



Review

Chronic stress-induced cellular changes in the medial prefrontal cortex and their potential clinical implications: Does hemisphere location matter?

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ABSTRACT

The prefrontal cortex (PFC) is implicated in a number of higher cognitive functions as well as processing emotions and regulation of stress responses. Hemispheric specialization of the PFC in humans in emotional processing is well documented, and there is evidence that a similar functional lateralization is present in all mammals. Recent findings suggest the possibility of an intrinsic structural hemispheric asymmetry in the rat medial PFC (mPFC). Specifically, interhemispheric differences have been found in the architecture of pyramidal cell apical dendritic trees together with hemispheric asymmetry in cell proliferation including gliogenesis. It is now well established that chronic stress has a profound impact on neural plasticity in a number of corticolimbic structures and affects the etiology, pathophysiology, and therapeutic outcome of most psychiatric disorders. We summarize recent experimental data documenting pronounced dendritic remodeling of pyramidal cells and suppressed gliogenesis in the mPFC of rats subjected to chronic stress or to artificially elevated glucocorticoid levels. The stress affect on these structural elements seems to be hemispheric specific, often abolishing or even reversing natural asymmetries seen at the cellular level. We discuss these preclinical observations with respect to clinical findings that show impaired function, altered lateralization and histopathological changes in the PFC in psychiatric patients. We argue that it is important to define the kinds of structural changes that result from long-term stress exposure because this knowledge will improve the identification of cellular endophenotypes in various psychiatric disorders.

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1. Introduction

The importance of the physiological and pathophysiological consequences of chronic stress is increasingly acknowledged, with many interdisciplinary studies showing that repetitive, uncontrollable stress affects well-being and leads to disease. The brain not only coordinates stress responses but also bears its consequences. Chronic stress has significant impact on the cellular integrity and function of certain brain areas, most notably the limbic structures [80,105]. In most studies, the hippocampal formation has been investigated as a model structure, but recently the prefrontal cortex and amygdala have been seen as equally or even more important. Our aim is to provide a brief overview of the current knowledge on chronic stress-induced structural plasticity in the prefrontal cortex of rats with an emphasis on hemispheric differences. We also attempt to relate our preclinical findings to human studies, although we are aware that these may not always mirror the human situation. However, it is now clear that many of the preclinical observations can help us to understand stress-related processes in the human brain.

2. The role of the medial prefrontal cortex in stress response regulation

The prefrontal cortex (PFC) in rats consists of anatomically and functionally distinct areas that are most commonly divided into two main subregions: the medial prefrontal cortex (mPFC) and the orbitofrontal cortex (OFC) [113,157]. The medial PFC can be further subdivided into the infralimbic (IL), prelimbic (PL), and dorsal anterior cingulate cortex (ACd) [87]. The substantial debate regarding the exact extent and nomenclature of the PFC subareas [157] is outside the scope of this paper. We also do not describe the afferent and efferent projections of the rat PFC, instead referring to the excellent, detailed anatomical literature (e.g., [63,71,76,140,158,159]). The medial areas of the rat prefrontal cortex participate in several higher-order functions including learning, memory, event association, the temporal sequencing of tasks, specific aspects of locomotor activity, spatial navigation, decision making and goal-directed behavior [152,159]. The PFC plays a key role in coordinating behavior that requires working memory, recalling memories from long-term storage as well as recent memories to guide behavior, while inhibiting inappropriate responses and distractions [131,132].

Prefrontal cortex has a significant role in modulating autonomic and endocrine responses to stress. Similarly to the hippocampus, the PFC contributes to negative feedback control of the hypothalamic–pituitary–adrenal (HPA) axis [72] and regulates the stress responses of other structures (e.g., [5,117]). Glucocorticoid receptors are abundantly present in the prefrontal cortical areas of rats and primates [50,106,108,137]. Corticosterone implants in the medial prefrontal region of rats diminished the stress-induced adrenocorticotrophic hormone (ACTH) release from the pituitary and corticosterone secretion from the adrenal cortex following acute or repeated immobilization stress [1,50]. Functional segregation of the different PFC subareas has been demonstrated by lesioning the anterior cingulate cortex (dorsal mPFC), which increased plasma levels of ACTH and corticosterone in response to restraint stress [50,124]. The restraint stress-induced corticosterone response was suppressed by lesions in the infralimbic cortex (ventral mPFC) [124,146]. This functional dissociation between dorsal and ventral regions of the mPFC has been confirmed by studies showing that these subareas have distinct anatomical connections [71,158,159].

Hemispheric specialization of the prefrontal cortex in emotional processing is well documented in humans [43], but there is evidence that a similar lateralized regulation of stress responses is present in lower mammals including rodents [22,23,68,146]. A

number of studies on rats have shown that whereas the right mPFC integrates emotional and physiological responses to long-term stressful situations, the left mPFC is more involved in regulation of immediate stress responses [23,147]. The right ventromedial PFC appears to play a primary role in optimizing cautious and adaptive behavior in potentially threatening situations [148]. The significance of hemispheric lateralization in the regulation of emotional reactivity and stress responses is not yet understood, but it is clear that this lateralization phenomenon transcends species and is not restricted to the PFC. One possible basis for such functional asymmetry is that right-hemispheric structures are more directly linked with the more basic autonomic and neuroendocrine life-sustaining functions [65].

3. Chronic stress-induced cellular changes in the medial prefrontal cortex

3.1. Stress-induced dendritic remodeling in the mPFC is subregion dependent and hemisphere dependent

It is well documented that repeated stressful experiences have a profound impact on neuronal plasticity in various brain areas, especially in the hippocampal formation, the prefrontal cortex and the amygdala. Probably the most thoroughly investigated neuromorphological change is the regression of the geometrical length of apical dendrites of pyramidal neurons first demonstrated in the hippocampus [163]. However, chronic stress alters dendritic morphology not only in the hippocampus but also in the medial prefrontal cortex and amygdala [62]. These three structures are all heavily interconnected and regulate the activity of the HPA axis [72].

