Neuroscience and Biobehavioral Reviews 33 (2009) 773–783

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review

Stress-induced prefrontal reorganization and executive dysfunction in rodents

Andrew Holmes [a,*], Cara L. Wellman [b]

[a] Section on Behavioral Science and Genetics, Laboratory for Integrative Neuroscience, National Institute on Alcoholism and Alcohol Abuse, National Institutes of Health, 5625 Fishers Lane, Room 2N09, Rockville, MD 20852-9411, United States
[b] Department of Psychological and Brain Sciences, Indiana University, Bloomington, IN, United States

ARTICLE INFO

Article history:
Received 15 January 2008
Received in revised form 26 November 2008
Accepted 30 November 2008

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

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

* Corresponding author. Tel.: +1 301 402 3519; fax: +1 301 480 1952.
E-mail address: holmesan@mail.nih.gov (A. Holmes).

0149-7634/$ – see front matter © 2009 Published by Elsevier Ltd.
doi:10.1016/j.neubiorev.2008.11.005

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.

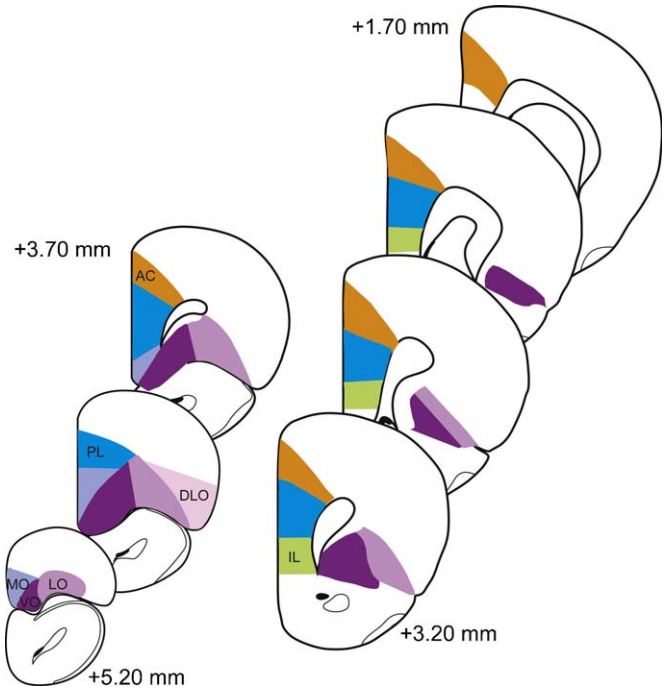

Fig. 1. Schematic diagram of coronal sections through PFC, with major subdivisions of rodent PFC orchestrating stress responses and mediating executive function identified. Coordinates given are relative to Bregma in mouse brain. AC = anterior cingulate; PL = prelimbic; IL = infralimbic; MO = medial 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

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 (Frysztak 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 oversimplification 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 potion 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, Cerquiera 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; Markowitsch 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.

Acknowledgments

This work was supported by the National Institute on Alcohol Abuse and Alcoholism Intramural Research Program (A.H.) and National Institute of Mental Health Grant MH067607 (C.L.W.).

References

Aggleton, J.P., Neave, N., Nagle, S., Sahgal, A., 1995. A comparison of the effects of medial prefrontal, cingulate cortex, and cingulum bundle lesions on tests of spatial memory: evidence of a double dissociation between frontal and cingulum bundle contributions. J. Neurosci. 15, 7270–7281.

Agid, O., Shapira, B., Zislin, J., Ritsner, M., Hanin, B., Murad, H., Troudart, T., Bloch, M., Heresco-Levy, U., Lerer, B., 1999. Environment and vulnerability to major psychiatric illness: a case control study of early parental loss in major depression, bipolar disorder and schizophrenia. Mol. Psychiatry 4, 163–172.

Ahima, R.S., Harlan, R.E., 1990. Charting of type II glucocorticoid receptor-like immunoreactivity in the rat central nervous system. Neuroscience 39, 579–604.

Akana, S.F., Chu, A., Soriano, L., Dallman, M.F., 2001. Corticosterone exerts site-specific and state-dependent effects in prefrontal cortex and amygdala on regulation of adrenocorticotropic hormone, insulin and fat depots. J. Neuroendocrinol. 13, 625–637.

Akirav, I., Maroun, M., 2007. The role of the medial prefrontal cortex-amygdala circuit in stress effects on the extinction of fear. Neural Plast. 30873.

Amat, J., Paul, E., Watkins, L.R., Maier, S.F., 2008. Activation of the ventral medial prefrontal cortex during an uncontrollable stressor reproduces both the immediate and long-term protective effects of behavioral control. Neuroscience 154, 1178–1186.

Amat, J., Baratta, M.V., Paul, E., Bland, S.T., Watkins, L.R., Maier, S.F., 2005. Medial prefrontal cortex determines how stressor controllability affects behavior and dorsal raphe nucleus. Nat. Neurosci. 8, 365–371.

Anisman, H., Hahn, B., Hoffman, D., Zacharko, R.M., 1985. Stressor invoked exacerbation of amphetamine-elicited perseveration. Pharmacol. Biochem. Behav. 23, 173–183.

Arnsten, A.F., 2006. Fundamentals of attention-deficit/hyperactivity disorder: circuits and pathways. J. Clin. Psychiatry 67 (Suppl. 8), 7–12.

Bacon, S.J., Headlam, A.J., Gabbott, P.L., Smith, A.D., 1996. Amygdala input to medial prefrontal cortex (mPFC) in the rat: a light and electron microscope study. Brain Res. 720, 211–219.

Barad, M., 2005. Fear extinction in rodents: basic insight to clinical promise. Curr. Opin. Neurobiol. 15, 710–715.

Bardgett, M.E., Taylor, G.T., Csernansky, J.G., Newcomer, J.W., Nock, B., 1994. Chronic corticosterone treatment impairs spontaneous alternation behavior in rats. Behav. Neural Biol. 61, 186–190.

Bechara, A., 2005. Decision making, impulse control and loss of willpower to resist drugs: a neurocognitive perspective. Nat. Neurosci. 8, 1458–1463.

Bechara, A., Damasio, H., Damasio, A.R., 2000. Emotion, decision making and the orbitofrontal cortex. Cereb Cortex 10, 295–307.

Birrell, J.M., Brown, V.J., 2000. Medial frontal cortex mediates perceptual attentional set shifting in the rat. J. Neurosci. 20, 4320–4324.

Bissiere, S., McAllister, K.H., Olpe, H.R., Cryan, J.F., 2006. The rostral anterior cingulate cortex modulates depression but not anxiety-related behaviour in the rat. Behav. Brain Res. 175, 195–199.

Bondi, C.O., Rodriguez, G., Gould, G.G., Frazer, A., Morilak, D.A., 2008. Chronic unpredictable stress induces a cognitive deficit and anxiety-like behavior in rats that is prevented by chronic antidepressant drug treatment. Neuropsychopharmacology 33, 320–331.

Brake, W.G., Flores, G., Francis, D., Meaney, M.J., Srivastava, L.K., Gratton, A., 2000. Enhanced nucleus accumbens dopamine and plasma corticosterone stress responses in adult rats with neonatal excitotoxic lesions to the medial prefrontal cortex. Neuroscience 96, 687–695.

Brann, D.W., 1995. Glutamate: a major excitatory transmitter in neuroendocrine regulation. Neuroendocrinology 61, 213–225.

