Review

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"Braking" the Prefrontal Cortex: The Role of Glucocorticoids and Interneurons in Stress Adaptation and Pathology

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ABSTRACT
The medial prefrontal cortex (mPFC) receives information regarding stimuli and appropriately orchestrates neurophysiological, autonomic, and behavioral responses to stress. The cellular and neurochemical heterogeneity of the mPFC and its projections are key to fine-tuning of stress responses and adaptation. Output of the mPFC is mediated by glutamatergic pyramidal neurons whose activity is coordinated by an intricate network of interneurons. Excitatory/inhibitory (E/I) balance in the mPFC is critical for appropriate responsiveness to stress, and E/I imbalance occurs in numerous neuropsychiatric disorders that co-occur with chronic stress. Moreover, there is mounting data suggesting that chronic stress may precipitate E/I imbalance. This review will provide information regarding the cellular and anatomical makeup of the mPFC and discuss the impact of acute and chronic stress in adulthood and early life on interneuron function, with implications for E/I balance affecting functional connectivity. Specifically, the review will highlight the importance of interneuron type, connectivity, and location (both layer- and subregion-specific). The discussion of local mPFC networks will focus on stress context, including stressor duration (acute vs. chronic) and timing (early life vs. adulthood), as these factors have significant implications for the interpretation of experiments and mPFC E/I balance. Indeed, interneurons appear to play a prominent role in prefrontal adaptation, and a better understanding of the interactions between stress and interneuron function may yield insight to the transition from adaptation to pathology. Ultimately, determining the mechanisms mediating adaptive versus pathologic plasticity will promote the development of novel treatments for neuropsychiatric disorders related to prefrontal E/I imbalance.

Keywords: Adaptation, GABA, Glucocorticoids, Interneurons, Prefrontal cortex, Stress

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The medial prefrontal cortex (mPFC) receives, processes, and integrates a variety of stimuli to plan and direct appropriate behavioral and physiological responses, especially to stress (1,2). The mPFC pyramidal neurons (PNs) that orchestrate these responses are under tight control by a complex network of gamma-aminobutyric acidergic (GABAergic) interneurons that gate information flow into and out of the mPFC. Balance between excitation and inhibition (E/I) is critical for ensuring appropriate information processing and response generation by the mPFC. Cortical E/I imbalance is linked to stress-related neurocognitive disorders, for example, major depressive disorder (MDD) (3,4). Moreover, chronic stress itself precipitates E/I imbalance, causing enhanced inhibition of PNs in the rat mPFC (5). In this review, we discuss the interplay among stress, the mPFC, and interneurons in both humans and rodents to outline a prominent role for interneurons in stress-induced prefrontal adaptation.

MEDIAL PREFRONTAL NEUROANATOMY AND CELLULAR COMPOSITION

The structure and function of various subregions of the PFC in humans is derived from focal lesions and neuroimaging studies (6). The human mPFC is divided into dorsomedial (Brodmann areas [BAs] 8, 9, 10, 24, and 32) and ventromedial (BAs 10, 12, 14, 25) subregions. On the basis of structure, connectivity, and function, human BAs 24b, 32, and 25 are thought to correspond to the dorsal (anterior cingulate cortex [ACC], dorsal prelimbic [PrL]) and ventral (ventral PrL and infralimbic [IL]) components of the mPFC in rodents (7,8). The rodent mPFC is composed of 5 principal layers, including layers I (mostly axons), II, III, V, and VI. Unlike humans, rodent mPFC is agranular, lacking a definitive layer IV (9) [see (8–11) for more comparative anatomy information]. The PNs in the superficial (II/III) and deep (V/VI) layers of the mPFC project to subcortical structures (7). The ACC in rats projects to oculomotor sites and regions involved in spatial navigation (12), suggesting involvement in motor behaviors and foraging decision making (13). Additionally, there is evidence for ACC involvement in pain reactivity (8,14). The PrL is linked to limbic and cognitive functions, whereas the IL is thought to have more of a role in visceral and autonomic responses [see (7,12,15–17)]. There is also a high degree of intracortical connectivity across all layers (mainly between layers II and III) (18), indicating integration of

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cognitive information with appropriate physiological responding.

The mPFC is composed primarily of glutamatergic PNs (~80%–90% of neurons) (19). These PNs are under tight inhibitory control by multiple types of interneurons [~10%–20% of neurons (11,20)] (see Table 1). Parvalbumin (PV) cells (basket and chandelier cells) represent the majority of mPFC GABAergic interneurons (52%). PV neurons are typically fast spiking, and they gate output of the mPFC by inhibiting PNs via contacts at the soma (basket) or axon initial segment (chandelier) (19,21–24). Moreover, PV interneurons generate gamma rhythms and regulate theta oscillations in the mPFC, which is important for activating salient neural networks during context-specific tasks (21,22,25–29). Functionally, PV interneurons exhibit sustained firing during goal-driven attentional processing, coordinate PN activity, contribute to processing of task-relevant information in downstream projections (30), and facilitate working memory (31). Dendritic inhibition of PNs is provided by somatostatin (SST) neurons, which comprise slow-spiking Martinotti and intermediate fast-spiking/low-threshold spiking subclasses (19,32–34). The Martinotti neurons, which represent the majority of SST neurons, gate input onto apical dendrites of PNs (35–37) [for review, see (19,38,39)]. Notably, working memory remains intact following ablation of SST neurons, suggesting that this function is subserved by PV interneurons (given findings linking PV interneurons and working memory) and/or other interneuron populations (31). Activity of PNs is also regulated by interneuron-interneuron disinhibition via irregular-spiking vasoactive intestinal polypeptide (VIP) interneurons (a small percentage of cortical interneurons). These neurons preferentially inhibit Martinotti interneurons, and to a lesser extent basket PV interneurons, to promote PN excitation (19,23,32,36,40,41). There are several other interneuron subtypes in the mPFC, including those expressing cholecystokinin (CCK), neuropeptide Y (NPY), calretinin (CR), and calbindin (CB), with overlapping expression of other GABAergic phenotypic markers (e.g., PV, SST, or VIP) (42–44) (see Figure 1). In addition, SST neurons can be further subdivided depending on whether NPY or CR is also expressed (44). However, the function of the latter chemical-specific subsets of interneurons remain to be determined.

