Neuroscience and Biobehavioral Reviews 105 (2019) 39–51

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

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

Review article

# Prefrontal excitatory/inhibitory balance in stress and emotional disorders: Evidence for over-inhibition

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ARTICLE INFO

*Keywords:*
Stress
Anxiety
Depression
Prefrontal cortex
GABA
Glutamate
Parvalbumin

ABSTRACT

Chronic stress-induced emotional disorders like anxiety and depression involve imbalances between the excitatory glutamatergic system and the inhibitory GABAergic system in the prefrontal cortex (PFC). However, the precise nature and trajectory of excitatory/inhibitory (E/I) imbalances in these conditions is not clear, with the literature reporting glutamatergic and GABAergic findings that are at times contradictory and inconclusive. Here we propose and discuss the hypothesis that chronic stress-induced emotional dysfunction involves hypoactivity of the PFC due to increased inhibition. We will also discuss E/I imbalances in the context of sex differences. In this review, we will synthesize research about how glutamatergic and GABAergic systems are perturbed by chronic stress and in related emotional disorders like anxiety and depression and propose ideas for reconciling contradictory findings in support of the hypothesis of over-inhibition. We will also discuss evidence for how aspects of the GABAergic system such as parvalbumin (PV) cells can be targeted therapeutically for reinstating activity and plasticity in the PFC and treating stress-related disorders.

## 1. Introduction: the other end of the spectrum

The prefrontal cortex (PFC) relies on a balance between excitatory and inhibitory neurotransmission for a range of higher-order functions, such as working memory, planning, decision-making, error monitoring, and emotional regulation (Fuster and Bressler, 2015). This excitatory/inhibitory (E/I) balance arises from a complex interplay of heterogeneous glutamatergic and GABAergic neurons interacting within a local circuit. In particular, GABAergic interneurons that express the calcium-binding protein parvalbumin (PV) are a major regulator of E/I balance as they represent more than 50% of the total population of GABAergic interneurons in the frontal cortex and provide strong, fast-spiking inhibitory control near or on the cell bodies of excitatory pyramidal cells (Ferguson and Gao, 2018a; Kubota et al., 1994). Consequently, PV cells play an important role in prefrontal-dependent emotional and cognitive behaviors (Ferguson and Gao, 2018a).

Dysregulations in prefrontal E/I balance have frequently been implicated in neuropsychiatric disorders such as schizophrenia, autism spectrum disorders, and intellectual disabilities. Most of these disorders are thought to involve deficient inhibitory control, largely mediated by deficiencies in PV-expressing GABAergic interneurons. On that subject, readers are referred to several comprehensive review articles about the psychopathology of reduced PV cell activity and over-excitation in prefrontal circuits (Ferguson and Gao, 2018a; Nelson and Valakh, 2015; Selten et al., 2018; Yizhar et al., 2011). The other end of the E/I spectrum – over-inhibition and reduced circuit activity – has not been as extensively studied. Increasing evidence suggests that the PFC is hypoactive in stress-induced affective disorders like anxiety and depression, and that the GABAergic system and PV cells play an important role in the stress response and emotional dysfunction (Maguire, 2014; McKlveen et al., 2016; Shepard et al., 2016; Shepard and Coutellier, 2018). Given the well-established link between chronic stress exposure and neuropsychiatric disorders like depression and anxiety (Duman and Monteggia, 2006; Kendler et al., 1999; Mineur et al., 2006), understanding the mechanistic connection between stress and emotional dysfunction is critical to developing effective treatments for these disorders.

The purpose of this review is to synthesize research about E/I imbalance in stress and emotional dysfunction in support of the hypothesis that over-inhibition in the PFC, in part mediated by increased activity of prefrontal PV cells, is a contributing factor to stress-related affective neuropsychiatric disorders. We will discuss glutamatergic and GABAergic dysfunction in stress and affective disorders with a specific focus on stress-induced anxiety and depression. We will conclude with evidence supporting the GABAergic system as a therapeutic target for reinstating activity and plasticity in the PFC.

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https://doi.org/10.1016/j.neubiorev.2019.07.024
Received 11 April 2019; Received in revised form 31 July 2019; Accepted 31 July 2019
Available online 01 August 2019

Included throughout the review will be a discussion of sex differences in the context of chronic stress and glutamatergic/GABAergic dysfunction. Women are at an increased risk for developing anxiety and depression in comparison to men, and also show higher rates of comorbidity between these disorders (de Graaf et al., 2002d; Kessler et al., 2012). Rodent studies show that the PFC responds to stress in a sex-specific manner (Bale and Epperson, 2015; Hodes et al., 2015; Seney and Sibille, 2014). As we will discuss, variations in the sensitivity of the prefrontal GABAergic system to stress may underlie some of the sex differences in stress vulnerability and the prevalence of emotional disorders.

## 2. Cellular regulators of prefrontal E/I balance

The PFC is involved in emotional expression and regulation (Dixon et al., 2017) and cognitive behaviors (Fuster and Bressler, 2015). The PFC is also highly stress-responsive (Arnsten, 2009; McEwen et al., 2016). The rodent medial PFC (mPFC) is subdivided into three subregions: the anterior cingulate cortex (ACC), prelimbic (PL) cortex, and infralimbic (IL) cortex. In the human brain, these subregions are thought to be homologous to Brodmann areas 24b, 32, and 25, respectively (McKlveen et al., 2015). The PL and IL cortices in particular show high connectivity with limbic regions of the brain such as the nucleus accumbens and amygdala and therefore play a substantial role in modulating emotional behaviors (Adhikari et al., 2015; Wood et al., 2019). The subregions of the PFC have distinct functional connectivity with other brain regions and thus differing roles in neuropsychiatric disorders (Heidbreder and Groenewegen, 2003). An investigation into the different subregions of the PFC is beyond the scope of this review, as many of the studies referenced here examine the PFC as a whole, but is nevertheless an important consideration when parsing the nature of prefrontal E/I balance.

In order to understand E/I imbalances that occur in stress and emotional disorders, it is first helpful to examine how E/I balance in the PFC is developed and regulated. E/I balance is established during adolescence and relies heavily on maturation of the GABAergic system. As we will discuss, some of the mechanisms behind this process may provide insight into how E/I balance is disrupted in stress and affective dysfunction and may also provide insight into novel therapeutic approaches for rebalancing glutamatergic and GABAergic transmission in stress-induced affective disorders.

Postnatal life is characterized by critical periods of plasticity in which brain regions show heightened activity-dependent sensitivity to experience with long-lasting effects. Like other young brain regions, the immature PFC is hyper-excitable and plastic. As development proceeds, the prefrontal GABAergic system matures to introduce more inhibitory control and stability into the network (Bavelier et al., 2010; Le Magueresse and Monyer, 2013). The mechanisms for increased network stability are numerous (Takesian and Hensch, 2013), but they include increased glutamatergic inputs onto prefrontal PV interneurons that enables greater inhibitory control over pyramidal cells (Caballero et al., 2016). PV immunoreactivity and mRNA/protein expression increases during juvenile and adolescent development (Caballero et al., 2014a; Ueda et al., 2015; Ueno et al., 2017). GABAergic maturation also includes increases in perineuronal net (PNN) density (Takesian and Hensch, 2013). PNNs are extracellular matrices of proteins that preferentially surround PV cells and enhance their excitability (Balmer, 2016). In the visual cortex, PNNs have been shown to increase inhibitory GABAergic currents during the critical period of plasticity (Liu et al., 2013). PNNs also protect PV cells from oxidative stress arising from their fast-spiking properties (Cabungcal et al., 2013). In the PFC, PNN density increases in the transition from juvenile life to adolescence (Baker et al., 2017; Ueno et al., 2017) and in the transition from adolescence to adulthood (Page and Coutellier, 2018). Increased PV cell activity and PNN coverage of PV cells is associated with the closing of critical periods of plasticity (Umemori et al., 2015) and the functional maturation of brain regions like the PFC. In adulthood, PV cells continue to play a major role in regulating the inhibitory side of E/I balance and thus in regulating prefrontal-dependent cognitive and emotional functions (Ferguson and Gao, 2018a).