A rapidly growing number of studies demonstrate that prolonged stress leads to changes in the dendritic arbors of the pyramidal neurons in layers II–III of the mPFC (Fig. 1) [30,91,118,125–127]. The main results from these studies are a significant reduction in total dendritic length of 20–35% with a significant decrease in branching and spine density of the distal apical dendrites. Even repeated injections of vehicle (a relatively mild stressor) result in similar although less-pronounced changes indicating that the morphology of mPFC neurons is more sensitive to external influences than those in the hippocampus [17,107]. However, it also appears that these changes are plastic and not degenerative in nature because they reverse spontaneously after a recovery period [125]. These studies, however, usually did not differentiate between the three PFC subregions (anterior cingulate, prelimbic and infralimbic). Instead, cells in all three, or in some cases only two, neighboring subregions were analyzed, and no distinction was made between hemispheres. Our recent, detailed analysis of the mPFC showed significant differences not only between the subareas but also between the hemispheres [118]. As shown in Fig. 2, whereas the dendritic complexity of layer III pyramidal cells in control rats had no inherent hemispheric asymmetry in the dorsal anterior cingulate cortex, neurons in the right prelimbic cortex had longer dendrites in middle and distal portions of the apical tree, as compared with those in the left prelimbic cortex [118]. Similarly, pyramidal neurons in the right hemisphere of the infralimbic cortex had longer apical dendrites proximal to the soma (Fig. 2 and [118]). Twenty-one days of immobilization stress affected mainly the right hemisphere and abolished the inherent hemispheric asymmetry (Fig. 2 and [118]). Furthermore, the effect of chronic stress was region specific. In neurons of the right dorsal anterior cingulate cortex, dendritic branch complexity substantially decreased in the distal part, but increased in the proximal portion of the dendritic tree (Table 2 of [118]). In the right prelimbic area, branches retracted both in the middle and distal regions of the dendritic tree (Fig. 2). In neurons of the right infralimbic region, dendritic atrophy was observed largely in the proximity of the soma, whereas elongation

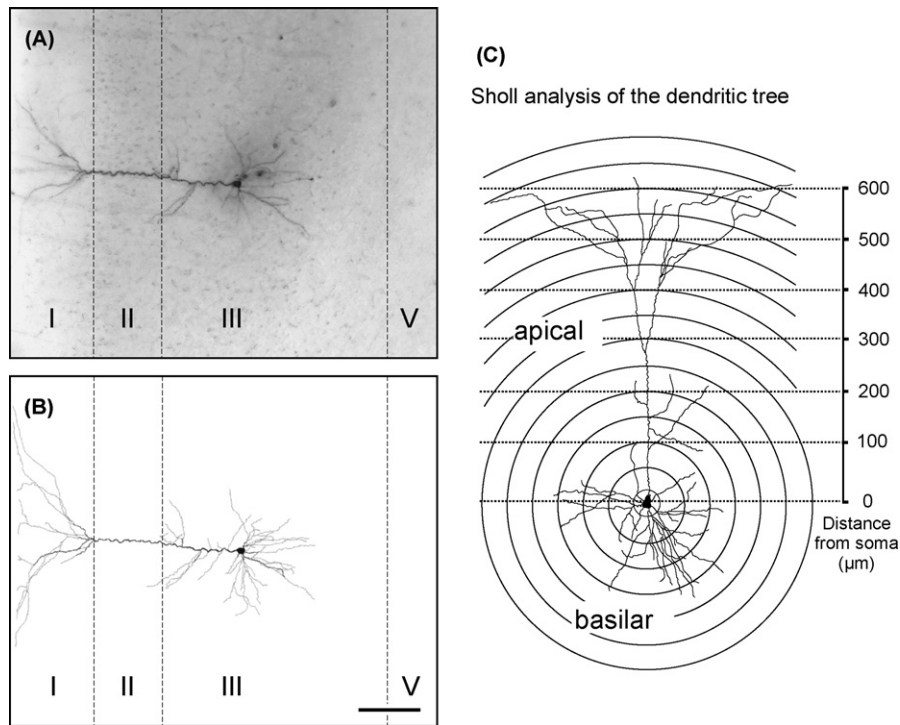


Fig. 1. Methodology for comprehensive dendritic arbour morphologic analysis of pyramidal neurons in the mPFC. (A–B) Example of an intracellularly labeled and then digitally reconstructed pyramidal neuron in layer III of the mPFC. Scale bar: 100 μm . (C) Schematic drawing illustrates the Sholl circles that correspond to the distances from soma. These Sholl rings are used for quantitative analysis of dendritic morphology.

of dendrites occurred in the distal part of the dendritic tree (Fig. 2). The importance of distinguishing between the different regions of the mPFC is supported by data shown in Fig. 3. Daily i.p. injections of saline for a period of 21 days – a relatively mild stressor – resulted in dendritic retraction only in the right prelimbic cortex. The importance of discriminating between mPFC subregions is underscored by a recent study demonstrating that a brief exposure to daily swim stress caused a significant retraction of neurons in the infralimbic, but not in the prelimbic, cortex [78].

The functional significance of the chronic stress-induced dendritic retraction within mPFC or hippocampus is unclear. It is well documented that stress results in increased glutamatergic neurotransmission in both the PFC and the hippocampus [111]. The accepted explanation for dendritic remodeling is that the neurons need to protect themselves from the excitotoxic effect of glutamate by reducing their surface area. A reduction in the neuronal surface area will diminish the amount of synaptic input, and indeed, stress-induced apical dendritic atrophy in the PFC results in decreased responses to apically targeted excitatory inputs [92]. In the hippocampus, a significant loss of synapses on the CA3 pyramidal cells and profound changes in the morphology of their afferent mossy fiber terminals have been observed in chronically stressed or corticosterone-treated animals [97,138,144]. Studies of the hippocampal formation demonstrate that the stress-induced retraction of the dendritic tree alters the electrical characteristics and excitability of these neurons [80]. These changes are likely to contribute to the various cognitive deficits that have been described as a result of chronic stress exposure. Another possible functional outcome of dendritic retraction may be a disturbance of HPA axis regulation, leading to unregulated glucocorticoid release [31]. Finally, neurons showing dendritic retraction may also be sensitive to other life events, and this may explain why the hippocampus is vulnerable to damage when chronic stress precedes or coincides with other harmful conditions [31,32]. In contrast to a brief exposure to stress (in which cellular changes are aimed at restoring homeostatic con-

rol and are therefore beneficial for the survival of the organism), when stress becomes chronic and uncontrollable, the system may deteriorate and become vulnerable to other adverse situations. To our knowledge, such a stress-induced enhanced cellular vulnerability has not yet been investigated in the prefrontal cortex.

3.2. Morphological changes as a result of artificially elevated glucocorticoid levels

As noted earlier, glucocorticoid receptors (GRs) are abundantly expressed in prefrontal cortical areas, and the PFC contributes to the negative feedback regulation of the HPA axis. Some of the chronic stress-induced effects are likely to be mediated by the activation of GRs because artificially elevated levels of adrenoglucocorticoids result in morphological changes similar to those seen following chronic stress exposure.