Interneurons express glucocorticoid receptors (GRs), suggesting the capacity to integrate systemic stress signals. While GRs are expressed in the majority of PV neurons, immunoreactivity is not present in CB-, SST-, or CCK-positive neurons, suggesting that individual interneuron populations may be differentially responsive to glucocorticoids (5). Notably, GRs are downregulated in PV interneurons following chronic stress, suggesting loss of glucocorticoid signaling in this population in the context of sustained adversity (5). In addition, corticotropin-releasing hormone-binding protein (CRH-BP) is predominantly expressed in GABAergic neurons in the prefrontal cortex, specifically SST and, to a lesser extent, CCK and PV interneurons (45) (see Figure 1). CRH-BP binds and modulates CRH cellular actions (45,46), suggesting that these interneurons may be receptive to stress signals communicated by ascending or intrinsic CRH neurons. Thus, there is growing appreciation for the role of interneurons in controlling the flow of information into and out of the mPFC and the impact of stress on these processes (Table 1).

PREFRONTAL REGULATION OF NEUROENDOCRINE RESPONSES

The hypothalamic-pituitary-adrenal (HPA) axis mediates neuroendocrine response to stress and facilitates physiological responding (2). Glucocorticoids are released into systemic circulation and bind to mineralocorticoid receptors (47) and GRs (48) in multiple bodily compartments, including the mPFC. The mPFC in turn controls stress reactivity. Lesions of the mPFC exacerbate Fos responses to restraint stress in the paraventricular nucleus of the hypothalamus (49,50) and increase adrenocorticotropic hormone (50,51) and corticosterone release (51), in a subregion-specific manner (49). Taken together, these studies are consistent with a central role of mPFC in processing glucocorticoid signals and regulating neuroendocrine responses to stress [for review, see (2)].

Central HPA axis regulation is mediated by glucocorticoid feedback via multiple sites, including the mPFC (51,52). Knockdown of PrL GR enhances HPA activation following acute restraint only, whereas IL GR knockdown exacerbates corticosterone responses to restraint, both acutely and following chronic stress (1). These findings suggest that following the transition from acute to chronic stress, the IL GR is selectively involved in regulation of HPA axis responses to novel stressors under chronic stress. Chronic stress decreases (53) or increases (54) cytosolic GR levels, increases FKBP5 (the cochaperone of HSP90 that negatively regulates GR sensitivity) (54), and decreases GR phosphorylation (53,54) in the mPFC as a whole, which may indicate impaired translocation and transcriptional activity of the GRs. Furthermore, the suppressive effect of dexamethasone on the HPA axis is abolished when infused directly into the mPFC or attenuated when administered systemically in chronically stressed rats, suggesting impaired regulation via the GRs (53). These preclinical studies suggest that the mPFC may modulate stress activation of the HPA axis via a GR-mediated mechanism, perhaps by modulating inhibitory tone; however, this hypothesis remains to be tested.

EFFECTS OF STRESS ON PREFRONTAL PHYSIOLOGY AND MORPHOLOGY

Acute stress appears to enhance excitation of PNs, while dampening input onto inhibitory neurons. For example, acute stress increases extracellular glutamate levels in the mPFC, as measured by microdialysis and in vivo voltammetric sampling (55–57). Similarly, foot shock stress increases the amplitude of excitatory postsynaptic currents (EPSCs) and depolarization-evoked glutamate release in isolated synaptosomes via a GR-dependent mechanism (58). In preadolescent and adolescent rats, acute stress increases surface expression of *N*-methyl-D-aspartate (NMDA) and alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors on the postsynaptic membranes, facilitating increased NMDA- and AMPA-mediated excitatory currents (59,60). Short exposure to a learned helplessness procedure also increases NMDA- and AMPA-mediated EPSC amplitude in activated PrL neurons (61). Additional studies using the same learned helplessness procedure demonstrated reduced amplitude of miniature EPSCs onto PV neurons in the PrL (62). Likewise, acute application of corticosterone decreases

Table 1. Interneurons of the mPFC in Rodents

	Top-Level Class									
	PV		SST		5-HT3aR					
	Subtype[a]		Subtype[a]		Subtype[a]					
	Basket	Chandelier	Martinotti	Non-Martinotti	VIP	CR	Neurogliaform	CCK	Calbindin	Reference
Morphology			Multipolar	Bitufted, small number of basket cells	Double bouquet, bipolar, and bitufted	Double bouquet, bipolar, multipolar; bitufted		Large and small basket cells; double bouquet	Multipolar; bitufted	(38,41,140)
Input	PNs, VIP	PNs	PNs, VIP	PNs	PNs	PNs	PNs	PNs	PNs	(19)
Short-Range Connectivity	Target other PVs (autaptic self-inhibition) and perisomatic region of PNs	Target axon initial segment of PNs; do not target spines	Project to LI and target LII/III PN dendrites; primarily located in LII/III and sparsely in LV/VI; also target other interneurons (non-self-inhibition)		Target somata of SST cells in LII/III and LV and to a lesser extent PVs; avoid PNs	Target dendritic shafts and spines	Target LII/III somata of PNs and apical tuft dendrites of LV PNs	Target somata of self and PNs; large basket cells do not target spines	Target dendritic shafts and spines	(38,141,142,143)
Physiology	FS	Most FS, but some that coexpress CRH are non-FS	RS, bursting, LTS, FS-like, or stuttering depending on layer, morphology, and type		Non-FS, irregular spiking	Unknown	Late-spiking	Non-FS	LTS	(38,144,145)
Function	Gain control network oscillation; temporal precision; feed-forward inhibition	Action potential initiation in PNs	Surround inhibition		Disinhibition	Unknown	GABA release via volume transmission and propagation via gap junctions	CB1R disinhibition; heterosynaptic learning	Unknown	(137,146)

Summary of major classes, subtypes, morphology, inputs to, local connectivity, intrinsic firing, and functional characteristics of interneurons. This table is not meant to be all-inclusive, but rather provides a synopsis of the present understanding of the major types of interneurons in cortex.

