1995; Ikemoto, 2002). However, a recent experiment indicated that the locomotor activating properties of cocaine depend upon DA transmission into the core, while rewarding effects of the psychostimulant depend upon DA transmission in the shell and into the olfactory tubercle (Sellings et al., 2006). It has also been shown that rats learn to self-administer the psychostimulant in the medial shell and in the medial tubercle, but not in the core, ventral shell and lateral tubercle (Ikemoto et al., 2005). Although these findings indicate that rewarding effects of psychostimulants are mediated by Nacc shell and olfactory tubercle, while the locomotor activating effects are mediated by the Nacc core, previous findings demonstrated that DA transmission in the core is necessary for some associative processes, for instance, the establishment of Pavlovian or instrumental conditioning (Parkinson et al., 1999, 2000; Hall et al., 2001; Hutcheson et al., 2001; Di Ciano et al., 2001).

Interestingly, DA transmission in the shell of the Nacc has different characteristics when compared with the transmission in the core. Basal extracellular DA levels are greater in the core and ventral medial pFC than the shell (King and Finlay, 1997; Hedou et al., 1999). However, studies in postmortem tissue punches revealed that basal DA levels are greater in the shell than the core, while the DOPAC/DA ratio is greater in the

[9] In our opinion, the frontal cortex controls and inhibits primary-process emotional processes such as those that may be disinhibited in attention deficit hyperactivity disorders (ADHD), leading to heightened levels of emotional acting out (Panksepp, 2001).

core (Deutch and Cameron, 1992). Although the total amount of DA (extracellular + intracellular) could be higher in the shell, the amount of extracellular DA could be greater in the core due to a faster rate of release and uptake. In fact, in vitro voltammetric studies show that the values of DA release and uptake in the shell Nacc are approximately one-third of those measured in the core region. Moreover, the density of [3H]mazindol binding sites in the Nacc was examined by autoradiography and the shell was found to have an average of half the number of DA uptake sites than those measured in the core region (Jones et al., 1996). Together, these findings suggest that DA transmission in the shell of the Nacc presents the characteristic of so-called slow (Greengard et al., 1999), non-synaptic (Vizi, 2003) or volume transmission (Sykova, 2004; Bach-Y-Rita, 2005). Conversely, DA transmission in the core seems to be more confined to the synaptic clefts.

Besides the neurochemical differences between the core and the shell of the Nacc, important functional differences appear to be associated with these subregions. The DA volume transmission in the shell of the Nacc may be involved in the generation and the maintenance of an aroused and positive affective state. On the other hand, the DA transmission in the core may be involved in the expression of this emotion in the BG–thalamocortical circuits and then in the "control of goal-directed behavior by associative process" (Ito et al., 2004). Indeed, excitotoxic lesions of Nacc core disrupt Pavlovian approach behavior (Parkinson et al., 2000), conditioned reinforcement (Parkinson et al., 1999) and Pavlovian to instrumental transfer (Hall et al., 2001), while coincident activations of D1 receptors and NMDA receptors in the Nacc core are necessary for associative learning (Smith-Roe and Kelley, 2000; Wickens et al., 2003; Hernandez et al., 2005).

2.5. *Electric activity of DA cells: phasic and tonic DA transmission*

Phasic DA transmission is the short-lasting and impulse-dependent release that appears as a consequence of neural burst firing (Gonon, 1988; Suaud-Chagny et al., 1992). Following such bursts, 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). In contrast, tonic DA levels are diffused in the extracellular space outside the synaptic clefts, but exist in very small concentrations (in the nanomolar range) and change relatively slowly (Grace, 2000).

It has recently been proposed that phasic DA in the Nacc is the key component in the process of reward (Grace, 1993, 2000; Wightman and Robinson, 2002; Self, 2003) and that the rewarding effect of electrical stimulation of the MFB is mediated, at least partially, by transient DA release (Wise, 2005). The role of phasic DA in reward processes is envisioned to reflect the fact that phasic DA is a time- and space-specific event, necessary for associative learning, and acts as a detector of coincidence when coupled with glutamatergic inputs directed into the Nacc (O'Donnell, 2003; Dalley et al., 2005). Since DA is transiently released before the execution of goal-directed movements (Phillips et al., 2003; Roitman et al., 2004), phasic DA may promote not only reward-related learning (Reynolds et al., 2001) but also motivated behaviors (Phillips et al., 2003; Ghitza et al., 2004, 2006).

The presence of unpredicted salient, novel and rewarding stimuli induces transient DA cell bursts (Miller et al., 1981; Freeman et al., 1985; Steinfels et al., 1983; Schultz et al., 1993; Mirenowicz and Schultz, 1996; Schultz et al., 1997; Horvitz et al., 1997; Schultz, 1998; Horvitz, 2000; Cooper, 2002), suggesting a role of phasic DA in the salience attribution process or the attentional-exploratory behavior that always follows such waking events. However, the overall mean DA cell bursting (and firing) appears independent from the tonic arousal state of the organism since DA neurons do not alter firing rates with waking and sleep (Trulson et al., 1981; Steinfels et al., 1983; Miller et al., 1983; Trulson and Preussler, 1984; Hyland et al., 2002). Effects of stress on DA cell bursting are also not clear with some reports of a reduction in bursts or no effect (Ungless, 2004), and increases in burst firing observed by others (Anstrom and Woodward, 2005).

In contrast, increased amounts of tonic extracellular DA levels exist during emotional arousal, either in aversive and appetitive conditions, or when organisms are actively engaged with the environment (Thierry et al., 1976; Roth et al., 1988; Cousins et al., 1999; Di Chiara et al., 1999a,b). Evidence from voltammetry (Trulson, 1985) and microdialysis (Smith et al., 1992; Feenstra et al., 2000; Lena et al., 2005) illustrates that tonic DA is sensitive to fluctuations in sleep–wake states, and there is also enhanced release during REM-dream episodes (Miller et al., 1983; Solms, 2000; Maloney et al., 2002; Gottesmann, 2002). Activating the D2-type inhibitory postsynaptic and presynaptic receptors, tonic DA generally reduces the influence that descending glutamatergic projections exert over neurons in the BG and VTA (Nicola et al., 2000; Schmitz et al., 2003). In such a way, tonic DA activity may block the cortical and limbic top–down control, favoring the expression of behaviorally aroused states generated subcortically (see Section 4).

It has been demonstrated that tonic DA reduces the firing of DA neurons and phasic DA release via D2 autoreceptor activation in terminal projections and soma (Fig. 3 left) (Grace, 2000; Schmitz et al., 2003). However, long-lasting elevations of tonic DA levels may also increase the quanta of DA molecules released per single burst (Fig. 3 right). Two lines of evidence suggests this hypothesis.

Psychostimulants increase tonic DA levels into the Nacc, and thereby enhance the rewarding properties of self-stimulation (Wise, 1996), by presumably potentiating the amount of phasic DA released after each stimulation. Moreover, amphetamine produces an impulse-dependent DA release into the Nacc (Ventura et al., 2004; Ventura and Puglisi-Allegra, 2005), which may be associated with its rewarding effect. Since amphetamine generally suppresses the electrical activity of DA neurons (Westerink et al., 1987), the impulse-dependent DA release may arise from an increased amount of molecules released per impulse.

Continuous electrical stimulations of DA cells progressively decrease impulse-released DA quanta (Garris et al., 1999). Therefore, investigators need to consider that if an electrically overactive system promotes blunted phasic DA release, a less excitable system may be characterized by the fact that each action potential now has a greater power of each impulse.

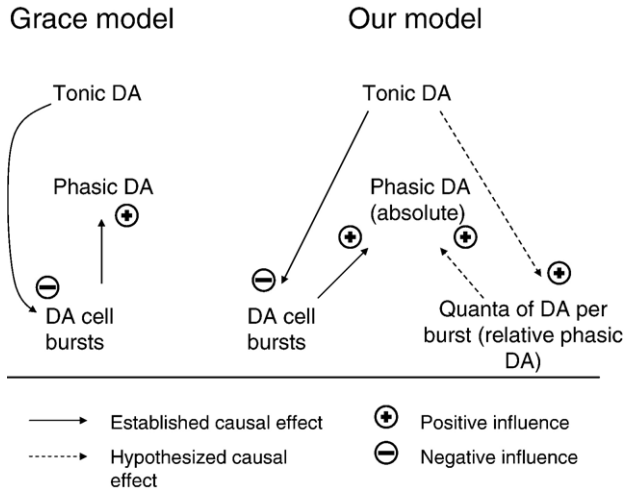

Fig. 3 – Functional feedbacks between tonic and phasic DA transmission. In the Grace model (Grace, 1991, 2000), tonic DA levels were indicated to inhibit phasic DA release since D2 autoreceptor activation decreases bursting (and firing) activity of DA neurons. Without questioning the validity of the Grace theory, our alternative model considers the existence of two different feedback loops between tonic and phasic DA transmission. The first one is well experimentally demonstrated, it acts in short-time periods and consists of the negative influences that tonic DA exerts over DA cell bursting (as in the Grace model). However, in our alternative model, a positive feedback loop has been hypothesized (but not demonstrated yet) since its existence may help in explaining some important empirical evidence. The supposed positive feedback loop should act in longer time frames and consist in tonic DA increasing the amount (or quanta) of DA released per single burst. We called this component the *relative phasic DA transmission* to distinguish it from the *absolute phasic DA transmission*, which is dependent upon the *relative phasic DA*, plus the *mean bursting activity of DA neurons*. In our model, tonic DA transmission increases the relative phasic DA (potentiating the efficiency of each burst) and inhibits the mean bursting activity of DA neurons, without strongly modifying the absolute phasic DA. In summary, the Grace model emphasizes the existence of a negative interaction between tonic and phasic DA, whereas our model individuates the existence of a positive feedback loop.

Therefore, although the inhibitory action of tonic DA over phasic DA has been emphasized (Grace, 2000), the possibility of positive reciprocal feedbacks should also be considered (Fig. 3). In particular, we suggest that high levels of tonic DA do not decrease the total amount of phasic DA per se, but reduce the excitability of DA cells to descending excitatory glutamatergic inputs, acting either indirectly via D2 receptors located on DA neurons or directly on glutamatergic terminals reaching the VTA. However, high levels of tonic DA will increase the quanta of DA released per single impulse, potentiating the effect that each impulse will produce in terms of extracellular DA release. In conclusion, we are tempted to hypothesize that high tonic DA levels will predispose to less excitable but more powerful ML-DA network influences.

