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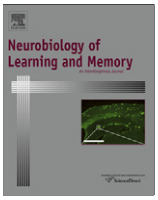

Review

An analysis of rat prefrontal cortex in mediating executive function

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ABSTRACT

While it is acknowledged that species specific differences are an implicit condition of comparative studies, rodent models of prefrontal function serve a significant role in the acquisition of converging evidence on prefrontal function across levels of analysis and research techniques. The purpose of the present review is to examine whether the prefrontal cortex (PFC) in rats supports a variety of processes associated with executive function including working memory, temporal processing, planning (prospective coding), flexibility, rule learning, and decision making. Therefore, in this review we examined changes associated with working memory processes for spatial locations, visual objects, odors, tastes, and response domains or attributes, temporal processes including temporal order, sequence learning, prospective coding, behavioral flexibility associated with reversal learning and set shifting, paired associate learning, and decision making based on effort, time discounting, and uncertainty following damage to the PFC in rats. In addition, potential parallel processes of executive function in monkeys and humans based on several theories of subregional differentiation within the PFC will be presented. Specifically, theories based on domain or attribute specificity (Goldman-Rakic, 1996), level of processing (Petrides, 1996), rule learning based on complexity (Wise, Murray, & Gerfen, 1996), executive functions based on connectivity with other brain regions associated with top-down control (Miller & Cohen, 2001), are presented and applied to PFC function in rats with the aim of understanding subregional specificity in the rat PFC. The data suggest that there is subregional specificity within the PFC of rats, monkey and humans and there are parallel cognitive functions of the different subregions of the PFC in rats, monkeys and humans.

1. Introduction

It is clear that the rodent PFC provides neither the anatomical nor the cognitive complexity that exist in humans or non-human primate brains. Given this premise, why might the rodent PFC be a useful model for understanding prefrontal function in general and psychiatric disease in particular? We argue that, in many ways, it is useful to use rodents to model prefrontal function for the same reasons that rodent models are useful in general. Most obviously, they provide a simpler system for study while sustaining many complex characteristics that are of interest to understanding the neurobiological basis of cognitive, motivational, and behavioral processes that are implicated in psychiatric disease. Moreover, genetic, molecular, cellular, systems approaches, and combinations of these techniques that would be unfeasible or costly in other study subjects can be applied in rodents, particularly in establishing proof of concept in preclinical studies. While it is acknowledged that species-specific differences are an implicit condition of comparative studies, rodent models of PFC function serve a significant role in the acquisition of converging evidence on PFC function across levels of analysis and research techniques. We maintain that the role of PFC, whether in rodents or humans, should be viewed within the context of its crucial role in brain wide orchestration of adaptive behavior, particularly through its involvement in executive functions.

We will review studies that reveal rodents capable of many complex behaviors that are supported by PFC. Thus, the present review examines whether the PFC in rats subserves functions associated with a variety of processes that define executive function. These processes include working memory, temporal processing, planning (prospective coding), flexibility, and decision making. Specifically, we will examine working memory processes through the lens of domain or attribute specificity such as spatial locations, visual objects, odors, tastes, and responses. We will also examine temporal processes such as temporal order, sequence learning, prospective coding, behavioral flexibility associated with rule

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learning, such as reversal learning and set shifting, as well as paired associate learning. Further consideration will be given to the role of the rodent PFC in decision making based on effort, time, and uncertainty. In addition, potential parallel processes involved in executive function based on subregional differentiation within the PFC of rats, monkeys, and humans will be presented, even though we recognize that a comparison of the function of rat PFC with monkeys and human PFC can be quite difficult.

Campbell and Hodos (1970) suggest that one can evaluate homologies between rats, monkeys, and humans based extensively on cytoarchitectonics, the absence of a granular layer, comparable connections with other brain regions, and recording of electrophysiological changes in the PFC in behavioral tasks, as well as behavioral changes following PFC lesions. In addition to considering these criteria, we will compare theories of subregional specificity of PFC, namely domain or attribute specificity, (Goldman-Rakic, 1996), level of processing (Petrides, 1996), rule learning based on complexity (Wise, Murray, & Gerfen, 1996), executive functions based on connectivity with other brain regions associated with top-down control (Miller & Cohen, 2001), and apply these theoretical views with the aim of understanding subregional specificity in the rat PFC.