5-HT3aR, serotonin receptor type 3a; CR, calretinin; CB1R, cannabinoid receptor type 1; CCK, cholecystokinin; CRH, corticotropin-releasing hormone; FS, fast-spiking; GABA, gamma-aminobutyric acid; L, layer; LTS, low-threshold-spiking; PNs, pyramidal neurons; PV, parvalbumin; RS, regular-spiking; SST, somatostatin; VIP, vasointestinal peptide.

[a] See (34,41,140).

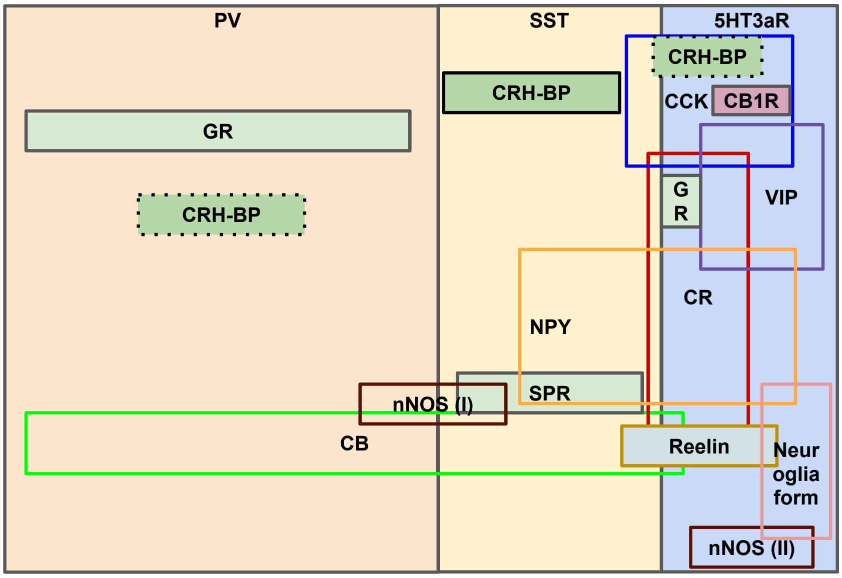

Figure 1. Molecular phenotyping of interneurons. There are three main classes of interneurons owing to differing developmental origin from the medial ganglionic eminence (somatostatin [SST], parvalbumin [PV]; >60% of interneurons) vs. caudal ganglionic eminence (serotonin receptor type 3a [5-HT3aR] ~30% of interneurons) (137,138). These populations are supplemented by interneurons originating from the preoptic area (e.g., neuropeptide Y [NPY]) and lateral ganglionic eminence (139). PV, SST, and vasoactive intestinal peptide (VIP) represent mostly nonoverlapping populations of interneurons. Each of these populations (PV, SST, or VIP), in turn, are coimmunoreactive for a number of molecular markers, as summarized in this figure. Please note in rat, calretinin (CR) expression is not thought to overlap with SST; however, in mouse cortex it does. Thus, we have represented CR immunoreactivity as slightly overlapped with SST. Figure based on (42,137). Please note while the three major classes of interneurons are illustrated to reflect approximate percentages of coimmunoreactive interneurons, the other boxes representing the various subtypes and receptor coimmunoreactive interneurons are not drawn to scale. The dotted line surrounding corticotropin-releasing hormone-binding protein (CRH-BP) also indicates more limited immunoreactivity. CB, calbindin; CB1R, cannabinoid receptor type 1; CCK, cholecystokinin; GR, glucocorticoid receptor; nNOS1, neuronal nitric oxide synthase I; SPR, substance p receptor.

miniature inhibitory postsynaptic currents in PNs and increases paired-pulse inhibition, further supporting disinhibition of mPFC output (63). Thus, acute stress seems to bring the mPFC "online," increasing excitation of PNs, to increase mPFC output and engage downstream targets (5) (Table 2).

A growing body of data suggests that the actions of chronic stress largely oppose those seen following acute stimulation. Chronic stress increases inhibition of IL PNs (5), in line with data suggesting chronic stress–induced decrements in prefrontal output and a switch to more habitual responding under chronic stress [as demonstrated in humans (64) and rodents (65)]. Yuen *et al.* (59) reported previously that chronic stress in preadolescence and adolescence decreases NMDA- and AMPA-mediated EPSCs in the mPFC through increased degradation of glutamate receptors. Adolescence is a developmental period marked by pruning of prefrontal glutamatergic synapses (66), which may account for the lack of an effect of stress on inhibitory neurons in this study. In adult male mice, chronic stress increases PV messenger RNA and immunoreactivity, increases pre- and postsynaptic markers of glutamatergic neurotransmission onto PV neurons, and decreases Fos activation in downstream targets of the mPFC in mice (more so in female than in male mice) (67,68). Chronic stress decreases GAD67 protein, perhaps driven by decreased SST and NPY, but with no effect on PV, VIP, CCK, CB, or CR (69). Conversely, a recent study from Czéh *et al.* (70) found reduced CR, PV, and CCK neuron number and reduced GABAergic neurotransmission in PNs in layers II/III of rat PrL and IL following an extended (9-week) chronic mild stress paradigm only in an "anhedonic" subpopulation of Wistar rats. These findings differ from GABA hyperactivity observed in layers V/VI after shorter (2-week) variable stress exposure in the absence of sucrose ingestion in Sprague Dawley rats (5).