3. Theoretical interpretations

Complex relationships among neural, behavioral and psychological levels guarantee the presence of substantial gaps in our understanding that remain to be filled. The adoption of novel integrative hypotheses may be essential for promoting empirical predictions that can help fill the remaining gaps.

3.1. *Neurocognitive behaviorism*

Much of today's experimental work is driven by a common theoretical perspective, here termed "neurocognitive behaviorism". It is characterized by two main assumptions: (1) Animal (and human) behaviors are the product of associative memories stored in the brain (Watson, 1913; Skinner, 1938; Martin and Levey, 1988; Ressler, 2004; Rolls, 2004; Pickens and Holland, 2004). (2) Cognitive processes, mediated by higher cortical functions, can be conceptualized as computations for unconscious control of behavior and modeled in accordance with information processing theories (Kihlstrom, 1987; Gerstner et al., 1997; Fuster, 2002; Miyashita, 2004; Vogel, 2005). Behavioristic and cognitive approaches have melded together since associative learning is considered the process through which organisms acquire and modify their predictive cognitions (Sutton and Barto, 1981).

Within this context, the principal focus of research is to clarify how DA modulates learning by sustained alterations of intracellular molecular mechanisms (Greengard et al., 1999; Hyman and Malenka, 2001; Barrot et al., 2002; Nestler, 2004), enhanced synaptic plasticity (Centonze et al., 2001; Li et al., 2003; Huang et al., 2004) and facilitated neural communication (White, 1996; Robinson and Kolb, 1999; Reynolds et al., 2001; Nestler, 2001a; Wickens et al., 2003; Centonze et al., 2003). Considering the motivational properties of ML-DA transmission, neurocognitive behaviorism is characterized by a top–down, incentive salience orientation of brain functioning rather than a bottom–up view that envisions brain DA to facilitate ingrained psychobehavioral subroutines necessary for survival. Motivations are viewed as cognitive representations of future goals elaborated in cortical structures, which thereby control the activities of motor circuitries. Within this worldview, DA regulates the communication between corticolimbic inputs and Nacc neurons and then manages information flow from cognitive representations (neocortical and higher limbic areas) to movements (BG areas) (Cepeda et al., 1998; Kalivas and Nakamura, 1999; Nicola et al., 2000; Schultz and Dickinson, 2000; Joel et al., 2002; Dayan and Balleine, 2002; Murer et al., 2002; West et al., 2003; O'Donnell, 2003; Carelli, 2004).

The neurocognitive behaviorist perspective has advanced hypotheses about the etiology of DA-related psychiatric diseases. Drug abuse, for example, is viewed as a product of abnormal learning, occurring when the associations between external predictors of the drug's presence and behaviors directed towards its acquisition and consumption progressively consolidate (Robbins and Everitt, 1999; Robinson and Berridge, 2000) (see Section 5). In the establishment of compulsive seeking behaviors, the critical step is the cortico-

striatal circuits fueling by drug-induced DA release (Pierce and Kalivas, 1997; Di Chiara, 1998; Di Chiara et al., 1999a,b; Berke and Hyman, 2000; Nestler, 2001b, Everitt et al., 2001; Wolf, 2002; Kelley, 2004; Self, 2004). Despite such theoretical successes, it remains difficult for such models to explain how increased ML-DA transmission also promotes certain kinds of unconditional responses, such as behavioral activation expressed in exploratory-investigatory behaviors (Panksepp, 1981a,b; Wise and Bozarth, 1987) and the generation of positive affective states (Drevets et al., 2001; Burgdorf and Panksepp, 2006). It is also unresolved why individuals show differences in dispositional vulnerability toward addiction (True et al., 1999; Uhl, 1999, 2004; Vanyukov and Tarter, 2000). If addiction is a learned process, what predisposes an individual to be a good or bad learner?

3.2. *Formal models of DA functioning*

Electrophysiological recordings from DA neurons generally demonstrate that these cells burst when a reward value is better than expected (Schultz, 1997, 2002). Phasic (or transient) DA transmission is thus viewed as key for organisms to change their internal cognitive schemata in relation to what happened around them (Grace, 2000; Waelti et al., 2001; Reynolds et al., 2001; Wightman and Robinson, 2002; Cooper, 2002; Ungless, 2004). DA transmission is thereby conceptualized as a *teaching signal*, which reorganizes cognitive representations by indicating *prediction errors* (Redgrave et al., 1999; Schultz and Dickinson, 2000).

The new data on DA transmission seem congruent with temporal difference (TD) models for reward learning in animals (Sutton and Barto, 1981). TD models, just like some ethological models (Panksepp, 1981a,b), view learned behavior as the product of anticipatory expectations processed within the brain. These expectations are modeled in algorithmic computations capable of predicting the reward value of stimuli which are dynamically modified by experience. Only recently have such models been utilized to explain DA functions within the brain (Schultz et al., 1997; Waelti et al., 2001; Dayan and Balleine, 2002; Montague et al., 2004).

TD models describe "the function of reward according to the behavior elicited. For example, appetitive or rewarding stimuli induce approach behavior that permits an animal to consume" (Schultz et al., 1997). Such formal models predict that each collection of sensory cues represents a specific reward value and that animals tend to seek out those that offer the greatest reward. A movement may be defined as activity leading to a sequence of perceptual configurations, whose rewarding value is measured by how strongly it entices the organism to approach or proceed with a sequence of learned configurations. A core problem of TD models concerns a stimulus' temporal representation (Schultz et al., 1997), which is essential for associating sensory cues with future rewards along a number of intermediate time points. Yet it remains unclear, in such formal models, how a representation of reward value is translated into concrete actions and how the animal behaves in novel situations, where no reward value has been solidified by previous learning.

These problems may be well addressed by considering that sensorial configurations are embedded into pre-motor sequences leading organisms to move within and between these configurations. In well-learned situations, past experiences determine the succession of perceptual configurations embedding them within the organism's motor–cognitive habits. In such cases, initial presentations of reward-predicting stimuli transiently stimulate the DA system, and phasic DA transmission activates the sequences leading to the predicted outcome. However, in novel situations (or when the reward delivery is maximally uncertain), fixed sequences of movements across sensorial configurations have not yet been established. The persistent increase of DA cell firing in such unpredictable conditions (Fiorillo et al., 2003) may promote the emergence of an unstable state, characterized by the release of instinctual behavioral arousal patterns, which drive organisms to explore external stimuli and to cope with life-challenging events in unpredictable environments (Panksepp, 1981a,b, 1998).

In summary, formal neurocognitive behaviorist models of DA functions are built upon a disconnection between brain information-processing modules responsible for the cognitive prediction of reward and those intrinsic brain circuits responsible for the natural behavioral patterns exhibited during reward seeking. In our view, these two aspects are part of the same integrated process: an intrinsic instinctual action tendency to move across perceptual/cognitive landscapes so as to approach towards specific outcomes within environments. In novel and unpredictable contexts, the reward value of a stimulus is the product of the sustained emotional tendency to unconditionally move towards certain objects within the environment. In learned situations, on the other hand, a series of configurations is evoked by previously acquired knowledge so the SEEKING urge is manifested in the tendency to run along the entire sequence until the final configuration is reached. It is possible that the neural circuitry that subsumes the SEEKING response is the only "ground state" in the brain upon which effective information processing can proceed. In other words, all emotional systems control sensory input gating, as well as selective responses to those stimuli. Thus incentive salience may be as much a reflection of changing action readiness as any changing properties of the perceptual field.

3.3. *The incentive salience hypothesis*

Recognition of a direct involvement of the ML-DA system in the behavioral effects of ESSB (see Wise and Rompre, 1989 for a review) led to a provocative and for a while seminal hypothesis to explain both motivational and learning effects of the ESSB (Wise et al., 1978). Stimulation of the ML-DA system induced a positive hedonic state and enhanced the pleasure derived from consummatory behaviors. Criticism of the hedonic hypothesis emerged from the demonstration that more intense activation of ML-DA occurs during the appetitive phase than during the consummatory phase of motivated behaviors (Blackburn et al., 1987, 1989; Panksepp, 1981a, 1982, 1986). ML-DA thus appears more concerned with "wanting" and less with "liking" (Berridge and Robinson, 1998). This idea is consistent with evidence from pharmacological manipulations of the ML-DA system in the context of instrumental behaviors. Blocking DA activity in the Nacc strongly dimi-

nishes maze-running speed, even though consummation of available rewards is unaffected (Ikemoto and Panksepp, 1996). Reduced DA activity diminishes the appetitive urge more than consummatory pleasure.[10] Likewise, by facilitating arousal of this system with amphetamine in instrumentally conditioned rats, those animals exhibit more directed appetitive behavior toward stimuli associated with rewards in the past (Wyvell and Berridge, 2000, 2001).

According to Berridge, DA is a promoter of the motivational salience of external stimuli, without implying any conscious experience of affective quality. "Liking" has been considered independent from DA transmission as DA does not seem to promote hedonic taste reactions (Berridge and Robinson, 1998). However, it is important to emphasize that taste pleasure may not exhaust the range of possible positive affects that may be facilitated by brain DA arousal. Moreover, many experiments have pointed to the involvement of ML-DA transmission in the consummatory phase of motivated behaviors, such as feeding (see MacDonald et al., 2004 for a review), while a recent study demonstrated that strongly valenced tastes, both pleasant and unpleasant, may promote DA arousal (Roitman et al., 2005).

Since animals self-stimulate the ML system, which is strongly controlled by brain DA availability, it also needs to be explained why the activation of an appetitive "wanting" state has its own rewarding properties despite being considered an unconscious process. Otherwise, it is unclear why animals would seek to self-activate their own general purpose, appetitive states. Focusing on this aspect, Berridge (2004) concluded that problems in the field arise when we wrongly believe that appetitive behaviors are direct expressions of what used to be called "drives". Indeed, in drive-reduction theories, only the reduction of a drive was originally related to the reward, while the drive itself was deemed to be aversive (Hull, 1943; Spence, 1956; Mowrer, 1960). As a solution to the dilemma, Berridge proposed that appetitive behaviors arise from the attribution of incentive properties to external stimuli (pursuant to the views of Bolles, 1972; Bindra, 1974; Toates, 1986), rather than from internal drives. Therefore, "when incentive salience is attributed to a stimulus representation, it makes the stimulus attractive [and] attention grabbing" (Berridge, 2004, p. 195). Since ML-DA transmission presumably helps an external stimulus to acquire incentive salience (Berridge and Robinson, 1998), it also influences the learning of stimulus-related contingencies and appetitive motivations to approach the stimulus.

