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Review

Stress-induced prefrontal reorganization and executive dysfunction in rodents

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ABSTRACT

The prefrontal cortex (PFC) mediates a range of higher order 'executive functions' that subserve the selection and processing of information in such a way that behavior can be planned, controlled and directed according to shifting environmental demands. Impairment of executive functions typifies many forms of psychopathology, including schizophrenia, mood and anxiety disorders and addiction, that are often associated with a history of trauma and stress. Recent research in animal models demonstrates that exposure to even brief periods of intense stress is sufficient to cause significant structural remodeling of the principle projection neurons within the rodent PFC. In parallel, there is growing evidence that stress-induced alterations in PFC neuronal morphology are associated with deficits in rodent executive functions such as working memory, attentional set-shifting and cognitive flexibility, as well as emotional dysregulation in the form of impaired fear extinction. Although the molecular basis of stress-induced changes in PFC morphology and function are only now being elucidated, an understanding of these mechanisms could provide important insight into the pathophysiology of executive dysfunction in neuropsychiatric disease and foster improved strategies for treatment.

Contents

1. Introduction

The prefrontal cortex (PFC) plays an integral role in mediating a range of executive functions that subserve the selection and processing of information necessary to plan, control and direct behavior in a manner appropriate to current environmental

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demands (Bush et al., 2000; Goldman-Rakic, 1996; Miller and Cohen, 2001; Robbins, 2005; Rolls, 1996; Tremblay and Schultz, 1999). A growing literature from studies in laboratory animals demonstrates that the PFC not only plays a major role in orchestrating the behavioral and systemic response to stress, but that neurons in the rodent PFC are highly sensitive to stress and undergo significant remodeling following stress exposure. These findings support the notion that stress-induced alterations in PFC function represent a principle neural insult underlying deficits in executive function observed in stressed rodents, and the executive component of many neuropsychiatric diseases.

In this article, we review this emerging field of research. We begin with a note on the anatomy and connectivity of the rodent PFC and current views about its functional homology with the corresponding anatomical region's in the primate brain. We then describe evidence demonstrating the important role of the PFC in regulating rodent neuroendocrine and autonomic responses to stress, and modulating anxiety- and depression-related behaviors. Next, we turn to the intriguing finding that the morphology of rodent PFC neurons is highly sensitive to stress and speculate on how this might impact PFC functions. Finally, we address how such stress-induced changes might manifest in terms of impairment of three forms of rodent behavior related to executive function (working memory, cognitive flexibility and fear extinction).

2. Anatomy and connectivity of the rodent PFC

The rodent provides an invaluable model system for studying neural processes underlying complex behaviors including higher order cognitive and executive functions. However, given the evolutionary differentiation of the primate and rodent PFC, a discussion of the utility of rodent models for studying the PFC must first acknowledge the issue of the cross-species functional and anatomical homology of this region. On the basis of criteria including granular cytoarchitecture and connectivity with the mediodorsal thalamus, there is general agreement that rodents have a frontal region that is an anatomical representation of the primate PFC (Divac et al., 1993; Groenewegen, 1988; Leonard, 1969; Uylings et al., 2003; van Eden et al., 1990). The degree of functional homology is more difficult to establish, however, and as a result has been more controversial. Consistent with the evolution of the dorsolateral (dl) division of the PFC from motor cortex and its close anatomical connections with striatum, human neuroimaging studies suggest a role for the dlPFC in directing 'cognitive actions' (Fuster, 2000; Wood and Grafman, 2003). In contrast, the ventromedial portion of human PFC is more tightly coupled to limbic regions and regulates emotion and responses to reward (Bechara, 2005; Everitt and Robbins, 2005; Hyman, 2005; Ressler and Mayberg, 2007). While the primate dlPFC does not have a direct anatomical homologue in the rodent, functions of the dlPFC and vmPFC are thought to be integrated within the phylogenetically ancient medial PFC (mPFC) (Conde et al., 1995; Heidbreder and Groenewegen, 2003; Preuss, 1995; Uylings et al., 2003; Uylings and van Eden, 1990; Vertes, 2002). Furthermore, the orbital division of the rodent PFC (OFC) appears to have functional homology with the primate orbital PFC (Floyd et al., 2001; Uylings et al., 2003).