Chronic stress also alters the structural integrity of mPFC neurons. Repeated restraint, chronic unpredictable stress, or chronic corticosterone induces a reversible loss of dendritic complexity in glutamatergic PNs in rodents (71–79). Loss of dendritic complexity is thought to reflect a reduction in the area available for excitatory synaptic connections, perhaps reflecting decreased excitability (80) and decreased synaptic plasticity (78,81). Dendritic retraction also predicts impaired PFC function (attentional set-shifting) in rodents (79). Moreover, chronic stress decreases asymmetric (excitatory) synapses and myelinated axons in the IL, further supporting decreased excitatory activity (82). Conversely, chronic restraint stress increases dendritic complexity and transcriptional activity of prefrontal GABAergic Martinotti interneurons, despite a decrease in GAD67-expressing somata (83). Chronic stress increases the number of inhibitory appositions and terminals onto glutamatergic output neurons across all layers of the IL, indicative of structural plasticity favoring enhanced inhibition (5). Taken together, the morphological and neurophysiological data suggest that chronic stress causes PN hypotrophy and interneuron hypertrophy and terminal sprouting, producing shifts in E/I balance in the mPFC (Table 3).

EARLY LIFE STRESS EFFECTS AND IMPLICATIONS FOR E/I BALANCE IN THE ADULT PREFRONTAL CORTEX

The developing brain is particularly vulnerable to stressors, and stress exposure can have effects that persist into adulthood, as discussed in Schmidt (84). In humans, there have been a number of gene × environment studies linking genetic sensitivity to stress (e.g., polymorphisms in FKBP5) and linking childhood trauma exposure to the severity of posttraumatic stress disorder symptoms in adulthood (85,86). In rodents, numerous models of early life and adolescent stress have been developed to better understand the mechanisms by which stress impacts the developmental trajectory through

Table 2. Effects of Acute Stress on the mPFC, by End Point

Manipulation	Type of Measurement	Effect	Reference
Neurophysiological and Membrane Effects			
Acute Stress—Tail Pinch, Restraint, or Forced Swim	Microdialysis and microelectrode sampling	↑ Extracellular glutamate levels	(55–57)
Foot Shock	Electrophysiology in synaptosomes	↑ Amplitude of EPSCs ↑ Depolarization-evoked glutamate release	(58)
Acute Stress in Adolescent Rats (Forced Swim, Restraint, Corticosterone IP Injection)	Western blot and electrophysiology	↑ NMDA and AMPA receptor expression ↑ NMDA- and AMPA-mediated EPSCs	(59–60)
Learned Helplessness	Electrophysiology	↑ NMDA- and AMPA-mediated EPSC amplitude	(61)
Learned Helplessness	Electrophysiology	↓ Amplitude of mIPSCs onto PV neurons	(62)
Acute Application of Corticosterone	Electrophysiology	↓ mIPSCs and ↑ paired-pulse inhibition	(63)
Neuroendocrine Effects			
shRNA GR Knockdown and Acute Restraint	Plasma corticosterone	↑ Corticosterone at 30 min for IL and 60 min for PrL	(1)
siRNA vGluT1 Knockdown and Acute Restraint	Plasma corticosterone and ACTH	↑ ACTH at 15 min and 30 min ↑ Corticosterone at 60 min	(16)
Lesion to mPFC and Acute Restraint	Plasma corticosterone and ACTH	↑ ACTH and corticosterone	(50,51)
Lesion to IL or PrL and Acute Restraint	Plasma corticosterone and ACTH, in situ hybridization	PrL: ↑ CRH mRNA in PVH ↑ Corticosterone and ACTH IL: ↑ PVN preautonomic activation	(49)
Pharmacological Stimulation of the mPFC and Acute Restraint and Hypoxia	Plasma corticosterone and ACTH	↓ ACTH and corticosterone to restraint ↑ Corticosterone but not ACTH to hypoxia	(147)
Effects in Humans			
Shock	fMRI and skin conductance from hand	↑ Higher skin conductance activation of vmPFC, hippocampus, and striatum	(148–150)

Summary of effects of acute stress on prefrontal mPFC-mediated neurophysiological, membrane, neuroendocrine, and autonomic end points in rodents and humans.

ACTH, adrenocorticotropic hormone; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; CRH, corticotropin-releasing hormone; EPSCs, excitatory postsynaptic currents; fMRI, functional magnetic resonance imaging; GR, glucocorticoid receptor; IL, infralimbic prefrontal cortex; IP, intraperitoneal; mIPSCs, miniature inhibitory postsynaptic currents; mPFC, medial prefrontal cortex; mRNA, messenger RNA; NMDA, *N*-methyl-D-aspartate; PrL, prelimbic prefrontal cortex; PV, parvalbumin; PVH, paraventricular nucleus of the hypothalamus; PVN, paraventricular nucleus; shRNA, short hairpin RNA; vGluT1, vesicular glutamate transporter 1; vmPFC, ventral medial prefrontal cortex; ↓, decreasing; ↑, increasing.

adulthood, as reviewed extensively in Molet *et al.* (87). For this review, we will focus attention on the effects of early life stress (ELS) and adolescent stress on interneurons in the rodent mPFC.

