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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.

Keywords

Prefrontal cortex; Infralimbic; Prelimbic; Orbitofrontal; Stress; Neuron; Dendrite; Executive function; Working memory; Cognitive flexibility; Attentional set-shifting; Glucocorticoid; Mouse; Rat

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 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

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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.

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 responses to drugs of abuse. Collectively, this profile of regional connectivity is consistent with the PFC being a major neural node both for the modulation of the stress response and top-down executive functions. In the next two sections we summarize evidence that the rodent PFC modulates neuroendocrine and autonomic responses to stress, and some of the behavioral correlates of stress exposure in the forms of anxiety- and depression-related behaviors.

3. PFC modulation of rodent neuroendocrine and autonomic responses to stress

By quantifying the expression of immediate-early genes such as c-Fos (Singewald, 2007), the rodent PFC, particularly the medial subregions (IL, PL, and AC), has been shown to be strongly activated by exposure to various forms of stress. These stressors include acute exposure to restraint (Cullinan et al., 1995; Ostrander et al., 2003), footshock (Morrow et al., 2000), forced swimming (Cullinan et al., 1995), loud noise (Campeau et al., 2002, 1997), tests for anxiety-like behavior (Duncan et al., 1996), and treatment with anxiety-provoking drugs (Schroeder et al., 2003; Singewald et al., 2003). Activation likely reflects the engagement of the PFC as a modulator of the endocrine and autonomic response to stress (for reviews see Herman et al., 2005; Sullivan, 2004). This is supported by the finding that lesions of the PL and AC can augment acute restraint stress-induced glucocorticoid release and c-Fos activation in the paraventricular nucleus of the hypothalamus (PVN) and medial amygdala (Brake et al., 2000; Diorio et al., 1993; Figueiredo et al., 2003; Radley et al., 2006a; Spencer et al., 2005) (cf. Crane et al., 2003; Sullivan and Gratton, 1999). An opposite effect is seen with corticosterone implants in the mPFC, which serve to inhibit acute restraint or cold stress-induced glucocorticoid release (Akana et al., 2001; Diorio et al., 1993). These effects likely occur via actions on glucocorticoid and mineralocorticoid receptors abundantly expressed in the rodent mPFC (Ahima and Harlan, 1990; Chao et al., 1989; Fuxe et al., 1985; Meaney and Aitken, 1985; Patel et al., 2000) and, as such, might be attenuated with repeated exposure to stress due to glucocorticoid receptor downregulation. In support of this, Mizoguchi et al. found that prolonged stress (4 weeks of daily restraint or water immersion) decreased glucocorticoid receptor protein and mRNA expression in the PFC and attenuated PFC-mediated negative feedback control over the HPA axis in rats (Mizoguchi et al., 2003).

An important but as yet unresolved issue is the degree to which different PFC subregions play functionally distinct roles in modulating autonomic and HPA-axis responses to stress. Early reports were mixed. Lesions of AC/dorsal PL reduced gastric ulcers resulting from acute stress (Sullivan and Henke, 1986). Ablation or temporary inactivation of the rat IL and ventral PL

reduced conditioned autonomic responses (heart rate and blood pressure) to shock and shock-associated context (Fryszak and Neafsey, 1991, 1994; Resstel et al., 2006), while stimulation of rabbit IL elicited sympathetic-like changes in heart rate and blood pressure (Powell et al., 1994). While these data suggest a role for IL in mediating sympathetic activation during stress, IL lesions failed to alter some autonomic components of the conditioned emotional response (Powell et al., 1994). The contradictory nature of these studies may stem in part from lack of regional specificity of the lesions (which were relatively diffuse and included parts of both IL and PL in these early studies), differential effects of electrolytic versus fiber-sparing excitotoxic lesions, and potentially differential roles of the subdivisions of mPFC in learned versus unlearned autonomic responses (e.g., Powell et al., 1994).

Radley et al. have conducted the most direct and comprehensive assessment of the regional specificity of mPFC modulation of sympathetic and HPA axis responsivity to date (Radley et al., 2006a). These authors found that IL lesions attenuated restraint stress-induced HPA axis activation reflected in plasma ACTH and corticosterone levels and decreased c-Fos and CRF mRNA expression in PVN nuclei mediating glucocorticoid release, while PL/AC lesions had opposite effects (Radley et al., 2006a). A subsequent study went on to show that stress-induced activation of PL but not IL, as assayed by c-Fos expression, was negatively correlated with c-Fos and CRF mRNA expression in the PVN (Radley et al., 2008a). Conversely, IL lesions increased activation of PVN neurons mediating sympathetic activation.