Though much of the work described above was conducted in male rodents, biological sex is a highly relevant factor for the mechanisms of E/I maturation during adolescence. Ovariecotomy prior to puberty onset blocks the increase in inhibitory neurotransmission in the frontal cortex of female mice, and pre-pubertal hormone treatment accelerates GABAergic maturation (Piekarski et al., 2017). The adolescent increase in PV protein expression and cell counts appears to occur earlier in females than in males (Du et al., 2018). At least in the hippocampus, an adolescent increase in PV expression in females is estradiol-dependent (Wu et al., 2014), though it is unknown whether this is also true for the PFC. Adolescent development of E/I balance also involves pruning of excitatory synapses in the PFC (Hoftman and Lewis, 2011; Petanjek et al., 2011). Loss of prefrontal excitatory synapses during adolescence is more pronounced in females according to rodent studies (Drzewiecki et al., 2016; Koss et al., 2014), and greater thinning of the PFC during adolescence correlates with increased emotional regulation abilities in women (Vijayakumar et al., 2014). In addition to synaptic pruning, loss of non-GABAergic cells also occurs in the PFC during adolescence (Markham et al., 2007; Willing and Juraska, 2015). Neuronal loss is more pronounced in females during this developmental period due to the effect of ovarian hormones (Koss et al., 2015).

In summary, the development of E/I balance in the PFC is necessary for the maturation of PFC-dependent functions, including emotional regulation. E/I balance involves GABAergic stabilization largely mediated by PV-expressing interneurons, though other GABAergic cell types like calretinin-expressing neurons are also involved (Caballero et al., 2016, 2014a). We will next discuss glutamatergic and GABAergic dysfunction in stress-induced affective disorders like anxiety and depression. These conditions appear to involve reduced activity and plasticity in the PFC, possibly through enhanced activity or strengthening of the same mechanistic brakes that stabilize E/I balance during development, such as PV cells and PNNs.

## 3. E/I imbalances in stress and affective disorders

Chronic stress in adulthood perturbs mature E/I balance in the PFC and contributes to emotional disturbances like those in depression and anxiety (Lener et al., 2017; Wieronska et al., 2011), though the precise nature and time course of this imbalance is far from clear. In this section, we will summarize research on glutamatergic and GABAergic disturbances in studies of adult chronic stress and affective disorders. As is evident from research on the topic (Table 1 and Table 2), there are conflicting and occasionally paradoxical results about glutamatergic and GABAergic dysfunction in chronic stress and emotional disorders. Some of these differences may be attributable to sex differences, while others might relate to variations in the stress paradigm or rodent model used. We propose here that chronic stress-induced affective disorders involve over-inhibition of the PFC due in part to cell type-specific GABAergic dysfunction. We will also discuss ideas that may help reconcile contradictory and inconclusive findings about the nature of E/I imbalance following chronic stress.

Glutamatergic and GABAergic alterations have been observed in human studies of emotional disorders and behaviors, including depression, panic disorder, post-traumatic stress disorder (PTSD), and trait anxiety (Table 1), as well as in rodent models of emotional disorders (Table 2). The majority of these disorders are modeled using chronic stress paradigms to evoke depression- and anxiety-related behaviors. It is important to note that depression, anxiety, and other emotional disorders are frequently co-morbid but nevertheless have distinct and differentiating features. For instance, depression can involve despair-related behaviors (measured by tests such as tail suspension and forced swim in rodents), anhedonia (measured by the

**Table 1**
Glutamatergic and GABAergic dysfunction in human studies of emotional disorders including depression, anxiety, and PTSD. The findings in this non-exhaustive list are limited to adults and to the prefrontal cortex.

| Model | Sex | Excitation-related Findings | Inhibition-related Findings | Behavioral Phenotype | Reference |
|---|---|---|---|---|---|
| Human Studies | | | | | |
| Post-mortem tissue from clinically depressed patients | unspecified | ↓ immediate early gene expression | Not tested | N/A | (Covington III et al., 2010) |
| Post-mortem tissue from clinically depressed patients | Men and women (not analyzed by sex) | ↓ NR2A, NR2B, and PSD-95 expression | Not tested | N/A | (Feyissa et al., 2009) |
| Post-mortem tissue from clinically depressed patients | Men and women (not analyzed by sex) | Not tested | ↓ GAD67 expression | N/A | (Karolewicz et al., 2010) |
| Magnetic resonance spectroscopy (MRS) in major depression patients | Men and women (not analyzed by sex) | ↓ glutamate/glutamine levels | ↓ GABA levels | Met DSM-IV criteria for current major depressive episode, high score on depression rating scale | (Hasler et al., 2007) |
| MRS in panic disorder patients | Women | Not tested | ↓ GABA levels | High scores on panic disorder severity scale and state anxiety level test | (Long et al., 2013) |
| MRS in healthy subjects | Men and women | | ↑ GABA levels correlated with ↑ trait anxiety; no sex differences | Trait anxiety measurements | (Delli Pizzi et al., 2016) |
| MRS in PTSD patients | Men and women (not analyzed by sex) | Not tested | ↑ GABA levels | High score on PTSD measurement scale | (Michels et al., 2014) |
| Post-mortem tissue from clinically depressed patients | Men and women (not analyzed by sex) | Not tested | ↓ SST expression | N/A | (Sibille et al., 2011) |
| Post-mortem tissue from clinically depressed patients | Men and women (not analyzed by sex) | Not tested | ↓ CB cell counts | N/A | (Rajkowska et al., 2007) |

sucrose preference test), and/or a lack of personal care/grooming (as indicated by the splash test and coat condition in rodents) (Hu et al., 2017). Similarly, subdomains of anxiety can manifest as different results in various anxiety tests, such as those that measure approach vs. avoidance (elevated plus and elevated zero mazes, light/dark box), social anxiety (social interaction tests), general exploratory behavior (open field test), and fear of novelty (novelty suppressed feeding task) (Bailey and Crawley, 2009). These behavioral phenotypes are all closely related in rodent models (Hu et al., 2017), but it is important to consider the different subdomains of emotional behaviors when interpreting results as they involve different brain regions and circuits (Janak and Tye, 2015; Miller et al., 2017; Stanton et al., 2019).

It is also important to note that the majority of studies reviewed focus on the PFC as a whole or report similar results across subregions. Subregions of the PFC are thought to play distinct roles in neuropsychiatric disorders and emotional behaviors (Adhikari et al., 2015; Heidbreder and Groenewegen, 2003), but at present there is insufficient evidence to parse the nature of prefrontal E/I imbalances in stress and emotional disorders according to subregion. Therefore, this review focuses on the PFC as a whole.

