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Impact of stress on excitatory and inhibitory markers of adolescent cognitive critical period plasticity

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ABSTRACT

Adolescence is a time of significant neurocognitive development. Prolonged maturation of prefrontal cortex (PFC) through adolescence has been found to support improvements in executive function. Changes in excitatory and inhibitory mechanisms of critical period plasticity have been found to be present in the PFC through adolescence, suggesting that environment may have a greater effect on development during this time. Stress is one factor known to affect neurodevelopment increasing risk for psychopathology. However, less is known about how stress experienced during adolescence could affect adolescent-specific critical period plasticity mechanisms and cognitive outcomes. In this review, we synthesize findings from human and animal literatures looking at the experience of stress during adolescence on cognition and frontal excitatory and inhibitory neural activity. Studies indicate enhancing effects of acute stress on cognition and excitation within specific contexts, while chronic stress generally dampens excitatory and inhibitory processes and impairs cognition. We propose a model of how stress could affect frontal critical period plasticity, thus potentially altering neurodevelopmental trajectories that could lead to risk for psychopathology.

1. Introduction

Adolescence is a distinct developmental period during which there is a transition from childhood to adulthood, delineated by biological markers such as puberty, as well as sociocultural milestones, such as the attainment of independence from caregivers (Spear, 2000). Behaviorally, adolescents begin to engage with their environments in novel ways, placing greater emphasis on social experiences and relationships, while also exhibiting more sensation-seeking and risk-taking behavior (Spear, 2000). Concurrently, adolescents' executive function continues to improve (Cepeda et al., 2001; Luna et al., 2015). Neurobiological maturation of prefrontal cortex (PFC) is thought to underlie this cognitive development. Histological studies have demonstrated continued synaptic pruning in PFC through adolescence, persisting through the 20 s (Petanjek et al., 2011). Neuroimaging studies have revealed developmental changes in the activation of regions core to executive functions including working memory (D. J. Simmonds et al., 2017) and inhibitory control (Ordaz et al., 2013), as well as maturation of white matter tracts (D. Simmonds et al., 2014) and thinning of gray matter throughout frontal cortex (Gogtay et al., 2004). Together, these changes support the transition into stable, reliable, adult-level cognition.

Accumulating research suggests that adolescence is also a time of heightened neuroplasticity of PFC reflective of a critical period (Larsen and Luna, 2018). Critical period plasticity would support heightened influence of experience and environmental factors optimizing specialization of systems underlying executive function. However, while a period of enhanced neuroplasticity can bring opportunity to establish functional trajectories, it can also be a period of vulnerability for impairment depending on the inputs the system receives during that time. Indeed, the adolescent/early adulthood period is also a time when mental illness often first emerges (Paus et al., 2008). Given the parallel timing of these dynamic neurobiological changes and increasing rates of psychiatric diagnoses, many of these disorders are thought to be at least partially the result of developmental trajectories that were disrupted by genetic and/or environmental factors. Importantly, given that adolescence is a significant time of cognitive maturation, it is notable that symptoms of many mental illnesses that emerge during adolescence include cognitive deficits, such as schizophrenia and mood disorders (Fioravanti et al., 2012; Jaeger et al., 2006). These cognitive deficits remain less well-understood when compared to other symptoms of psychopathology, and fewer treatments exist to ameliorate them. Thus,

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it is important to understand what mechanisms might underlie these cognitive symptoms. Understanding how environmental factors may affect neurobiological processes during adolescence can help identify novel targets for pharmacological, psychotherapeutic, public health, or policy intervention.

Stress is one such environmental factor that has been demonstrated to have the potential to impact neurodevelopmental trajectories (Callaghan and Tottenham, 2016). The literature to date has focused primarily on the outcomes of affective systems, which may undergo accelerated maturation as a result of early life adversity (Callaghan and Tottenham, 2016). However, relatively less is known about how stress during development could impact mechanisms of cognitive maturation, especially in PFC, as other regions such as hippocampus have been more widely studied thus far (Green and McCormick, 2013). Some literature has demonstrated that stress in childhood can have an impact on PFC, such as in a study showing that associations between cumulative early life stress and suboptimal working memory performance were mediated by smaller PFC volumes (Hanson et al., 2012). While childhood is a time of significant neural maturation, stress experienced during adolescence may interact uniquely with the maturation of adolescent-specific neural mechanisms in regions of the brain continuing to undergo protracted development past childhood. Further, much of the literature has focused on structural measures of brain maturation, while relatively less is known about functional and molecular mechanisms. In this review, we will integrate neural structural, functional, and molecular findings from animal model and human literature regarding excitation and inhibition in PFC. To accomplish this, we will discuss this prior work which we identified based on interrogation of critical period mechanisms related to excitation and inhibition (e.g., GABA, glutamate, etc.) and cognition. We will include studies that focus on the adolescent period specifically, and examine the impact of stress on cognition. Further, we will focus on frontal systems given their critical role in cognition, as well as the findings indicating that frontal systems are undergoing critical period plasticity (Larsen and Luna, 2018; Perica et al., 2022). Thus, we will integrate these bodies of literature to contextualize findings within the model of adolescence as a critical period for cognitive function.