One interpretation of these data is that IL and PL have somewhat opposing modulatory effects on stress-induced activation of the HPA-axis, with PL primarily having an inhibitory role and IL predominantly excitatory. This is likely to be an over-simplification however. For example, IL lesions also increase stress-induced c-Fos in a subregion of PVN involved in sympathetic regulation (Radley et al., 2006a), suggesting IL plays an additional inhibitory role in sympathetic activation. Moreover, there is evidence for hemispheric specialization in IL's modulation of HPA axis responses, with lesions of right but not left IL altering HPA axis activity (Sullivan and Gratton, 1999). Clearly, further work will be needed to dissect the precise role of PFC subregions in mediating the neuroendocrine and autonomic response to stress. Notwithstanding, the available data establish an important role for the PFC in mediating the autonomic and HPA-axis response to stress.

4. PFC modulation of rodent anxiety- and depression-related behaviors

Stress responsivity and anxiety are not synonymous, but are intimately linked in terms of rodent behavior and clinical pathology. For example, one consequence of stress exposure in rodents can be heightened anxiety (Cryan and Holmes, 2005). The PFC appears to have a rather complex role in mediating rodent anxiety-like behavior. Electrolytic lesions of the rodent IL have been shown to decrease state anxiety-like behavior in the elevated plus-maze, shock-probe burying and Vogel conflict tests (Lacroix et al., 2000; Maaswinkel et al., 1996; Shah and Treit, 2003; Sullivan and Gratton, 2002). Similar effects are produced by fiber of passage-sparing ibotenic acid lesions or temporary inactivation of the mPFC (Resstel et al., 2007; Shah and Treit, 2004; Wall et al., 2004). However, lesions or inactivation of AC plus dorsal part of PL are more variable in their effects, with decreases (Deacon et al., 2003; Gonzalez et al., 2000; Maaswinkel et al., 1996), increases (Holson, 1986; Jaskiw and Weinberger, 1990; Jinks and McGregor, 1997) and no change (Bissiere et al., 2006; Corcoran and Quirk, 2007; Lacroix et al., 1998) all being reported in various tests for anxiety-like behavior following ablation of these areas. Thus, if a tentative conclusion can be drawn from these data, it is that the IL appears to promote anxiety-like behavior, while the more dorsal portion of mPFC has a less well-defined role.

With regards studies of the role of the PFC in modulating rodent 'depression-related' behaviors, Muigg and colleagues found that rats selectively bred for high anxiety-like behavior exhibited an increased depression-related phenotype in the forced swim test, coupled with increased swim-induced PL activation, as compared to low anxiety counterparts (Muigg et al., 2007). Moreover, both the behavioral and neural abnormalities displayed by these rats were normalized by chronic antidepressant treatment. Another recent study found that lesions of the AC increased depression-related passive floating behavior in rats repeatedly subjected to forced swimming (Bissiere et al., 2006). This finding is reminiscent of work by Maier et al. which has demonstrated the importance of the rat mPFC in regulating the perception of stress 'controllability.' Their studies utilize an elegant task in which one group of rats has control over the cessation of shock while another, yoked, group passively receives an equivalent number of shocks. Rats exposed to the inescapable stress regime develop a passive behavioral response even when escape from shock becomes available: a phenomenon termed 'learned helplessness' (Seligman, 1972). The inescapable condition selectively elicits a number of neural responses including activation of the ascending serotonergic system and release of serotonin in the ventral part of mPFC (Grahn et al., 1999; Maswood et al., 1998). As already mentioned, there is a large projection from the IL/PL area to the serotonergic dorsal raphe nucleus (Gabbott et al., 2005; Jankowski and Sesack, 2004). Stimulation of this pathway inhibits activity of serotonin neurons via local GABAergic interneurons (Celada et al., 2001; Hajos et al., 1998). Amat et al. have shown that temporary inactivation of the IL/PL area is sufficient to induce learned helplessness in response to stress – i.e., lesioned rats given control over stress still develop a passive behavioral response and persistent serotonin activation akin to that produced by uncontrollable conditions (Amat et al., 2005). Conversely, pharmacological stimulation of the IL/PL region prevents the learned helplessness and persistent serotonin activation induced by inescapable stress (Amat et al., 2005, 2008). These intriguing findings suggest that one major consequence of stress-induced mPFC dysfunction is to produce a bias towards perceived lack of control and as a result a passive, maladaptive response to stress (for further discussion, see Maier et al., 2006; Maier and Watkins, 2005). In the next section we discuss recent evidence that these changes may in part result from stress-induced structural remodeling in PFC.