Brito, G.N., Brito, L.S., 1990. Septohippocampal system and the prelimbic sector of frontal cortex: a neuropsychological battery analysis in the rat. Behav. Brain Res. 36, 127–146.

Brog, J.S., Salyapongse, A., Deutch, A.Y., Zahm, D.S., 1993. The patterns of afferent innervation of the core and shell in the "accumbens" part of the rat ventral striatum: immunohistochemical detection of retrogradely transported fluorogold. J. Comp. Neurol. 338, 255–278.

Brown, G.W., Harris, T.O., 1989. Life events and illness. In: Brown, G.W., Harris, T.O. (Eds.), Depression. Guilford, New York, pp. 49–93.
Brown, S.M., Henning, S., Wellman, C.L., 2005. Mild, short-term stress alters dendritic morphology in rat medial prefrontal cortex. Cereb Cortex 15, 1714–1722.
Bush, G., Luu, P., Posner, M.I., 2000. Cognitive and emotional influences in anterior cingulate cortex. Trends Cogn. Sci. 4, 215–222.
Campeau, S., Dolan, D., Akil, H., Watson, S.J., 2002. c-fos mRNA induction in acute and chronic audiogenic stress: possible role of the orbitofrontal cortex in habituation. Stress 5, 121–130.
Campeau, S., Falls, W.A., Cullinan, W.E., Helmreich, D.L., Davis, M., Watson, S.J., 1997. Elicitation and reduction of fear: behavioural and neuroendocrine indices and brain induction of the immediate-early gene c-fos. Neuroscience 78, 1087–1104.
Cardinal, R.N., Pennicott, D.R., Sugathapala, C.L., Robbins, T.W., Everitt, B.J., 2001. Impulsive choice induced in rats by lesions of the nucleus accumbens core. Science 292, 2499–2501.
Carr, D.B., Sesack, S.R., 1996. Hippocampal afferents to the rat prefrontal cortex: synaptic targets and relation to dopamine terminals. J. Comp. Neurol. 369, 1–15.
Caspi, A., Moffitt, T.E., 2006. Gene-environment interactions in psychiatry: joining forces with neuroscience. Nat. Rev. Neurosci. 7, 583–590.
Cassell, M.D., Wright, D.J., 1986. Topography of projections from the medial prefrontal cortex to the amygdala in the rat. Brain Res. Bull. 17, 321–333.
Celada, P., Puig, M.V., Casanovas, J.M., Guillazo, G., Artigas, F., 2001. Control of dorsal raphe serotonergic neurons by the medial prefrontal cortex: involvement of serotonin-1A, GABA(A), and glutamate receptors. J. Neurosci. 21, 9917–9929.
Cerqueira, J.J., Mailliet, F., Almeida, O.F., Jay, T.M., Sousa, N., 2007a. The prefrontal cortex as a key target of the maladaptive response to stress. J. Neurosci. 27, 2781–2787.
Cerqueira, J.J., Taipa, R., Uylings, H.B., Almeida, O.F., Sousa, N., 2007b. Specific configuration of dendritic degeneration in pyramidal neurons of the medial prefrontal cortex induced by differing corticosteroid regimens. Cereb Cortex 17, 1998–2006.
Cerqueira, J.J., Pego, J.M., Taipa, R., Bessa, J.M., Almeida, O.F., Sousa, N., 2005a. Morphological correlates of corticosteroid-induced changes in prefrontal cortex-dependent behaviors. J. Neurosci. 25, 7792–7800.
Cerqueira, J.J., Catania, C., Sotiropoulos, I., Schubert, M., Kalisch, R., Almeida, O.F., Auer, D.P., Sousa, N., 2005b. Corticosteroid status influences the volume of the rat cingulate cortex—a magnetic resonance imaging study. J. Psychiatr. Res. 39, 451–460.
Chao, H.M., Choo, P.H., McEwen, B.S., 1989. Glucocorticoid and mineralocorticoid receptor mRNA expression in rat brain. Neuroendocrinology 50, 365–371.
Chudasama, Y., Robbins, T.W., 2006. Functions of frontostriatal systems in cognition: comparative neuropsychopharmacological studies in rats, monkeys and humans. Biol. Psychol. 17, 19–38.
Chudasama, Y., Passetti, F., Rhodes, S.E., Lopian, D., Desai, A., Robbins, T.W., 2003. Dissociable aspects of performance on the 5-choice serial reaction time task following lesions of the dorsal anterior cingulate, infralimbic and orbitofrontal cortex in the rat: differential effects on selectivity, impulsivity and compulsivity. Behav. Brain Res. 146, 105–119.
Clark, L., Cools, R., Robbins, T.W., 2004. The neuropsychology of ventral prefrontal cortex: decision-making and reversal learning. Brain Cogn. 55, 41–53.
Conde, F., Maire-Lepoivre, E., Audinat, E., Crepel, F., 1995. Afferent connections of the medial frontal cortex of the rat. II. Cortical and subcortical afferents. J. Comp. Neurol. 352, 567–593.
Conrad, C.D., LeDoux, J.E., Magarinos, A.M., McEwen, B.S., 1999. Repeated restraint stress facilitates fear conditioning independently of causing hippocampal CA3 dendritic atrophy. Behav. Neurosci. 113, 902–913.
Cook, S.C., Wellman, C.L., 2004. Chronic stress alters dendritic morphology in rat medial prefrontal cortex. J. Neurobiol. 60, 236–248.
Corcoran, C., Mujica-Parodi, L., Yale, S., Leitman, D., Malaspina, D., 2002. Could stress cause psychosis in individuals vulnerable to schizophrenia? CNS Spectr. 7 (33–38), 32–41.
Corcoran, K.A., Quirk, G.J., 2007. Activity in prelimbic cortex is necessary for the expression of learned, but not innate, fears. J. Neurosci. 27, 840–844.
Crane, J.W., Ebner, K., Day, T.A., 2003. Medial prefrontal cortex suppression of the hypothalamic-pituitary-adrenal axis response to a physical stressor, systemic delivery of interleukin-1beta. Eur. J. Neurosci. 17, 1473–1481.
Cryan, J.F., Holmes, A., 2005. The ascent of mouse: advances in modelling human depression and anxiety. Nat. Rev. Drug Discov. 4, 775–790.
Cullinan, W.E., Herman, J.P., Battaglia, D.F., Akil, H., Watson, S.J., 1995. Pattern and time course of immediate early gene expression in rat brain following acute stress. Neuroscience 64, 477–505.
Czeh, B., Perez-Cruz, C., Fuchs, E., Flugge, G., 2008. Chronic stress-induced cellular changes in the medial prefrontal cortex and their potential clinical implications: does hemisphere location matter? Behav. Brain Res. 190, 1–13.
Dalley, J.W., Cardinal, R.N., Robbins, T.W., 2004. Prefrontal executive and cognitive functions in rodents: neural and neurochemical substrates. Neurosci. Biobehav. Rev. 28, 771–784.
Davidson, R.J., Pizzagalli, D., Nitschke, J.B., Putnam, K., 2002. Depression: perspectives from affective neuroscience. Annu. Rev. Psychol. 53, 545–574.