2. Subregional differentiation of the prefrontal cortex in the rat

Based primarily on architectonics and connectivity with other brain structures, one can organize the subregions of the PFC in the rat according to the schema proposed by Groenewegen and Uylings (2000) and Uylings and van Eden (1990). These subregions include the medial, ventral medial, lateral and ventral PFC (see Fig. 1). Before presenting the interconnections of the PFC, it is important to state that we have concentrated on the connections within neocortex, limbic system, thalamus and caudate/putamen, since these regions are very important for supporting executive functions. The medial PFC can be subdivided into a dorsal medial region including the precentral cortex (PrCm), the dorsal and ventral anterior cingulate cortices (AC). The primary afferent and efferent connections of these areas are with sensory-motor input and association neocortical areas including associated thalamic areas as well as medial dorsal thalamic nuclei and the intralaminar thalamic nuclei. Furthermore, cortico-striatal projections from PrCm innervate the central part of caudate-putamen, whereas the AC terminates more medially and also innervate the core of the nucleus accumbens, (for more detail see Heidbreder & Groenewegen, 2003; Hoover & Vertes, 2007). The ventral medial PFC can be subdivided into the prelimbic and infralimbic as well as medial orbital cortices (PL–IL/MO). The primary afferent connections of these areas include the medial dorsal nucleus, parataenial nucleus of the thalamus, midline thalamic nuclei, the limbic system and limbic association areas, such as perirhinal cortex, entorhinal cortex, hippocampus, basal nucleus of the amygdala and medial basal forebrain. Efferent connections from the PL include the ventromedial part of the caudate-putamen, and the core of the nucleus accumbens, whereas the IL and MO project to the medial shell of the nucleus accumbens (for more detail see Heidbreder & Groenewegen, 2003; Hoover & Vertes, 2007). The lateral PFC can be subdivided into the dorsal and ventral agranular insular and the lateral orbital cortices (AI/LO). The primary afferent connections of these areas include olfactory cortex (pyriform cortex) and olfactory bulb, gustatory cortex and gustatory thalamus, parts of somatosensory I and II, visual association cortex, parietal cortex, perirhinal cortex, the medial dorsal nucleus and central medial nucleus of the thalamus. Efferent connections from the AI region include the ventrolateral part of the caudate-putamen, whereas the LO region projects to the central part of the caudate/putamen (for more detail see Ongur & Price, 2000; Reep, Corwin, & King, 1996). The ventral PFC can be subdivided into the ventral orbital and ventrolateral orbital cortices (VLO/VO). The primary afferent connections of these areas include parietal cortex, visual association cortex, medial dorsal nucleus, and central medial nucleus of the thalamus. Efferent connections from the VO and VLO regions project to dorsal central caudate, posterior parietal cortex, secondary visual cortex, pyriform cortex, and olfactory bulb. In summary, the dorsal medial region (AC/PrCm) has its major connections with the neocortex, the ventral medial PFC (PL–IL/MO) has its major connections with the limbic system, the lateral and ventral PFC (AI/LO) and (VO/VLO) have their major connection to neocortical areas, including connections with the olfactory and gustatory systems, but not the limbic system. The four different areas of PFC project to different parts of the caudate/putamen complex (Heidbreder & Groenewegen, 2003; Hoover & Vertes, 2007; Ongur & Price, 2000; Reep et al., 1996).

In order to make comparisons among the PFC of rats, monkeys, and humans, it is important to note that, based on architectonics,

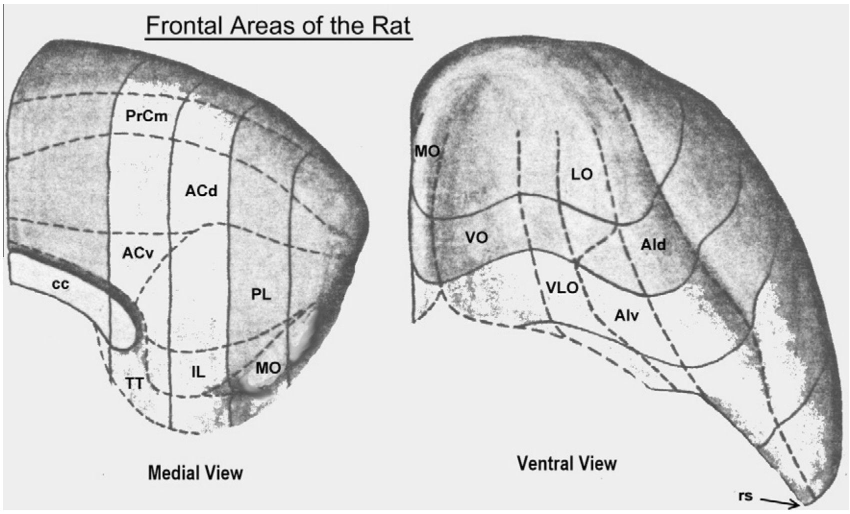

Fig. 1. Frontal areas of the rat: A. Medial view. B. Ventral view. *Abbreviations*: PrCm – precentral cortex; AC – dorsal and ventral anterior cingulate; PL–IL – prelimbic and infralimbic cortex; MO – medial orbital cortex; AI – dorsal and ventral agranular insular cortex; LO – lateral orbital cortex; VO – ventral orbital cortex; VLO – ventrolateral orbital cortex.