In this review, much of the research discussed has been performed in rodent models. In rodents, as in humans and non-human primates, the onset of puberty is one of the defining characteristics of early adolescence. However, adolescence also includes other important maturational processes that may occur prior to puberty or independent of pubertal hormones (McCormick et al., 2017; McCutcheon and Marinelli, 2009; Sisk and Foster, 2004). Further, many studies are inconsistent in reporting pubertal timing and staging within the pubertal period, and therefore, we use a broad definition of rodent adolescence spanning postnatal day (PND) 21–59, as opposed stricter definitions which may start around PND 28 and end at 42 (McCormick et al., 2017; Spear, 2000; Tirelli et al., 2003). Thus, our operationalization of adolescence can be thought of as including juvenile or early adolescence (PND 21 – 34), middle adolescence (PND 34–46), and late adolescence (PND 46–59) (Laviola et al., 2003). Studies in non-human primates and humans will also be discussed, and will include samples that span the late childhood/early adolescent to young adult age range. However, across all studies, we will be precise about what age we are referring to, and make comparisons between earlier developmental stages and later stages when possible.

Within these constraints, literature will be reviewed relating to the effect of stress during adolescence on cognition and on frontal cortex markers of critical period plasticity mechanisms, in particular relating to excitatory and inhibitory processes. We note that throughout this review, we refer to a specific set of plasticity and plasticity-related mechanisms defined in the context of critical periods, as we will discuss in the upcoming section. First, studies investigating the impact of stress during adolescence on cognition will be discussed. Second, literature will be reviewed pertaining to the impact of stress on mechanisms of excitatory and inhibitory processes in frontal cortex. Finally, this literature will be brought together to inform a model of how stress during adolescence could impact developmental trajectories of cognitive function and its underlying mechanisms, building upon the framework of adolescence as a critical period by exploring how stress might alter these critical period plasticity processes and outcomes.

1.1. Adolescence as a critical period

During critical period plasticity, relevant brain regions are particularly responsive to external, environmental input. This has been well-characterized in the visual system, starting with the seminal study done by Wiesel & Hubel that demonstrated that the organization of visual cortex circuitry of kittens was irreversibly altered if their eyes did not receive visual stimuli during a discrete time period immediately following the first opening of the kittens' eye (Wiesel and Hubel, 1963). This period during which the visual cortex must receive visual input to facilitate proper development is the visual system's critical period. Since then, the neurobiological mechanisms governing critical periods have been further characterized, and these mechanisms seem to be broadly conserved across neural systems (Reh et al., 2020). In both visual and auditory cortices, it has been demonstrated that the opening of a critical period is triggered by the transient excess of excitatory, glutamatergic neural activity that results from the sudden flood of external, environmental stimuli (such as light entering the eye for the first time). This has been found to lead to compensatory maturation of inhibitory neural circuitry, specifically parvalbumin-positive (PV) GABAergic interneurons, which re-establishes excitatory/inhibitory (E/I) balance (Dorrn et al., 2010; Espinosa and Stryker, 2012; Hensch and Fagiolini, 2005), leading to experience-driven, evoked neural activity becoming the primary driver of neural circuit organization over spontaneous neural activity (Toyoizumi et al., 2013). When the critical period is over, GABAergic inhibition and glutamatergic excitation are in balance with one another, resulting in fine-tuned neural circuitry that provides for optimal information processing and neuronal functioning.