de Bruin, J.P., Sanchez-Santed, F., Heinsbroek, R.P., Donker, A., Postmes, P., 1994. A behavioural analysis of rats with damage to the medial prefrontal cortex using the Morris water maze: evidence for behavioural flexibility, but not for impaired spatial navigation. Brain Res. 652, 323–333.
de Kloet, E.R., Joels, M., Holsboer, F., 2005. Stress and the brain: from adaptation to disease. Nat. Rev. Neurosci. 6, 463–475.
Deacon, R.M., Penny, C., Rawlins, J.N., 2003. Effects of medial prefrontal cortex cytotoxic lesions in mice. Behav. Brain Res. 139, 139–155.
Degenetais, E., Thierry, A.M., Glowinski, J., Gioanni, Y., 2003. Synaptic influence of hippocampus on pyramidal cells of the rat prefrontal cortex: an in vivo intracellular recording study. Cereb Cortex 13, 782–792.
Del Arco, A., Segovia, G., Garrido, P., de Blas, M., Mora, F., 2007. Stress, prefrontal cortex and environmental enrichment: studies on dopamine and acetylcholine release and working memory performance in rats. Behav. Brain Res. 176, 267–273.
Delatour, B., Gisquet-Verrier, P., 2000. Functional role of rat prelimbic-infralimbic cortices in spatial memory: evidence for their involvement in attention and behavioural flexibility. Behav. Brain Res. 109, 113–128.
Di Pietro, N.C., Black, Y.D., Green-Jordan, K., Eichenbaum, H.B., Kantak, K.M., 2004. Complementary tasks to measure working memory in distinct prefrontal cortex subregions in rats. Behav. Neurosci. 118, 1042–1051.
Dias, R., Aggleton, J.P., 2000. Effects of selective excitotoxic prefrontal lesions on acquisition of nonmatching- and matching-to-place in the T-maze in the rat: differential involvement of the prelimbic-infralimbic and anterior cingulate cortices in providing behavioural flexibility. Eur. J. Neurosci. 12, 4457–4466.
Diorio, D., Viau, V., Meaney, M.J., 1993. The role of the medial prefrontal cortex (cingulate gyrus) in the regulation of hypothalamic-pituitary-adrenal responses to stress. J. Neurosci. 13, 3839–3847.
Divac, I., Mogensen, J., Petrovic-Minic, B., Zilles, K., Regidor, J., 1993. Cortical projections of the thalamic mediodorsal nucleus in the rat. Definition of the prefrontal cortex. Acta Neurobiol. Exp. (Wars) 53, 425–429.
Drevets, W.C., Ongur, D., Price, J.L., 1998. Neuroimaging abnormalities in the subgenual prefrontal cortex: implications for the pathophysiology of familial mood disorders. Mol. Psychiatry 3 (220–226), 190–221.
Duncan, G.E., Knapp, D.J., Breese, G.R., 1996. Neuroanatomical characterization of Fos induction in rat behavioral models of anxiety. Brain Res. 713, 79–91.
Dupin, N., Mailliet, F., Rocher, C., Kessal, K., Spedding, M., Jay, T.M., 2006. Common efficacy of psychotropic drugs in restoring stress-induced impairment of prefrontal plasticity. Neurotox. Res. 10, 193–198.
Engels, A.S., Heller, W., Mohanty, A., Herrington, J.D., Banich, M.T., Webb, A.G., Miller, G.A., 2007. Specificity of regional brain activity in anxiety types during emotion processing. Psychophysiology 44, 352–363.
Enthoven, L., de Kloet, E.R., Oitzl, M.S., 2007. Effects of maternal deprivation of CD1 mice on performance in the water maze and swim stress. Behav. Brain Res. 187, 195–199.
Everitt, B.J., Robbins, T.W., 2005. Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. Nat. Neurosci. 8, 1481–1489.
Ferbinteanu, J., Ray, C., McDonald, R.J., 2003. Both dorsal and ventral hippocampus contribute to spatial learning in Long–Evans rats. Neurosci. Lett. 345, 131–135.
Ferino, F., Thierry, A.M., Glowinski, J., 1987. Anatomical and electrophysiological evidence for a direct projection from Ammon's horn to the medial prefrontal cortex in the rat. Exp. Brain. Res. 65, 421–426.
Ferry, A.T., Lu, X.C., Price, J.L., 2000. Effects of excitotoxic lesions in the ventral striatopallidal–thalamocortical pathway on odor reversal learning: inability to extinguish an incorrect response. Exp. Brain Res. 131, 320–335.
Figueiredo, H.F., Bruestle, A., Bodie, B., Dolgas, C.M., Herman, J.P., 2003. The medial prefrontal cortex differentially regulates stress-induced c-fos expression in the forebrain depending on type of stressor. Eur. J. Neurosci. 18, 2357–2364.
Fisk, G.D., Wyss, J.M., 2000. Descending projections of infralimbic cortex that mediate stimulation-evoked changes in arterial pressure. Brain Res. 859, 83–95.
Floresco, S.B., Seamans, J.K., Phillips, A.G., 1997. Selective roles for hippocampal, prefrontal cortical, and ventral striatal circuits in radial-arm maze tasks with or without a delay. J. Neurosci. 17, 1880–1890.
Floyd, N.S., Price, J.L., Ferry, A.T., Keay, K.A., Bandler, R., 2001. Orbitomedial prefrontal cortical projections to hypothalamus in the rat. J. Comp. Neurol. 432, 307–328.
Francis, D.D., Zaharia, M.D., Shanks, N., Anisman, H., 1995. Stress-induced disturbances in Morris water-maze performance: interstrain variability. Physiol. Behav. 58, 57–65.
Frysztak, R.J., Neafsey, E.J., 1991. The effect of medial frontal cortex lesions on respiration, ''freezing and ultrasonic vocalizations during conditioned emotional responses in rats. Cereb Cortex 1, 418–425.
Frysztak, R.J., Neafsey, E.J., 1994. The effect of medial frontal cortex lesions on cardiovascular conditioned emotional responses in the rat. Brain Res. 643, 181–193.
Fuster, J.M., 2000. Prefrontal neurons in networks of executive memory. Brain Res. Bull. 52, 331–336.
Fuxe, K., Wikstrom, A.C., Okret, S., Agnati, L.F., Harfstrand, A., Yu, Z.Y., Granholm, L., Zoli, M., Vale, W., Gustafsson, J.A., 1985. Mapping of glucocorticoid receptor immunoreactive neurons in the rat tel- and diencephalon using a monoclonal antibody against rat liver glucocorticoid receptor. Endocrinology 117, 1803–1812.
Gabbott, P., Headlam, A., Busby, S., 2002. Morphological evidence that CA1 hippocampal afferents monosynaptically innervate PV-containing neurons and NADPH-diaphorase reactive cells in the medial prefrontal cortex (Areas 25/32) of the rat. Brain Res. 946, 314–322.
Gabbott, P.L., Warner, T.A., Jays, P.R., Salway, P., Busby, S.J., 2005. Prefrontal cortex in the rat: projections to subcortical autonomic, motor, and limbic centers. J. Comp. Neurol. 492, 145–177.

