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Review

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

Antonio Alcaro[a,*], Jaak Panksepp[b]

[a] Santa Lucia Foundation, European Centre for Brain Research (CERC), Via del Fosso di Fiorano 65, 00143 Rome, Italy
[b] Department of Veterinary and Comparative Anatomy, Washington State University, Pullman, WA 99164-6520, USA

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ABSTRACT

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

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

Contents

* Corresponding author. Tel.: +39 06501703075; fax: +39 06501703319.
E-mail address: antonioalcaro@yahoo.it (A. Alcaro).

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1. Introduction

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

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

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

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

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

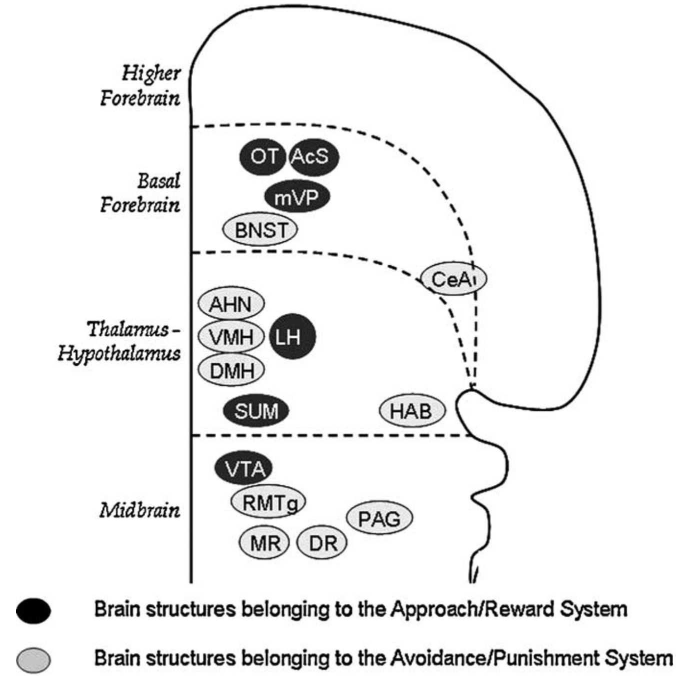

Fig. 1. The basic neuroanatomy of the Approach/Reward and Avoidance/Punishment systems. Schematic drawing shows a flat map of the rat brain adopted and modified from the one by Swanson (2004). Based on brain electrostimulation and drug microinjection studies, the figure indicates a set of subcortical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

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

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