Postmortem and in vivo human studies provide evidence suggesting that these critical period plasticity mechanisms may be present in frontal and association cortex during adolescence, providing evidence for adolescence as a critical period (Larsen et al., 2022; Larsen and Luna, 2018; Perica et al., 2022). Much like the visual system critical period requires visual input, the cognitive critical period would require more complex experiences that would optimally engage these higher-order regions of the brain in order to properly develop. Neurobiological changes that take place during adolescence, like a peak in dopamine, facilitate a heightened exploratory drive that encourages adolescents to engage with their environments in novel, autonomous, and cognitively challenging ways. Thus, the adolescent cognitive critical period is thought to be driven by more complex information coming from downstream circuitry which matured earlier in childhood. As in the visual system, where visual capabilities are permanently altered by the visual input the system receives from the environment during the critical period, cognitive developmental trajectories could be altered depending on the input the system receives during its critical period. This new, complex information being processed by PFC, in addition to pubertal processes and changes in sex hormones, have been proposed to act as a trigger for the maturation of GABAergic inhibitory circuitry and a shift in E/I balance (Delevich et al., 2021; Piekarski et al., 2017). Evidence for this shift in E/I balance has been found in rodents, where there are more PV GABAergic neurons in PFC and more inhibitory activity in PFC layer V of adolescents as compared to younger rodents (Caballero, Flores-Barrera et al., 2014; Caballero, Thomases et al., 2014). This has been extended in postmortem human studies, which have demonstrated more PV neurons following puberty as compared to prior to puberty in layer III dorsolateral PFC (Hoftman et al., 2017). In addition to changes in inhibition, changes in the excitatory glutamatergic system that support experience-dependent plasticity have also been observed in adolescent PFC (Henson et al., 2008). Although much of the work

informing this model was done in animals or postmortem human tissue studies, promising new evidence examining aspects of critical period plasticity in vivo in humans has emerged with recent advancements in noninvasive neuroimaging methodology. These studies have provided further evidence for a shift toward inhibition through adolescence as well as more E/I balance in regions of frontal and association cortex (Larsen et al., 2022; Perica et al., 2022; Silveri et al., 2013). Importantly, cognitive deficits in psychopathology have been associated with aberrant excitatory and inhibitory processes in PFC (Duman et al., 2019; Ferguson and Gao, 2018; Lisman, 2012; Nahar et al., 2021), although it remains to be thoroughly understood how this could arise as a result of disrupted developmental processes.

In addition to the presence of critical period opening factors, like the disruption of E/I balance, which begin the critical period process, there is also evidence for braking factors being present in frontal cortex during adolescence (Larsen and Luna, 2018). Critical period braking factors act to close the critical period window and prevent further plasticity once neural circuits have been established. This includes the development of perineuronal nets (PNNs), which are extracellular matrix structures that surround the soma and dendrites primarily of inhibitory PV neurons, thereby providing a physical barrier that regulates and limits plasticity (Fawcett et al., 2019). As such, PNNs increase in number toward the end of critical periods to dampen further plasticity, a phenomenon which has also been described in adolescent PFC (Drzewiecki et al., 2020; Larsen and Luna, 2018). PNNs maintain the inhibitory activity necessary for E/I balance that results from the maturation of PV neurons (Lensjø et al., 2017). Indeed, experimental removal of PNNs leads to reduced inhibitory activity and increased neural spiking variability, thus resembling a more immature state (Lensjø et al., 2017). In addition, myelination is also considered a braking factor by insulating axon tracts to speed neural transmission while also preventing further modifications (McGee et al., 2005).

In the context of discussing adolescence as a critical period, it is important to note that adolescence is often referred to as a "sensitive period" (Blakemore and Mills, 2014). While the biological mechanisms underlying critical period plasticity are also thought to apply to sensitive period plasticity (Hensch, 2004, 2005; Larsen and Luna, 2018), it is possible that the adolescent critical period might not close as permanently as early sensory system critical periods in order to maintain some degree of lifelong plasticity that could be adaptive for executive functions. However, given that a strong mechanistic distinction has not yet been made between critical and sensitive periods, the term "critical period" will be used throughout this review as mechanisms have been more thoroughly studied in critical periods.