3.4. *The affective neuroethological perspective*

With a focus on the unconscious attributions of salience to external representations, Berridge's perspective attempted to explain the role of DA transmission in the absence of any pleasure (specifically sensory "liking"). Berridge claims that motivations are commonly activated by the presence (or anticipatory representation) of external stimuli and not necessarily by internal drives nor affective states. Nevertheless, such a behavioristic shift of focus from the organism to the environment can be misleading. Although the role of external stimuli for guiding motivational processes is undeniable, an excessive reliance on how perceptual stimuli guide behavior could obscure an intrinsic, initially objectless, appetitive motivation as a real process within organisms. Indeed, the manner in which ML-DA transmission may increase the incentive salience of external stimuli is by changing the self-referential attitude of the organism towards those stimuli. In this "active-organism" view, which acknowledges the existence of experienced affect, an internally generated action tendency (i.e., the SEEKING instinct) lies at the very center of information processing.

Thus, in our estimation, ML-DA transmission subcortically promotes the emergence of the emotional SEEKING disposition, an intrinsic psychobehavioral function of the brain that evolved to cope with all varieties of life-challenging events in unpredictable environments (Panksepp, 1981a,b, 1998, 2005). This disposition consists of instinctual behavioral tendencies that help organism to move across sensorial configurations and to approach specific sources of stimulations, including salient non-reward events (Horvitz, 2000). The SEEKING disposition is manifested in energized behaviors such as forward locomotion, orienting movements, sniffing, investigating and ultrasonic 50-kHz vocalizations in rats (Ikemoto and Panksepp, 1994; Panksepp, 1998; Burgdorf and Panksepp, 2006). The SEEKING disposition, independent of world events, would also have its own hedonic properties, not the "pleasure of satisfaction", but "enthusiastic positive excitement", "interest", "desire", and "euphoria"[11] (for relevant subjective human data, see Drevets et al., 2001; Jönsson et al., 1971; Newton et al., 2001; Romach et al., 1999; Volkow and Swanson, 2003). Moreover, promoting the urge to project oneself forward in space and time, the SEEKING disposition, manifested at the cortical level (e.g., medial frontal cortex), may facilitate the generation of higher order "forethought", positive expectancies and anticipatory states (Panksepp, 1981a,b; Wise, 2005).

It is well-established that emotions affect memory consolidation and retrieval (Cahill, 1997; McGaugh, 2000; Packard and Cahill, 2001; Roozendaal et al., 2001, 2002; Berntson et al., 2003; Richter-Levin, 2004). By promoting the expression of the SEEKING disposition, ML-DA transmission may then facilitate learning, both through attentive processes as well as favoring the recollection of past events related to the arousal of the SEEKING state. The SEEKING disposition may be viewed as an affect-centered instinctual structure binding together perceptual and motor configurations. Indeed, associations between perceptual and motor representations may follow the connections that each of them has established with the SEEKING

[10] Nevertheless, every consummatory behavior also has an appetitive component (animals fluctuate between approaching/manipulating and consuming the food), and hence it is not surprising that DA transmission is enhanced during feeding, and partially controls food intake (Hernandez and Hoebel, 1988; Hoebel et al., 1989; Martel and Fantino, 1996; Ragnauth et al., 2000; Kelley and Berridge, 2002; MacDonald et al., 2004).

[11] This does not mean that DA arousal might not contribute to coping with aversive situations; we would simply predict that it generally tends to counteract negative feelings, even though it may not eliminate them.

state. Such an automatic, associative process relates to temporal and cue predictability of rewards. The role of the SEEKING disposition in learning is evident in the shaping of spontaneous sniffing behavior in rats during the free, fixed-interval delivery of rewards (Clark and Trowill, 1971; Panksepp, 1981a). Similarly, this phenomenon is also evident in 50 kHz chirping of rats (Burgdorf et al., 2000), an unconditioned component of ML-DA network activity (Burgdorf and Panksepp, 2006).

Additional evidence supports our view. In classical conditioning, novel or unusual stimuli can be associated with unconditioned stimuli whereas habitual stimuli in familiar environments do not condition readily (Rescorla and Wagner, 1972). It is noteworthy that neutral cues initially provoke sniffing, a DA energized response, but this effect habituates rapidly (Clark et al., 1970). Moreover, it has been demonstrated that operant responses for electrical brain stimulation are always preceded by some exploratory or investigative behaviors (Ikemoto and Panksepp, 1996). Unconditioned rewards may thus promote associative learning to the degree the SEEKING disposition has been aroused. In such a way, when the reward arrives and animals begin to exhibit consummatory behavior, the changing neurodynamic of the SEEKING state (e.g., diminished foraging) or perhaps those associated with the pleasurable interaction with the reward solidifies the previously related appetitive activity.

The activation of the emotional SEEKING disposition by particular environmental stimuli facilitates instrumental responding within other contexts. For example, the presentation of a conditioned stimulus enhances instrumental response also for unconditioned stimuli different from the one the conditioned stimulus had previously been paired with (Corbit and Balleine, 2005). Moreover, an environment associated with food delivery enhances the locomotor activating effects of amphetamine as well as an environment associated with the amphetamine (Yetnikoff and Arvanitogiannis, 2005). In these two cases, the effects of the stimulus (or the environment) on the animal's performance cannot be explained by direct stimulus–response associations simply because these associations have never occurred. On the other hand, it is very probable that associations have been established between the SEEKING disposition and the operant responses, so they are released whenever the SEEKING state is again activated (independently of the stimuli that were originally involved in the generation of that state).

In summary, the affective neuroethological perspective of the ML-DA system is centered on the SEEKING disposition concept, whose ability to explain both motivational and rewarding function of DA transmission is unique among existing scientific scenarios. Such perspective can easily incorporate most of the other views, including variants of enhanced incentive salience and the maintenance of effortful behaviors (Salamone et al., 2005). The core of the SEEKING affective state may be generated in midbrain and hypothalamic areas (Panksepp, 1998; Damasio, 1999; Parvizi and Damasio, 2001) and communicated, in part, to BG–thalamocortical circuits via midbrain DA neurons. As many empirical findings demonstrated (see Section 2), ventral BG-DA transmission is essential to the behavioral and mental expression of the SEEKING disposition. In contrast, DA projections to pFC may facilitate information processing without activating the affective-emotional, euphoric aspects of the SEEKING urge. In our view, the attentive and executive functions controlled by mesocortical DA projections (Goldman-Rakic et al., 2000; Nieoullon, 2002; Castner et al., 2004; Arnsten and Li, 2005) may constitute more sophisticated cognitive processes related to the SEEKING disposition. Since under stressful conditions DA transmission in the pFC inhibits DA release in the Nacc (Deutch et al., 1990; Karreman and Moghaddam, 1996; King et al., 1997; Wilkinson, 1997; Jentsch et al., 1988; Ventura et al., 2002), it is also likely that DA-promoted pFC functions may hinder the overt expression of the SEEKING disposition in such highly aroused situations and may potentially inhibit positive affective states.

4. New inroads of the affective neuroethological perspective

In the previous section, we described how the behavioral functions of ML-DA emerge from its ability to activate the SEEKING emotional disposition. It is now important to provide new hypotheses describing how this disposition is processed in the brain. Obviously, this proposal needs an elucidation of the role of DA in modulating neural activity across brain circuitries. Indeed, correlative neurophysiological observations obtained from recording DA neurons (which tell us much about what DA cells are listening to, but not necessarily what message they are passing on; see Panksepp, 2005), as is common in the otherwise excellent electrophysiology work of W. Schultz and colleagues, should be integrated with neurophysiological findings about the effects of DA in its projection areas (which better informs us about what DA is doing as it is being released downstream of the inputs).

4.1. *DA modulation of neural activity*

Binding to its receptors, DA activates a cascade of intracellular processes with many diverse neural influences (Missale et al., 1998; Greengard et al., 1999), from changing the activity of ion channels to altering the functionality of different membrane receptors. DA transmission also regulates gene expression and leads to permanent synaptic changes (Greengard, 2001a,b; Wolf et al., 2003; Nestler, 2004). Along with many other G-protein-coupled receptors (Hille, 1994), DA receptors alter neuronal excitability via modulation of voltage-dependent ion channels and influence behavioral processes by modulating large-scale neural activity in widespread neural networks.

DA release generally depresses spontaneous and evoked cell firing (Siggins, 1978; Dray, 1980; Rowlands and Roberts, 1980; Yim and Mogenson, 1982, 1986; Brown and Arbuthnott, 1983; Johnson et al., 1983; Yang and Mogenson, 1984; DeFrance et al., 1985; Chiodo and Berger, 1986; Hu and Wang, 1988; Nisenbaum et al., 1988; Hu et al., 1990; Pennartz et al., 1992; Harvey and Lacey, 1996, 1997; Nicola et al., 1996; Peoples and West, 1996; Peoples et al., 1998; Nicola and Deadwyler, 2000; Zhang et al., 2002). It has been argued that behavioral arousal emerges from a DA disinhibitory role obtained by the block of an inhibitory pathway. Indeed, the main targets of DA neurons

are BG GABA inhibitory neurons (Graybiel, 2001; Groenewegen, 2003), and DA decreases firing in the globus pallidus and the substantia nigra, the two main BG output nuclei (Alexander et al., 1986; Albin et al., 1989; Gerfen et al., 1990; Bergman et al., 1994; Nini et al., 1995; Brown and Marsden, 1998; Gerfen, 2000; Gurney et al., 2001; Brown et al., 2001).

Despite a predominantly inhibitory role, DA also enhances spontaneous and evoked neural activity in striatal as well in cortical neurons[12] (Gonon and Sundstrom, 1996; Hernandez-Lopez et al., 1997; Hu and White, 1997; Gonon, 1997; Cepeda et al., 1998; Lewis and O'Donnell, 2000; West and Grace, 2002; Charara and Grace, 2003; Chen et al., 2004; Bandyopadhyay et al., 2005). The general interpretation of such bidirectional effects is that DA, in a manner similar to NE, enhances the signal-to-noise ratio in neural networks. In other words, DA may filter spurious activity and suppress background noise, while facilitating and enhancing neural activities related to significant incoming signals (Rolls et al., 1984; DeFrance et al., 1985; Kiyatkin and Rebec, 1996; O'Donnell and Grace, 1996; Nicola et al., 2000; West and Grace, 2002; West et al., 2003; Brady and O'Donnell, 2004). The signal-to-noise ratio hypothesis is a computational theory based on the idea that DA facilitates the selection of Nacc competing neuronal ensembles (Pennartz et al., 1994; Redgrave et al., 1999) that receive multiple converging inputs from pFC, hippocampus and amygdala (Pennartz et al., 1994; O'Donnell and Grace, 1995; Groenewegen et al., 1999; French and Totterdell, 2002). DA then modulates synaptic communication (West et al., 2003) and gates information to the Nacc, favoring the entrance of salient signals in BG–thalamocortical executive circuits (Mogenson et al., 1980a; Pennartz et al., 1994; Groenewegen et al., 1999; West et al., 2003; O'Donnell, 2003) and translating motivational representations into executive motor plans (Mogenson et al., 1980a; Willner and Sheel-Krüger, 1991; O'Donnell, 2003). ML-DA also strengthens synaptic associations between descending glutamatergic projections and BG neural ensembles, influencing long-term memory processes (Wise, 2004).