5. Stress effects on rodent PFC neuronal morphology

The seminal work of McEwen, Sapolsky, de Kloet and others has shown how prolonged exposure to glucocorticoids or stress produces significant neuronal atrophy in the hippocampus, characterized by a retraction of dendrites on pyramidal neurons in the CA3 subregion (de Kloet et al., 2005; McEwen and Milner, 2007; Sapolsky, 2003). It was subsequently found that neurons in other limbic regions also undergo morphological changes following stress. Of particular note, Chattarji and co-workers have found increased dendritic growth and spine density in pyramidal neurons of the basolateral nucleus of the amygdala in rats and mice exposed to chronic restraint stress (Govindarajan et al., 2006; Mitra et al., 2005; Vyas et al., 2006, 2002).

In the first demonstration that pyramidal neurons in the rodent medial PFC exhibit morphological changes in response to stress, Wellman found that 3 weeks of corticosterone administration reorganized dendrites of pyramidal neurons in layer II–III of the dorsal part of the PL as well as the AC (Wellman, 2001). In a follow-up study, a marked reduction in dendritic material in this area was seen following exposure to stress itself; in this case, 3 weeks of 3 h daily restraint (Cook and Wellman, 2004). In these studies, dendritic remodeling was specific to the apical but not basilar branches, with the most dramatic reductions in branch number and length occurring in terminal branches relatively distal to the soma. A similar pattern of apical dendritic retraction and debranching in mPFC neurons following chronic restraint stress or corticosterone treatment has been independently documented in a series of excellent studies

by Liston et al. (2006), Radley et al. (2005a, 2006b, 2004), and Cerqueira et al. (2005a,b, 2007a,b) (see also recent work by Czeh et al., 2008). Importantly, this work has shown that stress-induced debranching of apical dendrites is also associated with a significant decrease in the density of dendritic spines, particularly in their mature functional form (Michelsen et al., 2007; Radley et al., 2006a, 2008b; Silva-Gomez et al., 2003).

The restriction of remodeling and spine loss to apical dendrites provides some clues as to the mechanisms driving these alterations. Cortical pyramidal neurons segregate their inputs. In piriform cortex for instance, distal apical dendrites of layer III pyramidal neurons receive extrinsic inputs, while more proximal portions of the apical dendrite, as well as the basilar dendrites, receive intrinsic inputs (Price, 1973). While the segregation of inputs to pyramidal neurons in neocortex appears to be less straightforward, mPFC pyramidal neurons also tend to segregate inputs. For example, there is some evidence that extra-cortical afferents (e.g., from mediodorsal thalamus and CA3 region of hippocampus) predominantly synapse on layer I distal dendrites (Groenewegen, 1988; Swanson and Cowan, 1977) while local cortical afferents tend to cluster more on proximal portions of the apical and basilar arbor (Scheibel and Scheibel, 1970). Thus, the stress-induced retraction of relatively distal apical dendrites could be a response to alterations in activity of subcortical inputs. Because stimulation of the apical tufts of cortical pyramidal neurons disproportionately excites the cell (Rhodes and Llinas, 2001), apical retraction would serve as a relatively effective adaptive response to over-excitation. However, precisely how stress-induced morphological alterations in mPFC neurons translates into changes in their physiological properties remains a critical but largely unanswered question. Interestingly in this context, one recent study found that stress-induced reductions in branch length of apical tufts in layer V mPFC neurons correlated with reduced neuronal responses (i.e., excitatory post-synaptic currents) to serotonin application (Liu and Aghajanian, 2008). Further work along these lines will be an important area for future study.

5.1. Sensitivity, reversibility and subregion specificity of stress effects on rodent PFC neurons

One somewhat unexpected finding from Wellman's initial finding of dendritic remodeling after corticosterone treatment was that control rats receiving subcutaneous vehicle injections showed the same pattern of changes, albeit to a lesser extent (Wellman, 2001). Earlier data had shown that a similar regime of vehicle injections did not alter dendritic morphology in hippocampal CA3 pyramidal neurons (Woolley et al., 1990). This suggested that mPFC neurons might be relatively more 'susceptible' to stress than neurons in other brain regions. Subsequent findings have borne this out. For example, repeated exposure to brief restraint (10 min per day for 7 days) has been shown to cause dendritic retraction in PL and AC (Brown et al., 2005) similar in pattern but lesser in extent to that produced by lengthier (3–6 h) restraint protocols (Cook and Wellman, 2004; Radley et al., 2004). Even more strikingly, a single 10-min forced swim followed by tone-shock Pavlovian fear conditioning was sufficient to produce apical dendritic retraction in the IL of mice (Izquierdo et al., 2006). Brief stress also affects the synaptic plasticity of mPFC neurons. In rats, a single 30-min bout of elevated platform stress impaired a form of long-term potentiation in PL produced by theta-burst stimulation of the basolateral amygdala (Maroun and Richter-Levin, 2003). Jay and co-workers have found that the same single stressor also impaired LTP in the hippocampus-mPFC pathway (Dupin et al., 2006; Jay et al., 2004; Mailliet et al., 2008; Rocher et al., 2004), mimicking the effects of chronic restraint stress (Cerqueira et al., 2007a). Collectively, these findings speak to the exquisite morphological and physiological sensitivity of mPFC neurons to stress.

