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Invited Minireview

The stressed prefrontal cortex. Left? Right!

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Abstract

The prefrontal cortex (PFC) plays an important role in the integration of cognitive and affective behavior and regulating autonomic and neuroendocrine functions. This region of the brain, which may be considered analogous to the RAM memory of a computer, is important for translating stressful experience into adaptive behavior. The PFC responds to stress and modulates the response to stress through regulation of the hypothalamic paraventricular nucleus (PVN) which, in turn, controls sympathoadrenal and hypothalamic–pituitary–adrenal (HPA) activity. Interestingly, the latter convey the signals that link the CNS with the immune system.

The present review highlights findings that contribute to elucidate the involvement of the PFC in the control of behavioral and neuroendocrine responses to chronic stress. It also considers the implications of these regulatory links for disorders of the nervous and immune systems.

Keywords: Prefrontal cortex; Stress; HPA axis; Hippocampus; Handedness; Hemispheric asymmetry; Lateralization; Immune response; Autonomic nervous system

1. Introduction to the prefrontal cortex (PFC)

Effective communication requires a code that is comprehensible to both the transmitter (the author) and the receiver (the reader). Accordingly, we will approach this task keeping in mind Leonardo da Vinci's words "simplicity is the ultimate sophistication" or those of Albert Einstein "make things simple ... but not simpler".

The PFC was defined after Brodmann's pioneering classification of the cortex. It includes all areas of the frontal lobe that have an inner granular layer IV and lie rostral to the agranular (pre)motor region. These areas, which are well-developed in man, consist of several anatomically distinct subfields, roughly divided into dorsolateral, medial (anterior cingulate) and orbital regions (Fuster, 1997). Different cognitive and emotional functions have been ascribed to these subdivisions of the primate PFC (Goldman-Rakic, 1995). Work by Damasio and co-workers in lesioned patients has led to the view that the PFC is involved in working memory, decision making, planning and behavioral flexibility, as well as in social interactions and emotional processing (Damasio, 2000).

It was previously inferred from the large size of the primate (especially human) frontal lobes that the PFC is a uniquely primate structure. However, based on the common patterns of connectivity among all mammals, the predominance of reciprocal relations with the mediodorsal nucleus of the thalamus and the existence of "class-common functions", such as working memory, temporal organization of behavior and social skills, a region at the frontal pole of the rat brain is now widely considered to be the rodent equivalent of the primate PFC (Uylings et al., 2003). The areas that constitute the rat PFC can be grossly grouped into two main subdivisions: a medial region (mPFC, comprising frontal area 2 (Fr2), dorsal and ventral anterior cingulate areas (ACd and ACv), prelimbic area (PL), infralimbic area (IL) and medial orbital area (MO))

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that has characteristics of the human dorsolateral and medial PFC, and a lateral and ventral region (OFC, comprising dorsal agranular insular area (AId), ventral anterior insular area (AIv), lateral orbital area (LO) and ventral orbital area (VO)) that resembles the primate orbitofrontal cortex (Zilles and Wree, 1995; Dalley et al., 2004).

The PFC has extensive connections with the thalamus (particularly the mediodorsal thalamic nucleus) and basal ganglia (Uylings et al., 2003), its different parts being involved in various basal ganglia–thalamo–cortical circuits. Of particular importance is the input from the midline thalamic nuclei to ventral mPFC areas (IL and PL) through which subcortical limbic information, including from the hypothalamus, is conveyed to the PFC. Available data suggest that the PFC has also extensive, mainly ipsilateral, connections with the other cortical areas, including the hippocampus (CA1 and subiculum). While for long considered a homogeneous region, histochemical and connectivity studies have revealed that the PFC represents a group of distinct areas. Of notice, each of these regions has generally distinct functions (see Table 1).

Furthermore, there is consensus that the dorsal (composed by the prelimbic (PL) and anterior cingulate (Cg)) and ventral (mainly infralimbic (IL)) portions of the rat mPFC are, in fact, two distinct sub-areas (Uylings et al., 2003), although correspondence with equivalent regions in the primate brain remains to be established. For example, the ventral (IL) and dorsal (PL/Cg) zones of the mPFC appear to have opposing effects in the expression of emotional behaviors such as avoidance of aversive outcomes (Jinks and McGregor, 1997), conditioned fear (Vidal-Gonzalez et al., 2006) and habit formation (Killcross and Coutureau, 2003). Importantly, our understanding of the pathogenesis of mood and emotional disorders has changed remarkably since the demonstration of the impact of stress in the aetiology of these disorders (see Sheline, 2000). We have recently gained insights into the interplay between the hippocampus, amygdala/bed nucleus of the stria terminalis (BNST) and mPFC in rats (Sousa et al., 2007). Briefly, stress-induced changes in the hippocampus downgrade some PFC functions (Cerqueira et al., 2007a), allowing the amygdala/BNST (responsible for coordinating emotive responses to stimuli) to assume a dominant function (Fig. 1). These findings are consistent with imaging and post-mortem histological studies that describe alterations in these brain areas of patients suffering from chronic anxiety and depression.

As with its regulation of emotional behavior, the ventral and dorsal PFC areas exert a dual control over the autonomic system. Electrical stimulation of more dorsal zones (prelimbic/anterior cingulate), activates the parasympathetic system, whereas stimulation of the ventral zone (IL) typically elicits sympathetic responses (Powell et al., 1994). Interestingly, human patients with damage in the ventromedial PFC fail to show autonomic responses to emotionally-charged stimuli and exhibit greatly impaired emotional and social functioning, decision-making and risk assessment (Damasio, 2000). Moreover, fMRI studies have documented the activation of mPFC regions by procedures that evoke autonomic changes (Harper et al., 2000).

The PFC appears to be strategically positioned to modulate cognitive and emotional responses to stress. Summa-

Table 1
Behavioral impairments observed after lesions of the two major divisions of the PFC (Adapted and abridged from Uylings et al., 2003 and Chudasama and Robbins, 2006)

Behavioral impairment	Key references
mPFC lesions	
Spatial working memory	Kolb et al. (1974), Ragozzino et al. (1998)
Strategy formation	Kolb et al. (1994), Chudasama et al., (2001)
Spatial reversal	Divac (1971), Delatour and Gisquet-Verrier (2000), Chudasama and Robbins (2003)
Habituation	Kolb (1974a)
Skilled reaching	Whishaw et al. (1992a)
Motor sequencing	Kolb and Whishaw (1983)
Attention	Muir et al. (1996), Chudasama et al. (2003)
Attention set shift	Birrell and Brown (2000), Barense et al. (2002)
Food hoarding	Kolb et al. (1974b)
Fear extinction	Quirk et al. (2000)
Conditioned emotional responses	Frysztak and Neafsey (1994)
Spontaneous alternation	Wikmark et al. (1973)
Decision making	Haddon and Killcross (2006)
Motor responses to pain	LaBuda and Fuchs (2005)
OFC lesions	
Hyperactivity	Kolb (1974c)
Social behavior	Kolb (1974d), de Bruin (1990)
Incentive association	Gallagher et al. (1999), Schoenbaum and Setlow (2001)
Odor and taste working memory	Otto and Eichenbaum (1992), Ragozzino and Kesner (1999)
Configural odor learning	Whishaw et al. (1992b)
Feeding	Kolb and Nonneman (1975)
Impulsivity	Mobini et al. (2002), Winstanley et al. (2004)