4.2. *DA modulation of global field dynamics*

It is remarkable that cognitive, top–down perspectives of ML-DA system are largely built on the observation of DA effects on single neuron firing (Schultz, 1997, 1998, 2001, 2002, 2004, 2006). Based on information from large-scale populations of neurons, an alternative picture is now emerging. DA transmission desynchronizes slow rhythms and induces fast-wave oscillations within the BG–thalamocortical circuits (Brown and Marsden, 1998; Brown, 2003; Lee et al., 2004; Sharott et al., 2005). It also promotes a greater autonomy of BG neural patterns from a strict cortical control, blocking the spread of cortical synchronous oscillations into the BG (Marsden et al., 2001; Brown, 2003; Priori et al., 2002; Williams et al., 2002; Heimer et al., 2002; Cassidy et al., 2002; Goldberg et al., 2002; Magill et al., 2004; Sharott et al., 2005) (Fig. 4A). Such network effects may offer the best overall explanation of DA induced psychobehavioral arousal (Steriade, 1996, 2000). Collectively, local field potential studies support the hypothesis that DA promotes the emergence of characteristic rhythms and their diffusion in the brain:

(1) DA decreases the power and coherence of cortically derived beta-frequency oscillations (~15 Hz) and promotes the emergence of high-frequency gamma oscillations (>60 Hz). The prevalence of beta rhythm in BG–thalamocortical circuits is associated with motor impairments characteristic of Parkinson's disease (Deuschl et al., 2000; Vitek and Giroux, 2000; Brown, 2003; Dostrovsky and Bergman, 2004; Hutchison et al., 2004).
(2) DA suppresses slow firing oscillations and regular bursting of BG neurons (~1 Hz) in anesthetized and sleeping rats (Pan and Walters, 1988; MacLeod et al., 1990; Murer et al., 1997; Tseng et al., 2000, 2001). Since rhythmic bursts have been interpreted as the result of spreading of cortical activity into BG nuclei, these changes may reflect a barrier between cortex and BG.
(3) DA increases the multisecond temporal oscillatory patterns (from ~30 s to ~ 10 s) of BG nuclei's spike trains and increases the spectral power of these oscillations (Ruskin et al., 1999, 2001, 2003).

The DA capacity to promote gamma rhythms needs specific attention since these oscillatory waves are involved in diverse behavioral and psychological processes, while their alteration has been observed in neuropsychiatric disorders (Herrmann and Demiralp, 2005). The generation of gamma rhythms is essential for synaptic plasticity and memory processes (Paulsen and Sejnoski, 2000; Buzsaki and Draguhn, 2004; Sederberg et al., 2007), voluntary movement execution (Cassidy et al., 2002; Courtemanche et al., 2003; Kuhn et al., 2004; Sharott et al., 2005), attentive functions (Brown, 2003) and "binding of sensory object features into a coherent conscious percept" (Engel and Singer, 2001). It has also been suggested that gamma waves preside over the emergence of active intentional brain states (Freeman, 2003), which underlie all of the abovementioned functions.

In summary, the behavioral arousal function of ML-DA transmission may be explained on the basis of a DA-promoted emergence of high-frequency oscillations in BG–thalamocortical circuits. According to this view, motivated behaviors do not arise from cognitive signals activating executive motor plans, but from instinctual behavioral and emotional drives originating in midbrain and hypothalamic areas and communicated through DA within BG–thalamocortical circuits. We will next explore the possibility that gamma rhythms favor the release of specific neural activity patterns expressing intentional behavioral dispositions.

[12] The impact of DA transmission on neural activity seems to depend on three main factors: (1) *DA receptors*: D2-type receptors are inhibitory, while D1-type receptors feature both excitatory and inhibitory roles (Hernandez-Lopez et al., 1997; Reynolds et al., 2001; Floresco et al., 2001a,b; Chao et al., 2002; West and Grace, 2002); (2) *Steady-state membrane potentials*: DA inhibits hyperpolarized neurons (down-state) and excites depolarized ones (up-state) (Cepeda et al., 1998; Nicola et al., 2000; West and Grace, 2002); and (3) *Concentration*: evoked concentrations of DA in the range of 600 nM elicit excitation (Gonon, 1997) while higher concentrations inhibit firing rates (Williams and Millar, 1990).

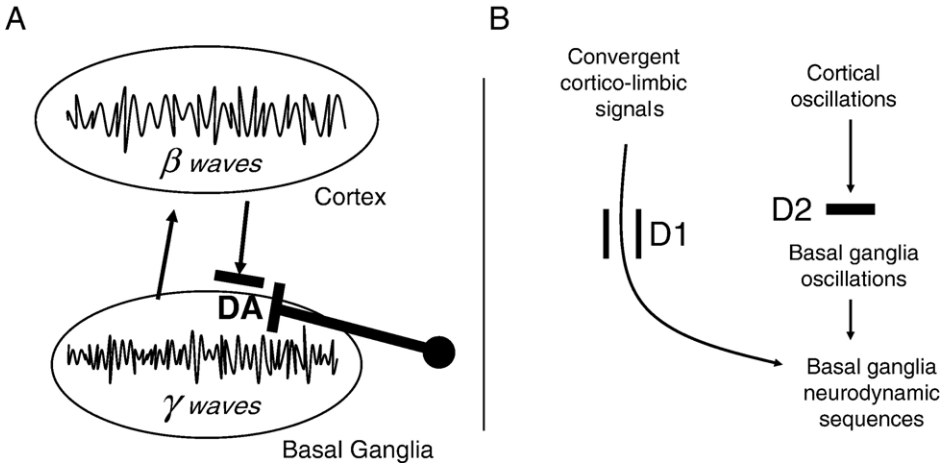

Fig. 4 – DA-promoted BG activity patterns. Much evidence has shown that the release of DA into BG blocks the spreading of cortical rhythms in BG structures (A). For example, DA inhibits *cortically derived beta oscillatory patterns* and promotes the emergence of *BG characteristic oscillatory patterns* (in the gamma range) in BG–thalamocortical circuits (Brown and Marsden, 1998; Brown, 2003; Courtemanche et al., 2003; Magill et al., 2004; Lee et al., 2004; Sharott et al., 2005). The inhibitory function of DA transmission on the spreading of cortical rhythms is mainly mediated by the activation of D2-type receptors (D2) since they have an inhibitory role over descending glutamatergic transmission into BG areas (Nicola et al., 2000; West et al., 2003; O'Donnell, 2003) (B). The consequent emergence of gamma and other BG rhythms may favor the release of neurodynamic sequences and their diffusion in BG–thalamocortical circuits. On the other hand, transient activation of D1-type receptors (D1) may have an excitatory function and seems to favor the entrance of specific and highly convergent cortical and limbic information into BG (West et al., 2003; O'Donnell, 2003) (B). Those signals may control the release of neurodynamic sequences in accordance with the representation of the organism–environment relationship. The global function of DA may then be conceptualized as a widespread modulation favoring the elaboration of relevant cortico-limbic information into a BG *intentional code*.

4.3. *DA effects on sequential neural activity patterns*

It has been shown that GABA neural networks are involved in the desynchronization of slow-wave oscillations (Sloviter, 1987) and in the promotion of high-frequency rhythmic oscillations in the gamma band (Llinas et al., 1991; Steriade, 2000). GABAergic neurons also preside over the release of repetitive sequential patterns (or neurodynamic sequences) (Laurent, 2002; Lagier et al., 2004; Beggs and Plenz, 2003, 2004). Capturing brain activity within dynamic attractors (Freeman, 2000, 2001, 2003; Lewis, 2005), the GABAergic basal forebrain neurodynamic sequences direct activity consistent with the sequence and constitute the intrinsic structure of intentional behaviors and cognitions. Viewed as impulses to act, they translate neural activity into the intentional code[13] necessary for active movements.

It is not known how GABAergic networks produce fast-wave rhythms and sequential neural activity patterns or the exact relationship between gamma rhythms and the release of neurodynamic sequences. However, it is reasonable that ML-DA favors the release of basal forebrain neurodynamic sequences reflected within fast-wave oscillatory gamma rhythms. As demonstrated for gamma rhythms (Brown, 2003), optimal levels of DA are also important for the release of neurodynamic sequences[14] (Stewart and Plenz, 2006).

In classic theory of BG functions (Alexander et al., 1986; Albin et al., 1989; Gerfen et al., 1990; Gerfen, 2000; Gurney et al., 2001), DA transmission relieves thalamic and brainstem nuclei from chronic inhibition by BG output nuclei. DA arousal is supposed to emerge from a global increase in thalamocortical activity, while the activity of BG output nuclei is considered antikinetic. This view may be contradicted by evidence where electrical stimulation of BG output nuclei relieves Parkinsonian symptoms (Hamani et al., 2006). BG output nuclei may rather exert an antikinetic effect primarily when they oscillate at low frequencies, but not when normal BG oscillatory activity is restored through DA-facilitating medications or

[13] We refer to intentional code as the dynamic structure of the neural activity produced in basal forebrain and basal ganglia areas. The intrinsic organization of these areas evolved to favor the emergence of sequential activity patterns that may be easily translated in movements because of their procedural shape. In other words those areas have been predisposed to release coherent sequences of movements.