The mPFC and OFC together encompass quite a large area of the rodent forebrain. This area is anterior to the genu of the corpus callosum and extends rostrally as far as the olfactory bulbs. These areas are further subdivided into different subregions (Paxinos and Franklin, 2001) (Fig. 1). The mPFC is comprised of the anterior cingulate (AC), prelimbic (PL), and infralimbic (IL) cortices, while the OFC is made up of the medial (MO), ventral (VO) and lateral orbital (LO) subregions. We will attempt to refer to specific subregions in cases where they were specifically studied and this is made clear in the primary source. However, there are many instances, especially in the older literature, where studies use the more generic terms 'mPFC' or 'OFC' and in these cases our description remains faithful to the original citation.

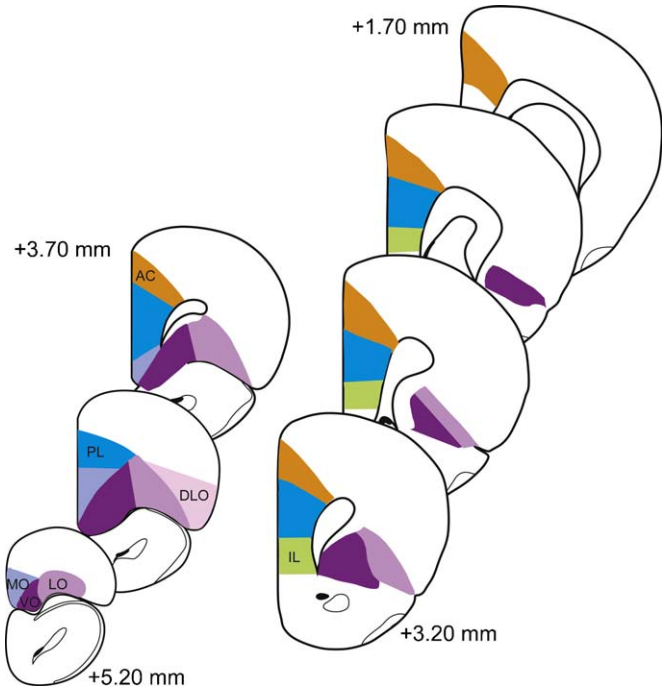

Fig. 1. Schematic diagram of coronal sections through PFC, with major subdivisions of rodent PFC orchestrating stress responses and mediating executive function identified. Coordinates given are relative to Bregma in mouse brain. AC = anterior cingulate; PL = prelimbic; IL = infralimbic; MO = medial orbitofrontal; VO = ventral orbitofrontal; LO = Lateral Orbitofrontal; DLO = dorsolateral orbitofrontal (adapted from Paxinos and Franklin, 2001).

The majority of neural connections within the PFC are between layers and subregions – reflecting a high degree of intrinsic activity and regulation within PFC (Jones et al., 2005). The anatomical connectivity of the PFC with the rest of the brain makes it ideally positioned to orchestrate higher order behavioral functions. We will not attempt to describe this extensive network in detail (for primary references, see (Bacon et al., 1996; Brog et al., 1993; Carr and Sesack, 1996; Cassell and Wright, 1986; Conde et al., 1995; Degenetais et al., 2003; Ferino et al., 1987; Fisk and Wyss, 2000; Gabbott et al., 2002, 2005; Hurley et al., 1991; Jankowski and Sesack, 2004; Jay et al., 1989, 1992; Jay and Witter, 1991; Laroche et al., 1990; Leonard, 1969; McDonald et al., 1996; Neafsey, 1990; Ottersen, 1982; Owens and Verberne, 1996; Resstel and Correa, 2006; Sesack et al., 1989; Swanson, 1981; Takagishi and Chiba, 1991; Thierry et al., 2000; Tierney et al., 2004; Vertes, 2004). However, four pathways are particularly worth emphasizing in the context of PFC modulation of stress. First is a bidirectional connection between PFC and the amygdala (a major neural locus subserving emotion- and reward-related processes among other behaviors), and a descending projection from the PFC to the hypothalamus and brainstem nuclei that mediate neuroendocrine and autonomic responses to stress, respectively. Second is the reciprocal connection between the PFC and the major monoamine systems arising from the midbrain and brainstem that are activated by stress and which are known modulators of executive functions. Third is the reciprocal pathway between the mPFC and hippocampus, which provides a channel for the transfer of complex environmental information between the two regions. Fourth, the PFC is highly interconnected with dorsal and ventral striatal regions that control reward-related behaviors and neuroadaptive