Given the rapid response of mPFC neurons to stress, a corollary question is how quickly these neurons recover from stress. Dendritic retraction in the hippocampus caused by chronic restraint is ameliorated within 10 days of stress cessation (Conrad et al., 1999). By comparison,

chronic restraint stress-induced dendritic retraction in the dorsal portion of PL and AC was no longer evident 3 weeks after stress (Radley et al., 2005b). A detailed time course of the progression of recovery would be very useful. Notwithstanding, the more general finding that stress effects on mPFC neuronal morphology are reversible further underscores the plasticity of these neurons. Critically, it also implies that the mechanisms mediating this plasticity can be identified and manipulated to expedite the process of recovery.

Given increasing evidence that different subregions of the rodent PFC have dissociable functions in mediating stress and behavioral (including executive, as discussed below) functions, another important issue is whether stress differentially targets specific subregions. Sousa, Cerqueira et al. have demonstrated that rats chronically treated with either corticosterone or the glucocorticoid receptor agonist dexamethasone, or exposed to chronic unpredictable mild stress, results in decreases in volume and apical dendritic length (and sometimes cell loss) that are equivalent in the IL, PL and AC (but not motor or retrosplenial cortex) (Cerqueira et al., 2005a,b, 2007a,b). While this suggests that stress-induced dendritic retraction generalizes across subregions of mPFC, there is preliminary evidence that changes in OFC may actually be quite different. This stems from the finding that the same chronic restraint procedure that produces dendritic retraction in the AC actually increased dendritic material in the rat lateral OFC (Liston et al., 2006). This intriguing finding suggests that stress produces opposite effects on the morphology of mPFC and OFC neurons. That mPFC and OFC show divergent changes in response to an environmental insult is not without precedent. For example, repeated exposure to psychostimulants produces increased spine density in mPFC neurons but decreased spine density in OFC neurons (Robinson and Kolb, 2004), as well as contrasting changes in the firing properties of mPFC and OFC neurons (for further discussion, see Moghaddam and Homayoun, 2008). This raises the possibility that behavioral functions mediated by mPFC and OFC might be differentially sensitive to stress. We will take up this issue in the next section where we discuss some of the literature describing the effects of stress on rodent executive functions.

6. Stress effects on rodent executive functions

The rodent PFC subserves a range of cognitive and behavioral processes analogous to some of the executive functions mediated by the human PFC (Heidbreder and Groenewegen, 2003; Marko-witsch and Pritzel, 1977; Robbins, 2005; Uylings et al., 2003). Executive functions measurable in rats and mice include working memory (e.g., delayed alternation in the T-maze), cognitive flexibility (e.g., reversal learning and set-shifting), sustained attention (e.g., 5-choice serial reaction time task), and inhibitory response control (e.g., delay discounting, Go/No-Go). A number of laboratories have now convincingly shown that the rodent PFC mediates these processes and does so with a remarkable degree of subregional specialization (reviewed in Chudasama and Robbins, 2006; Dalley et al., 2004). However, although a significant corpus of data describes the effects of stress on various forms of rodent learning and memory, chiefly those involving the hippocampus (Kim and Diamond, 2002; McEwen, 1999; Sandi, 2004; Shors, 2006), stress effects on PFC-mediated executive functions is only now being elucidated. We will summarize some of the main findings to date.

6.1. Stress effects on rodent working memory

The T-maze delayed alternation test and the 8-arm radial maze are two of the more common rodent assays for working memory (Lalonde, 2002; Olton, 1987). Lesions encompassing most of the rodent mPFC, or the IL and PL subregions specifically, impair working memory performance on these and related tasks such as the Y-maze and appear to do so in part at least by impairing inhibitory response control (Aggleton et al., 1995; Brito and Brito, 1990; Chudasama et al., 2003; Di Pietro et al., 2004; Dias and Aggleton, 2000; Floresco et al., 1997; Granon et al., 1994; Kellendonk et al., 2006; Kolb, 1984; Ragozzino et al., 1998;