[14] Massive, cortical, glutamatergic input to basal forebrain and BG nuclei blocks neurodynamic sequences through the reciprocal GABAergic connections characteristic of basal forebrain ensembles. With a metaphor taken from Dante's Inferno, basal forebrain neurons are like the damned souls of the envious kept in a cauldron. They cannot escape because when "one does manage to escape, the others pull him/her back in! And so the cauldron closes itself" (Llinas, 2002, p. 138). However, when only a subset of basal forebrain neurons receives excitation (and this effect may be potentiated by DA transmission), a behavioral coherent neurodynamic sequence is properly released.

electrical stimulation[15] (Garcia et al., 2005). Rather than conceiving DA behavioral effects as a consequence of BG output nuclei inhibition, we propose that DA transmission promotes high-frequency oscillatory patterns (Fig. 4A) and the release of BG neurodynamic sequences. The overall DA inhibition of excitatory input, mainly mediated by D2-type receptors of the indirect pathway of BG[16] (Fig. 4B), reduces the diffusion of cortical rhythms and promotes BG characteristic rhythms.[17] On the other hand, acting upon D1 receptors of depolarized striatal neurons belonging to the direct pathway, phasic DA may increase their responsiveness to convergent descending excitatory influences (Gerfen, 2000; Nicola et al., 2000; Murer et al., 2002; West et al., 2003). This may promote the release of neurodynamic sequences in accordance with specific information coming from cortico-limbic structures (Fig. 4B). Convergent glutamatergic input may thus form a switching signal (Redgrave et al., 1999), allowing new information to enter basal forebrain/BG areas and new sequential activity patterns to be generated in BG–thalamocortical circuits. Consistent with this view, an imbalance between phasic and tonic DA transmission may promote attention deficit hyperactivity disorders (Levy, 2004) and probably also Tourette's syndrome. BG–thalamocortical circuits of these subjects may be overcharged by switching signals as external stimuli continuously release new neurodynamic sequences. Conversely, excesses of BG tonic DA transmissions may promote stereotypical behaviors and obsessive-compulsive disorders (Korff and Harvey, 2006). In these cases, the abnormal presence of tonic DA may completely suppress the influence that cortical and limbic areas exert over subcortical nuclei, leading neurodynamic sequences to be produced autonomously and without any input from the external environment.

4.4. *ML-DA and the SEEKING neurodynamic sequences*

Limbic neurodynamics in the ventral BG serve as vectors for the expression of the SEEKING emotional disposition, translating a general arousal state into active exploration. They are the neural bases of instinctual internalized movements or action tendencies directed to actively investigate elements of the external and in humans perhaps the internal (mental) environment. SEEKING tendencies are comprised of specific types of locomotor activities, associated autonomic changes, and other responses directed to attain perceptual information and to progressively orient the organism toward affectively enticing and eventually desired sources of stimulation (e.g., via whole body exploratory sequences, eye and head movements, sensory-information sampling with continuous sniffing).

The SEEKING neurodynamic sequences presumably drive motor-action pattern generators via connections from ventral BG output to brainstem motor nuclei. By integrating incoming perceptual information into SEEKING action tendencies, the organism may coordinate its relationship with the environment in flexible ways. Perceptual information from both external and internal sources receives a preliminary evaluation of its survival value as it enters the Nacc through limbic structures like olfactory bulb, pFC, amygdala, and hippocampus. The diffusion of SEEKING sequences in the BG–thalamocortical circuits brings about exploration and approach to the most prominent sources of positive affective stimulation. Going beyond formal models (Schultz and Dickinson, 2000; Waelti et al., 2001; Dickinson and Balleine, 2002; Schultz, 2004; Niv et al., 2005), we think that the SEEKING neurodynamic sequences are the procedural structures that concretely lead organisms to move across landscapes of perceptual configurations. Instead of being processed in abstract algorithmic computations, the rewarding value of external stimuli depends on the ability to activate such instinctual psychobehavioral sequences. Raw emotional feeling may be highly linked to the neurodynamics that generate instinctual emotional behaviors. From this perspective, it is likely that positive emotional affects, such as DA facilitated euphoria, emerge relatively directly from instinctual SEEKING dynamics (Panksepp, 2005).

The SEEKING neurodynamic sequences in the limbic BG–thalamocortical circuit interface continuously with other neural activities. Therefore, the role of ML-DA transmission in learning emerges when such neurodynamics intermesh with other cognitive and perceptual representations (see Lewis, 2005 for another elaboration of this type of view in emotion theory). This forms a tight linkage between external stimulus configurations and the SEEKING urge, where external environmental configurations gain the ability to activate SEEKING sequences, acquiring incentive motivational value[18] (via classical conditioning). When unexpected positive outcomes (sensory pleasures) emerge for a behavior in a novel environment, motor sequences that were stimulated by the presence of rewards and reward-related stimuli become linked to the SEEKING sequences. Discrete operant behavior thereby becomes embedded progressively into ever narrowing SEEKING sequences, connecting the original configurations of stimuli to final reward configurations. Such behaviors eventually become habitual, and perhaps largely affectively

[15] The current interpretation of the therapeutic effects of deep brain stimulation is that such electric currents disorganize and block the activity of BG output nuclei. However, it is interesting to note that the frequencies of such stimulations are around the gamma range (~100 Hz) (Garcia et al., 2005). Why not hypothesize then that the deep brain stimulation is effective because it restores basal ganglia characteristic oscillatory rhythms?

[16] But partially also by D1-type receptors belonging to hyperpolarized neurons of the direct pathway (Nicola et al., 2000).

[17] DA transmission tonically inhibits the entrance of glutamatergic descending input in BG areas either via D2-type receptors of striatal neurons belonging to the indirect pathway or via D1-type receptors of down-state, striatal neurons from the direct pathway (Nicola et al., 2000).

[18] SEEKING neurodynamic sequences may simply promote approach or operant behaviors via activation of motor routines. By activating these sequences, external stimuli may acquire an unconscious incentive value (Berridge, 2004). However, it is also possible that SEEKING sequences actively contribute to the emergence of positive hedonic state—not sensory pleasure but euphoria. Indeed, hypothalamic and midbrain nuclei receive abundant direct and indirect connections from the Nacc shell, the ventral pallidum, and the pFC, and empirical data, such as conditioned place preferences, indicate that all these brain regions contribute to affective experiences (Panksepp, 2005).

unconscious, when ML-DA arousal is no longer necessary to activate appetitive SEEKING urges (Choi et al., 2005).

In summary, the neurodynamics of SEEKING sequences within BG–thalamocortical circuits should be viewed as essential neural integrative substrates for associative and operant learning processes. As described in the next section, considering the SEEKING disposition as the affective substrate for appetitive learning could have profound implications in understanding addictions.

5. The ML-DA system in drug addiction

5.1. *Current theories*

Drug abuse has been defined as a chronically relapsing disorder, in which the addict experiences uncontrollable compulsion to take drugs, while the repertoire of behaviors not related to drug seeking, taking and recovery declines dramatically (White, 2002). The development of addiction is attributed to the action of drugs in the brain (Leshner, 1997). Chronic drug use causes permanent neural changes at many levels of analysis, from molecular and cellular levels to neural circuits (Hyman and Malenka, 2001; Everitt and Wolf, 2002; White, 2002; Nestler, 2004; Koob et al., 2004; Robinson and Kolb, 2004). Activity of the ML-DA system represents a key aspect of the chain of events that leads from a molecular action of drugs to the establishment of compulsive habits. In fact, most common drugs of abuse stimulate the release of DA, which modulates both their rewarding and the psychomotor arousal effects (Wise and Bozarth, 1987; Di Chiara and Imperato, 1988; White, 1996; Di Chiara, 1998). Permanent functional changes in the ML system and in BG–thalamocortcal circuits, arising from repetitive DA stimulation, are involved in the development of compulsive drug-taking behaviors (Berke et al., 1998; Robinson and Kolb, 1999; Nestler, 2001a, 2004; Hyman and Malenka, 2001; Koob and Le Moal, 2001; Li et al., 2003; Kalivas et al., 2003). Through the complex reorganization of brain circuits, drugs gradually acquire a tremendous motivational power as organisms become captivated by drug-related activities.

Initial studies of drug abuse in the 1960–1970s considered dependence as the cardinal feature of the disease. Dependence is the physiological state of organisms necessitating continuous drug intake to avoid withdrawal symptoms. In the "opponent process theory", Solomon (1977) proposed that drug abuse arises substantially from homeostatic imbalance caused by compensatory adaptations to chronic drug usage. Concurrently, Panksepp and colleagues (1978, 1980) envisioned that the natural negative emotional processes that sustain drug addictions are related psychologically to the separation-distress process that young animals exhibit when isolated from their caretakers. In other words, endogenous opioids mediate the rewards of social reunion, which is a powerful evolutionary force for creating social bonds, and hence addictive tendencies. Thus, much of drug abuse may reflect self-medication to alleviate aversive feelings, partly engendered by drug withdrawal (see Khantzian, 2003, with commentaries). This perspective has also been adopted by Koob and his coworkers who have sought to identify the neurochemical processes directly involved in generating dependence (Koob and Le Moal, 1997, 2001, 2005; Koob, 2003). As a "hedonic homeostatic dysregulation", drug abuse has a cyclic and progressive nature and is characterized by a pathological alteration of the reward state. As a result of ML-DA hypofunctionality, the deficit in reward functioning throws organisms into a "spiraling distress cycle" and drugs become necessary to restore the normal homeostatic state (Koob and Le Moal, 2001).

Criticism of the affective theory of drug abuse relates to the presence of relapse episodes. Specifically, the affective-homeostatic perspective fails to explain why "after prolonged drug-free periods, well after the last withdrawal symptom has receded, the risk of relapse, often precipitated by drug associated cues, remains very high" (Hyman, 2005, p. 1414). Moreover, in animal models, re-exposure to drugs or drug-related stimuli reinstates drug-seeking behaviors more strongly than withdrawal (Stewart and Wise, 1992). Relapse is then interpreted as the result of unconscious associative memories that, once activated, mechanistically drive the behaviors of addicts without the involvement of any hedonic-homeostatic process (Shaham et al., 2003). Such a conclusion is not probable from the Panksepp et al. (1978, 1980) analysis, where the neurological substrates of drug addiction are strongly linked to the natural social–emotional reward processes of animals that are always experienced at the affective, if not cognitive, level.

In the neurocognitive behavioristic perspective, drugs act on the neurochemical processes involved in the formation of associative and procedural memories (Di Chiara, 1999; Berke and Hyman, 2000; Nestler, 2002; Robbins and Everitt, 2002). Addiction is thus viewed as a "pathological usurpation of the mechanisms of reward-related learning" (Hyman, 2005). This interpretation has received support from work showing many common molecular pathways in addiction and memory processes[19] (Nestler, 2002; Hyman et al., 2006).

A widely heralded attempt to integrate this approach with a motivational perspective argues that repetitive drug usage causes a sensitization of the ML-DA system (see next paragraph), which is involved in mediating the incentive salience of external stimuli (Robinson and Berridge, 1993, 2000, 2003). The attractiveness of drugs and drug-associated cues depends on the capacity of those cues to activate a motivational appetite ("wanting") through the stimulation of the ML-DA system. This theoretical perspective focuses on the influence of the sensory and perceptual processes that regulate the SEEKING urge and has had little to say about the emotional characteristics of brain states. Moreover, a pure incentive sensitization view might wrongly predict that addicts consume less drugs as their system gets sensitized to it. Namely, they are getting more effect from a smaller amount of drug.

