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REVIEW

Neurobiological basis of motivational deficits in psychopathology

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Abstract
In recent years, there has been increasing emphasis on the importance of motivational symptoms in depression, schizophrenia and other disorders. The present review discusses the conceptual background related to the construct of motivation, and provides a framework that for research on both physiological and pathological aspects of motivation. Particular emphasis is placed on what is known about the neurobiological basis of activational aspects of motivation, including studies from animal models. The role of limbic/prefrontal/striatal circuitry in behavioral activation and effort-related functions is examined, and the utility of behavioral tasks of effort-based decision making as models of motivational symptoms is discussed. We also review the neurobiology of motivational symptoms in relation to psychopathology, and issues related to the language used to characterize motivational dysfunctions are considered. The literature suggests that research on the neurobiology of motivational dysfunction in psychopathology, at both clinical and preclinical levels, could inform the development of novel and more effective treatments for a range of CNS disorders.

1. Introduction

Although it has been recognized for some time that motivational dysfunctions are commonplace in psychopathology, this subject has been receiving increasing interest in the recent literature (Demyttenaere et al., 2005; Salamone et al., 2006; Gard et al., 2009; Barch and Dowd,

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2010; Treadway and Zald, 2011; Salamone and Correa, 2012; Markou et al., 2013; Fava et al., 2013; Davis et al., 2014; Barch et al., 2014; Arango et al., 2014). The present review will provide some conceptual background on the construct of motivation, and propose a framework that is relevant for research on both normal and pathological aspects of motivation. Particular emphasis will be placed on what is known about the neurobiological basis of activational aspects of motivation, including studies from animal models and human psychopathology (i.e., depression, schizophrenia and other disorders).

2. Conceptual background: motivation

Motivation has been defined in several different ways, although there are common threads to these diverse definitions. Young (1961) defined motivation as the process of arousing actions, sustaining this activity in progress, and regulating its pattern. Motivation also has been defined as the behaviorally-relevant processes that enable an organism to regulate its external and/or internal environments (Salamone, 1992, 2010; Ryan and Deci, 2000). Motivational functions often involve sensory, motor, cognitive and emotional functions working together (Pezzulo and Castelfranchi, 2009; Salamone, 2010). Moreover, motivational processes are complex and multifaceted. In general, motivationally relevant stimuli are at some physical or psychological distance from the organism (Ryan and Deci, 2000; Salamone, 2010; Salamone and Correa, 2012; Pezzulo and Castelfranchi, 2009). Thus, there are sequences of behaviors that bring the organism into physical proximity with the goal object (e.g., reward or reinforcer) or increase the chances that the goal object will be presented (appetitive, preparatory, approach, or "seeking" behavior), and then a terminal phase that involves the direct interaction with the motivational stimulus or goal object (i.e., consummatory or "taking" behavior; Craig, 1917; Markou et al., 2013). Furthermore, motivation is said to have directional and activational aspects (Cofer and Appley, 1964; Salamone 1988, 1992, 2010). Motivated behavior is directed towards or away from particular stimulus conditions (e.g. towards food or money, away from pain or other aversive stimuli). In addition, motivated behavior can be instigated or sustained with a high degree of activation (i.e., vigor, speed, persistence, and exertion of effort). Activational aspects of motivation are highly adaptive because they enable organisms to exert effort to overcome the work-related response costs that separate them from significant stimuli (Salamone and Correa, 2002, 2012).

In a complex environment, organisms frequently must engage in motivational decision making, when the perceived value or utility of the motivational stimulus is weighed against the costs involved in the instrumental phase (Salamone and Correa, 2002). Reinforcement can occur with varying magnitudes, frequencies, delays or probabilities. There are neural circuits that process information about the value of motivational stimuli, the value and selection actions, and the regulation of cost/benefit decision making processes that integrate this information in order to guide behavior (Phillips et al., 2007; Kable and Glimcher, 2009; Roesch et al., 2009; Guitart-Masip et al., 2014). Furthermore, organisms must be sensitive to effort-related response costs, and make decisions based upon cost/benefit analyses. Taking all this into account, it is clear that motivational dysfunctions can manifest themselves as psychopathological symptoms in multiple ways. A person could have impairments in directional aspects of motivated behavior (e.g. reduced or excessive appetite) or problems with the temporal organization or regulation of motivated behavior (e.g. compulsive food seeking, binge eating, or gambling). In addition, someone could have a pathology related to goal-directed aspects of motivation, or habitual aspects of behavior (see de Wit et al. (2012)). Furthermore, an individual could have an intact emotional response to a motivational stimulus, but still show impairments in the pursuit of their goals. A thorough review of this entire literature is beyond the scope of the present paper. Instead, the discussion below will focus on animal and human studies of impairments in activational aspects of motivation, with a focus on amotivational conditions associated with depression, schizophrenia and other disorders.

3. Preclinical studies of behavioral activation and effort-related aspects of motivation

One brain system that has been consistently implicated in activational aspects of motivation is the mesolimbic dopamine (DA) system (Robbins and Everitt, 2007; Salamone et al., 2006). In rats, neurotoxic depletion of DA in the nucleus accumbens (i.e., NAcc; part of ventral striatum) reduces the motor activity instigated by psychomotor stimulant drugs (Koob et al., 1978), as well as the behavioral activities induced by motivational conditions such as periodic presentation of food to food-restricted animals (Robbins and Koob, 1980; McCullough and Salamone, 1992). Furthermore, NAcc DA depletion reduces the tendency of rats to work for food on operant lever pressing schedules. As the number of lever presses required for obtaining reinforcement increases, rats with NAcc DA depletion show greater sensitivity than controls to this work requirement, and display markedly reduced responding (Aberman and Salamone, 1999; Salamone et al., 2001; Ishiwari et al., 2004). Moreover, this effect is due to the magnitude of the lever pressing requirement, but not the time requirements or intermittency that are part of the operant schedule (Correa et al., 2002; Mingote et al., 2005). NAcc DA is thought to be involved in mediating the instigation of flexible approach behavior (Nicola, 2010), and recent electrophysiological studies indicate that activity of NAcc neurons can be a correlate of the response invigoration seen on tasks involving approach (McGinty et al., 2013). Although NAcc DA is critical for mediating the exertion of effort and response-related vigor, manipulation of accumbens DA transmission does not alter the hedonic reactivity to the taste stimulus (Berridge and Robinson, 1998; Smith et al., 2011).

NAcc DA is also involved in effort-related decision making. In this type of study, animals are given a choice between a more valued reinforcer that can only be obtained by engaging in a high effort activity vs. a low effort/low value option. The behavioral procedures used include a T-maze task that provides an effort-related challenge by having a vertical barrier in the arm with the higher reward value (Salamone et al., 1994; Cousins et al., 1996), operant

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