It has been shown that induced hypercortisolism in rats can decrease the volume of the anterior cingulate cortex especially in the left hemisphere, while the right anterior cingulate region reacts to a smaller extent [25]. The cellular mechanisms contributing to the shrinkage of these brain areas involve decreases in dendritic branching and perhaps neurodegeneration. Treatments with glucocorticoid receptor agonists such as dexamethasone or corticosterone significantly reduce the total length of apical dendrites of pyramidal neurons in lamina II–III of the ACd, PL, and IL cortices [28]. Although these treatments are associated with decreased branching in the distal portions of the apical dendrites, changes in the architecture of the basal dendrites have not been observed [28]. Daily injections of corticosterone for 3 weeks increased the amount of dendritic material proximal to the soma of pyramidal neurons in layers II–III of the mPFC whereas the distal dendrites were reduced by the treatment [164]. Another study demonstrated that treatment with the synthetic glucocorticoid dexamethasone induced neuronal loss in layer II in all three mPFC regions [27]. Apparently, glucocorticoids act in a region-specific manner because no other

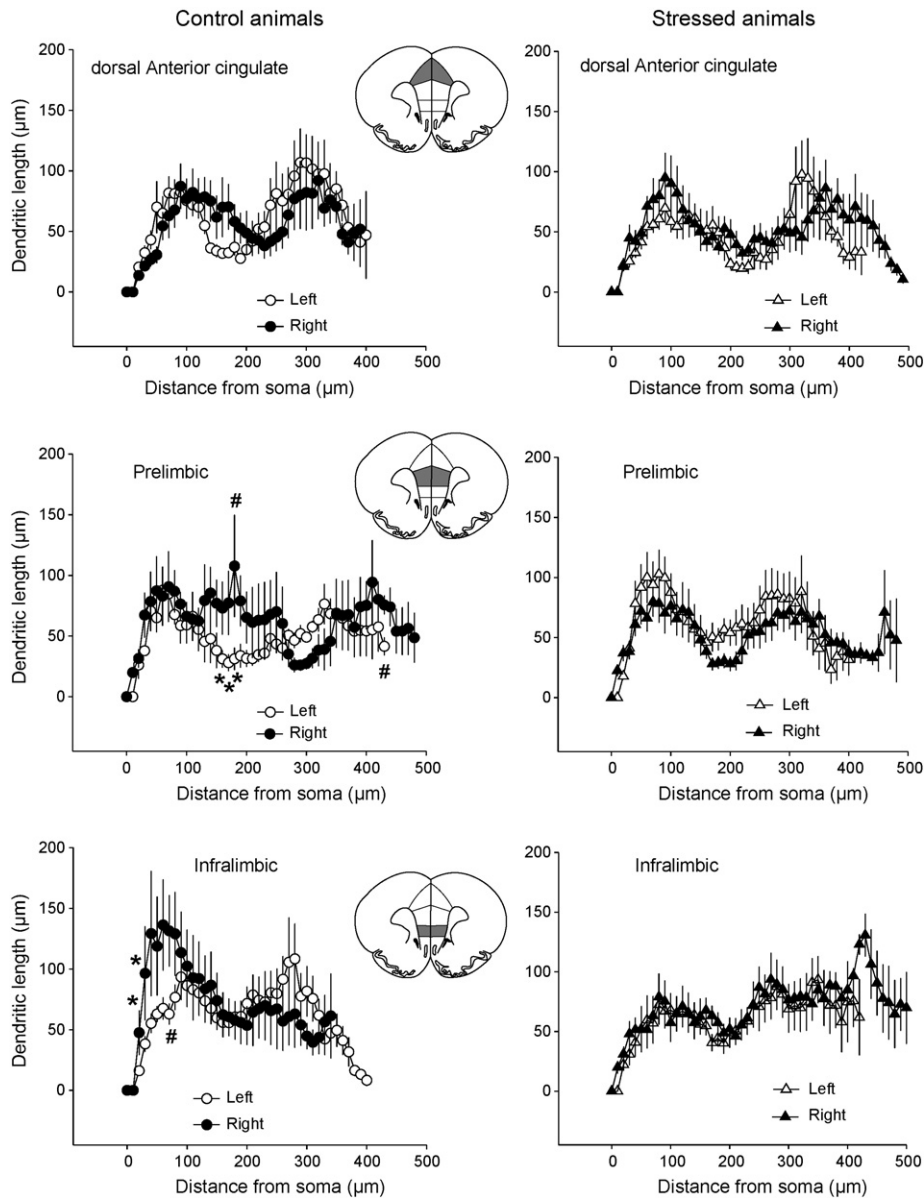


Fig. 2. Apical dendritic lengths of layer III pyramidal cells in the three different subregions of the mPFC in control (left panel) and stressed animals (right panel). Data points represent the sum of all dendrites detected at the respective distance (radius) from the soma center set as zero (mean \pm S.E.M.). Note that there are clear left–right differences in the control animals that mostly disappear after chronic stress exposure. Data are results of a Sholl analysis of digitally reconstructed neurobiotin filled pyramidal cells (for details see Ref. [118]). The number of cells/control animals: in dorsal anterior cingulate cortex: left 10/9; right 9/9; in prelimbic cortex: left 5/5; right 5/5; in infralimbic cortex: left 9/9; right 8/7. The number of cells/stressed animals: in dorsal anterior cingulate cortex: left 6/7; right 7/6; in prelimbic cortex: left 11/10; right 14/12; in infralimbic cortex: left 9/8; right 9/9. Symbols indicate significant differences within each 10 μ m ring (* $p < 0.05$, # $p < 0.01$).

cortical layers or areas were affected. The number of glial cells was not investigated in these studies. In contrast to dexamethasone (a high-affinity GR agonist), high levels of corticosterone (a physiological adrenocortical steroid that binds with high affinity to the mineralocorticoid receptor [MR] and with lower affinity also to the GR) did not cause a significant reduction in the numbers of mPFC neurons [27]. These studies suggest that shorter treatment periods, e.g., a 7-day dexamethasone treatment, do not result in obvious morphologic changes. Longer treatments, e.g., 21 days, are necessary to induce noticeable structural changes such as the diminution and rearrangement of neurons and their dendrites [167].

3.3. Adult neurogenesis and gliogenesis

During the last decade, the capacity of the adult nervous system to replace its cells has attracted considerable interest in the sci-

entific community. The demonstration of ongoing neurogenesis in the adult human hippocampus [57] has been a turning point in our understanding of neuroplasticity. The findings that stress inhibits adult hippocampal neurogenesis [67], whereas antidepressant treatment has an opposite effect [136], and that patients with mood disorders often have smaller hippocampal volumes [21] rapidly led to the formulation of the “neurogenic hypothesis” of depression. This theory proposed adult hippocampal neurogenesis as a candidate substrate, for both the etiology and the treatment of major depressive disorders [54]. Since then, this view has been refined. According to the current view, newborn hippocampal granule cells may not be critical contributors to the development of depression but nevertheless may be required for certain behavioral antidepressant effects [136]. The demonstration that various antidepressant treatment strategies can stimulate neurogenesis in the adult dentate gyrus [98] has been followed by studies showing