Goldman-Rakic, P.S., 1996. The prefrontal landscape: implications of functional architecture for understanding human mentation and the central executive. Philos. Trans. R. Soc. Lond. B: Biol. Sci. 351, 1445–1453.
Gonzalez, L.E., Rujano, M., Tucci, S., Paredes, D., Silva, E., Alba, G., Hernandez, L., 2000. Medial prefrontal transection enhances social interaction. I: behavioral studies. Brain Res. 887, 7–15.
Govindarajan, A., Rao, B.S., Nair, D., Trinh, M., Mawjee, N., Tonegawa, S., Chattarji, S., 2006. Transgenic brain-derived neurotrophic factor expression causes both anxiogenic and antidepressant effects. Proc. Natl. Acad. Sci. U.S.A. 103, 13208–13213.
Grahn, R.E., Will, M.J., Hammack, S.E., Maswood, S., McQueen, M.B., Watkins, L.R., Maier, S.F., 1999. Activation of serotonin-immunoreactive cells in the dorsal raphe nucleus in rats exposed to an uncontrollable stressor. Brain Res. 826, 35–43.
Granon, S., Vidal, C., Thinus-Blanc, C., Changeux, J.P., Poucet, B., 1994. Working memory, response selection, and effortful processing in rats with medial prefrontal lesions. Behav. Neurosci. 108, 883–891.
Groenewegen, H.J., 1988. Organization of the afferent connections of the mediodorsal thalamic nucleus in the rat, related to the mediodorsal-prefrontal topography. Neuroscience 24, 379–431.
Hahn, B., Zacharko, R.M., Anisman, H., 1986. Alterations of amphetamine elicited perseveration and locomotor excitation following acute and repeated stressor application. Pharmacol. Biochem. Behav. 25, 29–33.
Hajos, M., Richards, C.D., Szekely, A.D., Sharp, T., 1998. An electrophysiological and neuroanatomical study of the medial prefrontal cortical projection to the midbrain raphe nuclei in the rat. Neuroscience 87, 95–108.
Harrison, P.J., Weinberger, D.R., 2005. Schizophrenia genes, gene expression, and neuropathology: on the matter of their convergence. Mol. Psychiatry 10, 40–68.
Hefner, K., Whittle, N., Juhasz, J., Norcross, M., Karlsson, R.M., Saksida, L.M., Bussey, T.J., Singewald, N., Holmes, A., 2008. Impaired fear extinction learning and cortico-amygdala circuit abnormalities in a common genetic mouse strain. J. Neurosci. 28, 8074–8085.
Heidbreder, C.A., Groenewegen, H.J., 2003. The medial prefrontal cortex in the rat: evidence for a dorso-ventral distinction based upon functional and anatomical characteristics. Neurosci. Biobehav. Rev. 27, 555–579.
Herman, J.P., Ostrander, M.M., Mueller, N.K., Figueiredo, H., 2005. Limbic system mechanisms of stress regulation: hypothalamo-pituitary-adrenocortical axis. Prog. Neuropsychopharmacol. Biol. Psychiatry 29, 1201–1213.
Herry, C., Ciocchi, S., Senn, V., Demmou, L., Muller, C., Luthi, A., 2008. Switching on and off fear by distinct neuronal circuits. Nature 454, 600–606.
Hill, M.N., Patel, S., Carrier, E.J., Rademacher, D.J., Ormerod, B.K., Hillard, C.J., Gorzalka, B.B., 2005. Downregulation of endocannabinoid signaling in the hippocampus following chronic unpredictable stress. Neuropsychopharmacology 30, 508–515.
Holmes, A., 2008. Genetic variation in cortico-amygdala serotonin function and risk for stress-related disease. Neurosci. Biobehav. Rev. 32, 1293–1314.
Holmes, A., Hariri, A.R., 2003. The serotonin transporter gene-linked polymorphism and negative emotionality: placing single gene effects in the context of genetic background and environment. Genes Brain Behav. 2, 332–335.
Holson, R.R., 1986. Mesial prefrontal cortical lesions and timidity in rats. I. Reactivity to aversive stimuli. Physiol. Behav. 37, 221–230.
Hurley, K.M., Herbert, H., Moga, M.M., Saper, C.B., 1991. Efferent projections of the infralimbic cortex of the rat. J. Comp. Neurol. 308, 249–276.
Hyman, S.E., 2005. Addiction: a disease of learning and memory. Am. J. Psychiatry 162, 1414–1422.
Hyman, S.E., 2007. The neurobiology of addiction: implications for voluntary control of behavior. Am. J. Bioeth. 7, 8–11.
Hyman, S.E., Malenka, R.C., Nestler, E.J., 2006. Neural mechanisms of addiction: the role of reward-related learning and memory. Annu. Rev. Neurosci. 29, 565–598.
Izquierdo, A., Wellman, C.L., Holmes, A., 2006. Brief uncontrollable stress causes dendritic retraction in infralimbic cortex and resistance to fear extinction in mice. J. Neurosci. 26, 5733–5738.
Jankowski, M.P., Sesack, S.R., 2004. Prefrontal cortical projections to the rat dorsal raphe nucleus: ultrastructural features and associations with serotonin and gamma-aminobutyric acid neurons. J. Comp. Neurol. 468, 518–529.
Jaskiw, G.E., Weinberger, D.R., 1990. Ibotenic acid lesions of the medial prefrontal cortex potentiate FG-7142-induced attenuation of exploratory activity in the rat. Pharmacol. Biochem. Behav. 36, 695–697.
Jay, T.M., Witter, M.P., 1991. Distribution of hippocampal CA1 and subicular efferents in the prefrontal cortex of the rat studied by means of anterograde transport of Phaseolus vulgaris-leucoagglutinin. J. Comp. Neurol. 313, 574–586.
Jay, T.M., Glowinski, J., Thierry, A.M., 1989. Selectivity of the hippocampal projection to the prelimbic area of the prefrontal cortex in the rat. Brain Res. 505, 337–340.
Jay, T.M., Thierry, A.M., Wiklund, L., Glowinski, J., 1992. Excitatory amino acid pathway from the hippocampus to the prefrontal cortex. Contribution of AMPA receptors in hippocampo-prefrontal cortex transmission. Eur. J. Neurosci. 4, 1285–1295.
Jay, T.M., Rocher, C., Hotte, M., Naudon, L., Gurden, H., Spedding, M., 2004. Plasticity at hippocampal to prefrontal cortex synapses is impaired by loss of dopamine and stress: importance for psychiatric diseases. Neurotox. Res. 6, 233–244.
Jinks, A.L., McGregor, I.S., 1997. Modulation of anxiety-related behaviours following lesions of the prelimbic or infralimbic cortex in the rat. Brain Res. 772, 181–190.