1.2. The stress response during adolescence

Experience-dependent plasticity allows for environmental influences to shape neural development, thereby producing neural circuity that is adapted to the individual's specific environmental demands. While there are many such environmental factors that have the potential to impact neurodevelopmental processes, stress has been recognized as one such factor. Stress has been broadly defined as an event that an individual perceives to be uncontrollable, novel, or unpredictable, and therefore, leads to a specific set of physiological and behavioral responses (Koolhaas et al., 2011). However, different types of stressors and varying duration or intensity of stressors can lead to unique outcomes (Slavich, 2019). Biological responses to stress are multi-dimensional. Much of the work examining the mechanisms of stress on outcomes like cognition have focused on glucocorticoids, such as corticosteroids, as the primary biological mediator of interest. Glucocorticoids are the end products of the hypothalamic-pituitary-adrenal (HPA) axis, which along with the fast-acting sympathetic-adreno-medullar (SAM) axis, make up the "fight or flight" response (Chrousos and Gold, 1992). Like all hormones, glucocorticoids are secreted by endocrine glands, specifically the adrenal cortex, and are released into the peripheral bloodstream, thereby traveling through the bloodstream to reach their end targets. Thus, glucocorticoids are able to bind to any tissue that contains a corresponding receptor, thereby exerting varied and widespread effects throughout the body. Therefore, glucocorticoids, such as cortisol, are able to reach the brain by crossing the blood-brain-barrier to exert effects on the central nervous system (Banks, 2012; Joëls, 2018; Raymond et al., 2018), allowing for peripheral levels of cortisol to be reflected centrally (Joëls and Baram, 2009). Peripheral glucocorticoids are able to bind onto neurons specifically in PFC (Joëls et al., 2012). Mechanistically, glucocorticoid binding to receptors on the surface of PFC neurons could recruit other mediators, such as endocannabinoid signaling processes, that could lead to changes in downstream neural activity (Hill et al., 2011; Joëls et al., 2012). However, corticosteroids can also directly modulate neural activity by binding to glucocorticoid (GR) and mineralocorticoid (MR) receptors on neuronal membranes as well in nuclear form (Popoli et al., 2012). MRs have a much higher affinity for corticosteroids than GRs, and therefore, they are usually occupied even at low levels of stress (Joëls and Baram, 2009). GRs have a lower affinity for stress hormones and thus are only occupied at higher levels of stress. This MR/GR ratio has been proposed as a mechanism underlying the inverted-U effects of stress on performance, wherein about half occupancy of GR receptors can have positive effects on performance but saturation of GR receptors could be underlying detrimental effects (de Kloet et al., 1999).

While it has been assumed that glucocorticoids, such as cortisol, are secreted in response to a stressor and this secretion scales with the intensity and/or duration of that stressor, the relationship between cortisol and stress has been shown to be more complex, particularly in humans (Michaud et al., 2008). Humans may have lower cortisol responses to laboratory stressors as compared to rodents, in addition to a variety of moderating factors that can impact how the stress response proceeds, such as stressor appraisal, controllability, predictability, or the type of stressor (Dickerson and Kemeny, 2004; Michaud et al., 2008). It should also be noted that cortisol responses to the same stressor acclimate over time, in addition to some studies showing that patients with Post-Traumatic Stress Disorder may have blunted cortisol responses (Michaud et al., 2008; Yehuda, 2002). Thus, while cortisol is an important factor in the acute stress response, there are many factors involved in the chronic stress response that could be involved in producing the wide-ranging effects seen as a result of long-term stressors in addition to glucocorticoids, such as inflammatory processes (Slavich and Irwin, 2014). However, the biological processes underlying the transition between an acute and chronic stressor are still not well understood (Rohleder, 2019).

Through adolescence, there are developmental changes in the stress response system that may render adolescents more susceptible to its effects. Rodent models have found that adolescents exhibit protracted stress hormone compared to adults (Romeo, 2013) and human studies show elevated cortisol levels in adolescence (Shirtcliff et al., 2012), suggesting prolonged and elevated stress responses. These normative developmental changes in the stress response system during adolescence could interact or be related to frontal maturation impacting its trajectory. In particular, early life stress has been associated with numerous neurobiological changes such as structural and functional changes in PFC, hippocampus, and amygdala, in addition to executive function deficits and emotional difficulties (Hanson et al., 2012; Herzberg and Gunnar, 2020; Teicher et al., 2016). Models have been proposed to delineate how stress may alter developmental trajectories. The Stress Acceleration Hypothesis proposes that early life adversity leads to a compensatory mechanism of premature development of emotional and associative learning systems, which comes at a cost to prolonged, adaptive plasticity needed for optimal specialization of cognitive systems (Callaghan and Tottenham, 2016). The Diathesis-Stress Model of Schizophrenia underscores how, in combination with heightened genetic risk for the disorder, early life and adolescent stress may be a trigger for the emergence of schizophrenia symptoms (Gomes and Grace,

2017; Mittal and Walker, 2019; Pruessner et al., 2017). However, stress experienced at different stages of development could have unique effects on different regions of the brain. Stress experienced during adolescence could have greater impact on the frontal cortex given its peak plasticity and maturational trajectory through adolescence into adulthood (Gogtay et al., 2004; Lupien et al., 2009; D. Simmonds et al., 2014).