[19] The relevance given to associative learning overlaps the emphasis on overt behavioral expression as the only appropriate level of analysis. Drug addiction is now diagnosed exclusively on the basis of observable "behavioral abnormalities" and is defined "as a loss of control over drug use, or compulsive drug seeking and taking despite adverse consequences" (Nestler, 2001b, p. 119). The emotional aspects of addiction are typically underemphasized.

5.2. *The addiction cycle*

One of the big problems in addiction studies concerns how compulsive habits get established from the occasional use of drugs. The process of sensitization is now considered a key step in the addiction development cycle where repetitive drug intake further enhances the desire to consume drugs and further leads to uncontrollable urges. It has been shown that previous drug use, especially that of psychostimulants, increases locomotion, stereotypic responses ("behavioral sensitization"), or the ML-DA response ("biochemical sensitization") to a subsequent acute dose of the same drug (Vanderschuren and Kalivas, 2000; Sax and Strakowski, 2001; Ungless et al., 2001). And this happens not just for drug rewards, but a variety of natural rewards (Nocjar and Panksepp, 2002), especially social ones (Nocjar and Panksepp, 2007).

The concept of sensitization was originally utilized to describe the fact that the application of electrical stimuli induces a "progressively excitable neuronal locus" showing an enhanced sensitivity to subsequent application of the original stimulus or associated cues (Goddard et al., 1969; Janowsky et al., 1980). Since enhanced behavioral and ML-DA responses to drugs correspond to the enhancement of rewarding properties, a study of sensitization should foster our understanding of why drugs and drug-related stimuli acquire an increasing motivational and incentive value (Robinson and Berridge, 1993, 2000; Morgan and Roberts, 2004).

Sensitized responsiveness to drugs often depends on particular stimuli and environmental conditions previously associated with drug intake (Robinson and Berridge, 2000; Weiss et al., 1989). "Context-dependent sensitization" can thus be used to explore how drug-associated stimuli acquire their incentive value. It also provides an explanation for the phenomenon of relapse, where drug-associated memories maintain the ability to activate the ML-DA system long after the withdrawal has subsided (Shaham et al., 2003). On the other hand, "context-independent sensitization" may reflect the increasing ability of drugs to activate the ML-DA system, without contributions from external stimuli (Patridge and Schenk, 1999). In such cases, it is possible that the specific response to the pharmacological action of drugs is potentiated in some way or that the activity of the ML-DA system is globally increased after drug use.

It has been shown that repetitive administration of psychostimulants causes an increased activity of midbrain DA neurons (White and Wang, 1984; Henry et al., 1989; Wolf et al., 1993; Kalivas, 1995). Furthermore, molecular and cellular adaptations responsible for a sensitized DA activity have been found in the VTA (Vanderschuren and Kalivas, 2000; Kalivas et al., 2003; Vezina, 2004; Borgland et al., 2004) or along DA projections. A subsensitivity of D2 autoreceptors, which inhibit DA cell firing, also exists after repeated drug usage (White and Wang, 1984; Volkow et al., 2002a,b). Although a general enhancement of ML-DA functions after chronic drug treatment has been postulated (Robinson and Berridge, 2000; Vezina, 2004), adequate evidence of enhanced ML-DA release under basal testing conditions in chronically drugged animals is missing. On the contrary, as predicted by the hedonic homeostatic dysregulation hypothesis (Koob and Le Moal, 1997, 2001, 2005; Koob, 2003), a deficiency in ML-DA transmission and consequent motivational changes have been observed after repetitive drug use (Parsons et al., 1991; Weiss et al., 1992; Koob and Le Moal, 1997, 2005; Nestler, 2004). Moreover, as already noted, it is difficult for ML-DA sensitization theories to explain why the rewarding power of drugs is enhanced, while natural rewards are commonly ignored by human addicts.

In summary, two different and opposite molecular pathways activated by drugs have been discovered (Nestler, 2004), which are being related to the experience-dependent motivational power of drugs. On one hand, compensatory adaptations responsible for a decreased ML-DA functioning induce motivational impairments and loss of interest in activities not associated with drug consumption (Koob and Le Moal, 1997, 2001; Nestler, 2001b; Volkow et al., 2005b; Barrot et al., 2002; Aston-Jones and Harris, 2004). On the other hand, changes responsible for a sensitized DA responsiveness to drug and drug-related stimuli (Vanderschuren and Kalivas, 2000; Nestler, 2002, 2004) may lead drug-related memories to acquire an increasing motivational value (Robinson and Berridge, 2000).

5.3. *The affective neuroethological perspective of addiction*

Like the affective-homeostatic perspective of Koob and his coworkers, our view is centered on naturally occurring internal affective states. We have envisioned how natural "social reward" chemicals, such as endogenous opioids, participate in addictive urges (Panksepp, 1981b; Panksepp et al., 2004). However, affectivity in our view is conceptualized not only as a result of homeostatic self-regulatory processes, but also of basic intention-in-action type emotional dispositions (Panksepp, 1998, 2003, 2005). Compared with the "psychomotor stimulant theory" (Wise and Bozarth, 1987) and with the "incentive-sensitization theory" of addiction (Robinson and Berridge, 2000), our perspective attempts to specify that the appetitive motivational component stimulated by drugs is an ancestral emotional urge (the SEEKING disposition) regulated by DA transmission and characterized by specific neurodynamic patterns along ventral striatum and ventral BG–thalamocortical circuits. Moreover, this emotion is characterized by neural, behavioral and affective components linked together in complex and synchronized ways.

According to this perspective, drugs of abuse, especially psychostimulants, provide an artificial way to stimulate the emergence of the SEEKING disposition, through which motivated behavior is normally expressed and certain positive affective feelings, such as the euphoria and exhilaration of exploration and reward pursuit, arise. The role of the SEEKING disposition in mediating drug reward is indicated by the similarity between the unconditioned effects of drugs and those of novelty. Novelty may be considered the unconditioned stimulus to which the SEEKING system is naturally predisposed to react (explaining why novelty promotes exploration), while drugs activate the same system in a pharmacological way. Interestingly, novel environments enhance the rewarding and psychomotor activating properties of drugs, leading to environment specific sensitization (Badiani et al., 1995a, 1998; Badiani and Robinson, 2004). From our point of view, the disposition to seek and explore, already active in the

presence of novelty, is further activated by drugs, creating an amplified effect.[20]

Strong associative memories between the SEEKING disposition and drug-related stimuli create the neural conditions for drugs to progressively increase their incentive value. Indeed, in this view, drug-related memories push organisms to consume drugs primarily by activating the SEEKING emotional disposition (at least at the first stages of the addiction process). The involvement of the SEEKING disposition in the first stages of addiction is consistent with evidence that sensitization arising from repeated drug injections not only promotes the establishment of drug-seeking behaviors, but also increases the vigor of normal motivational, non-drug-related activities, such as a pursuit of sexual and food rewards in rats (Nocjar and Panksepp, 2002, 2007; Panksepp et al., 2004).

Molecular, cellular and synaptic learning processes stimulated by drugs could be related to the emergence of the SEEKING disposition, in the way we think this disposition is manifested at the whole brain/mind level (as neurodynamic patterns emerging into ventral BG and spreading into BG–thalamocortical circuits). It seems unlikely to us that molecular and cellular adaptations observed after drug use correspond to the storage of specific information into a linear input-to-output way of processing (Fig. 5A). To the contrary, we think that those brain changes more likely affect the way global reverberatory activity patterns within BG–thalamocortical circuits are generated, how they are supported by ML-DA transmission, and how they are related to incoming activity elaborated through the rest of the brain. We envision the SEEKING neurodynamics being the affective-action centered functional structures, whereby drug-related memories and drug-seeking behaviors become linked together (Fig. 5B).

The abnormal and continuous activation of the SEEKING disposition by drugs is also responsible for the consolidation of compulsive habits, when behavioral routines to find and consume drugs become part of epigenetic changes in the SEEKING dispositions (Ikemoto and Panksepp, 1999). We can imagine that SEEKING neurodynamics activated in ventral BG by drug-associated memories are progressively transformed into behavioral sequences associated with compulsive habits and expressed habitually in dorsal BG circuitry. In such cases, addicts may no longer seek drugs not just because of subjectively experienced elevated desire and euphoria but because of the power of automatically expressed habitual stereotypical compulsive behaviors (that are also well suited to effectively alleviate withdrawal distress).

[20] Commonalities between novelty and drug reward explain why addiction is so pervasive and difficult to stop. Indeed, if natural rewards activate the ML-DA system in unpredictable and novel situations, a DA-induced activation of the SEEKING urge will help the animal to both achieve its goal and to learn from its current experiences. As environments become increasingly familiar, the SEEKING disposition is not activated as intensely. However, drugs of abuse will continue to activate the ML-DA system pharmacologically even in familiar situations, bringing about the experience of novelty and of its associated euphoric effects. This process will cause repetitive and abnormal learning until the motivational and behavioral repertoire of an organism becomes thoroughly captivated by drug-related activities.

A novel feature of this model is that it offers some unique unconditional indicators of SEEKING urges for monitoring drug desire and craving independently of formal conditioning paradigms (Panksepp et al., 2002, 2004). For instance, rat vocalizations may serve as an instinctual "self-report" of appetitive drug desire or aversion since rats exhibit more 50 kHz ultrasonic vocalizations (USVs) when returned to environments in which they received rewarding drugs and more 22 kHz USVs when returned to environments in which they received aversive drugs (Burgdorf et al., 2001a). Indeed, the 50 kHz USV system is intimately related to ascending brain DA networks (Burgdorf and Panksepp, 2006; Burgdorf et al., 2007), and the placement of amphetamine directly into the Nacc, especially the shell region, effectively promotes 50 kHz USVs (Burgdorf et al., 2001b; Thompson et al., 2006). Such affective vocalizations may be capable of being used to track fluctuating affective changes during various phases of the addiction cycle (Panksepp et al., 2002, 2004).

As highlighted in the next paragraph, the affective neuroethological perspective provides a new way of envisioning individual vulnerability to psychostimulant addictions and perhaps other drugs as well. An ethological description of normal SEEKING behavior, together with the knowledge of the neural circuits involved in other emotions (Panksepp, 1998), especially negative ones such as social separation distress (Panksepp, 1981a,b), permits a conceptualization of addiction vulnerability as the consequence of the cascade of natural but specific emotional-affective liabilities. In particular, a deficit in the ML-DA may lead individuals to become compulsive drug consumers, by promoting an enhanced ML-DA responsiveness to drugs. In other words, drugs will acquire an enhanced euphoria-producing (rewarding) power since the hypofunctional DA system is characterized by a deficient development of self-inhibitory mechanisms that usually counteract the neurochemical effects of drugs.