Jones, B.F., Groenewegen, H.J., Witter, M.P., 2005. Intrinsic connections of the cingulate cortex in the rat suggest the existence of multiple functionally segregated networks. Neuroscience 133, 193–207.
Kalivas, P.W., Volkow, N.D., 2005. The neural basis of addiction: a pathology of motivation and choice. Am. J. Psychiatry 162, 1403–1413.
Kalivas, P.W., Volkow, N., Seamans, J., 2005. Unmanageable motivation in addiction: a pathology in prefrontal-accumbens glutamate transmission. Neuron 45, 647–650.
Kellendonk, C., Simpson, E.H., Polan, H.J., Malleret, G., Vronskaya, S., Winiger, V., Moore, H., Kandel, E.R., 2006. Transient and selective overexpression of dopamine D2 receptors in the striatum causes persistent abnormalities in prefrontal cortex functioning. Neuron 49, 603–615.
Kesner, R.P., Rogers, J., 2004. An analysis of independence and interactions of brain substrates that subserve multiple attributes, memory systems, and underlying processes. Neurobiol. Learn. Mem. 82, 199–215.
Kim, J., Ragozzino, M.E., 2005. The involvement of the orbitofrontal cortex in learning under changing task contingencies. Neurobiol. Learn. Mem. 83, 125–133.
Kim, J.J., Diamond, D.M., 2002. The stressed hippocampus, synaptic plasticity and lost memories. Nat. Rev. Neurosci. 3, 453–462.
Kolb, B., 1984. Functions of the frontal cortex of the rat: a comparative review. Brain Res. 320, 65–98.
Koob, G.F., Ahmed, S.H., Boutrel, B., Chen, S.A., Kenny, P.J., Markou, A., O'Dell, L.E., Parsons, L.H., Sanna, P.P., 2004. Neurobiological mechanisms in the transition from drug use to drug dependence. Neurosci. Biobehav. Rev. 27, 739–749.
Lacroix, L., White, I., Feldon, J., 2002. Effect of excitotoxic lesions of rat medial prefrontal cortex on spatial memory. Behav. Brain Res. 133, 69–81.
Lacroix, L., Broersen, L.M., Weiner, I., Feldon, J., 1998. The effects of excitotoxic lesion of the medial prefrontal cortex on latent inhibition, prepulse inhibition, food hoarding, elevated plus maze, active avoidance and locomotor activity in the rat. Neuroscience 84, 431–442.
Lacroix, L., Spinelli, S., Heidbreder, C.A., Feldon, J., 2000. Differential role of the medial and lateral prefrontal cortices in fear and anxiety. Behav. Neurosci. 114, 1119–1130.
Lalonde, R., 2002. The neurobiological basis of spontaneous alternation. Neurosci. Biobehav. Rev. 26, 91–104.
Lapiz-Bluhm, M.D., Soto-Pina, A.E., Hensler, J.G., Morilak, D.A., 2008. Chronic intermittent cold stress and serotonin depletion induce deficits of reversal learning in an attentional set-shifting test in rats. Psychopharmacology (Berl).
Laroche, S., Jay, T.M., Thierry, A.M., 1990. Long-term potentiation in the prefrontal cortex following stimulation of the hippocampal CA1/subicular region. Neurosci. Lett. 114, 184–190.
Leonard, C.M., 1969. The prefrontal cortex of the rat. I. Cortical projection of the mediodorsal nucleus. II. Efferent connections. Brain Res. 12, 321–343.
Lewis, D.A., Gonzalez-Burgos, G., 2006. Pathophysiologically based treatment interventions in schizophrenia. Nat. Med. 12, 1016–1022.
Liston, C., Miller, M.M., Goldwater, D.S., Radley, J.J., Rocher, A.B., Hof, P.R., Morrison, J.H., McEwen, B.S., 2006. Stress-induced alterations in prefrontal cortical dendritic morphology predict selective impairments in perceptual attentional set-shifting. J. Neurosci. 26, 7870–7874.
Liu, R.J., Aghajanian, G.K., 2008. Stress blunts serotonin- and hypocretin-evoked EPSCs in prefrontal cortex: role of corticosterone-mediated apical dendritic atrophy. Proc. Natl. Acad. Sci. U.S.A. 105, 359–364.
Luine, V., Villegas, M., Martinez, C., McEwen, B.S., 1994. Repeated stress causes reversible impairments of spatial memory performance. Brain Res. 639, 167–170.
Maaswinkel, H., Gispen, W.H., Spruijt, B.M., 1996. Effects of an electrolytic lesion of the prelimbic area on anxiety-related and cognitive tasks in the rat. Behav. Brain Res. 79, 51–59.
Maier, S.F., Watkins, L.R., 2005. Stressor controllability and learned helplessness: the roles of the dorsal raphe nucleus, serotonin, and corticotropin-releasing factor. Neurosci. Biobehav. Rev. 29, 829–841.
Maier, S.F., Amat, J., Baratta, M.V., Paul, E., Watkins, L.R., 2006. Behavioral control, the medial prefrontal cortex, and resilience. Dialogues Clin. Neurosci. 8, 397–406.
Mailliet, F., Qi, H., Rocher, C., Spedding, M., Svenningsson, P., Jay, T.M., 2008. Protection of stress-induced impairment of hippocampal/prefrontal LTP through blockade of glucocorticoid receptors: implication of MEK signaling. Exp. Neurol. 211, 593–596.
Manikandan, S., Padma, M.K., Srikumar, R., Jeya Parthasarathy, N., Muthuvel, A., Sheela Devi, R., 2006. Effects of chronic noise stress on spatial memory of rats in relation to neuronal dendritic alteration and free radical-imbalance in hippocampus and medial prefrontal cortex. Neurosci. Lett. 399, 17–22.
Markowitsch, H.J., Pritzel, M., 1977. Comparative analysis of prefrontal learning functions in rats, cats, and monkeys. Psychol. Bull. 84, 817–837.
Maroun, M., 2006. Stress reverses plasticity in the pathway projecting from the ventromedial prefrontal cortex to the basolateral amygdala. Eur. J. Neurosci. 24, 2917–2922.
Maroun, M., Richter-Levin, G., 2003. Exposure to acute stress blocks the induction of long-term potentiation of the amygdala-prefrontal cortex pathway in vivo. J. Neurosci. 23, 4406–4409.
Maswood, S., Barter, J.E., Watkins, L.R., Maier, S.F., 1998. Exposure to inescapable but not escapable shock increases extracellular levels of 5-HT in the dorsal raphe nucleus of the rat. Brain Res. 783, 115–120.
McAlonan, K., Brown, V.J., 2003. Orbital prefrontal cortex mediates reversal learning and not attentional set shifting in the rat. Behav. Brain Res. 146, 97–103.
McDonald, A.J., Mascagni, F., Guo, L., 1996. Projections of the medial and lateral prefrontal cortices to the amygdala: a Phaseolus vulgaris leucoagglutinin study in the rat. Neuroscience 71, 55–75.