Though the effects of early life adversity on responses to stress in adulthood have been known for quite some time (88), the effects of ELS on interneurons has been explored only recently. These studies were made possible in large part by the advent of new tools for visualizing interneuron populations. Following early life separation stress in rodents (*Octodon degus*), CB immunoreactivity decreases in ACC interneurons at puberty (89). In adulthood, CB levels in the ACC normalize, while PV immunoreactivity increases. There were no effects of separation on PrL or IL interneurons, indicating temporal and regional specificity of ELS actions (89). Maternal separation in rats, however, decreases PV protein and immunoreactivity in the PrL of adolescents, but not in the ACC (90). The discordance between these two studies might be explained by the difference in rodent species used. Subsequent studies in adolescent rats showed that maternal separation increases the NR2A subunit and postsynaptic density 95 expression in the mPFC, leading to loss of PV immunoreactivity (91–94). Notably, maternal separation also induces dendritic atrophy and decreases spine density in layers II/III PNs, which could have implications for the processing of information coming into the mPFC (92).

A double-hit model, combining isolation stress with a perinatal NMDA receptor antagonist (MK801) injection (to impair later stages of neocortical development), increases dendritic complexity in SST neurons (95,96). The density of vGlut1-positive divided by the density of vGat-positive puncta also increases in the mPFC of double-hit mice, interpreted as an increase in E/I balance (96). In contrast to the aforementioned studies, social isolation increases the number of PV-expressing neurons, perineuronal nets (PNNs), and PV neurons surrounded by PNNs in the IL, which is reversed in the double-hit mice (96). Similarly, chronic mild stress during adolescence increases the number of PV neurons surrounded by PNNs in the PFC of adult mice (97). Following neonatal exposure to ketamine, which similarly disrupts NMDA receptor function as the previously discussed double-hit model, PV expression increases in the boutons of PV interneurons and

Table 3. Effects of Chronic Stress on the mPFC, by End Point

Manipulation	Type of Measurement	Effect	Reference
Neurophysiological and Membrane Effects			
Chronic Variable Stress	Electrophysiology	↑ mIPSCs in layer 5 IL	(5)
Chronic Variable Stress	Protein immunohistochemistry	↑ Glutamatergic synapses onto PV neurons in IL	(5)
Repeated Restraint or Chronic Variable Stress in Adolescence	Electrophysiology and Western blot	↓ NMDA- and AMPA-mediated EPSCs ↓ Glutamate receptors	(59)
Repeated Restraint	Golgi, lucifer yellow intracellular loading	↓ Dendritic complexity of pyramidal neurons (apical dendrite length, branch number, intersection number)	(71–74,76–79)
Repeated Restraint	Immunohistochemistry and RT-PCR	↓ Number of somata but ↑ dendritic arborization in SST and calretinin interneurons ↑ In synaptophysin, NCAM, and GABAa1 receptor	(83)
Chronic Mild Stress	Immunohistochemistry and RT-PCR	↑ PV mRNA and immunoreactivity ↑ Synaptic markers of glutamatergic input onto PV neurons ↓ Fos protein in downstream targets of the mPFC	(67,68)
Chronic Mild Stress	Electrophysiology in "anhedonic" subpopulation of rats	↓ GABAergic neurotransmission in layers II/III of PrL and IL	(70)
Chronic Mild Stress	Immunoreactivity in "anhedonic" subpopulation of rats	↓ CR, PV, and CCK	(70)
Chronic Water Immersion	Immunoprecipitation with Western blot, in situ hybridization	↓ Cytosolic GR (nuclear unchanged)	(53)
Chronic Variable Stress	Immunohistochemistry	↓ GR (nuclear) in PV neurons	(5)
Chronic Unpredictable Stress	Immunohistochemistry and RT-PCR	↓ GAD67 protein ↓ SST and NPY mRNA No effect on VIP or CCK mRNA No effect on PV, CR, or CB protein	(69)
Chronic Social Defeat Stress	Immunohistochemistry	↓ Zif268 and arc in PrL and IL in "susceptible" mice	(118)
Chronic Social Defeat Stress	1H-[13C]-nuclear magnetic resonance spectroscopy together with infusion of [1,6-13C2] glucose	↓ Glutamate, glutamine, *N*-acetylaspartate, and taurine ↓ Glutamatergic and GABAergic metabolism and neurotransmitter cycling ↓ Gad1	(116)
Neuroendocrine Effects			
shRNA GR Knockdown Followed by Chronic Variable Stress—Response to Acute Restraint	Plasma corticosterone	IL: ↑ corticosterone at 30 min exacerbated by CVS PrL: ↓ corticosterone at 60 min	(1)
siRNA vGluT1 Knockdown and Chronic Variable Stress—Response to Acute Restraint	Plasma corticosterone and ACTH	↓ ACTH at 15 min ↑ Corticosterone at 0, 30, and 60 min	(16)
Effects in Humans			
Prolonged Psychosocial Stress	Hemoglobin spectroscopy	Decreased activity of the mPFC	(103)
Chronic Occupational Stress	fMRI	Uncoupling of connectivity between anterior cingulate cortex and the amygdala	(110)
Prolonged Stress	fMRI	Connections between dorsal and ventral mPFC with the amygdala reduced, inversely correlated with severity in female subjects	(135)

Summary of effects of chronic stress on prefrontal mPFC-mediated neurophysiological, membrane, neuroendocrine, and autonomic end points in rodents and humans.