### 3.1. The biphasic effect of stress on glutamatergic transmission

The literature supports evidence for both increased and decreased glutamatergic transmission in the PFC in the context of chronic stress and affective disorders (Sanacora et al., 2012). Some of the contradictory findings may be attributable to the time course of stress effects. Stress has a biphasic effect on glutamatergic transmission that is mirrored in its effects on dendritic arborization and spine density of pyramidal neurons in the PFC. The effects of stress on glutamatergic transmission in the PFC and on pyramidal cell morphology and excitatory synapse number have been comprehensively reviewed (Musazzi et al., 2015; Popoli et al., 2011). Acute stress increases prefrontal glutamatergic transmission and enhances dendritic complexity and spine density of pyramidal neurons, often accompanied by mild cognitive enhancement (Musazzi et al., 2015). Chronic stress causes dendritic atrophy of these same neurons in the PFC, according to studies conducted in male rodents (Cook and Wellman, 2004; Radley et al., 2006). This decrease in dendritic arborization and spine density of prefrontal pyramidal neurons is thought to be one of the mechanisms behind reduced activity and plasticity in the PFC following stress and in affective disorders. Chronic stress reduces activity in the PFC, impairing its function and contributing to emotional dysregulation (Negrón-Oyarzo et al., 2016). PFC tissue from both chronically stressed mice and from clinically depressed human patients display reduced expression of immediate early genes (IEGs), indicative of decreased activity of this brain region (Covington III et al., 2010). Magnetic resonance spectroscopy (MRS) studies in depressed patients also reveal decreased glutamate in the PFC (Hasler et al., 2007) (reduced GABA levels were also found; see “Integrating glutamatergic and GABAergic findings” section for discussion).

If reduced prefrontal activity is associated with emotional dysfunction, one would expect that increased activity of the PFC would contribute to healthy emotional functioning. Engagement of the PFC is indeed associated with stress resilience and recovery. Increased prefrontal activity during chronic stress appears to promote coping and resilience in human and rodent studies (Sinha et al., 2016; Vialou et al., 2014). Stimulation of the PFC has also been shown to reduce anxiety- and depression-related behaviors in rodents (Covington III et al., 2010; Fuchikami et al., 2015; Kumar et al., 2013; Reznikov et al., 2018). PFC activation is also necessary for the extinction of learned fear (Fucich et al., 2018; Ramanathan et al., 2018) via decreasing activity in the amygdala (Quirk et al., 2003).

The rodent studies cited above were conducted exclusively in male mice, and the human studies did not analyze sex differences. There is increasing evidence to suggest that the PFC of females may respond

**Table 2**
Glutamatergic and GABAergic dysfunction in stress and emotional dysfunction in rodent studies. The findings in this non-exhaustive list are limited to adults and to the prefrontal cortex.

| Model | Sex | Excitation-related Findings | Inhibition-related Findings | Behavioral Phenotype | Reference |
|---|---|---|---|---|---|
| Rodent Studies | | | | | |
| $GABA_AR$ γ2(+/-) mice | unspecified | ↓ glutamate receptor expression<br>↓ glutamatergic synapses | ↓ GABAergic synapses | Anxiety- and depression-like behaviors | (Ren et al., 2016) |
| Chronic variable stress (14-day) in rats | Males | ↑ inhibitory synapses on glutamatergic cells | ↑ mIPSC frequency, ↓ glucocorticoid receptor on PV cells | Impaired decision-making | (McKlveen et al., 2016) |
| Chronic restraint stress (21-day) in rats | Males | ↓ dendritic arborization of pyramidal cells<br>↓ pyramidal cell spine density | Not tested | Not tested | (Cook and Wellman, 2004; Radley et al., 2006) |
| Chronic restraint stress (7-day) in rats | Males and females | Pyramidal cell dendritic branching: males ↓, females ↑ | Not tested | Not tested | (Garrett and Wellman, 2009) |
| Unpredictable chronic mild stress (28-day) in mice | Males and females | Females: ↓ immediate early gene expression | Females: ↑ PV expression and cell counts | Females: anxiety- and depression-like behaviors<br>Males: depression-like behaviors | (Shepard et al., 2016) |
| Unpredictable chronic mild stress (14-day) in mice | Males and females | Males: ↓ NR2B expression | Females: ↑ PV expression and cell counts, Vglut1 puncta on PV cells, and pERK-labeled PV cells | Males and females: anxiety-like behaviors<br>Females: depression-like behaviors, impaired cognition | (Shepard and Coutellier, 2018) |
| Chronic mild stress (9-week) in rats | Males | ↑ pyramidal cell excitability | ↓ PV, CR, CCK cell counts<br>↓ mIPSC frequency | Anhedonia, impaired cognition | (Czéh et al., 2018) |
| Chronic social isolation stress (21-day) in rats | Males | Not tested | ↓ PV cell counts | Depression-like behaviors | (Todorović et al., 2019) |
| Chronic social defeat stress (10-day) in mice | Males | ↓ immediate early gene expression | Not tested | Depression-like behaviors, reduced social interaction | (Covington et al., 2010) |
| Chronic restraint stress (21-day) in mice | Males | Not tested | ↑ dendritic arborization of GAD-expressing cells<br>↓ GAD67-expressing somata<br>↑ $GABA\text{-}A_{\alpha}1$ expression | Not tested | (Gilabert-Juan et al., 2013) |
| Chronic unpredictable stress (5-week) in rats | Males | Not tested | ↓ GAD67, SST, NPY expression | Not tested | (Banasr et al., 2017) |
| Social isolation stress (28-day) in mice | Males | ↓ immediate early gene and mGluR-1 and -2 expression | Not tested | Anxiety- and depression-like behaviors | (Ieraci et al., 2016) |
| Social intruder stress (5-day) in rats | Males and females | Females: ↓ pyramidal cell excitability | Not tested | Not tested | (Urban and Valentino, 2017) |
| Social defeat stress (10-day) in mice | Males | ↓ glutamate, glutamine, EAAT2 expression | ↓ GABA, GAD1 expression | Depression-like behaviors | (Veeraiah et al., 2014) |

differently to stress (Wellman et al., 2018). Females show unique, estrogen-dependent patterns of pyramidal cell dendritic remodeling in the PFC and PFC-amygdala connections following chronic stress (Garrett and Wellman, 2009; Shansky et al., 2010). Following chronic stress, males show the above-mentioned dendritic retraction in the PFC, but females do not (or even show dendritic hypertrophy), possibly due to protective effects of estrogen (Wei et al., 2014; Wellman et al., 2018). After a period of rest from stress, dendritic retraction in males recovers but does not change in females. This suggests that in the days following chronic stress, the PFC of females is less plastic than that of males. If this is the case, females may be more susceptible to a "second hit" of a novel stressor: while prior chronic stress exposure blunts novel acute stress-induced neuronal activation in males, females may have a more exaggerated response to subsequent stressors. Therefore, dendritic retraction may be an adaptive, protective mechanism against initial stress exposure that males employ but females do not, rendering females more susceptible to chronic stress and emotional dysfunction (Moench and Wellman, 2017; Wellman et al., 2018). Supporting the hypothesis that females are more susceptible to a "second hit" of stress, chronically stressed female rats given a rest period show enhanced activity in limbic brain regions following a novel acute stressor compared to their unstressed counterparts. By contrast, male rats showed blunted activity in the PFC and limbic brain regions under the same conditions (Moench et al., 2019). This research implies that plasticity of the PFC following stress is important for resilience and recovery, and that chronic or repeated stress may impair prefrontal plasticity especially in females.