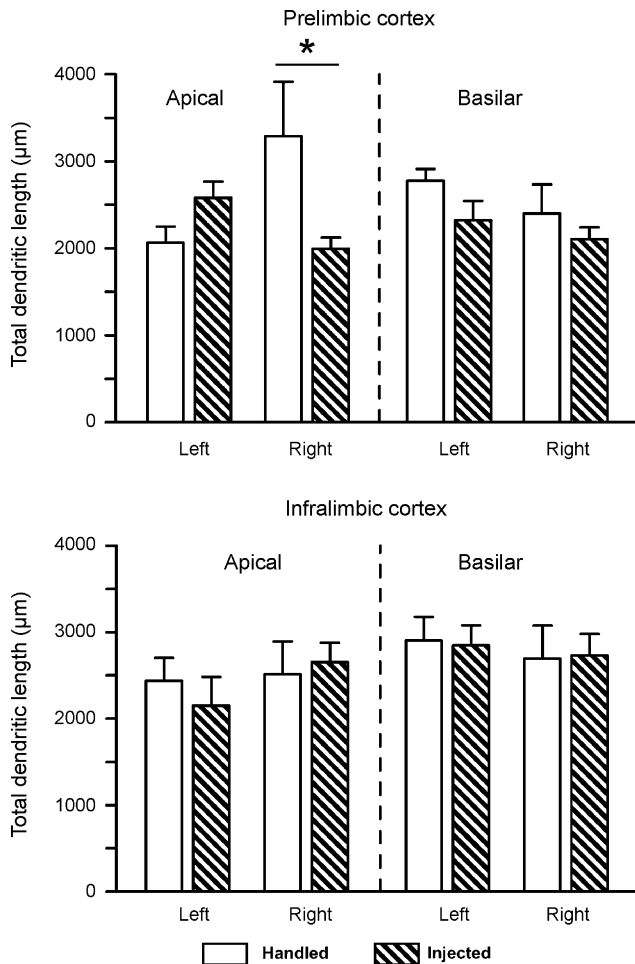


Fig. 3. Remodelling of dendrites of layer III pyramidal neurons in the mPFC after daily i.p. injections of saline for 21 days. Note that this relatively mild although chronic stressor induced dendritic retraction in the apical dendritic tree of pyramidal cells located only in the right hemisphere of the prelimbic cortex. The dorsal anterior cingulate cortex was not analysed. Data are results of a Sholl analysis of digitally reconstructed neurobiotin filled pyramidal cells (for details see Ref. [118]). The number of cells/animals in the prelimbic cortex: left: 5/5 handled rats; 6/4 injected rats. Right: 5/5 handled rats; 8/8 injected rats. In the infralimbic cortex: left: 8/9 handled rats; 5/5 injected rats. Right: 8/8 handled rats; 7/7 injected rats.

similar stimulatory effects on cell proliferation and gliogenesis in the rat medial prefrontal cortex [85,96,116]. Moreover, it has recently been shown that chronic stress inhibits cell proliferation not only in the hippocampus but also in the rat medial prefrontal cortex, and that this inhibitory effect can be counteracted by antidepressant treatment [8,41]. The significance of these observations is strengthened by *in vivo* neuroimaging studies of patients with mood disorders that consistently point to the involvement of prefrontal sites in the pathophysiology of the disease [53,103]. These imaging findings are further supported by reports on human postmortem material revealing that not only neurons but also the glial cell numbers in these same prefrontal areas are affected in patients with mood disorders [129,130] (see Chapter 4.4).

Chronic stress-induced inhibition of gliogenesis and changes in total glial cell numbers has been reported in the hippocampus [39,40]. These changes may be mediated by glucocorticoids as these substances inhibit gliogenesis both *in vivo* and *in vitro* [4,37,166]. It appears that stress has to be long-term and chronic to reduce gliogenesis in the mPFC because acute stress, or just a shorter stress period, did not have as much of an inhibitory effect [8]. This is in sharp contrast to the prompt suppression of dentate neurogenesis in the hippocampal formation after the experience of a single social

defeat [155]. It is, however, possible that the effect is not restricted to the mPFC because Banasr et al. reported that 2 weeks of unpredictable stress suppresses cell proliferation not only in the mPFC but also in the motor cortex [8]. We also found a substantial decrease in cell proliferation in the primary motor cortex after 5 weeks of social defeat stress, but the same paradigm had no effect on the survival rate of the newly generated cells in the same cortical area (see Fig. 7 in [41]). The generation of new neurons or glia is the end product of a series of steps consisting of proliferation, survival, migration, and differentiation and, with respect to neurons, the establishment of functional connections with other neurons. Therefore, it is important to differentiate between the proliferation rate of the precursor cells and the survival rate of newborn cells. Measurement of cell proliferation is possible by killing the animals shortly (i.e., 2–24 h) after the injection of the proliferation marker 5-bromo-2'-deoxyuridine (BrdU, which is incorporated into DNA during replication), and then visualizing the newborn cells by immunohistochemistry using an antibody against BrdU. The survival rate can be measured by killing the animals after a longer survival time (i.e., several weeks) following BrdU injection. A large portion of the newly generated cells die spontaneously shortly after their birth with only 40–50% differentiating into mature cells. According to current knowledge, both the *proliferation* and *survival* rates may be affected by numerous internal and external factors [60].

A further surprising outcome of our study was the observation that gliogenesis in the mPFC shows an intrinsic hemispheric asymmetry [41]. Whereas adult neurogenesis in the hippocampal dentate gyrus of control animals shows no hemispheric lateralization [142], in the left mPFC, both the *proliferation* rate and *survival* of the newborn cells were always higher as shown in Figs. 4 and 5. This intrinsic lateralization of cell proliferation was significant in the anterior cingulate and in the prelimbic cortex with a similar trend observed in the infralimbic cortex (Fig. 4). The most pronounced hemispheric asymmetry was seen when data collected from these three subareas were pooled and expressed together as cell proliferation in mPFC (Fig. 4). A similar pattern of hemispheric asymmetry, although less pronounced, was detected in the *survival* rate of the newly generated cells in the mPFC of control rats (Fig. 5). The functional significance of this intrinsic lateralization in the mPFC is yet to be determined, but it is tempting to relate adult gliogenesis to the clinical observations of lateralized emotional processing (see Chapter 4.2). Lateralized gliogenesis in the mPFC might reflect functional asymmetry. The higher occurrence of gliogenesis in the left PFC may indicate the left “dominance” of this region in normal unchallenged animals. Chronic stress exposure abolished this intrinsic lateralization in all three subregions. When data from the three subareas were pooled, and the data from the entire mPFC in control and stressed animals were compared, a reversed asymmetry emerged showing significantly more newborn cells present in the right mPFC (Figs. 4 and 5). Higher levels of cytogenesis in the right hemisphere in stressed animals may reflect hyperactivation of this area during chronic stress. This hypothesis is based on clinical and preclinical findings detailed in Chapters 2 and 4.2.

The detailed phenotypic analysis of the newborn cells in the mPFC revealed that most develop into glia [41,99]. Ongoing neurogenesis has been reported in the prefrontal cortex of adult rats and nonhuman primates [47,66,99], but these findings have been questioned by other investigators [86]. Up to now, there is no evidence that cortical neurogenesis is affected either by stress or drug treatment. Current knowledge in humans indicates that neocortical neurogenesis is restricted to prenatal developmental stages [12], and neurogenesis in the adult human neocortex has not yet been documented.