McEwen, B.S., 1999. Stress and hippocampal plasticity. Annu. Rev. Neurosci. 22, 105–122.
McEwen, B.S., Milner, T.A., 2007. Hippocampal formation: shedding light on the influence of sex and stress on the brain. Brain Res. Rev. 55, 343–355.
Meaney, M.J., Aitken, D.H., 1985. [3H]Dexamethasone binding in rat frontal cortex. Brain Res. 328, 176–180.
Michelsen, K.A., van den Hove, D.L., Schmitz, C., Segers, O., Prickaerts, J., Steinbusch, H.W., 2007. Prenatal stress and subsequent exposure to chronic mild stress influence dendritic spine density and morphology in the rat medial prefrontal cortex. BMC Neurosci. 8, 107.
Milad, M.R., Quirk, G.J., 2002. Neurons in medial prefrontal cortex signal memory for fear extinction. Nature 420, 70–74.
Miller, E.K., Cohen, J.D., 2001. An integrative theory of prefrontal cortex function. Annu. Rev. Neurosci. 24, 167–202.
Miracle, A.D., Brace, M.F., Huyck, K.D., Singler, S.A., Wellman, C.L., 2006. Chronic stress impairs recall of extinction of conditioned fear. Neurobiol. Learn. Mem. 85, 213–218.
Mitra, R., Jadhav, S., McEwen, B.S., Vyas, A., Chattarji, S., 2005. Stress duration modulates the spatiotemporal patterns of spine formation in the basolateral amygdale. Proc. Natl. Acad. Sci. U.S.A. 102, 9371–9376.
Mizoguchi, K., Ishige, A., Aburada, M., Tabira, T., 2003. Chronic stress attenuates glucocorticoid negative feedback: involvement of the prefrontal cortex and hippocampus. Neuroscience 119, 887–897.
Mizoguchi, K., Ishige, A., Takeda, S., Aburada, M., Tabira, T., 2004. Endogenous glucocorticoids are essential for maintaining prefrontal cortical cognitive function. J. Neurosci. 24, 5492–5499.
Mizoguchi, K., Yuzurihara, M., Ishige, A., Sasaki, H., Chui, D.H., Tabira, T., 2000. Chronic stress induces impairment of spatial working memory because of prefrontal dopaminergic dysfunction. J. Neurosci. 20, 1568–1574.
Mobini, S., Body, S., Ho, M.Y., Bradshaw, C.M., Szabadi, E., Deakin, J.F., Anderson, I.M., 2002. Effects of lesions of the orbitofrontal cortex on sensitivity to delayed and probabilistic reinforcement. Psychopharmacology (Berl) 160, 290–298.
Moghaddam, B., 2002. Stress activation of glutamate neurotransmission in the prefrontal cortex: implications for dopamine-associated psychiatric disorders. Biol. Psychiatry 51, 775–787.
Moghaddam, B., Jackson, M., 2004. Effect of stress on prefrontal cortex function. Neurotox. Res. 6, 73–78.
Moghaddam, B., Homayoun, H., 2008. Divergent plasticity of prefrontal cortex networks. Neuropsychopharmacology 33, 42–55.
Morgan, M.A., Schulkin, J., LeDoux, J.E., 2003. Ventral medial prefrontal cortex and emotional perseveration: the memory for prior extinction training. Behav. Brain Res. 146, 121–130.
Morrow, B.A., Elsworth, J.D., Lee, E.J., Roth, R.H., 2000. Divergent effects of putative anxiolytics on stress-induced fos expression in the mesoprefrontal system of the rat. Synapse 36, 143–154.
Muigg, P., Hoelzl, U., Palfrader, K., Neumann, I., Wigger, A., Landgraf, R., Singewald, N., 2007. Altered brain activation pattern associated with drug-induced attenuation of enhanced depression-like behavior in rats bred for high anxiety. Biol. Psychiatry 61 (6), 782–796.
Murphy, B.L., Arnsten, A.F., Goldman-Rakic, P.S., Roth, R.H., 1996a. Increased dopamine turnover in the prefrontal cortex impairs spatial working memory performance in rats and monkeys. Proc. Natl. Acad. Sci. U.S.A. 93, 1325–1329.
Murphy, B.L., Arnsten, A.F., Jentsch, J.D., Roth, R.H., 1996b. Dopamine and spatial working memory in rats and monkeys: pharmacological reversal of stress-induced impairment. J. Neurosci. 16, 7768–7775.
Neafsey, E.J., 1990. Prefrontal cortical control of the autonomic nervous system: anatomical and physiological observations. Prog. Brain. Res. 85, 147–165 (discussion 165–146).
Nishimura, J., Endo, Y., Kimura, F., 1999. A long-term stress exposure impairs maze learning performance in rats. Neurosci. Lett. 273, 125–128.
Olton, D.S., 1987. The radial arm maze as a tool in behavioral pharmacology. Physiol. Behav. 40, 793–797.
Ostrander, M.M., Richtand, N.M., Herman, J.P., 2003. Stress and amphetamine induce Fos expression in medial prefrontal cortex neurons containing glucocorticoid receptors. Brain Res. 990, 209–214.
Ottersen, O.P., 1982. Connections of the amygdala of the rat. IV: Corticoamygdaloid and intraamygdaloid connections as studied with axonal transport of horseradish peroxidase. J. Comp. Neurol. 205, 30–48.
Owens, N.C., Verberne, A.J., 1996. An electrophysiological study of the medial prefrontal cortical projection to the nucleus of the solitary tract in rat. Exp. Brain Res. 110, 55–61.
Pani, L., Porcella, A., Gessa, G.L., 2000. The role of stress in the pathophysiology of the dopaminergic system. Mol. Psychiatry 5, 14–21.
Pare, D., Quirk, G.J., Ledoux, J.E., 2004. New vistas on amygdala networks in conditioned fear. J. Neurophysiol. 92, 1–9.
Patel, P.D., Lopez, J.F., Lyons, D.M., Burke, S., Wallace, M., Schatzberg, A.F., 2000. Glucocorticoid and mineralocorticoid receptor mRNA expression in squirrel monkey brain. J. Psychiatr. Res. 34, 383–392.
Paxinos, K.B.J., Franklin, G., 2001. The Mouse Brain in Stereotaxic Coordinates, 2nd ed. Academic Press, London.
Piazza, P.V., Le Moal, M., 1998. The role of stress in drug self-administration. Trends Pharmacol. Sci. 19, 67–74.
Pierard, C., Liscia, P., Valleau, M., Drouet, I., Chauveau, F., Huart, B., Bonneau, D., Jouanin, J.C., Beaumont, M., Beracochea, D., 2006. Modafinil-induced modulation of working memory and plasma corticosterone in chronically-stressed mice. Pharmacol. Biochem. Behav. 83, 1–8.