The biphasic effects on glutamatergic transmission in the PFC (an initial increase in stress-evoked glutamate release followed by prefrontal hypoactivity), as well as sex differences inherent in this process, may explain in part the discrepancies in the literature about glutamatergic imbalances in stress and emotional disorders presented in Table 1 and Table 2. Glutamatergic findings will vary depending on factors like whether the stressor is acute or chronic, stress duration, recovery time, and sex of the animal, and genetic vulnerabilities (Fig. 1). Collectively, the literature supports the conclusion that under most chronic stress conditions and emotional dysfunction, activity and plasticity of the PFC is impaired and reduced.

### 3.2. Bidirectional GABAergic dysfunction

The literature on GABAergic dysfunction in stress and affective disorders is inconclusive and at times contradictory, with many studies reporting decreased GABAergic function but some finding evidence for increased inhibition (Table 1 and Table 2). The time course of GABAergic dysfunction has also not yet been comprehensively studied, but similarly to the glutamatergic system, there may be biphasic or even multiphasic effects of stress on the GABAergic system that help explain the bidirectional findings. Many studies report reduced GABA concentrations and markers of the GABAergic system in the stressed and/or anxious and depressed PFC, which has been previously reviewed (Fogaça and Duman, 2019; Ghosal et al., 2017). An MRS study of humans with panic disorder found decreased GABA levels in the anterior cingulate cortex and medial PFC (Long et al., 2013), as did an MRS study of major depressive disorder patients (Hasler et al., 2007). In rodent studies, chronic stress also reduces inhibitory transmission in the PFC (Czéh et al., 2018; Veeraiah et al., 2014). Support for the GABAergic deficit hypothesis of stress and affective dysfunction (Luscher et al., 2011) also comes from studies in mice deficient for the γ2 subunit of the $GABA_A$ receptor ($GABA_AR$), which show anxiety- and depression-like phenotypes along with suppressed GABAergic and glutamatergic system activity (Ren et al., 2016).

There are several studies that report findings indicative of increased GABAergic system activity and prefrontal inhibition in conditions of stress and affective dysfunction. Chronic stress increases the frequency of miniature inhibitory postsynaptic currents (IPSCs) in the PFC and increases inhibitory synapses onto glutamatergic cells (McKlveen et al., 2016). Chronic stress also induces dendritic hypertrophy in a subpopulation of GAD-expressing inhibitory interneurons identified as Martinotti cells, and has bidirectional effects on the expression of certain GABAergic system markers (decreased GAD67 and increased $GABA_A\alpha1$ expression) (Gilabert-Juan et al., 2013). These studies were conducted in male rodents. Knowledge of the effects of chronic stress on the prefrontal GABAergic system in females remains limited, but may involve increased activity of PV cells (Shepard et al., 2016; Shepard and Coutellier, 2018) (see "Prefrontal hypoactivity: the role of parvalbumin cells" for more discussion).

### 3.3. Integrating glutamatergic and GABAergic findings

How is it possible to reconcile inconsistent or contradictory findings about glutamatergic and GABAergic dysfunction in stress and affective disorders? More specifically, how does hypoactivity in the PFC fit with reports of GABAergic deficits? In both human and rodent studies (Table 1 and Table 2), the most consistent findings suggest suppression of both glutamatergic and GABAergic systems in stress and emotional dysregulation, with some exceptions. The time course of stress may provide some insight. Stress is a highly heterogeneous and variable experience, depending on factors like duration of exposure, time since exposure, severity, controllability, and predictability (Anisman and Matheson, 2005). The stress paradigm used, as well as when during that stress paradigm data are collected, will impact the direction of glutamatergic and GABAergic findings due to the biphasic and bidirectional effects of stress on these systems. A critical challenge for stress research in the coming decades will be to map the variable effects of stress onto the complex landscape of excitatory and inhibitory interactions in the PFC and other brain regions. Such a map would help provide a clear scale for the axes in Fig. 1, which as of now are undefined and hypothetical.

Another core concept that may help reconcile glutamatergic and GABAergic findings in stress and affective dysfunction is homeostatic

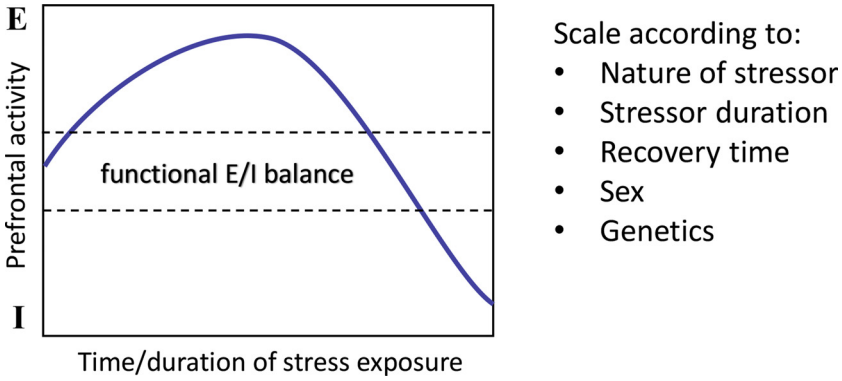


**Fig. 1.** Time course of stress effects on the glutamatergic transmission and activity in the prefrontal cortex. Acutely, stress exposure increases glutamatergic transmission and prefrontal activity. In cases of chronic stress exposure, this initial increase eventually results in reduced excitation and prefrontal hypoactivity. The nature of this trajectory is heterogeneous and impacted my multiple different factors including external ones relating to the stress itself, as well as internal ones such as sex and genetic vulnerability. E: excitation; I: inhibition.