The studies demonstrating opposing effects of stress and antidepressant treatments on cytogenesis in the mPFC reveal that the majority of the affected newly generated cells express the chon-

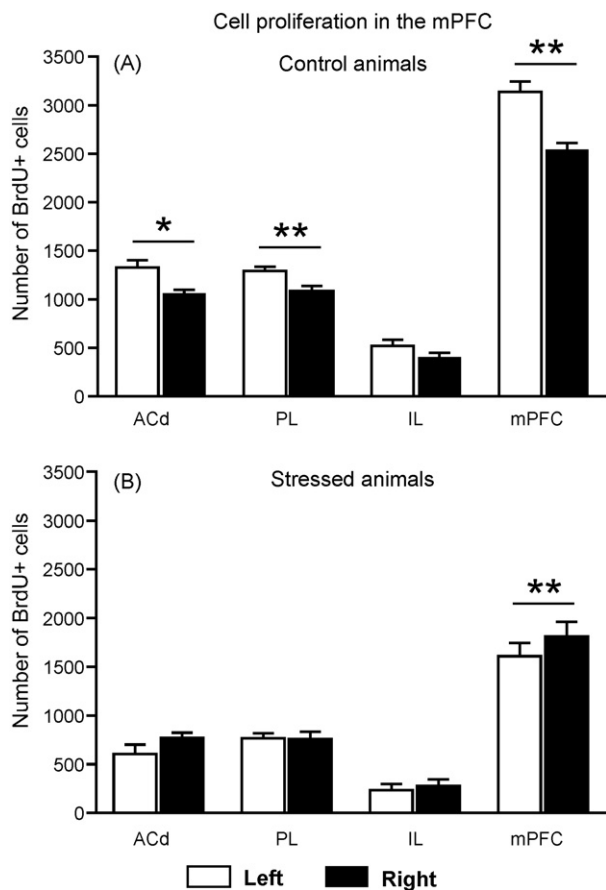


Fig. 4. Chronic psychosocial stress inhibits cell proliferation in the medial prefrontal cortex of rats. Cell proliferation was assayed by a pulse injection of BrdU at the end of a 5-weeks chronic stress period with daily social defeat. Newborn cells in the brain were visualized by immunohistochemistry and the total number of BrdU-positive cells was counted by stereological means (for details see Ref. [41]). (A) Cytogenesis was always higher in the left hemisphere of control animals. This intrinsic hemispheric asymmetry was most pronounced when values of the three subregions (ACd, PL, IL) were pooled (shown as mPFC). (B) Chronic stress abolished the hemispheric difference. When data was pooled (mPFC = ACd + PL + IL) a reversed asymmetry emerged, with significantly smaller incidence of newborn cells in the left mPFC. Statistics: paired *t*-test: **p* < 0.05, ***p* < 0.01. ACd: dorsal anterior cingulate cortex; PL: prelimbic; IL: infralimbic; mPFC: medial prefrontal cortex (including ACd + PL + IL).

droitin sulfate proteoglycan neuron-glia 2 (NG2; [8,41,85,96,116]). NG2 identifies a glial cell population that is widely and uniformly distributed throughout gray and white matter of the mature CNS, representing 5–8% of the total glial cell population [19,20,89]. The exact functional role of this glia type is still largely unknown, especially because NG2-positive cells most probably represent functionally heterogeneous populations. *In vivo* studies have shown that one group of NG2-positive cells represent the major cycling cell population in the normal adult rat CNS [46]. These preferentially differentiate into oligodendrocytes [45,90]. However, this may not be the only fate of NG2-positive cells. Recent evidence indicates that NG2-positive cells have the ability to differentiate into neurons, under both *in vitro* and *in vivo* conditions, suggesting that they may have stem-like or stem-cell-like properties [9,90]. In the hippocampal formation, the progeny of postnatal NG2-positive precursors appears to differentiate *in vivo* into GABAergic neurons capable of propagating action potentials with functional synaptic inputs [9]. A second group of NG2-positive cells have many of the morphological features of astrocytes. They are stellate cells with elaborate multiple branching processes that form numerous contacts with neurons, astrocytes and oligodendrocytes [19,20].

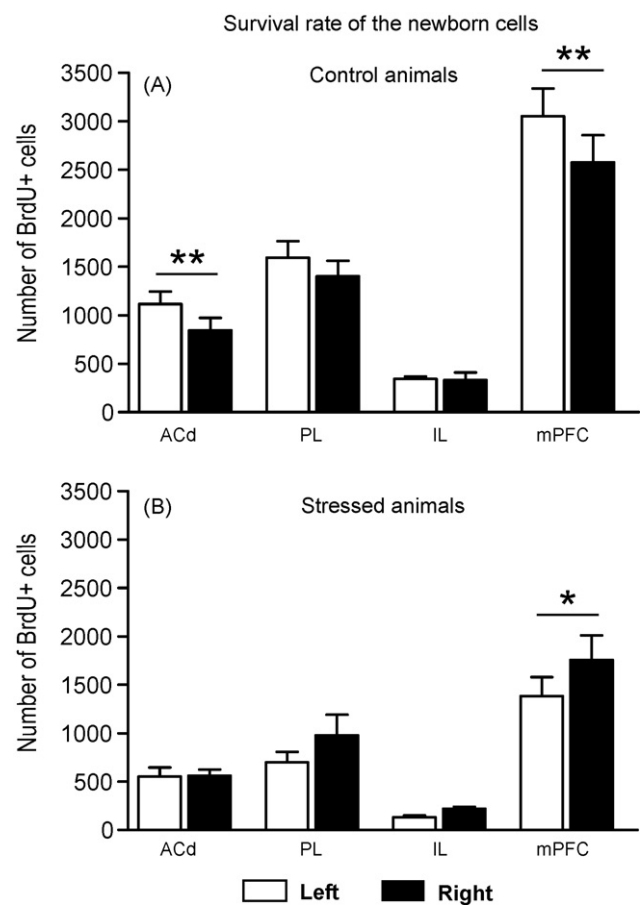


Fig. 5. Chronic stress reduces the survival rate of the newborn cells in the medial prefrontal cortex of rats. The effect of stress on cell survival rate was assessed by a pulse injection of BrdU, after which animals were subjected to a daily social defeat stress for 3-weeks. For details on the methods see Czéh et al. [41]. (A) The survival rate of the newly generated cells was higher in the left ACd of control animals, and when values of the three subregions were pooled and displayed as mPFC. (B) Chronic stress resulted in a reversed hemispheric asymmetry in cell survival rate. Statistics: paired *t*-test: **p* < 0.05, ***p* < 0.01. ACd: dorsal anterior cingulate cortex; PL: prelimbic; IL: infralimbic; mPFC: medial prefrontal cortex (including ACd + PL + IL).

These cells may be specialized to monitor signals from neurons and glia, and to respond to changes in the integrity of the CNS [19,20]. A further unique feature of the NG2-positive cells is that they form direct synaptic junctions with both glutamatergic and GABAergic neurons, and exhibit physiological properties distinct from neurons and other classes of glial cells [122].

3.4. Potential factors modulating stress-induced cellular plasticity in the PFC

The quantity of data on stress-induced plasticity in the brain, namely changes in the morphology of dendrites and spines as well as alterations in numbers of neurons and glia, has exploded during recent years with a concomitant steady increase in the number of known factors mediating these processes. Today, it is clear that there is a wide range of substances that act at all functional levels on brain cells. Although the current knowledge concerning factors regulating neural plasticity comes from a large number of studies, most focus on limbic structures with only a few investigations on the prefrontal cortex.