5.4. *Individual vulnerability*

An important issue in drug abuse research concerns why some individuals develop vigorous compulsive drug use after modest consumption of drugs. Human family studies demonstrate that addictive vulnerability is influenced both by genes and environmental conditions (Uhl, 1999, 2002; True et al., 1999; Vanyukov and Tarter, 2000). Similarly, individual vulnerability to drug abuse in animal models depends on both genetic (Carney et al., 1991; Belknap et al., 1993a,b; Meliska et al., 1995) and environmental risk factors for addiction (Bowling et al., 1993; Bowling and Bardo, 1994; Cabib et al., 2000; De Jong and de Kloet, 2004; Nader and Czoty, 2005).

It has been demonstrated that vulnerable animals show higher locomotor and exploratory activity in novel environments (Piazza et al., 1989; Rouge-Pont et al., 1993; Deroche et al., 1995; Grimm and See, 1997; Pierre and Vezina, 1997; Kabbaj et al., 2000; Marinelli and White, 2000; Shimosato and Watanabe, 2003; Orsini et al., 2004). Because of their preference for novel environments (Dellu et al., 1996; Stansfield et al., 2004), they have been described as novelty seekers (Bardo et al., 1996; Klebaur and Bardo, 1999) and compared to human sensation seekers, namely individuals characterized by lower levels of internal arousal who are strongly attracted

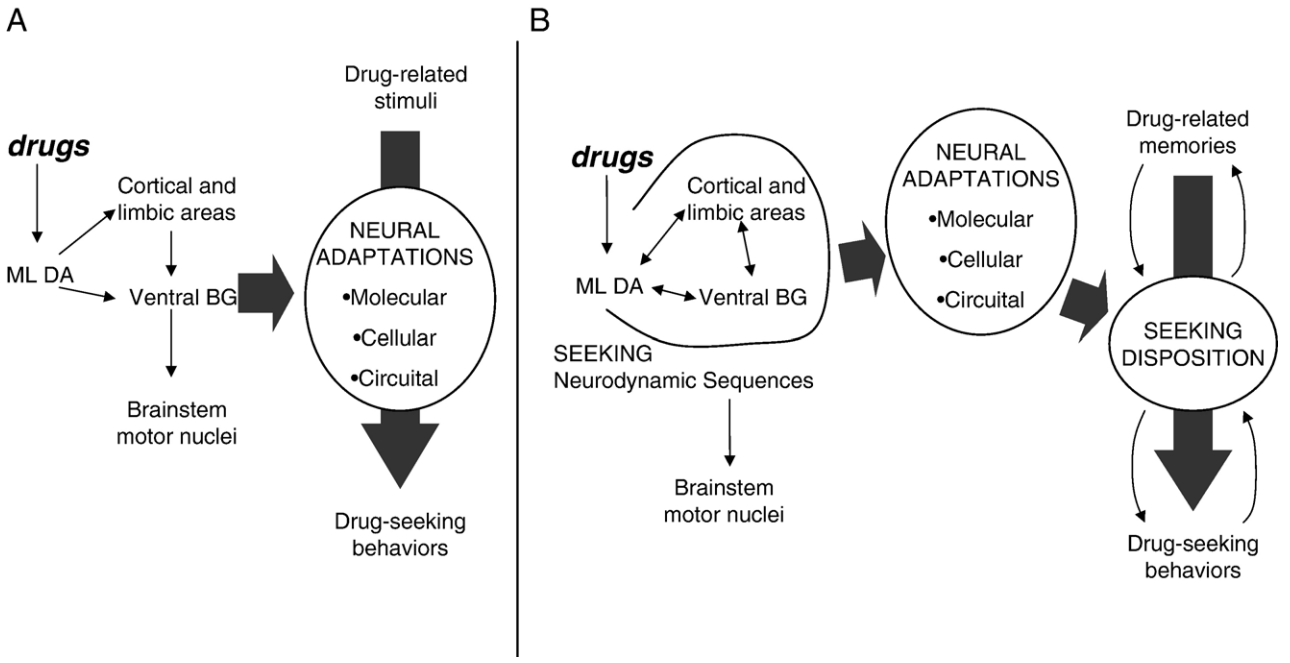

Fig. 5 – The process of drug addiction development. In the *neurocognitive behavioristic* perspective, addiction has been explained as the consequence of drug-induced brain adaptations "stamping" specific associative memories in neural circuits (A). The over-representation of drug-related memories should be caused by synaptic modifications connecting cortico-limbic areas (involved in the representation of motivationally relevant stimuli) to BG areas (involved in the expression of motivated and intentional behaviors). The flow of activity through which compulsive memories are expressed is a linear input–output way of processing, while the ML-DA transmission (especially into the Nacc) is supposed to be particularly important in the drug-induced reinforcement process. The *affective neuroethological* perspective advanced here diverges from the previous one in considering the drug-induced activation of the SEEKING emotional disposition as the cardinal element in the formation of those memories that make drugs and drug-related stimuli always more attractive (B). In particular, we think that ML-DA release after drug intake facilitates the emergence of specific neurodynamic sequences along the BG–thalamocortical circuits, which constitute the patterns through which the SEEKING disposition is expressed at the neural level. Once generated, these sequences match the representations of specific information about the environment (which are elaborated in BG–thalamocortical circuits and related structures). In line with the "Hebbian" dynamic conception of synaptic plasticity, we think that the match between SEEKING sequences and drug-related memories permanently modifies the functional organization of the brain (from the molecular to the systemic level). Therefore, the cascade of neuroadaptations observed after drug use (from molecular to cellular level) represents the tendency of the SEEKING disposition to be activated by drug-related memories and expressed through drug-seeking behaviors.

to intense sources of stimulation (Zuckerman, 1990; Dellu et al., 1996). In accordance with such views, vulnerability to addiction has been seen as the result of an endogenous deficiency in the reward state and, more specifically, in the ML-DA functioning. Indeed, in laboratory animals, low basal levels of ML-DA are related to drug-seeking behaviors, either in individuals with genetic- and history-induced vulnerabilities (Kellogg, 1976; Kempf et al., 1976; Nestler, 1993; George et al., 1995; Gardner, 1999; Misra and Pandey, 2003) or in acute withdrawal from drugs (Parsons et al., 1991; Weiss et al., 1992). In an attempt to maintain "optimal levels of arousal" (Hebb, 1955), individuals with a lower endogenous DA transmission may be preferentially attracted to the hedonic effects of drug-promoted arousal of the ML-DA system since drugs may constitute a way to compensate for endogenous arousal deficits and to pharmacologically increase internal levels of activation. On the other hand, since positive affective states are influenced by arousal following an inverted-U shaped function, drugs of abuse may constitute an excessive source of stimulation for individuals with higher basal levels of arousal, generating unpleasant states in them. Therefore, the "self-medication hypothesis" (Markou et al., 1998; Khantzian, 2003) and the "reward deficiency hypothesis" (Comings and Blum, 2000) look at drug-taking behaviors as instruments of self-regulation and thereby emphasize the relevance of affective feelings as signals of addiction relevant internal states.

Criticism against these theories of vulnerability came from studies showing that novelty- and drug-seeking rats are characterized by overactive ML-DA neurons (Marinelli and White, 2000; Vezina, 2004). Indeed, rats selected for high responsiveness to novelty and psychostimulants (high responders, HR) present an increased firing and bursting activity of ML-DA neurons in basal conditions (Marinelli and White, 2000). These findings have been considered strong evidence for an endogenous sensitization of the ML-DA system. Such endogenous sensitization has been attributed to a potentiation of synapses connecting glutamatergic excitatory projections and DA neurons in the VTA and has been suggested as the cause for

increased activating and rewarding properties of novelty and drugs. Indeed, animals that are more vulnerable to developing drug self-administration show higher levels of behavioral activation after drug intake (Piazza et al., 1989). This effect is explained by a greater drug response in the ML-DA system of these individuals (Bradberry et al., 1991; Hooks et al., 1992; Rouge-Pont et al., 1993; Piazza and Le Moal, 1996; Zocchi et al., 1998; Robinson and Berridge, 2000).

A challenge to the endogenous sensitization hypothesis has emerged from experiments in which high responding rats have a slower rate of DA release and uptake in the Nacc compared with low responders (Chefer et al., 2003). The greater electrical activity of DA neurons (Marinelli and White, 2000) thus correlates with a less rapid DA transmission in projection areas[21] (Chefer et al., 2003). Since DA influences the responsiveness of ML cells to external input, low DA levels should be accompanied by a prevalence of glutamatergic transmission and a hyper-excitability of DA neurons to glutamate. Indeed, DA usually reduces the amount of glutamate released or the intensity of glutamate-evoked cell firing (Siggins, 1978; Dray, 1980; Yim and Mogenson, 1982, 1986; Bradley et al., 1987; Maura et al., 1988; Harsing and Vizi, 1991). The prevalence of glutamatergic transmission in the VTA and higher ML-related regions may also cause the spreading of slow-wave cortical rhythms into the midbrain and BG. The increased bursting activity of DA neurons (Marinelli and White, 2000) may then be caused by a deficiency in DA transmission and may arise from the diffusion of cortical synchronized activity, as manifested in animals treated with chloral hydrate (Steinfels et al., 1981) and in BG output nuclei of Parkinsonian patients[22] (Wichmann and DeLong, 2003).

If the ML-DA deficiency is one predisposing factor in addiction vulnerability,[23] it is also true that sensitivity to the rewarding effects of drugs forms a key component (De Wit et al., 1986; Seale and Carney, 1991; O'Brien et al., 1986; Brunelle et al., 2004; Uhl, 2004). Therefore, it remains to be established why individuals with a blunted ML-DA transmission should present an enhanced ML-DA response to drugs and novelty. An important consequence of endogenous DA hypofunctionality is the reduced expression of neuronal self-inhibitory mechanisms in the ML system. Vulnerable individuals, after drug experiences, show fewer or less functional D2 autoreceptors (White and Wang, 1984; Cabib et al., 2002; Volkow et al., 2002a,b; Nader and Czoty, 2005). Mice of the C57 strain (the addiction vulnerable phenotype) not only show lower levels of D2 autoreceptors in the VTA (Puglisi-Allegra and Cabib, 1997), but also a reduced concentration of DA transporter proteins (DAT) responsible for the re-uptake of extracellular DA in ventral striatal areas (Janowsky et al., 2001). Maternally separated rats, which are more vulnerable to addiction, exhibit lower levels of DAT in adulthood compared with controls, with direct implications for greater responsiveness to drugs and stress (Meaney et al., 2002). On the other hand, socially dominant monkeys present higher levels of D2 receptors, protecting them against the rewarding effects of cocaine (Morgan et al., 2002). It has also been shown that the pFC DA response to amphetamine in the C57 "vulnerable" mice strain is considerably lower compared with that of the DBA addiction "resistant" mice strain (Ventura et al., 2004), and prefrontal DA transmission exerts an inhibitory control over DA release in ventral striatal areas (Deutch et al., 1990; Karreman and Moghaddam, 1996; King et al., 1997; Wilkinson, 1997; Jentsch et al., 1988; Ventura et al., 2002).