Schwabe et al., 2004; Seamans et al., 1995; Sloan et al., 2006). The detrimental effects of these lesions can be mimicked by stressors including chronic exposure to restraint, cold water immersion, loud noise, high illumination, or footshock, as well as acute stressors such as handling and anxiogenic drug treatment (Anisman et al., 1985; Del Arco et al., 2007; Hahn et al., 1986; Manikandan et al., 2006; Mizoguchi et al., 2000; Murphy et al., 1996a,b; Nishimura et al., 1999; Pierard et al., 2006; Shanks and Anisman, 1988). Interestingly, either adrenalectomy (Mizoguchi et al., 2004), acute or chronic corticosterone treatment (Bardgett et al., 1994; Roozendaal et al., 2004), or infusion of a glucocorticoid receptor agonist directly into the PL and AC (Roozendaal et al., 2004) also impairs performance on working memory tasks. These effects are reminiscent of the aforementioned finding that either adrenalectomy or corticosterone administration produces dendritic retraction in mPFC (Cerqueira et al., 2007b; Wellman, 2001). Thus, there appears to be an inverted U-shaped relationship between glucocorticoid activity and both mPFC neuronal morphology and mPFC-mediated working memory, with either hypo- or hypercortisolemia causing dendritic retraction and behavioral impairment.

While the similarities between the effects of stress and mPFC lesions on working memory suggest the possibility of a causative link between stress-induced changes in mPFC neuronal morphology and concomitant impairment of the behavior, direct evidence of such a link has not yet been obtained. In fact, this issue is raised in a recent study by Cerqueira et al. Using the Morris water maze, a paradigm typically used to assess spatial reference memory, but which has also been adapted to assay spatial working memory (Steele and Morris, 1999), these authors found that 6 days of unpredictable stress impaired water maze spatial working memory and caused dendritic atrophy in the IL, PL and AC (Cerqueira et al., 2007a). As the authors note, this deficit could reflect functional changes in either the mPFC or the hippocampus (or both) given evidence that both regions mediate this behavior (de Bruin et al., 1994; Ferbinteanu et al., 2003; Lacroix et al., 2002; Steele and Morris, 1999; Sullivan and Gratton, 2002; Wolf et al., 1987). This illustrates a general caveat when attributing stress-induced changes in behavior to functional changes in PFC per se because executive functions including working memory are subserved by a distributed network of brain regions in which the PFC has a special but by no means exclusive role (e.g., Floresco et al., 1997; Kesner and Rogers, 2004). In other words, a full understanding of the effects of stress on the PFC and its associated functions will ultimately have to be at the systems level, and account for interactions between PFC and other structures that are influenced by stress and/or critical components of the circuitry subserving executive functions.

6.2. Stress effects on rodent cognitive flexibility (reversal learning, attentional set-shifting)

There is growing evidence that stress-induced impairments extend to executive functions other than working memory. The Morris water maze task has been used to test for cognitive flexibility in the form of spatial reversal learning; by measuring the ability to learn to swim to a submerged platform after its trained location has been switched. A number of studies have now shown that spatial reversal learning on this task is impaired by exposure to stressors including chronic unpredictable stress, postnatal maternal separation and acute foot shock (Enthoven et al., 2007; Francis et al., 1995; Hill et al., 2005; Szuran et al., 2000). In studying the link of such deficits to mPFC neuronal changes, Cerqueira et al. demonstrated that 6 days of unpredictable stress impaired spatial reversal learning but did not alter the volume of IL, PL or AC (Cerqueira et al., 2005a). On the other hand, these authors found that either chronic corticosterone treatment or adrenalectomy was sufficient to impair spatial reversal learning (not working or reference memory) in a manner that correlated with reduced mPFC volume (Cerqueira et al., 2007a, 2005a). They also showed that their unpredictable stress paradigm impaired plasticity in the hippocampal-mPFC pathway (Cerqueira et al., 2007a). This latter observation is particularly noteworthy given the finding that chronic restraint stress produces spatial maze

reversal deficits that parallel morphological changes in the CA3 region of the hippocampus (Luine et al., 1994). The conclusion from these data therefore is that while stress effects on spatial working memory are coupled to morphological alterations in mPFC neuronal morphology, they likely stem from changes at the level of the mPFC-hippocampus circuit.