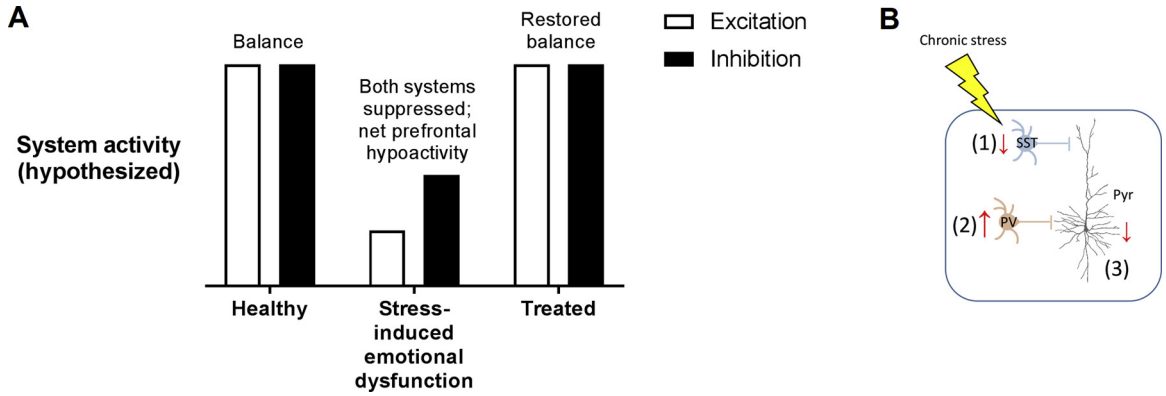


**Fig. 2.** Hypothesized explanation for reconciling GABAergic deficits in chronic stress and affective disorders with evidence for increased prefrontal inhibition. **(A)** The glutamatergic systems and GABAergic systems may be suppressed in conditions of chronic stress-induced depression and anxiety, but increased inhibition relative to excitation can still result in a net effect of prefrontal hypoactivity. The activity of both systems may be elevated by treatment. **(B)** The phenomenon hypothesized in (A) could arise if (1) decreased local dendritic inhibition by SST cells causes (2) over-compensation by PV cells which provide global, soma-targeting inhibition, (3) thus reducing the activity of pyramidal neurons and contributing to prefrontal hypoactivity. SST: somatostatin; PV: parvalbumin: Pyr: pyramidal cell.

plasticity. Homeostatic plasticity mechanisms help keep excitation and inhibition in balance. If a network is hyper-excitable beyond a set point, mechanisms of inhibitory control engage in order to keep excitation in check. For example, elevated activity levels can cause compensatory increases in the amplitude and/or frequency of IPSCs (Wenner, 2011). And vice-versa – if excitation is suppressed, levels of inhibition subsequently decrease in order to maintain a certain level of activity. In this way, the glutamatergic and GABAergic systems can concordantly be suppressed or elevated depending on changes in network activity. GABAergic deficits in stress-induced emotional dysfunction, therefore, may still be compatible with the hypothesis of prefrontal hypoactivity and over-inhibition. The glutamatergic and GABAergic systems may both be suppressed, but inhibition can still outweigh excitation resulting in a net effect of prefrontal hypoactivity (Fig. 2A). Such a phenomenon could arise if GABAergic deficits are over-compensated for by an increase in inhibition, which could be explained by the heterogeneity of GABAergic interneuron subtypes that differentially regulate the activity of pyramidal cells. For instance, a stress-induced loss of local, dendritic inhibition to pyramidal cells mediated by somatostatin (SST)-expressing interneurons (Lin and Sibille, 2015) could result in over-compensation by PV-mediated soma-targeting inhibition, thus reducing overall cortical excitation (Ghosal et al., 2017) (Fig. 2B). Fig. 2 represents this possible explanation for how the hypothesis of over-inhibition in the PFC fits with reports of GABAergic deficits in stress and affective dysfunction, though this remains to be tested. It has been suggested that rapid-acting antidepressants like ketamine re-engage homeostatic plasticity to elevate both glutamatergic and GABAergic systems again and restore proper E/I balance (Raab-Graham et al., 2016; Workman et al., 2018). In support of this idea, mice deficient for the γ2 subunit of the $GABA_AR$, which show emotional dysfunction, show suppressed glutamatergic and GABAergic system activity, both of which are restored by ketamine treatment (Ren et al., 2016).

A cell type-specific approach to understanding GABAergic imbalances in stress may be key to untangling inconclusive results. The PFC contains a highly heterogeneous population of GABAergic interneurons with different inputs, spiking properties, and cellular targets. The involvement of different GABAergic interneuron subtypes in major depressive disorder and animal models of depression was recently reviewed comprehensively (Fogaça and Duman, 2019). We will discuss cell-type specific findings in the following sections, with a primary focus on prefrontal PV cells and their micro- and macro-circuit interactions.

### 3.4. Prefrontal hypoactivity: the role of parvalbumin cells

A main driver for over-inhibition in the PFC may be increased activity of PV interneurons. Chronic stress exposure increases the number of cells that are immunoreactive for PV, as well as PV mRNA expression, in female mice (Shepard et al., 2016; Shepard and Coutellier, 2018). The reported increase in the number of PV-positive cells most likely reflects an activity-dependent increase in PV protein expression levels (Filice et al., 2016; Kinney et al., 2006) that allows for immunohistochemistry detection. Chronic stress also increases the number of PV cells double-labeled with pERK and increases the number of VGlut1 puncta on PV neurons in females, indicative of increased neuronal activity and increased excitatory input (Shepard and Coutellier, 2018). This immunohistochemical evidence indicates that chronic stress increases PV cell activity in the PFC in both sexes, though predominately in females. This may be a mechanism contributing to prefrontal hypoactivity following chronic stress. A stress-induced elevation in PV cell counts corresponds with a reduced number of PV-negative, cFos-positive cells in the PFC of female mice (Shepard et al., 2016), suggestive of reduced activity levels in the PFC, given that the majority of total neurons in the PFC are glutamatergic (Granato and De Giorgio, 2014; Tremblay et al., 2016). In male rats, chronic stress increases prefrontal inhibitory currents and decreases glucocorticoid receptor immunoreactivity specifically in PV neurons in the PFC. These findings suggest that chronic stress increases prefrontal inhibition possibly through a loss of a glucocorticoid receptor-mediated brake on PV cell activity (McKlveen et al., 2016). The hypothesis that increased PV cell activity following chronic stress is a mechanism of prefrontal hypoactivity is supported by electrophysiological studies showing that activation of PV cells increases IPSCs in target pyramidal cells and reduces network excitability (Safari et al., 2017; Winkelmann et al., 2014). At the behavioral level, increased PV expression correlates with increased emotionality behaviors in females but not males (Shepard et al., 2016). According to preliminary data from our lab, chronically driving the activity of PV cells in the PFC in the absence of chronic stress using chemogenetics (DREADDs; designer receptors exclusively activated by designer drugs) is anxiogenic in females but not males, establishing a sex-specific causal relationship between increased PV cell activity and increased anxiety (Wellman et al., 2018). Collectively, these findings indicate that prefrontal PV cells are sensitive to stress in both sexes but mediate anxiety behaviors specifically in females.

Another study used targeted expression of gain-of-function glycine receptors in PV cells to increase their activity, and found that this decreases network excitability and results in an anxious phenotype (Winkelmann et al., 2014). Increased PV cell activity using the same

genetic manipulation also reduces extinction of contextual fear memory (Çaliskan et al., 2016), again suggesting that PV cells represent a cellular substrate for fear and anxiety behaviors. These gain-of-function studies were conducted in male mice and were also not brain-region specific, so more research is needed to parse out the role of PV cells in different brain regions on emotional behaviors in male and female mice.