3.4.1. Neurotrophins

Neurotrophins have attracted particular attention in the context of stress and neuroplasticity [24]. These target derived neurotrophic

growth factors are important not only in the development of the CNS but also in mediating neuroplastic changes in the adult brain. One of these is nerve growth factor (NGF), which regulates outgrowth of neuronal processes [56,154] and affects neuronal survival by blocking apoptosis [82]. NGF expression has been shown to be downregulated in the hippocampal formation by chronic social stress [2], and a similar effect of stress in the prefrontal cortex is likely, but this has not been carefully investigated.

The most extensively studied factor of the NGF family in the context of stress and related disorders is brain-derived neurotrophic factor (BDNF) [55]. In the adult mammalian brain, BDNF is produced and released by neurons in an activity-dependent manner, and it is the most abundant and widely distributed neurotrophin. Although the main function of BDNF in the adult brain is to regulate synaptic plasticity, BDNF may also mediate cell survival and growth. *In vitro* studies show that BDNF stimulates the growth of dendrites and increases the spine density of cortical pyramidal neurons [77,104]. Exposure to stress and corticosterone reduced BDNF expression in several brain regions including rat prefrontal cortex [13,55,143]. Therefore, altered BDNF expression may be a candidate mechanism for the reduced dendritic length and spine density present in stressed animals. Recent evidence, however, suggests that suppressed BDNF expression alone does not appear to be sufficient to alter dendritic morphology. A study analyzing pyramidal neuron morphology in mice with an inducible knockout of the BDNF gene found that, despite an 80% reduction in BDNF mRNA levels in knockouts, neither spine density nor other dendritic or somal measures was decreased in the prelimbic and anterior cingulate cortices of adult mice, regardless of whether the reduction in BDNF mRNA levels was induced prenatally or in early adulthood [73]. A possible explanation for this negative finding is that reduced levels of both BDNF and TrkB might be required to produce a measurable decrease in dendritic morphology. Recent evidence suggests that neuronal activity-induced BDNF release may induce morphological changes not only in neurons but also in glial cells in the rodent neocortex, indicating that the BDNF–TrkB.T1 signaling pathway may influence astrocytic plasticity [114].

Neurotrophins regulate morphology of brain cells partly through effects on gene transcription. BDNF binding to the TrkB receptor (which is a kinase) in the plasma membrane of a target cell initiates an intracellular signaling cascade. As suggested by Berton and Nestler [11], TrkB receptor activation stimulates cAMP response element binding protein (CREB)-directed transcription. Phosphorylated CREB dimerizes and the dimer binds to the cAMP response element (CRE) in the promoter region of many genes. Stress is known to activate CREB-directed gene transcription in both neurons and glial cells [14]. However, CREB activity is regulated by many factors other than BDNF, including all those that activate a kinase (i.e., those able to phosphorylate CREB). Among the genes that contain a CRE is synapsin I [75], a protein in presynaptic nerve terminals involved in the regulation of neurotransmitter release [74]. Stress has been shown to downregulate synapsin I expression in the hippocampal formation [64], and it is possible that in the PFC also, stress affects expression of this protein, although there is currently no direct experimental evidence for this.

3.4.2. Neurotrophic effects of monoamines

Monoamines regulate CREB-directed gene transcription via stimulation of the G-protein coupled receptors that modulate the activity of adenylyl-cyclase, the enzyme that synthesizes cAMP. Stress activates noradrenergic neurons in the brain stem that innervate almost all brain regions including PFC, and this activation of the noradrenergic pathway results in various physiological and behavioral changes [149,153]. High levels of monoamines are thought to be necessary for an adequate stress response but may also lead to the development of psychopathologies such as anxiety disorders

and depression in individuals that are susceptible to stress [16].

Norepinephrine (NE) is widespread throughout the brain, and in the PFC, it is thought to modulate cognitive functions such as working memory and attention. Moderate levels of NE improve PFC functioning via alpha-2 adrenoceptors whereas high NE concentrations impair PFC function [131]. In male tree shrews, 10 days of daily social stress induced a transient downregulation of alpha-2 adrenoceptors, but after 4 weeks, these receptors were finally upregulated indicating a NE deficit in the PFC after several weeks of chronic stress [59]. The stress-induced changes in adrenoceptors probably contribute to changes in gene transcription, presumably through CREB-directed gene transcription in neurons because alpha-2 adrenoceptor stimulation inhibits cAMP formation.

The mesocortical dopaminergic system, another important element in stress response regulation, has been heavily investigated with ample evidence indicating that this pathway contributes significantly to the lateralized function of the PFC [145]. Sullivan [145] proposed a theory of the lateralized function of the mPFC in regulation of the stress response. According to this theory, when an animal is exposed to a mildly stressful challenge, the initial coping attempt is accompanied by activation of the left prefrontal cortex (the left prefrontal cortex is less emotional and more motor dominant than the right PFC). Because most normal-life stressors are manageable, the left prefrontal dominance successfully deals with mildly challenging situations without the need to activate the right prefrontocortex. However, when attempts to cope with the stress fail, activity in the stress-sensitive right PFC will be dominant. According to this theory, both left and right mesocortical dopamine activation is adaptive, although each may be preferentially associated with distinct stages or strategies of coping with stressful experiences of varying intensities [145].

There is evidence that dopamine (DA) partly exerts its effects on the PFC by changing the architecture of neurons. Modulating dopaminergic activity with psychostimulants alters the number of dendritic branches and spine density of layer V pyramidal neurons in the PFC [133]. Lesioning neurons in the ventral tegmental area, which provides dopaminergic input to the PFC, with the neurotoxin 6-hydroxy-dopamine caused a decrease in length of basal dendrites and spine density of layer V pyramidal neurons in the prelimbic cortex [161].

In addition to the monoamines NA and DA, serotonin (5-HT) has also been shown to exert trophic effects on PFC neurons. Destroying the serotonergic input to the PFC by lesioning 5-HT neurons in the dorsal raphe nucleus with the neurotoxin 5,7-dihydroxytryptamine reduced the length of apical and basal dendrites in layer III of the dorsomedial PFC [119]. In the serotonin transporter knockout mice that have abnormal 5-HT levels in their brains, the apical dendrites of pyramidal neurons in the infralimbic cortex were significantly longer than in wild-type mice [165].