Another way to ask how stress affects rodent cognitive flexibility is via the use of assays for attentional set-shifting. An illustrative example of set-shifting in rodents is an assay developed by Birrell and Brown (2000). In this task, rodents first learn to dig for food reward using sand texture and sand smell and then to reverse the learned association (e.g., if smooth sand previously signaled reward, now dig in rough sand). There is then a subsequent phase known as an extra-dimensional shift in which the subject must use a different stimulus 'set' to guide their digging behavior (e.g., if sand texture previously discriminated reward, now use sand smell to discriminate). In a now classic study, Birrell and Brown found that lesions of most of the rat mPFC selectively impaired the extra-dimensional component on this task. Similarly, combined IL and PL lesions impairs extra-dimensional set-shifting on various exploration-based tasks (Delatour and Gisquet-Verrier, 2000; Ragozzino et al., 1999a,b). Using the Birrell and Brown digging task, Bondi et al. demonstrated that 2 weeks of unpredictable stress impaired reversal learning and extra-dimensional set-shifting (Bondi et al., 2008). Along similar lines, Liston et al. (2006) found that 3 weeks of restraint stress produced a (in this case selective) deficit in extra-dimensional set-shifting and, furthermore, that the magnitude of the impairment correlated with the extent of dendritic retraction in the AC (Liston et al., 2006). Although it again should be emphasized that correlations alone cannot demonstrate that the dendritic atrophy in AC neurons caused the stress-induced disruption in set-shifting, this is the best evidence to date that the two are related.

Lesion studies have shown that, in contrast to the effects of mPFC lesions, ablation of the lateral OFC impaired reversal performance in the Birrell and Brown digging task while leaving the extra-dimensional set-shifting component intact (McAlonan and Brown, 2003). This effect is highly reminiscent of the finding that ventral and lateral OFC lesions disrupt the ability of rats to shift their responses for reward when stimulus-reinforcement contingencies are reversed (Chudasama et al., 2003; Ferry et al., 2000; Kim and Ragozzino, 2005; Schoenbaum et al., 2002, 2003; Stalnaker et al., 2007), and work by Schoenbaum and co-workers showing that the activity of OFC neuronal activity tracks reversal performance (Saddoris et al., 2005; Schoenbaum et al., 1999, 2000). Collectively, these observations support a model in which the OFC (in concert with subcortical regions including BLA and ventral striatum) guides behavioral responses according to their current incentive value of reward-related stimuli (Bechara et al., 2000; Clark et al., 2004; Rolls, 1996; Schoenbaum et al., 2006). This in turn provides a conceptual framework for explaining how OFC dysfunction might underlie the cognitive and behavioral rigidity characteristic of disorders ranging from drug addiction to obsessive compulsive disorder (Kalivas et al., 2005; Schoenbaum and Shaham, 2008).

A better understanding of how stress might affect OFC neuronal morphology and the behavioral functions supported by this region is of great topical interest. However, potential effects of stress-induced changes in OFC for measures of rodent cognitive flexibility such as reversal learning have not yet been well studied. One study found that 14 days of cold stress impaired reversal (but not extra-dimensional set-shifting) in the Birrell and Brown task (Lapiz-Bluhm et al., 2008) – i.e., mimicking the effects of OFC lesions. In addition, as discussed above, there is one report that chronic restraint stress produced increased dendritic length in lateral OFC neurons (Liston et al., 2006). However, this study did not find any correlation between the extent of the morphological changes and intra-dimensional set-shifting on the Birrell and Brown task. Although it is not certain that dendritic elongation of OFC would necessarily lead to an improvement (as opposed to an impairment) in this behavior, the authors speculate that their negative finding may have been due to the fact that stress improved rather

than impaired performance but the task was unable to detect this due to a 'ceiling effect'. Thus, precisely how stress might affect cognitive flexibility and other executive functions subserved by the OFC (e.g., certain forms of impulsivity Cardinal et al., 2001; Mobini et al., 2002) remains another important avenue for future work.

6.3. Stress effects on rodent fear extinction

Extinction of fear memories does not fit the definition of an executive function, but this behavior does have certain features that make it pertinent to the current discussion. First, fear extinction requires the ability to flexibly alter behavior by inhibiting a previously learned response – with extinction deficits manifesting as a form of 'emotional perseveration' somewhat akin to the 'cognitive perseveration' caused by OFC lesions (Morgan et al., 2003; Sotres-Bayon et al., 2004). Second, the evidence implicating the rodent mPFC in fear extinction is compelling. For example, IL is strongly activated (as assayed by immediate-early gene expression and neuronal firing) during extinction, while IL lesions or inactivation impair fear extinction learning and/or memory (reviewed in Quirk and Mueller, 2008).