On the other hand, others reported decreased PV cell counts in the PFC following chronic stress (Czéh et al., 2018; Todorović et al., 2019), countering the hypothesis of increased prefrontal inhibition mediated by prefrontal PV cells. The study by Czéh et al. also reported reduced counts of other GABAergic cells, including CR and CCK, along with increased pyramidal cell excitability. These findings are more in line with hypotheses of GABAergic deficits in stress and affective disorders. When attempting to reconcile these findings, it is important to consider the heterogeneity of stressful experiences. Czéh et al. utilized a 9-week chronic mild stress protocol, much longer than the 2- and 4-week protocols utilized when increased PV cell counts were found (Shepard et al., 2016; Shepard and Coutellier, 2018). Todorović et al. utilized social isolation, a stressor that varies fundamentally in nature from chronic mild stress protocols. The length and type of stressor may therefore play a role in the effects of chronic stress on prefrontal PV cells (increased vs. decreased). Additionally, the studies that reported decreased prefrontal PV cell counts utilized only male rodents and focused on anhedonia. It is possible that reduced prefrontal PV cell counts are associated with anhedonia in males (Czéh et al., 2018; Todorović et al., 2019), while increased prefrontal PV cell counts are associated with anxiety in females (Shepard et al., 2016; Wellman et al., 2018), emphasizing the importance of considering sex differences as well as the different domains of emotional dysfunction. Chemogenetic studies have also reported that acute activation of prefrontal PV cells is anxiolytic (Ferguson and Gao, 2018b), and acute suppression of prefrontal PV cell activity promotes helplessness (Perova et al., 2015). Both studies were conducted in male rodents, again emphasizing the possible role of sex differences. These studies were also acute manipulations, which likely have different behavioral effects than chronic excitation or inhibition. Independent of the nature of the changes to PV neurons after stress, these results altogether show that prefrontal PV cells are highly sensitive to stress and regulate aspects of emotional behaviors. Because changes in prefrontal activity has been reliably implicated in depression and anxiety (Thompson et al., 2015), these findings emphasize the importance of studying in depth the contribution of prefrontal PV neurons to mood disorders.

### 3.4.1. *In the context of GABAergic microcircuitry*

Other GABAergic cell types also contribute to prefrontal E/I imbalances in stress-induced affective disorders (Fig. 3). Both human and animal studies have identified SST-expressing inhibitory interneurons as a major culprit in emotional dysfunction. SST cells inhibit the dendrites of excitatory pyramidal cells (Tremblay et al., 2016). Mice lacking SST show increased anxiety and depression-like behaviors, and chronic stress decreases expression of SST (Banasr et al., 2017; Lin and Sibille, 2015). SST cells are also thought to modulate some of the sex-specific effects of chronic stress and sex biases in the prevalence of comorbid anxiety and mood disorders (Seney and Sibille, 2014). SST cells inhibit PV cells (Pfeffer et al., 2013), proposing the hypothesis that impaired functioning of SST cells results in disinhibition of PV cells. In support of this idea, increased activity of SST cells has antidepressant and anti-anxiety benefits (Fuchs et al., 2016). It has not yet been tested whether PV cells mediate the connection between SST cells and affective behavior, nor if chronic stress decreases SST-mediated inhibitory inputs to PV cells. If this is the case, this microcircuit would contribute to resolving the previously-discussed paradox in the literature: anxiety, depression, and chronic stress are simultaneously associated with both prefrontal hypoactivity and reduced GABAergic transmission in the PFC. These observations are not mutually exclusive if reduced

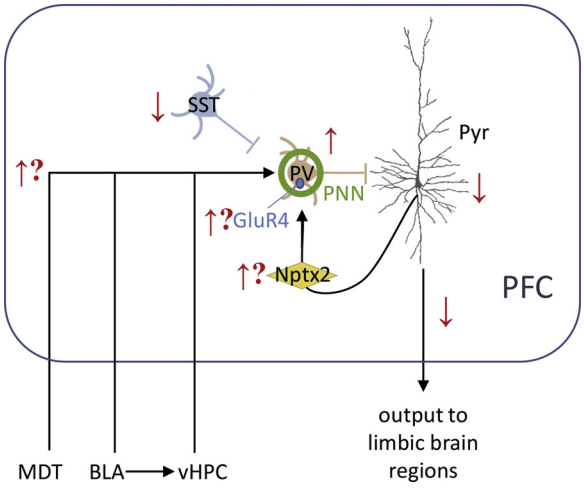


**Fig. 3.** Micro- and macro-circuit interactions with parvalbumin cells in the prefrontal cortex. PV cells are inhibited by local SST cells. A decrease in SST functionality as seen in stress and affective disorders may result in disinhibition of prefrontal PV cells and thus increased inhibition of target pyramidal neurons. Similarly, activity-dependent increases in Nptx2 may facilitate the accumulation of GluR4-subunit containing AMPA receptors into the membrane of PV cells via interactions with PNNs, enhancing PV cell excitability. At the macro-circuit level, inputs from the MDT, BLA, and vHPC may also drive activation of PV cells in the PFC. PV: parvalbumin; SST: somatostatin; PNN: perineuronal net; Pyr: pyramidal cell; PFC: prefrontal cortex; MDT: medial dorsal thalamus; BLA: basolateral amygdala; vHPC: ventral hippocampus.

GABAergic transmission is observed due in part to impaired SST cell functioning, while hypoactivity is observed due to the subsequent increase in PV cell activity. This hypothesis has been posited but not yet directly tested (Ghosal et al., 2017).

The stress-induced increase in PV cell activity could also come from direct excitatory connections within the PFC. Pyramidal cells excite local PV cells as part of maintaining network homeostasis (Spampanato et al., 2016). Pyramidal cell activity can also potentiate PV cells for receiving other excitatory inputs. One mechanism of this is Nptx2 (also known as Narp [neuronal activity-regulated pentraxin]), an activity-dependent, immediate early gene that is expressed in pyramidal cells. When translated, Nptx2 is secreted into the extracellular space where it accumulates at excitatory synapses of nearby PV cells and facilitates the insertion of GluR4-containing AMPA receptors into their membrane. PNNs also encourage the accumulation of Nptx2 on PV cells (Chang et al., 2010), which may be one of the mechanisms by which PNNs enhance PV cell excitability (Balmer, 2016). In this way, Nptx2 is a mechanism of homeostatic synaptic plasticity: it increases excitatory drive onto PV cells in response to pyramidal cell activity, increasing inhibition and keeping the network in a stable state (Doyle et al., 2010). As previously discussed, stress exposure initially increases pyramidal cell activity in the PFC, but chronic stress eventually leads to hypoactivity (Popoli et al., 2011). One possible mechanism for this biphasic stress effect is that stressinduced excitation causes overproduction of Nptx2 which progressively leads to an overdrive of PV cells and hypoactivity of downstream pyramidal cells (Fig. 3). Nptx2 has been implicated in schizophrenia (Manchia et al., 2017) but has not yet been examined in the context of chronic stress and prefrontal inhibition.

### 3.4.2. *Macrocircuit inputs possibly driving GABAergic changes in the PFC*

PV cells in the PFC receive inputs from subcortical structures that drive their activity and thus drive feedforward inhibition in the PFC (Fig. 3). For example, monosynaptic stimulation of the basolateral amygdala (BLA) activates prefrontal PV cells, increasing prefrontal inhibition (Dilgen et al., 2013; Gabbott et al., 2006). BLA-to-PFC inputs

are strongest on PV and SST interneurons over pyramidal cells, and this feedforward inhibition predominately contacts corticoamygdala neurons that provide reciprocal connections back to the BLA, highlighting a complex modulatory circuit that is likely involved in prefrontal-dependent control over emotional behaviors (McGarry and Carter, 2016). Some, but not all, chronic stress paradigms increase activity in the BLA (Lowery-Gionta et al., 2018; Shepard et al., 2016; Zhang et al., 2019), enhancing excitatory output at BLA-to-PFC synapses and inducing an anxiety phenotype. Whether a stress-induced increase in excitatory BLA projections to the PFC is driving the activity of prefrontal PV cells remains to be determined. Chronic stress also increases spine density and glutamatergic signaling in BLA projections to the ventral hippocampus, increasing activity of this region (Zhang et al., 2019). The ventral hippocampus directly innervates the PFC and excites PV interneurons (Caballero et al., 2014b; Gabbott et al., 2002). Again, it is unknown whether stress increases activity of prefrontal PV neurons via increased connectivity from the BLA to the ventral hippocampus to the PFC.