3.4.3. Effects of steroid hormones on the PFC

Hyperactivity of the HPA axis with the associated elevation of corticosteroid levels is a main neuroendocrine feature of stress [49]. Like other steroid hormones, glucocorticoids regulate gene transcription via interaction with intracellular receptors forming steroid-receptor complexes that bind to specific recognition sequences in the promoter regions of distinct target genes. Most of the corticosteroid-responsive genes are regulated by either activated GR or MR, although only a few genes are responsive to both receptor complexes [42]. In several species, different environmental challenges such as social defeat stress downregulate GR mRNA in the dentate gyrus and hippocampal CA3 and CA1 areas [93,109]. Alterations in GR expression have 'downstream effects' on many genes [42], and some of the steroid receptor-mediated changes in expression of structural proteins probably underlie

the alterations in neuroarchitecture. A recent study indicated that cyclin-dependent kinase 5, an enzyme that regulates transcriptional activity of the GR, is critically involved in the formation of dendritic spines [84]. It has been reported that MR is one of the genes that are downregulated by intermittent social stress in the medial prefrontal cortex of squirrel monkeys [83]. Gonadal steroids also affect the morphology of PFC neurons. In ovariectomized young adult female rhesus monkeys, estrogen increased spine density in layer III pyramidal neurons in the PFC while reducing dendritic length [69]. It is therefore possible that a balance between corticosteroids and gonadal steroids determines the shape of PFC neurons and that stress upsets this balance.

3.4.4. Stress-regulated genes in the PFC

Recent studies demonstrate that stress reduces the expression of many genes in the PFC that are involved in synaptic plasticity, cell-cycle progression and nuclear receptor signaling [83,139]. Several genes in the hippocampus known to be involved in neuronal differentiation were found to be downregulated by chronic social defeat stress (e.g., those encoding the membrane glycoprotein M6A, CDC-like kinase 1, and a DNA sequence representing a distinct subunit of certain G-proteins, GNAQ) [2]. All of these genes influence neurite outgrowth and neuronal differentiation, supporting the view that alterations in neuronal morphology and/or formation of neurons are primarily affected by stress [3].

A recent study focused on the molecular mechanisms related to susceptibility and resistance to repeated social stress. This study demonstrated that the expression of a considerably larger number of genes was either up- or downregulated in brain reward regions of mice impervious to chronic stress compared with stress-susceptible animals [88]. These data suggest that the resistant phenotype may reflect an active neurobiological process, associated with a heightened degree of molecular plasticity, and not simply the absence of vulnerability [88].

3.5. Functional consequences

The stress-induced structural changes described above are likely to affect the electrical properties of single neurons as well as the physiology of prefrontocortical networks, but very little is known about the effects of acute or chronic stress on neuronal excitability and network function in the prefrontal cortex.

Recording single unit activity in the mPFC of awake rats during acute stress exposure shows that 75% of mPFC neurons respond to the stress, displaying either transient or sustained increased activity [79]. This coincides with earlier observations demonstrating activation of glutamate neurotransmission in the PFC as a result of stress [111]. Pyramidal cells with apical dendritic atrophy display reduced responses to apically targeted excitatory inputs [92]. *In vivo* recordings show that acute stress blocks the induction of long-term potentiation (LTP) evoked via either the hippocampus-mPFC or the amygdala-mPFC pathway [26,101,134]. Under normal conditions, the projections from the mPFC to the amygdala do not induce LTP but instead promote long-term depression (LTD). Exposure to stress reverses this pattern of neuroplasticity, resulting in the promotion of LTP and the inhibition of LTD in the amygdala [100]. The function of this reversal may be used to encode memories of fear. These studies clearly demonstrate that stress experiences affect neuronal network functioning in the mPFC, but more data are needed before these findings can be generalized and related to cognitive functions or to changes in morphology of neurons or gliogenesis.

A number of behavioral studies demonstrate stress-induced impairment of performance in behavioral tasks that specifically depend on the integrity of the PFC, such as working memory and behavioral flexibility [15,26]. Although a recent study found

that the decreased dendritic arborization in the mPFC in chronically stressed rats predicted impairment of attentional set-shifting performance [91], earlier studies describing the impairment of working memory as a result of chronic stress usually attributed the cognitive deficit to an alteration of dopaminergic input to the PFC [6,7,110,112,151].

4. Human studies

Stressful life events are the major nongenomic factors contributing to the manifestation of various psychiatric illnesses, as well as to the exacerbation of acute psychiatric symptoms and to recurrence or relapse after a period of remission. Dysfunction of prefrontal cortical areas as a result of severe or chronic stress is likely to contribute to the core symptoms of affective disorders, schizophrenia and addiction. Because experimental paradigms using chronic stress exposure have recently emerged as valuable animal models of mood disorders [61,121] we briefly summarize related human data on the involvement of prefrontal cortical areas in the regulation of stress responses and mood disorders.

4.1. The involvement of the prefrontal cortex in stress response regulation

There are a few studies of healthy individuals using functional imaging to record changes in brain activation associated with the perception of stress and the regulation of the stress response. These studies exposed healthy volunteers to challenging mental tasks (typically arithmetic calculation) combined with social evaluative threat components that were considered to be psychosocial stressors [48]. Wang et al. [162] used functional MRI (fMRI) scans to show that such stress exposure was specifically associated with right ventral PFC activation, and that this activity persisted beyond the stress-task period. They also found that cerebral blood flow was reduced in the left ventrolateral PFC and in the left orbitofrontal cortex, parallel with the activation of the right PFC during stress. They argued that the right PFC is important in the central stress response because they could associate the changes in cerebral blood flow in this area with both subjective and objective measures of stress responses. These findings corroborate the traditional view that the activation of the right PFC is associated with negative emotions and increased alertness [29].

A somewhat different picture has emerged from a more recent study by Pruessner et al. [123], who employed a similar psychological stressor and assessed brain activation by positron emission tomography (PET) and fMRI scans. The authors observed a profound bilateral deactivation of the limbic system as a result of acute stress. In their PET study, reduced cerebral blood flow was detected in the dorsal and ventral medial prefrontal cortex including the anterior cingulate cortex and in a number of other limbic structures. The fMRI data generally replicated the findings of their PET study, with limbic system structures showing signs of reduced brain activity under stress. Results of this study imply that higher limbic structures such as the hippocampus and prefrontal cortex provide a tonic inhibition to the activity of the HPA axis. In response to a stressor, these limbic structures appear to reduce their activity, which then disinhibits the HPA axis and initiates stress hormone release. However, the authors were unable to confirm the hemispheric asymmetries reported by Wang et al. [162].

The major drawback of the current *in vivo* imaging techniques is their limited temporal resolution, so that they may not capture the real-time dynamics of brain function. These dynamics may well be the essence of emotional and cognitive processing. Further studies are required before any final conclusions can be drawn.

4.2. Hemispheric asymmetries of the prefrontal cortex in emotional experience and processing

The frontal lobe in humans occupies nearly 30% of the neocortex, and it has been implicated in emotional processing. Hemispheric specialization of mood regulation is a well-documented phenomenon. Not only does this functional asymmetry exist under normal conditions but also altered hemispheric lateralization has been demonstrated in various psychopathological conditions [10,29,43,102,120]. Current brain models of emotional processing suggest that positive (or approach-related) emotions are lateralized toward the left hemisphere, whereas negative (or withdrawal-related) emotions are lateralized toward the right hemisphere [135]. Some researchers regard this view as oversimplified, but many investigations have shown that damage to the left hemisphere is usually accompanied by depressed mood, whereas right-hemispheric damage is associated with euphoric reactions (e.g., [135,141,150]). According to the balance model of cerebral lateralization of emotions proposed by Tucker and Frederick [156], deactivation of one cerebrum leads to increased relative activation of the opposite cerebrum. Deactivation of the left cerebrum may therefore result in an increase in negative emotions. This view is supported by the clinical observations in patients with unilateral PFC lesions, by the electroencephalographic evidence that relates reduced left-hemisphere activation to depressive conditions, and by the hyperfunctioning of the right hemisphere with anxiety disorders [29,120,141].