ACTH, adrenocorticotropic hormone; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; CB, calbindin; CCK, cholecystokinin; CR, calretinin; CVS, chronic variable stress; EPSCs, excitatory postsynaptic currents; fMRI, functional magnetic resonance imaging; GABA, gamma-aminobutyric acid; GR, glucocorticoid receptor; IL, infralimbic prefrontal cortex; mIPSCs, miniature inhibitory postsynaptic currents; mPFC, medial prefrontal cortex; mRNA, messenger RNA; NCAM, neural cell adhesion molecule; NMDA, *N*-methyl-D-aspartate; NPY, neuropeptide Y; PrL, prelimbic prefrontal cortex; PV, parvalbumin; RT-PCR, real-time polymerase chain reaction; shRNA, short hairpin RNA; siRNA, small interfering RNA; SST, somatostatin; vGluT1, vesicular glutamate transporter 1; VIP, vasoactive intestinal polypeptide; ↓, decreasing; ↑, increasing.

decreases in the cell bodies of PV interneurons, and there is a PV-selective decrease in Npas4. Notably, Npas4 is a transcription factor that regulates E/I balance and promotes excitation of interneurons and is expressed in PV, SST, and VIP interneurons (98,99). Adolescent stress decreases PV immunoreactivity in the PrL of male mice, whereas it increases PV immunoreactivity and PNN coverage in the PrL and IL of female mice in adolescence (97). When Npas4 knockdown in

Table 4. Effects of Early Life Stress on the mPFC, by End Point

Manipulation	Type of Measurement	Effect	Reference
Neurophysiological and Membrane Effects			
Maternal Separation	Immunohistochemistry	↓ Calbindin immunoreactivity in ACC at puberty ↑ PV immunoreactivity in ACC in adulthood	(89)
Maternal Separation	Immunohistochemistry, Western blot	↓ PV immunoreactivity in PFC in adolescence	(90)
Maternal Separation	Immunohistochemistry, Western blot	↑ NR2A subunit in PrL ↓ PV immunoreactivity in PrL in adolescence	(91)
Maternal Separation	Golgi-Cox staining	↑ Dendritic atrophy ↓ Spine density in layers II/III of glutamatergic neurons in the mPFC	(92)
Maternal Separation	Immunohistochemistry, Western blot	↑ PSD-95 expression in mPFC ↑ NR2A+ cells in PrL and IL ↓ PV immunoreactivity in PrL and IL in adolescence	(93)
Social Isolation (Weaning Until Adulthood)	Immunohistochemistry	↑ PV-expressing neurons ↑ PNNs ↑ PV neurons surrounded by PNNs in the IL in adulthood	(95)
Perinatal NMDA Receptor Antagonist (MK801) Injection (PND 7) + Social Isolation (Weaning Until Adulthood)	Immunohistochemistry	↑ Density of vGlut1/density of vGat+ puncta in mPFC in adulthood	(96)
Chronic Mild Stress (Adolescence)	Immunohistochemistry	↑ PV+ neurons surrounded by PNNs in the IL of female mice in adolescence ↓ PV immunoreactivity in the PrL of male mice in adolescence	(97)
Chronic Mild Stress (Adolescence) ± Npas4 Deficiency	Immunohistochemistry, PCR	↑ PNN coverage of PV+ cells in WT male mice No change in Npas4 HET mice ↑ vGat in stressed Npas4-deficient mice	(100)
Neonatal Ketamine Exposure	Immunohistochemistry, Western blot	↑ PV protein expression (WB) in PFC ↓ PV+ somata in PFC ↑ PV+ boutons in PFC ↓ PV+ cells expressing Npas4	(99)

Summary of effects of early life stress on prefrontal mPFC-mediated neurophysiological, membrane, neuroendocrine, and autonomic end points in rodents and humans.

ACC, anterior cingulate cortex; HET, heterogeneous; IL, infralimbic prefrontal cortex; mPFC, medial prefrontal cortex; NMDA, *N*-methyl-D-aspartate; PCR, polymerase chain reaction; PFC, prefrontal cortex; PND, postnatal day; PNNs, perineuronal nets; PrL, prelimbic prefrontal cortex; PSD, postsynaptic density; PV, parvalbumin; vGat, vesicular gamma-aminobutyric acidergic transporter; vGluT1, vesicular glutamate transporter 1; WB, Western blot; WT, wild-type; ↓, decreasing; ↑, increasing.

mice is combined with adolescent stress, the stress-induced increase of PNN coverage is blocked, indicating an important gene × environment susceptibility to the effects of stress that can have long-term implications for neurocognitive status in adulthood (100). Thus, although specific effects are not always consistent across all models (see Table 4), ELS has profound effects on the development of prefrontal inhibitory circuitry and can have lasting effects on E/I balance.

CHRONIC STRESS EFFECTS ON PREFRONTAL FUNCTIONAL CONNECTIVITY

Local networks within the mPFC fine-tune the delicate balance of E/I signaling that ultimately regulates activity of output neurons. Perturbations of E/I balance in the mPFC, as well as altered connectivity in specific mPFC output circuits, are implicated in a variety of pathological affective states (101,102). Additionally, chronic psychosocial stress affects local networks regulating activity within the mPFC. For instance, prolonged psychosocial stress decreases activity of the mPFC as measured by hemoglobin spectroscopy (103). Activity within a specific region, BA 25, associates with sadness in healthy control subjects (104), as well as pathological depression (105). Importantly, increased regional cerebral blood flow and glucose metabolism in BA 25 is reduced by several antidepressant therapies, including deep brain stimulation (102,105). Furthermore, mPFC postmortem analyses indicate that changes in gene expression related to E/I balance occur in patients with depression, as transcripts related to glutamatergic and GABAergic synaptic transmission are increased in the ACC (106,107). Ultimately, changes in local E/I balance are manifest in the activity of glutamate projections from mPFC. Both human and rodent studies have examined mPFC circuits that may precipitate maladaptive stress responses (76,104). In particular, circuits emanating from mPFC that target subcortical limbic regions, including the amygdala, thalamus, and basal forebrain, have been implicated in mood and anxiety disorders (108,109).