In summary, the lower expression or functionality of self-inhibitory processes in the ML system may compensate for the endogenous hypofunctionality of ML-DA transmission. Although basal levels of DA are restored, the ML-DA system will become less capable of self-regulating its own activity. In situations where unusual stimuli, such as drugs of abuse or novel environments, induce a consistent release of DA into the Nacc and related basal forebrain regions, the deficiencies in the inhibitory mechanisms in the ML system will cause abnormally elevated DA responses. Therefore, vulnerable individuals may experience greater rewarding effects of drugs partly, we would propose, due to a higher activation of the SEEKING emotional disposition.

When the system "crashes" because effective reward-seeking is thwarted, animals exhibit depressive responses partly because of the emerging dysphoria producing dominance of dynorphinergic tone over the whole ML-DA SEEKING apparatus (Nestler and Carlezon, 2006). Although we have not focused on this aspect of the ML-DA seeking urge, it would be predicted that kappa receptor antagonists might not only be excellent antidepressants but they will tend to restore SEEKING urges in the behaviorally dysfunctional syndrome of clinical depression. Most other theoretical perspectives of the ML-DA functions, especially the neurocognitive "teaching signal" views, might have difficulty generating comparably straightforward predictions.

6. Conclusion

The analysis of ML-DA functions has become an enormous field of inquiry, and new findings and theoretical interpretations are emerging at a steady pace. As this paper was completed, a whole issue of the journal "Psychopharmacology" (2007, vol. 191, issue 3) appeared that was dedicated to the topic. There is no need to modify our position with respect to the cornucopia of these additional perspectives, which are mostly elaborations of previous positions. We would simply highlight that the view advanced here is one of the earliest and most holistic attempts to conceptualize how trans-hypothalamic reward circuitry, energized by the ML-DA

[21] It is interesting to note that the same paradoxical correlation is present in animals chronically treated with drugs.

[22] On the other side, GABA projections into the VTA exert a general inhibition on DA cell firing (Hyland et al., 2002). Keeping the DA neurons in a hyperpolarized state, GABA inputs permit the progressive accumulation of DA molecules in the presynaptic vescicles and the increase of quanta of DA released per impulse. Moreover, GABA transmission promotes the emergence and the diffusion of basal forebrain and BG oscillatory rhythms. Under GABA control, the ML system may then be regulated by those neurodynamic patterns forming the procedural structure of intentional behaviors.

[23] Although the existence of an endogenous hypofunctionality of ML-DA transmission is considered the first link in the chain, it is not clear where this deficit arises. It is easy to speculate that it may have developmental origins, based either upon genetic or environmental factors.

system, energizes a coherent organismic response to the world (Panksepp, 1981a,b to Panksepp and Moskal, in press). It can readily accommodate and be synergistic with many of the more specific views that exist in abundance in the literature.

Many theories of ML-DA still envision this system participating in goal-directed behaviors in relatively passive cognitive ways, such as "reward prediction error", which do not clearly envision or recognize the energetic psychobehavioral states this system mediates. Those alternative views remain encumbered by the failure to sift correlates from causes. Most eletrophysiological studies have been characterizing what DA neurons are listening to, truly a wide array of information, rather than what these systems are passing on in the global regulation of behavioral states (Panksepp, 2005). In our affective neuroethological perspective, the ML-DA is part of a general purpose appetitive foraging system (the SEEKING system) that allows animals to become acquainted with the diverse configurations and rewards of their environments and thereby establish realistic and adaptive expectations. This system, perhaps some subcomponents more than others, also participates in protecting animals against the vicissitudes of their world (punishing contingencies) by promoting the seeking of safety.

Our view openly acknowledges affective psychological changes, which emerge from related, but poorly understood, emotional network functions (Panksepp, 2005). In its primal form the ML-DA-SEEKING system can generate a special kind of positive affect that is characterized by a euphoric engagement with the world. To the extent that we can define the normal range of arousal of this system, we would suggest that it routinely tends to promote an affectively positive engagement with the world, even though it may not be able to completely counteract a negative affective state that has been concurrently aroused by various punishing events that require the seeking of safety. It is also likely that excessive arousal of this system may be experienced as affectively extreme, leading to feelings such as cravings and excessive feelings of urgency.

We have hardly touched upon the human brain imaging data that are beginning to highlight how important this system is in all varieties of appetitive human motivation, from the excitement of anticipating monetary rewards (Breiter et al., 2001; Knutson et al., 2002) to the delights of love (Fisher et al., 2006) and music (Blood and Zatorre, 2001). These issues have been well reviewed elsewhere (Knutson and Wimmer, 2007) and generally support the long-standing thesis that has been updated and mechanistically developed here. Indeed, some of the new wave of "neuroeconomic" brain imaging goes back to animal work affirming the appetitive nature of some of the spontaneous signs of ML-DA arousal, such a 50 kHz ultrasonic vocalizations (USVs) in rats (Knutson et al., 2002). This vocal index of positive social engagement, especially the "frequency modulated" (FM) variety, is strongly affected by ML-DA dynamics (Burgdorf et al., 2001a,b, 2007). Another, putative direct index of the arousal of this SEEKING system in rats is the appetitive invigoration of sniffing (Clark and Trowill, 1971) and this measure exhibits spontaneous temporal conditioning that helps explain why animals behave the way they do (i.e., exhibit scalloped, expectancy-type, operant responding) on fixed-interval schedules of reinforcement (Panksepp, 1981a,b, 1998). Thus, we have at least three measures of spontaneous arousability of the SEEKING urge in rodents: (i) sniffing, (ii) 50 kHz FM USVs, and (iii) general exploratory-foraging activities. Such unconditional indices, above and beyond DA release, should help us better characterize how the SEEKING disposition helps various behavior patterns become part of the learned repertoires of animals – both "realistic" and "delusional" – as the brains of organisms try to make causal sense of the correlated events to which they are exposed.

Many modern theories of ML-DA function still reflect the old battles between behaviorists and ethologists (Burkhardt, 2005). Obviously, the two views must work together, and they need to be integrated into a seamless whole. However, it needs to be reaffirmed that, as an initial step, organisms do have certain complex behavioral abilities before those abilities get restructured and channeled by learning. In its primal form, the ML-DA energized brain SEEKING system provides a "goad without a goal" (Panksepp, 1971), promoting the emergence of specific neurodynamic sequences first associated with instinctual exploratory and with learning, appetitive-approach patterns. Thereby DA transmission rapidly becomes enmeshed in all varieties of object relations that allow animals to effectively pursue all exteroceptively detectable resources needed for survival.

Several recent publications exhibit a growing interest in integrating dorsal BG-DA and ventral BG-DA behavioral functions (Robbins and Everitt, 2007; Nicola, 2007). Unfortunately, only single-neuron electrophysiological findings are presented as new empirical evidence without consideration of global-field dynamics studies that first revealed their usefulness in understanding Parkinson's disease. Most of the work in the field is still motivated by computational views of ML-DA functions (see Phillips et al., 2007; Nicola, 2007; Phillips et al., 2007), focusing largely "on a role of phasic dopamine in controlling the discrete selection between different actions" (Niv et al., 2007). Moreover, such views have difficulty specifying which kinds of actions are modulated by ML-DA since there is no evidence that "stimulus-evoked firing of DA neurons encodes specific movements" (Nicola, 2007). Such important questions recur in many of the most recent theoretical papers. How the behavioral activating effect of DA may be translated into specific motor patterns? Which kinds of actions are represented in the Nacc and other ventral BG areas? How are such actions adaptive in novel environments?

In our affective neuroethological perspective, the activating effects of DA are translated into instinctual (i.e., unconditioned) action tendencies, psychobehaviorally represented in ventral BG–thalamocortical circuits, since DA-promoted high-frequency rhythms facilitate the release of SEEKING neurodynamic sequences. Such sequences lead to explicit orienting, seeking and approaching movements when coupled with various external stimulus representations that have been experienced in the context of reward acquisitions. Our model integrates dorsal and ventral BG-DA functions in a new way since we considered the procedural routines represented in dorsal BG as learned *subsequences* of the SEEKING disposition that have become habitual (also see discussion in Ikemoto and Panksepp, 1999). Therefore, in novel and unpredictable environments, instinctual actions of exploration and approach to previously uninvestigated stimuli prevail, while in

well-learned situations those patterns are no longer needed (i.e., functional) and instinctual habitual sequences, reflecting more predictable and linear input–output relations, elaborated by dorsal BG circuits, prevail.[24] It is noteworthy that the latter patterns are more unconscious than the affectively rich SEEKING patterns elaborated by the more medial, and hence evolutionarily more ancient, ML-DA circuits.

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[24] It has been interestingly hypothesized that the key difference between dorsal and ventral BG is that dorsal BG control action selection in response to predictable stimuli, while the latter in response to unpredictable stimuli (Nicola, 2007). However, the maintenance of a strict associationistic perspective prevents Nicola from drawing what we believe is the right conclusion from this evidence. Indeed, to explain the role of ML-DA in novel and unpredictable situations, he postulates that stimulus–response associations may also be formed in the absence of a pairing between stimuli and action. But why should ML-DA affect behavior only by acting through the auspices of stimulus–response associations? Why are so many investigators resistant to envisioning that ML-DA arousal can liberate some instinctual action tendencies, evolutionary tools for living in the world, independently of previous learning? We suspect that this reflects the implicit assumption by many investigators interested in this system that the battle between behaviorists and ethologists during the 1950s (see Burkhardt, 2005) was, or should have been, won by the behaviorists. That is a deeply flawed, and evolutionarily improbable, view of animal life. If anything, both sides of that debate provided half the solution to the problem that still needs to be solved. This paper is dedicated to the neuroethological view that still needs to be recognized by neurobehaviorists if we are going to construct a more complete and coherent picture of how evolutionarily designed brain emotional and motivational systems actually operate.

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