Powell, D.A., Watson, K., Maxwell, B., 1994. Involvement of subdivisions of the medial prefrontal cortex in learned cardiac adjustments in rabbits. Behav. Neurosci. 108, 294–307.
Price, J.L., 1973. An autoradiographic study of complementary laminar patterns of termination of afferent fibers to the olfactory cortex. J. Comp. Neurol. 150, 87–108.
Preuss, T.M., 1995. Do rats have a prefrontal cortex? The Rose–Woolsey–Akert program reconsidered. J. Cogn. Neurosci. 7, 1–24.
Quirk, G.J., Mueller, D., 2008. Neural mechanisms of extinction learning and retrieval. Neuropsychopharmacology 33, 56–72.
Radley, J.J., Arias, C.M., Sawchenko, P.E., 2006a. Regional differentiation of the medial prefrontal cortex in regulating adaptive responses to acute emotional stress. J. Neurosci. 26, 12967–12976.
Radley, J.J., Williams, B., Sawchenko, P.E., 2008a. Noradrenergic innervation of the dorsal medial prefrontal cortex modulates hypothalamo-pituitary-adrenal responses to acute emotional stress. J. Neurosci. 28, 5806–5816.
Radley, J.J., Rocher, A.B., Janssen, W.G., Hof, P.R., McEwen, B.S., Morrison, J.H., 2005a. Reversibility of apical dendritic retraction in the rat medial prefrontal cortex following repeated stress. Exp. Neurol. 196, 199–203.
Radley, J.J., Rocher, A.B., Janssen, W.G.M., Hof, P.R., McEwen, B.S., Morrison, J.H., 2005b. Reversibility of apical dendritic retraction in the rat medial prefrontal cortex following repeated stress. Exp. Neurol. 196, 199–203.
Radley, J.J., Sisti, H.M., Hao, J., Rocher, A.B., McCall, T., Hof, P.R., McEwen, B.S., Morrison, J.H., 2004. Chronic behavioral stress induces apical dendritic reorganization in pyramidal neurons of the medial prefrontal cortex. Neuroscience 125, 1–6.
Radley, J.J., Rocher, A.B., Miller, M., Janssen, W.G., Liston, C., Hof, P.R., McEwen, B.S., Morrison, J.H., 2006b. Repeated stress induces dendritic spine loss in the rat medial prefrontal cortex. Cereb Cortex 16, 313–320.
Radley, J.J., Rocher, A.B., Rodriguez, A., Ehlenberger, D.B., Dammann, M., McEwen, B.S., Morrison, J.H., Wearne, S.L., Hof, P.R., 2008b. Repeated stress alters dendritic spine morphology in the rat medial prefrontal cortex. J. Comp. Neurol. 507, 1141–1150.
Ragozzino, M.E., Adams, S., Kesner, R.P., 1998. Differential involvement of the dorsal anterior cingulate and prelimbic-infralimbic areas of the rodent prefrontal cortex in spatial working memory. Behav. Neurosci. 112, 293–303.
Ragozzino, M.E., Detrick, S., Kesner, R.P., 1999a. Involvement of the prelimbic-infralimbic areas of the rodent prefrontal cortex in behavioral flexibility for place and response learning. J. Neurosci. 19, 4585–4594.
Ragozzino, M.E., Wilcox, C., Raso, M., Kesner, R.P., 1999b. Involvement of rodent prefrontal cortex subregions in strategy switching. Behav. Neurosci. 113, 32–41.
Rajkowska, G., 2000. Histopathology of the prefrontal cortex in major depression: what does it tell us about dysfunctional monoaminergic circuits? Prog. Brain Res. 126, 397–412.
Ramos, B.P., Arnsten, A.F., 2007. Adrenergic pharmacology and cognition: focus on the prefrontal cortex. Pharmacol. Ther. 113, 523–536.
Rau, V., Decola, J.P., Fanselow, M.S., 2005. Stress-induced enhancement of fear learning: an animal model of posttraumatic stress disorder. Neurosci. Biobehav. Rev. 29, 1207–1223.
Rauch, S.L., Shin, L.M., Phelps, E.A., 2006. Neurocircuitry models of posttraumatic stress disorder and extinction: human neuroimaging research—past, present, and future. Biol. Psychiatry 60, 376–382.
Ressler, K.J., Mayberg, H.S., 2007. Targeting abnormal neural circuits in mood and anxiety disorders: from the laboratory to the clinic. Nat. Neurosci. 10, 1116–1124.
Resstel, L.B., Correa, F.M., 2006. Involvement of the medial prefrontal cortex in central cardiovascular modulation in the rat. Auton. Neurosci. 126–127, 130–138.
Resstel, L.B., Souza, R.F., Guimaraes, F.S., 2007. Anxiolytic-like effects induced by medial prefrontal cortex inhibition in rats submitted to the Vogel conflict test. Physiol. Behav..
Resstel, L.B., Joca, S.R., Guimaraes, F.G., Correa, F.M., 2006. Involvement of medial prefrontal cortex neurons in behavioral and cardiovascular responses to contextual fear conditioning. Neuroscience 143, 377–385.
Rhodes, P.A., Llinas, R.R., 2001. Apical tuft input efficacy in layer 5 pyramidal cells from rat visual cortex. J. Physiol. 536, 167–187.
Robbins, T.W., 2005. Chemistry of the mind: neurochemical modulation of prefrontal cortical function. J. Comp. Neurol. 493, 140–146.
Robinson, T.E., Kolb, B., 2004. Structural plasticity associated with exposure to drugs of abuse. Neuropharmacology 47 (Suppl. 1), 33–46.
Rocher, C., Spedding, M., Munoz, C., Jay, T.M., 2004. Acute stress-induced changes in hippocampal/prefrontal circuits in rats: effects of antidepressants. Cereb Cortex 14, 224–229.
Rolls, E.T., 1996. The orbitofrontal cortex. Philos. Trans. R. Soc. Lond. B: Biol. Sci. 351, 1433–1443 (discussion 1443–1434).
Roozendaal, B., McReynolds, J.R., McGaugh, J.L., 2004. The basolateral amygdala interacts with the medial prefrontal cortex in regulating glucocorticoid effects on working memory impairment. J. Neurosci. 24, 1385–1392.
Saddoris, M.P., Gallagher, M., Schoenbaum, G., 2005. Rapid associative encoding in basolateral amygdala depends on connections with orbitofrontal cortex. Neuron 46, 321–331.
Sandi, C., 2004. Stress, cognitive impairment and cell adhesion molecules. Nat. Rev. Neurosci. 5, 917–930.
Sapolsky, R.M., 2003. Stress and plasticity in the limbic system. Neurochem. Res. 28, 1735–1742.