Numerous functional imaging studies highlight the importance of mPFC-amygdala circuits for stress-related processing (101). Resting-state functional magnetic resonance imaging indicates that ACC and amygdala connectivity is uncoupled in individuals experiencing chronic occupational stress, which correlates with impaired ability to downregulate negative emotion (110). Functional changes in circuit interactions due to chronic stress are similar to abnormalities in

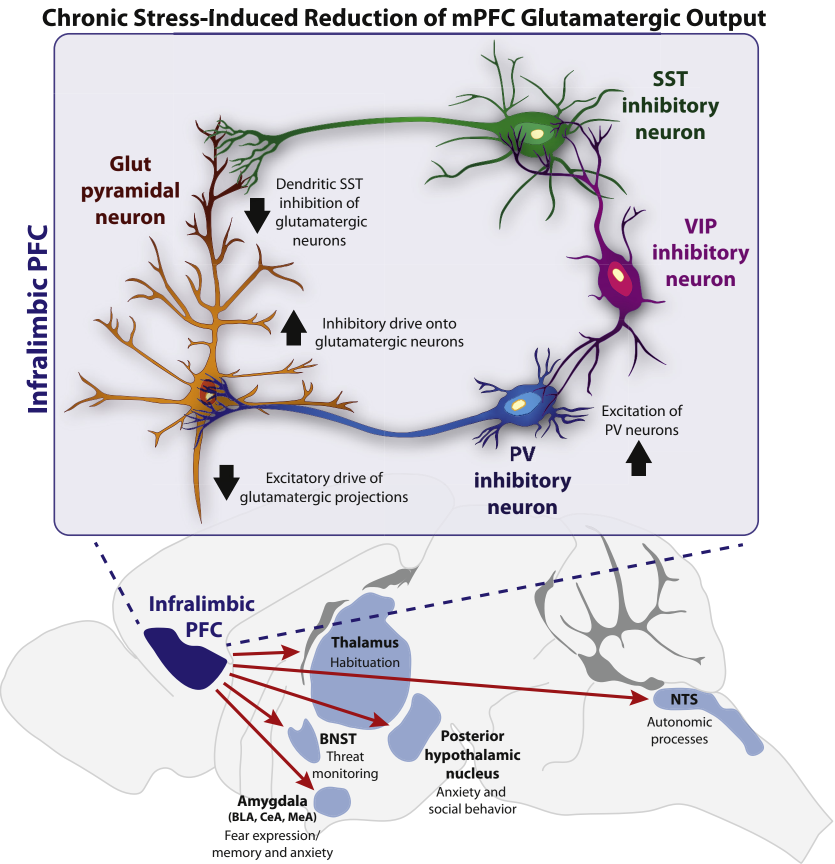

Figure 2. Chronic stress-induced reduction of medial prefrontal cortex (mPFC) glutamatergic output. Schematic of proposed high-level mechanistic model underlying chronic stress–induced hyperinhibition of mPFC glutamatergic (glut) pyramidal neurons (PNs). The inset shows proposed microcircuitry changes among interneurons and PNs of the infralimbic mPFC. We propose that under chronic stress, somatostatin (SST) neurons provide reduced dendritic inhibition of glut PNs, reducing filtering of information flow into the prefrontal cortex. Work from our lab points to hyperinhibition of glut PNs perhaps by perisomatic-located parvalbumin (PV) interneurons. Further work is needed to better understand the microcircuit changes within the mPFC including alterations to other interneuron subtypes, if any (e.g., calretinin, calbindin, cholecystokinin, and/or vasoactive intestinal polypeptide), and mechanism by which chronic stress increases inhibition [e.g., attenuated glucocorticoid receptor brake on PV activity, as our data suggest (5)]. Enhanced inhibitory drive onto glutamatergic PNs in turn reduces prefrontal innervation of downstream targets, such as the thalamus, bed nucleus of the stria terminalis (BNST), amygdala (including basolateral amygdala [BLA], medial amygdala [MeA], and central nucleus of the amygdala [CeA]), posterior hypothalamic nucleus, and/or nucleus of the solitary tract (NTS). While we propose reduced connectivity of the infralimbic mPFC with downstream targets under chronic stress, it is possible that some connections may become selectively enhanced. Further examination of the circuit-level changes under and following chronic stress will help elucidate the directionality of connectivity changes between the infralimbic mPFC and downstream targets, if any, illustrated by the red arrows in this figure. The existing literature indicates that interneurons may be integral to the transition from adaptation to pathology, thus better understanding the mechanisms underlying this transition and specific neurocircuit effects, is vital to developing more effective treatments for stress-related diseases. VIP, vasoactive intestinal peptide.

mPFC connectivity observed in patients with MDD (101,108). Recent data also highlight the importance of GABA in shaping prefrontal-amygdala connectivity, as high GABA content in the mPFC is associated with low inhibitory strength of top-down connection specifically between the mPFC and amygdala (111). Furthermore, functional connectivity between mPFC and the amygdala may represent a biomarker for antidepressant treatment response, as decreased resting-state mPFC-amygdala functional connectivity is observed only in pharmacotherapy-resistant patients (112).

There are a number of instances of coherence between rodent and human studies (113–115). Multimodal functional imaging/spectroscopy studies in mice indicate that chronic psychosocial stress (social defeat) results in mPFC-amygdala functional connectivity reductions analogous to those described in depression and anxiety (113). Repeated social stress reduces metabolic activity in mPFC neurons and overall levels of glutamate (116). In experimental models, the balance of mPFC activity can be directly manipulated to examine causal relationships between altered mPFC outflow and chronic stress responsiveness. In fact, reduction of glutamate outflow from ventral mPFC leads to exaggerated glucocorticoid responses to chronic stress (16). These studies, and others specifically targeting glucocorticoid signaling in subregions of the ventral mPFC, have pointed to the IL as a primary mediator of chronic stress responsiveness (1,16).