How stress affects fear extinction is not yet fully clear. In part this is because stress can enhance the acquisition or expression of conditioned fear memories per se (Rau et al., 2005), making it difficult to disentangle a selective deficit in the ability to extinguish the fear memory from increased fear itself. However, stress-induced deficits in fear extinction that are dissociable from any apparent increase in fear learning have been observed. Izquierdo et al. (2006) showed that 1 or 3 days of forced swimming prior to fear conditioning retarded fear extinction learning in mice, concomitant with significant retraction of apical dendrites in IL. In rats, 1 week of restraint was also found to impair extinction memory (Miracle et al., 2006), which is interesting in light of evidence that IL is preferentially recruited during extinction recall (Milad and Quirk, 2002). Moreover, Maroun and co-workers have shown that a single bout of elevated platform stress both impaired fear extinction and caused a shift in plasticity (LTP to long-term depression) in the IL-amygdala pathway subserving extinction (Akirav and Maroun, 2007; Maroun, 2006; Maroun and Richter-Levin, 2003). Together, these findings demonstrate that stress can selectively impair fear extinction, and may do so via alterations in PFC function.

Current models posit that fear extinction occurs in part by IL inhibition of amygdala output via activation of the intercalated cell masses (ITC) found in the amygdala (Hefner et al., 2008; Pare et al., 2004). One model is that stress-induced deficits in fear extinction result from loss of ITC-mediated IL inhibitory control over the amygdala. The situation is likely to be more complex, however. For example, recent work from Quirk and co-workers has shown that PL appears to play an opposing role to IL in fear extinction (i.e., PL stimulation impairs extinction and PL inactivation increases fear (reviewed in Quirk and Mueller, 2008). Thus, because, as discussed above, most stressors produce morphological changes in both PL and IL, the net effect of these changes for fear extinction is unclear. Another consideration is that the basolateral amygdala is also an important locus for fear extinction (Barad, 2005; Herry et al., 2008) and chronic restraint stress causes dendritic elongation and increased spine density in this region (Mitra et al., 2005; Vyas et al., 2002). How changes at the level of the amygdala contribute to stress-induced impairment of fear extinction is another issue that awaits clarification.

7. Concluding remarks

In this review, we have described how the PFC plays a significant, if as yet not fully clarified, role in regulating rodent neuroendocrine and autonomic responses to stress, and anxiety- and depression-related behaviors. We also discussed the important discovery that pyramidal neurons in several regions of the rodent PFC undergo dramatic remodeling with exposure to stressors, even those of brief or ostensibly mild nature. These pronounced structural changes

likely result in important functional changes in PFC neurons and the behavioral processes they support, including higher-order executive functions. Although these functional changes have also to be fully elucidated, there is accumulating evidence that stress can impair measures of working memory, cognitive flexibility and fear extinction in rodents.

These findings open up a number of avenues for future research. One key objective is to uncover the mechanisms mediating stress-induced changes in PFC structure and function. A review of the large literature describing the neurotransmitters and molecular signaling pathways within the PFC that have been shown to be altered by stress is beyond the scope of this article. Nonetheless, the available evidence supports a potential role in this regard for the monoaminergic transmitters serotonin (Holmes, 2008; Lapiz-Bluhm et al., 2008; Maier et al., 2006; Robbins, 2005), dopamine (Mizoguchi et al., 2004, 2000; Murphy et al., 1996a,b; Pani et al., 2000) and norepinephrine (Ramos and Arnsten, 2007), as well as glutamate (Brann, 1995; Moghaddam, 2002; Moghaddam and Jackson, 2004) and glucocorticoids (Liu and Aghajanian, 2008). Parsing how these and other mechanisms cause stress-induced alterations in PFC structure and function will be a massive undertaking, but ultimately a worthy one that could provide important insights into the pathophysiology of neuropsychiatric illness

Risk for a number of neuropsychiatric disease states is strongly linked to psychological trauma and stress. For example, stress is associated with increased prevalence and poorer long-term prognosis in anxiety disorders (Yehuda and LeDoux, 2007), bipolar disorder (Agid et al., 1999), depression (Brown and Harris, 1989), schizophrenia (Corcoran et al., 2002; Ventura et al., 1989), and drug addiction (Koob et al., 2004; Piazza and Le Moal, 1998; Stewart, 2000). Moreover, many of these same conditions are associated with abnormalities in PFC structure and function, including anxiety disorders (Davidson et al., 2002; Engels et al., 2007; Rauch et al., 2006), depression (Drevets et al., 1998; Rajkowska, 2000; Ressler and Mayberg, 2007), drug addiction (Hyman, 2007; Hyman et al., 2006; Kalivas and Volkow, 2005), Attention Deficit Hyperactivity Disorder (Arnsten, 2006), and schizophrenia (Harrison and Weinberger, 2005; Lewis and Gonzalez-Burgos, 2006). It is extremely difficult to disentangle a causative effect of stress from other factors, including genetic predisposition, on PFC dysfunction and risk for complex disease; in all likelihood these factors interact to determine disease risk (Caspi and Moffitt, 2006; Holmes and Hariri, 2003; Uher and McGuffin, 2008). However, the emerging data obtained from rodents tested under controlled laboratory conditions reviewed herein demonstrate that the PFC is a key target of stress, and supports the hypothesis that stress-induced PFC dysfunction is a major pathophysiological factor underlying these disorders. Further insights into the role of the PFC in stress-related disorders will improve our understanding of these devastating conditions and could ultimately foster the development of novel therapeutic approaches that serve to protect and promote the functional integrity of the PFC.