The mediodorsal thalamus (MDT) also helps regulate prefrontal E/I balance (Ferguson and Gao, 2018b). Past research has shown that excitatory projections from MDT neurons synapse directly on PV cells in the PFC, driving feedforward inhibition (Delevich et al., 2015; Rotaru et al., 2005). Increased activity of the MDT would hypothetically increase excitation onto prefrontal PV neurons and increase anxiety-related behaviors. The effect of chronic stress on activity in the MDT, and the relation of the MDT to anxiety disorders via connectivity with prefrontal PV cells, has not been studied. The sex-specific nature of macrocircuit alterations in stress and emotional disorders involving the BLA, ventral hippocampus, MDT, and others, also remains to be studied.

## 4. Inhibition as a therapeutic target

If chronic stress and affective disorders involve reduced prefrontal activity, in part due to increased activity of prefrontal PV cells, reducing activity of the prefrontal GABAergic system may be a therapeutic strategy for affective disorders like depression and anxiety. For example, reducing PV-cell mediated inhibition may restore levels of activity in the PFC, lifting brakes on plasticity and allowing for therapeutic rewiring of local and long-range circuits. This hypothesis has yet to be directly tested, but there is some supporting evidence from pharmaceuticals and from other brain regions and behavioral paradigms.

### 4.1. GABA agonism or antagonism?

GABA agonism is typically anxiolytic and many common anti-anxiety medications, such as benzodiazepines, exert their therapeutic effects by enhancing GABAergic transmission (Lydiard, 2003). A recent study even reported fast-acting antidepressant effects of novel $GABA_AR$ agonists in both males and females (McMurray et al., 2018). However, there is also recent evidence to suggest that GABA antagonism can be therapeutic for emotional disorders, in support of the hypothesis presented here that these disorders involve over-inhibition in the PFC. For example, quercetin, a negative allosteric modulator for $GABA_ARs$, reduces GABAergic transmission in the PFC (Fan et al., 2018) and has stress-protective and anxiolytic effects at least in male rodents (females were either not tested or the sex was unspecified) (Bhutada et al., 2010; Mehta et al., 2017; Samad et al., 2018). Other negative allosteric modulators for α5-containing $GABA_ARs$, MRK-016 and L-655,708, also exhibit antidepressant actions in males (females were not tested) (Fischell et al., 2015; Zanos et al., 2017). In humans, GABA content in the ventral PFC is positively correlated with trait anxiety with no sex differences observed (Delli Pizzi et al., 2016), suggesting that reducing prefrontal GABA may alleviate anxiety.

The contradictory findings about GABA agonism vs. antagonism may be explainable by differences in GABAergic dysfunction across brain regions in stress and emotional disorders. For instance, GABA agonism by benzodiazepines may exert its therapeutic effects within the amygdala specifically (Nuss, 2015). Due to the heterogeneity of GABAergic interneurons in the PFC, a cell-type specific approach to GABA agonism or antagonism may also be warranted to maximize therapeutic efficacy of intervening in the GABAergic system in this brain region. For example, certain reports indicate that facilitation of SST cell activity is anxiolytic while PV cell excitation is anxiogenic (Fuchs et al., 2016; Wellman et al., 2018). The anxiolytic effects of both GABA agonism and antagonism may also relate to the complex and bidirectional effects of chronic stress on GABAergic transmission.

### 4.2. Antidepressants and parvalbumin cells

Antidepressants are frequently used for the treatment of comorbid depression and anxiety or for anxiety alone (Feighner, 1999; Zohar and Westenberg, 2000). Both fluoxetine and ketamine reduce PV expression in the PFC (Ohira et al., 2013; Zhou et al., 2015). A previous study found that the ketamine-induced loss of PV expression involves activation of NADPH oxidase (Behrens et al., 2007). The NADPH oxidase inhibitor apocynin prevents ketamine-induced loss of PV expression in the PFC and also prevents ketamine's antidepressant effects (Zhou et al., 2015), strongly suggesting that at least part of the therapeutic efficacy of antidepressants comes from reducing the activity of prefrontal PV cells. In further support of this, fluoxetine also reduces PNNs around PV cells (Guirado et al., 2014). Venlafaxine reduces PNN integrity in the hippocampus by upregulating matrix metalloproteinase (MMP)-9 (Alaiyed et al., 2019). These studies were conducted in male rodents (or pooled male and female groups). Whether antidepressants reduce the activity of PV interneurons in females remains to be determined.

The activation of PV cells is driven in part by the potassium channel Kv3.1, which allows PV cells to send inhibitory signals at high frequencies to excitatory pyramidal cells (Rudy and McBain, 2001). Unstressed male Kv3.1 knockout (KO) mice that lack the Kv3.1 channel, and thus have reduced PV cell activation, display less anxious behaviors than wildtype (WT) mice (Parekh et al., 2018). Antidepressants like fluoxetine and paroxetine also block the Kv3.1 channel (Lee et al., 2018; Sung et al., 2008). These findings also lend support to the hypothesis that increased PV cell activity is part of the pathogenesis of stress-induced affective disorders like anxiety and depression and that reducing PV cell activity, or prefrontal GABAergic transmission in general, may be therapeutic.

### 4.3. Evidence from other brain regions

We are presenting the hypothesis that chronic stress-induced emotional dysfunction, as seen in disorders such as anxiety and depression, involves increased inhibition in the PFC. This increased inhibition may involve an increase in brakes on plasticity, such as PV cells and PNNs, that are typically associated with the closing of developmental critical periods of plasticity. Therapeutic interventions may involve lifting these brakes and reinstating activity and plasticity in the PFC. Further support for this hypothesis comes from research in other regions of the brain and other behaviorally-relevant networks: the visual cortex and ocular dominance plasticity, the amygdala and fear learning, and the hippocampus and anxiety and other behaviors.

Like the PFC, the visual cortex of early postnatal rodents is highly plastic. One of the first (and one of most well-documented) forms of critical period plasticity relates to sensory experience and occurs in the visual cortex in early postnatal life. During this time, mice display ocular dominance plasticity: if one eye is sutured shut, circuits in primary visual cortex will rewire to reduce inputs from that eye and the cortical territory will be taken over by inputs from the other, open eye. This rewiring can be corrected if the closed eye is re-opened during the critical period. If the closed eye is re-opened during adulthood, the rewiring remains permanent and cannot be reversed without the aid of

interventions (Castrén and Hen, 2013). Adult animals are thus unable to express this ocular dominance plasticity; however, it can be re-instated by chronic fluoxetine administration or degradation of PNNs, such as for the treatment of amblyopia (Lensjø et al., 2017; Maya-Vetencourt et al., 2008; Pizzorusso et al., 2002).