Primary outputs of PrL include the striatum, midline thalamus, amygdala, bed nucleus of the stria terminalis, hypothalamus, and brainstem monoaminergic nuclei such as the raphe (12). The IL also targets the midline thalamus, bed nucleus of the stria terminalis, and hypothalamus but more diversely innervates the amygdala, while also targeting brain stem autonomic centers, including the nucleus of the solitary tract (12,17). Specific cell groups in the anterior bed nucleus of the stria terminalis and posterior hypothalamus have been implicated in conveying the influence of PrL and IL, respectively, to neurosecretory neurons of the paraventricular nucleus (15,117). Collectively, significant strides have been made toward understanding prefrontal control of stress-related behaviors, while a relatively few, but growing, number of studies have examined how specific mPFC projections are altered by exposure to chronic stress, in rodents. Chronic social defeat stress decreases mPFC activity, and activation in the mPFC of susceptible animals reverses social defeat–induced social avoidance and anhedonia (118). Subsequent studies found that CCK-B, induced by delta FosB, in the PrL-nucleus accumbens circuit mediates depression-like behavior after chronic defeat (119). Furthermore, chronic defeat decreases the strength of the PrL-nucleus accumbens circuit (120). Other studies have found that chronic social defeat induces preferential activation of GABA neurons in the dorsal raphe by the ventral mPFC (encompassing both PrL and IL) and that activation of this circuit in the presence of an aggressor's social cues increases subsequent social avoidance (121). Another recent study combining electrophysiology, machine learning, and targeted chemogenetics after chronic social defeat generated a model of mPFC-mediated circuit dysfunction, potentially accounting for susceptibility to chronic stress–induced behavioral disturbances. Specifically, chronic stress disrupts mPFC-dependent coordination of synchronized activity between the amygdala and ventral tegmental area (122), which is reversible by activating ventral mPFC–amygdala connection, identifying an intervention to promote behavioral resilience following chronic stress (122). Similarly, activation of prefrontal PNs restores the PFC-amygdala inhibitory neuron connection, restores behavior, and rescues feed-forward inhibition of the amygdala after prolonged stress (123). A greater understanding of prefrontal E/I balance, inhibitory × pyramidal neuron interactions, and functional interactions with specific cell groups of the limbic forebrain is needed to shed light on numerous aspects of adaptation/maladaptation to chronic stress.

DISCUSSION

We have attempted to highlight the considerable complexity of the interneuron network and the critical importance of interneuron subtype, location, connectivity, stress duration (acute vs. chronic), and timing (early life vs. adulthood) on E/I balance in the mPFC. The importance of interneurons in prefrontal cortical signaling suggests a prominent role in promoting adaptation and perhaps in driving pathologies. The adaptive nature of chronic stress exposure bears consideration, in that many of the behavioral and physiological reactions to chronic stress are appropriate to the "newly hostile" world experienced by the individual. It seems appropriate to limit the potential for harm (rely on what is safe, limit potential risk, ready physiological defense mechanisms) when the environment is unsafe; appraisal decisions that the mPFC is uniquely geared to make. Pathological processes may well disrupt the appraisal process, driving "out-of-context" decisions that promote behaviors ill-suited for nonstress conditions (124). The adaptation and pathology distinction is important, given that chronic stress experiments in rodents may largely address adaptation, whereas human studies address pathology.

It is important to consider the GABAergic deficit of MDD hypothesis, given that stress is thought to precipitate or exacerbate neuropsychiatric disorders, such as MDD (3,125). This hypothesis is based largely on studies of human postmortem tissue or proton magnetic resonance spectroscopy that identified deficits in GAD67, the GABA-synthesizing enzyme (126,127); decreased GABA concentrations (128–131); reduced numbers of CB (but not PV) neurons; and reduced SST gene expression (132–134) in the neocortices of MDD patients. For more discussion of the GABA deficit hypothesis, we recommend excellent reviews that extensively cover this topic (3,125). Our data, along with other cited data in this review, suggest that chronic stress reduces functional connectivity of the IL with downstream targets as a result of hyperinhibition of PNs. These data contrast with evidence for GABAergic hypofunction seen in human disease states (see Figure 2). It is important to consider that the GABAergic deficit in MDD occurs in the context of pathology, not adaptation, a likely product of chronic stress in the absence of pathology. Thus, though MDD is thought to be a stress-associated disorder, the circuit-level activity of responses to chronic stress may differ from MDD, as the brain transitions from an adaptive to a pathological state. There is work in humans that supports the finding of reduced PFC connectivity under chronic stress (103,110,135), once again highlighting the importance of distinguishing adaptive stress responses from pathologies. It is important to also consider that pathological reductions in GABA in MDD are linked to reduced activation of specific interneuron subtypes (e.g., SST neurons) (136). Given the complexity of cortical GABAergic neurons, future studies need to focus on defined interneuron arrangements affected under adaptive versus pathological conditions.

Overall, emerging data do not support a singular mechanism linking brain stress coping processes and pathologies, such as MDD, and indeed they highlight the enormous complexity of factors that influence how the brain responds to stress. It will be critical to understand the long-term transition from adaptation to pathology to get at the core processes that drive stress-related diseases. Indeed, the literature suggests that interneurons may be instrumental for the adaptation-pathology transition. Understanding transitions in interneuron control of cortical activation may help predict or treat stress-related disorders in the adaptive, as opposed to pathological, phases of disease progression. The addition of interneuron dysregulation is an important conceptual advance in our understanding of stress adaptation and pathology, and there is no doubt that interneurons already are and will continue to remain a target of intense study as the field moves forward. In this regard, future studies will need to strongly consider the interneuron type, connectivity, and location (both layer- and subregion-specific), paired with attention to stressor duration (acute vs. chronic) and developmental timing (early life [e.g., prenatal, perinatal, preadolescence, adolescent] and adult stress), as each of these factors has profound implications for stress effects on prefrontal E/I balance.

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