Scheibel, M.E., Scheibel, A.B., 1970. Organization of spinal motoneuron dendrites in bundles. Exp. Neurol. 28, 106–112.
Schoenbaum, G., Shaham, Y., 2008. The role of orbitofrontal cortex in drug addiction: a review of preclinical studies. Biol. Psychiatry 63, 256–262.
Schoenbaum, G., Chiba, A.A., Gallagher, M., 1999. Neural encoding in orbitofrontal cortex and basolateral amygdala during olfactory discrimination learning. J. Neurosci. 19, 1876–1884.
Schoenbaum, G., Chiba, A.A., Gallagher, M., 2000. Changes in functional connectivity in orbitofrontal cortex and basolateral amygdala during learning and reversal training. J. Neurosci. 20, 5179–5189.
Schoenbaum, G., Roesch, M.R., Stalnaker, T.A., 2006. Orbitofrontal cortex, decision-making and drug addiction. Trends Neurosci. 29, 116–124.
Schoenbaum, G., Nugent, S.L., Saddoris, M.P., Setlow, B., 2002. Orbitofrontal lesions in rats impair reversal but not acquisition of go, no-go odor discriminations. Neuroreport 13, 885–890.
Schoenbaum, G., Setlow, B., Nugent, S.L., Saddoris, M.P., Gallagher, M., 2003. Lesions of orbitofrontal cortex and basolateral amygdala complex disrupt acquisition of odor-guided discriminations and reversals. Learn. Mem. 10, 129–140.
Schroeder, B.E., Schiltz, C.A., Kelley, A.E., 2003. Neural activation profile elicited by cues associated with the anxiogenic drug yohimbine differs from that observed for reward-paired cues. Neuropsychopharmacology 28, 14–21.
Schwabe, K., Enkel, T., Klein, S., Schutte, M., Koch, M., 2004. Effects of neonatal lesions of the medial prefrontal cortex on adult rat behaviour. Behav. Brain Res. 153, 21–34.
Seamans, J.K., Floresco, S.B., Phillips, A.G., 1995. Functional differences between the prelimbic and anterior cingulate regions of the rat prefrontal cortex. Behav. Neurosci. 109, 1063–1073.
Seligman, M.E., 1972. Learned helplessness. Annu. Rev. Med. 23, 407–412.
Sesack, S.R., Deutch, A.Y., Roth, R.H., Bunney, B.S., 1989. Topographical organization of the efferent projections of the medial prefrontal cortex in the rat: an anterograde tract-tracing study with Phaseolus vulgaris leucoagglutinin. J. Comp. Neurol. 290, 213–242.
Shah, A.A., Treit, D., 2003. Excitotoxic lesions of the medial prefrontal cortex attenuate fear responses in the elevated-plus maze, social interaction and shock probe burying tests. Brain Res. 969, 183–194.
Shah, A.A., Treit, D., 2004. Infusions of midazolam into the medial prefrontal cortex produce anxiolytic effects in the elevated plus-maze and shock-probe burying tests. Brain Res. 996, 31–40.
Shanks, N., Anisman, H., 1988. Stressor-provoked behavioral changes in six strains of mice. Behav. Neurosci. 102, 894–905.
Shors, T.J., 2006. Stressful experience and learning across the lifespan. Annu. Rev. Psychol. 57, 55–85.
Silva-Gomez, A.B., Rojas, D., Juarez, I., Flores, G., 2003. Decreased dendritic spine density on prefrontal cortical and hippocampal pyramidal neurons in post-weaning social isolation rats. Brain Res. 983, 128–136.
Singewald, N., 2007. Altered brain activity processing in high-anxiety rodents revealed by challenge paradigms and functional mapping. Neurosci. Biobehav. Rev. 31, 18–40.
Singewald, N., Salchner, P., Sharp, T., 2003. Induction of c-Fos expression in specific areas of the fear circuitry in rat forebrain by anxiogenic drugs. Biol. Psychiatry 53, 275–283.
Sloan, H.L., Good, M., Dunnett, S.B., 2006. Double dissociation between hippocampal and prefrontal lesions on an operant delayed matching task and a water maze reference memory task. Behav. Brain Res. 171, 116–126.
Sotres-Bayon, F., Bush, D.E., LeDoux, J.E., 2004. Emotional perseveration: an update on prefrontal-amygdala interactions in fear extinction. Learn. Mem. 11, 525–535.
Spencer, S.J., Buller, K.M., Day, T.A., 2005. Medial prefrontal cortex control of the paraventricular hypothalamic nucleus response to psychological stress: possible role of the bed nucleus of the stria terminalis. J. Comp. Neurol. 481, 363–376.
Stalnaker, T.A., Franz, T.M., Singh, T., Schoenbaum, G., 2007. Basolateral amygdala lesions abolish orbitofrontal-dependent reversal impairments. Neuron 54, 51–58.
Steele, R.J., Morris, R.G., 1999. Delay-dependent impairment of a matching-to-place task with chronic and intrahippocampal infusion of the NMDA-antagonist D-AP5. Hippocampus 9, 118–136.
Stewart, J., 2000. Pathways to relapse: the neurobiology of drug- and stress-induced relapse to drug-taking. J. Psychiatry Neurosci. 25, 125–136.
Sullivan, R.M., 2004. Hemispheric asymmetry in stress processing in rat prefrontal cortex and the role of mesocortical dopamine. Stress 7, 131–143.
Sullivan, R.M., Henke, P.G., 1986. The anterior midline cortex and adaptation to stress ulcers in rats. Brain Res. Bull. 17, 493–496.
Sullivan, R.M., Gratton, A., 1999. Lateralized effects of medial prefrontal cortex lesions on neuroendocrine and autonomic stress responses in rats. J. Neurosci. 19, 2834–2840.
Sullivan, R.M., Gratton, A., 2002. Behavioral effects of excitotoxic lesions of ventral medial prefrontal cortex in the rat are hemisphere-dependent. Brain Res. 927, 69–79.
Swanson, L.W., 1981. A direct projection from Ammon's horn to prefrontal cortex in the rat. Brain Res. 217, 150–154.
Swanson, L.W., Cowan, W.M., 1977. An autoradiographic study of the organization of the efferent connections of the hippocampal formation in the rat. J. Comp. Neurol. 172, 49–84.
Szuran, T.F., Pliska, V., Pokorny, J., Welzl, H., 2000. Prenatal stress in rats: effects on plasma corticosterone, hippocampal glucocorticoid receptors, and maze performance. Physiol. Behav. 71, 353–362.
Takagishi, M., Chiba, T., 1991. Efferent projections of the infralimbic (area 25) region of the medial prefrontal cortex in the rat: an anterograde tracer PHA-L study. Brain Res. 566, 26–39.
Thierry, A.M., Gioanni, Y., Degenetais, E., Glowinski, J., 2000. Hippocampo-prefrontal cortex pathway: anatomical and electrophysiological characteristics. Hippocampus 10, 411–419.
Tierney, P.L., Degenetais, E., Thierry, A.M., Glowinski, J., Gioanni, Y., 2004. Influence of the hippocampus on interneurons of the rat prefrontal cortex. Eur. J. Neurosci. 20, 514–524.
Tremblay, L., Schultz, W., 1999. Relative reward preference in primate orbitofrontal cortex. Nature 398, 704–708.
Uher, R., McGuffin, P., 2008. The moderation by the serotonin transporter gene of environmental adversity in the aetiology of mental illness: review and methodological analysis. Mol. Psychiatry 13, 131–146.
Uylings, H.B., van Eden, C.G., 1990. Qualitative and quantitative comparison of the prefrontal cortex in rat and in primates, including humans. Prog. Brain Res. 85, 31–62.
Uylings, H.B., Groenewegen, H.J., Kolb, B., 2003. Do rats have a prefrontal cortex? Behav. Brain Res. 146, 3–17.
van Eden, C.G., Kros, J.M., Uylings, H.B., 1990. The development of the rat prefrontal cortex. Its size and development of connections with thalamus, spinal cord and other cortical areas. Prog. Brain Res. 85, 169–183.
Ventura, J., Nuechterlein, K.H., Lukoff, D., Hardesty, J.P., 1989. A prospective study of stressful life events and schizophrenic relapse. J. Abnorm. Psychol. 98, 407–411.
Vertes, R.P., 2002. Analysis of projections from the medial prefrontal cortex to the thalamus in the rat, with emphasis on nucleus reuniens. J. Comp. Neurol. 442, 163–187.
Vertes, R.P., 2004. Differential projections of the infralimbic and prelimbic cortex in the rat. Synapse 51, 32–58.
Vyas, A., Jadhav, S., Chattarji, S., 2006. Prolonged behavioral stress enhances synaptic connectivity in the basolateral amygdala. Neuroscience 143, 387–393.
Vyas, A., Mitra, R., Shankaranarayana Rao, B.S., Chattarji, S., 2002. Chronic stress induces contrasting patterns of dendritic remodeling in hippocampal and amygdaloid neurons. J. Neurosci. 22, 6810–6818.
Wall, P.M., Blanchard, R.J., Yang, M., Blanchard, D.C., 2004. Differential effects of infralimbic vs. ventromedial orbital PFC lidocaine infusions in CD-1 mice on defensive responding in the mouse defense test battery and rat exposure test. Brain Res. 1020, 73–85.
Wellman, C.L., 2001. Dendritic reorganization in pyramidal neurons in medial prefrontal cortex after chronic corticosterone administration. J. Neurobiol. 49, 245–253.
Wolf, C., Waksman, D., Finger, S., Almli, C.R., 1987. Large and small medial frontal cortex lesions and spatial performance of the rat. Brain Res. Bull. 18, 1–5.
Wood, J.N., Grafman, J., 2003. Human prefrontal cortex: processing and representational perspectives. Nat. Rev. Neurosci. 4, 139–147.
Woolley, C.S., Gould, E., McEwen, B.S., 1990. Exposure to excess glucocorticoids alters dendritic morphology of adult hippocampal pyramidal neurons. Brain Res. 531, 225–231.
Yehuda, R., LeDoux, J., 2007. Response variation following trauma: a translational neuroscience approach to understanding PTSD. Neuron 56, 19–32.