4.3. The involvement of the prefrontal cortex in mood disorders

Human imaging studies using PET and fMRI to investigate the neuroanatomic correlates of emotional disorders repeatedly show the involvement of the prefrontal cortex, a structure that is apparently deregulated in both mood and anxiety disorders [51,52,102,120]. Depressed mood has been specifically associated with hypometabolism and volumetric reduction of the left PFC [51,53]. PET resting-state studies reveal reduced cerebral blood flow and metabolism in the left dorsolateral PFC (dlPFC) and hypermetabolism in the right dlPFC in acute states of major depressive disorder (MDD) [102,120]. Normalization of hemispheric imbalances of prefrontal function in mood disorders has been related to the efficacy of repetitive transcranial magnetic stimulation (rTMS). Depressed patients benefit from high-frequency rTMS stimulation (which increases cortical activity) over the left dlPFC and low-frequency TMS (which suppresses cortical activity) over the right dlPFC [18,58]. These findings have led to the “imbalance hypothesis of MDD”, which postulates prefrontal asymmetry with relative hypoactivity in the left dlPFC and relative hyperactivity in the right dlPFC [44]. This view is further supported by brain imaging studies identifying a key corticolimbic circuit involved in the top-down regulation of subcortical affective circuitry. The cognitive processes that downregulate negative emotions in healthy individuals are related to increased left prefrontal and decreased amygdala activation [81]. In contrast, depressed individuals show bilateral PFC activation during the same task with no left-lateralized activation, indicating an inappropriate or inefficient engagement of prefrontal regulatory circuitry [81].

4.4. Glial abnormalities in the PFC of patients with mood disorders

The observations described above from *in vivo* imaging studies are supported by postmortem cell-counting studies showing that mood disorders are characterized by alterations in the density and size of neuronal and glial cells in frontolimbic brain regions [33–35,128–130]. The most consistent finding from these

histopathological investigations is the demonstration of decreased glial cell numbers in specific areas of the prefrontal, orbitofrontal, and cingulate cortex [34,35,70,115,128,130]. It has been suggested that abnormalities in glial function are likely to contribute to the impairment of structural plasticity and thus to the overall pathophysiology underlying mood disorders [35,36,130].

In contrast to the traditional concept that attributed passive, housekeeping functions to glial cells, recent developments reveal that glia perform complex functions including the control of neurotransmitter turnover and release, regulation of synaptic strength and synaptogenesis, the control of adult neuro-, glio- and angiogenesis, and adjustment of cerebral blood flow [130,160]. Although the majority of the postmortem histopathological studies on reduction in glial elements in frontolimbic structures do not identify which populations of glial cells were reduced, there are indications that both astrocytes and oligodendrocytes are involved [130]. The loss of astrocytes or their impaired metabolism may account for the observed altered signal in fMRI and PET studies commonly reported in the PFC of depressed patients [94,130]. Oligodendrocyte pathologies are likely to account for the white matter abnormalities that have been repeatedly reported on the basis of *in vivo* imaging studies of the PFC, in both elderly and first-episode, treatment-naive young patients with MDD [95,130].

Hemispheric asymmetry was not specifically examined in most of the postmortem histopathological studies. One exception is the report by Cotter et al. [34]. This study investigated the anterior cingulate cortex and found higher glial densities in all six cortical layers of the left hemisphere in control subjects, whereas in patients with MDD, this hemispheric asymmetry in glial cell density was not observed. These results indicate a disease-induced loss of glial cells in the left hemisphere. Hemispheric asymmetry of neuronal densities was not reported in that study in controls or in patients with MDD. Another study reported higher neuronal densities in the left dorsolateral PFC of control subjects, whereas patients with schizophrenia displayed a decreased neuronal density in the left hemisphere with an increased neuronal density in the right hemisphere [38]. In summary, there is some evidence of inherent hemispheric asymmetry in neuronal and glial cell numbers in prefrontal cortical areas, together with the loss or perhaps even a reversal of cerebral asymmetry in patients with stress-related psychiatric disorders. These findings need confirmation.

Glial cells, unlike neurons, retain their ability to renew throughout human adult life [12]. It is tempting to speculate that the preclinical findings on the inhibition of gliogenesis following chronic stress exposure may relate to the abnormalities of glial cell numbers reported in the frontolimbic areas of depressed patients. Human studies focusing on gliogenesis in the prefrontal cortex of depressed patients are needed to confirm this hypothesis.

5. Summary and conclusions

Research on stress-induced morphological plasticity in the prefrontal cortex is in its infancy compared with the knowledge gained by studying the hippocampal formation. It is evident, however, that the significant structural changes occurring as a result of stress in the medial PFC of rats are similar to those observed in the hippocampus, with some significant differences. In both structures, chronic stress results in dendritic remodeling and suppression of cytogenesis, but pyramidal neurons in the mPFC apparently react more rapidly with dendritic reorganization, even in response to milder stress, compared with hippocampal neurons. There is also evidence that neurons within different subregions of the mPFC react to stress differently. Neurons in the ventral region of the mPFC are more susceptible to stress compared with the dorsal region, and there is a suggestion of differences between the prelimbic and infralimbic areas. Research on the stress-induced suppression of

cell proliferation has so far focused on neurons in the hippocampal dentate gyrus, whereas in the mPFC, until now, the major cycling cell population affected by the stress exposure seems to be NG2-positive cells. A fraction of these NG2-expressing progenitors may eventually differentiate into new GABAergic neurons, but more detailed investigations are needed to evaluate whether this process is affected by stress. The functional significance of the cellular changes induced by stress listed here is yet to be determined, but it is likely that they contribute to cognitive impairments commonly observed in chronically stressed individuals.

We have summarized recent findings from our laboratory indicating that structural asymmetry at the cellular level appears to be an innate feature of the medial PFC in rats. The stress-induced morphological changes seem to affect this hemispheric lateralization. More data are needed to validate the robustness of these observations.

Stressful life events are important factors contributing to the development of various psychiatric illnesses, especially in cases of affective disorders, schizophrenia and addiction. Preclinical experimental paradigms using chronic stress are nowadays commonly regarded as valuable animal models for mood disorders. It is therefore tempting to compare the knowledge on structural plasticity gained in such preclinical studies with the clinical situation. Certain similarities are found between the human and animal data that underscore the importance and relevance of adequate animal experiments. We believe that it is crucial to understand exactly what kinds of structural changes occur after long-term stress exposure because that knowledge will facilitate the identification of distinct neuroanatomical endophenotypes associated with various psychiatric disorders.

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