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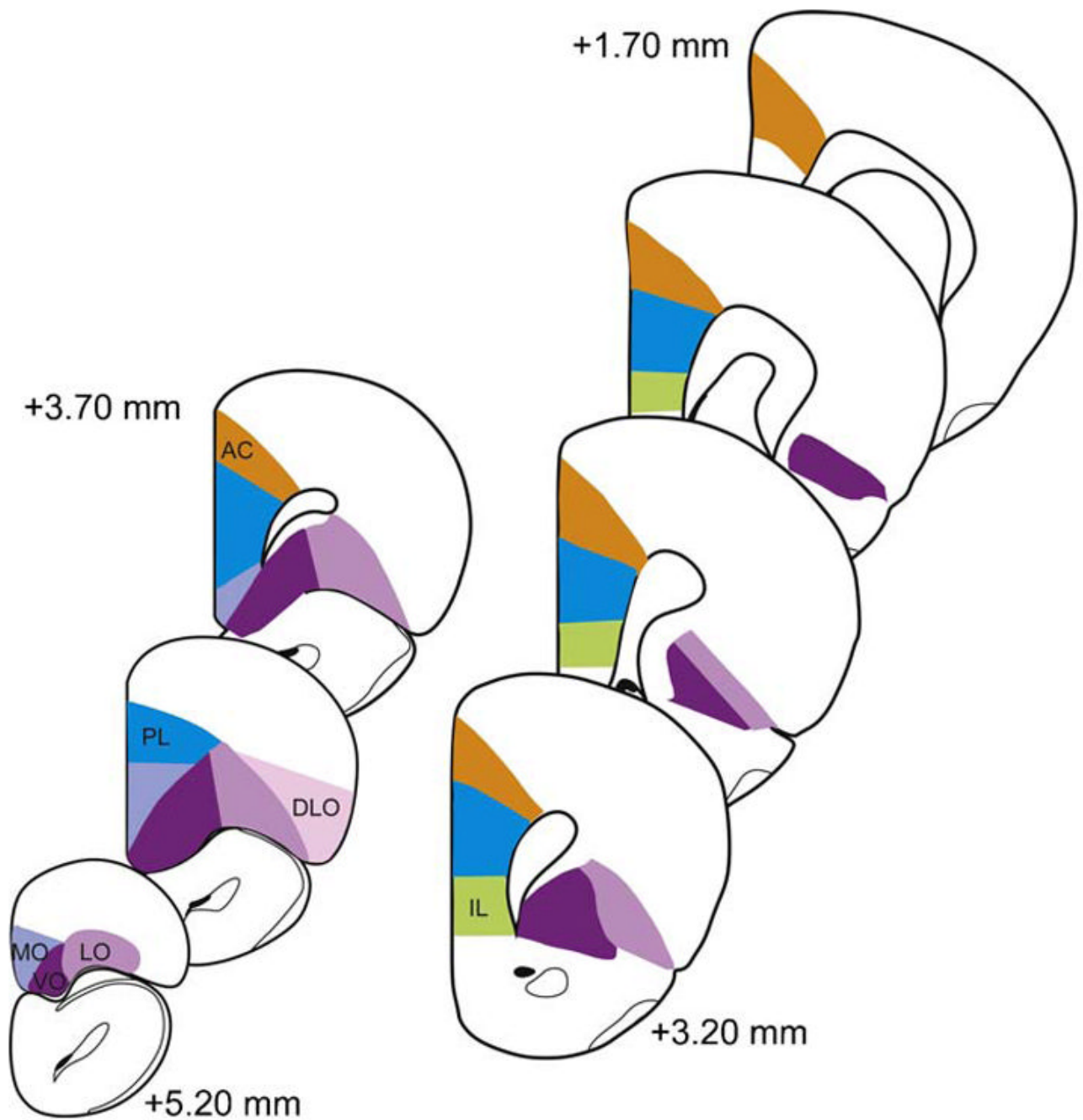


Fig. 1. Schematic diagram of coronal sections through PFC, with major subdivisions of rodent PFC orchestrating stress responses and mediating executive function identified. Coordinates given are relative to Bregma in mouse brain. AC = anterior cingulate; PL = prelimbic; IL = infralimbic; MO = medial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