In the amygdala, a similar concept has been applied to fear circuitry with therapeutic implications for post-traumatic stress disorder (PTSD) (Nabel et al., 2013). Fear associations in infant animals are rapidly forgotten and easily extinguished, while adults have long-lasting fear memories that are highly prone to reinstatement after extinction. Infant animals subjected to chronic stress in early life also show "adult-like" long-lasting and relapse-prone fear memories (Callaghan et al., 2013). In adult mice, simple extinction does not erase the fear memory. However, two landmark *Science* papers demonstrated that extinction training combined with degradation of PNNs in the amygdala or fluoxetine treatment does result in fear erasure (Gogolla et al., 2009; Karpova et al., 2011).

In the hippocampus, early life stress leads to a premature increase in PV cells (Bath et al., 2016). Conversely, chronic fluoxetine administration leads to a "dematuration" of the dentate gyrus, noted by reduced expression of the mature granule cell marker calbindin, increased granule cell excitability, and reduced connectivity between the dentate gyrus and CA3. These molecular changes were associated with behavioral destabilization, including fluctuating levels of activity and anxiety (Kobayashi et al., 2011, 2010). Electroconvulsive therapy, used for treating depression, also causes a rapid dematuration of hippocampal granule cells (Imoto et al., 2017). Chronic stress has also been shown to increase PNN coverage of PV cells in CA1 (Riga et al., 2017).

A common theme in these brain networks is that during particular developmental periods, a certain level of plasticity exists that allows for circuit rewiring in response to environmental experience due to the hyper-excitable state of the network. As development progresses into adulthood, these critical periods of plasticity close due to GABAergic maturation and increased inhibitory control, and less experience-dependent rewiring is possible. Chronic stress during early life or adulthood appears to accelerate or strengthen developmental brakes on plasticity, such as PV cell activity or PNN coverage of PV cells. Antidepressant treatments like fluoxetine, ketamine, electroconvulsive therapy, or others assist in lifting brakes on plasticity like PV cells and PNNs and restore activity levels and plasticity in brain networks to again allow for a healthy level of experience-dependent rewiring (Fig. 4). Treatment does not appear to re-induce a true "critical period", which is a positive finding, as critical periods of plasticity are associated with their own vulnerabilities to stress (Chaby et al., 2013; Hoftman and Lewis, 2011). A recent study in the visual cortex supports the trajectory presented in Fig. 4: fluoxetine treatment does not induce expression of molecular markers indicative of a "juvenile-like" state, but rather increased expression of markers associated with mature and functional E/I balance, specifically mature glutamate and GABA receptor subunits (Beshara et al., 2015).

The effects of chronic stress during early life and adulthood described here are not generalizable across the lifespan. Chronic stress appears to have an entirely different effect on the prefrontal GABAergic system when it occurs prenatally or during the adolescent critical periods. Here, chronic stress disrupts GABAergic development and leaves prefrontal networks in an immature state, with decreased PV and PNN expression and cognitive deficits like those indicative of schizophrenia phenotypes (de Araújo Costa Folha et al., 2017; Enwright et al., 2016). Stress during adolescence also disrupts emotional maturation (Page and Coutellier, 2018). In adolescence, enhancing PV cell activity is therapeutic and protective against stress (Chen et al., 2018; Ng et al., 2018). These differences between developmental periods are beyond the scope of this review but are an important consideration.

## 5. Concluding remarks

The evidence synthesized in this review supports the hypothesis that chronic stress and affective disorders involve E/I imbalances in the PFC, specifically over-inhibition and prefrontal hypoactivity. Some of the mechanisms behind over-inhibition may be the same as those that increase inhibition during the developmental transition from adolescence to adulthood. Specifically, during adolescent prefrontal maturation, the GABAergic system matures in part through increased activity of PV cells and increased PNN coverage of PV cells. Recent evidence suggests that these brakes on activity and plasticity may be increased by chronic stress and in conditions of anxiety and depression. Therapeutic interventions for these disorders involve reducing the activity of PV cells and/or reducing their coverage by PNNs, for instance. In this way, treatment involves restoring activity and plasticity in the PFC to healthy levels and reinstating E/I balance necessary for proper emotional functioning. As many reviews and experiments on the topic of E/I imbalances in stress and affective disorders have focused on the GABAergic deficit hypothesis of these conditions, we believe it is important to consider the evidence for over-inhibition. We also present ideas for how these two hypotheses can be reconciled. The time course of stress, differing magnitudes of glutamatergic vs. GABAergic deficits, mechanisms of homeostatic plasticity, and cell type-specific analyses are all critical factors to consider when investigating E/I imbalances in stress and emotional disorders. Acknowledging the evidence for over-inhibition in the PFC and integrating it into our current understanding of stress and emotional disorders will be invaluable for developing effective interventions. Sex differences in this research is also an essential

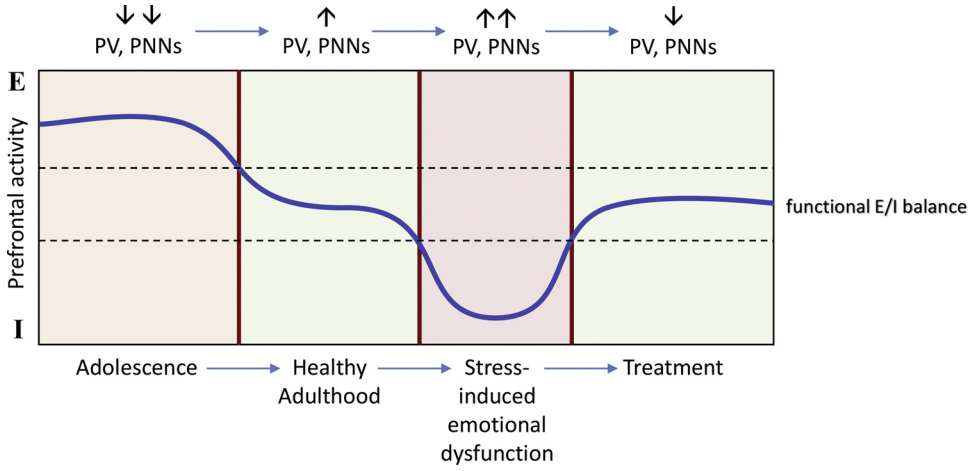


**Fig. 4.** Hypothesized changes in E/I balance due to development and chronic stress/emotional dysfunction. In adolescence, the PFC is more hyper-excitable and plastic. As development progresses into adulthood, increased PV cell activity and PNN coverage of PV cells enhances inhibition to stabilize the network, resulting in mature E/I balance and healthy prefrontal-dependent emotional functioning. Chronic stress and affective disorders like anxiety and depression may involve increases in the same molecular mechanisms that are involved in GABAergic maturation, such as PV cells and PNNs, inducing hypoactivity. Treatment involves restoring levels of activity, potentially in part through reducing brakes on excitation such as PV cells and PNNs to restore a mature, functional E/I balance. E: excitation; I: inhibition; PV: parvalbumin; PNN: perineuronal net.

consideration. The glutamatergic and GABAergic systems of males and females respond differently to stress, which may be important to understanding sex differences in the prevalence of anxiety and depression and developing sex-specific treatments. Future studies must continue to take sex differences into account, as well as continue to investigate the complex interplay between excitatory and inhibitory transmission both in and out of balance.

## Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## Declaration of Competing Interest

None.

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