2. Impact of stress during adolescence on cognition

There is consensus in the literature that stressors can have profound influences on cognition. Generally, short-term or acute stressors of low-to-moderate intensity have the potential to enhance cognition, while more chronic or sustained stressors or stressors that are acute but of high intensity have been found to have impairing effects on cognition (for review see Sandi, 2013). This literature on stress and cognition has fit in with the inverted-U model, wherein there is a "sweet spot" or optimal amount of stress that enhances cognitive abilities, but too little and too much stress may be detrimental to performance (summarized in Lupien et al., 2007; Sapolsky, 2004). As discussed previously, although this model is useful and biologically plausible, it has been criticized for being overly simplistic as many more dimensions to stressors can influence outcome and response (Schwabe et al., 2012), which we will examine where the literature allows. Throughout this review, the studies will be considered within the groupings of acute stressors and chronic stressor in order to consider the dimension of duration in depth and to understand how neural mechanisms may be differentially impacted depending on stressor duration.

2.1. Acute stress

Human and rodent studies find that acute stressors, across developmental contexts, can have impairing or enhancing effects on cognition, depending on specific factors and contexts (see Table 1 and Table 3). Male mice that underwent one of 3 different acute stress paradigms (forced swim, restraint stress, elevated platform) sometime between PND25 and 28 had enhanced working memory ability when measured 4 h post-stress or 1 day post-stress (Yuen et al., 2009). The boost in working memory ability post-stress was no longer present 2 days following cessation of stressor. Similarly, 17–25 year old humans showed improved cognitive flexibility mediated by salivary cortisol after the Trier Social Stress Task, where participants have to make a presentation followed by a math test to a not-encouraging audience (Gabrys et al., 2019). Importantly, participants who expressed that the stressful situation was controllable performed better. Finally, enhanced inhibitory control following acute social stressors was also found in human adolescents and young adults (19–25 years old, Chang et al., 2020; 20–32 years old, Schwabe et al., 2013).

However, the timing of the administration of the stressor relative to the cognitive task may be an important moderator of the association between acute stress and cognition. Undergraduates (mean age = 20, SD=3.86) who did the Trier Social Stress Task, inhibitory control was found to be impaired when inhibitory control was measured immediately after the stressor (Roos et al., 2017). Similarly, 18–25 year old year old human females who completed a working memory task immediately after watching stressful movie clips had impaired working memory (Qin et al., 2009). In contrast, the other studies that found enhancing effects did the cognitive tasks following a delay period. Therefore, the immediate effects of an acute stressor may be more impairing for cognition, while the enhancing effects of acute stress may not emerge until after a short delay period. Within the acute stress response period when sympathetic nervous system activation is high, fast-acting mediators of the stress response, such as norepinephrine, may activate the amygdala and interact with glucocorticoids in such a way to produce short-term impairing effects on cognition in favor of more immediately necessary responses (Qin et al., 2009; Roozendaal et al., 2006). However, over time when the fast-acting biological mediators subside, glucocorticoids

Table 1
Summary of findings from studies of impact of stress on cognition. Sample size for rodents reflects range used throughout experiments as group sizes varied between experiments. Sample size was reported with the information that was provided.

Reference	Stress paradigm	Cognitive paradigm	Sample	Effect on cognition
Acute Stressors				
Gabrys et al. (2019)	Trier Social Stress Task	Berg's Card Sorting task	64 undergraduate students (17 – 25 y.o.; 44 F)	⇑ cognitive flexibility
Chang et al. (2020)	Trier Social Stress Task	Stop Signal Task	30 (19–25 y.o., 14 F)	⇑ inhibitory control
Schwabe et al. (2013)	Socially Evaluated Cold Pressor Test	Stop Signal Task	72 university students (20–32 y.o., 40 F)	⇑ inhibitory control
Roos et al. (2017)	Trier Social Stress Task	Stop Signal Task	97 undergraduate students (age range not reported; 51 F)	⇓ inhibitory control
Qin et al. (2009)	Watching stressful movie clips	n-back task	29 18 – 25 y.o. healthy females on oral contraceptives to control for hormonal fluctuations	⇓ working memory
Rahdar and Galván (2014)	Self-reported, ecological momentary assessment of discrete, daily stressors	Go/No-Go task	22 adolescents (15–17 y.o.; 9 F) 23 adults (25–30 y.o.; 13 F)	⇓ inhibitory control in high stress state in both adolescents & adults, but effect was more pronounced in adolescents
Chronic Stressors				
Novick et al. (2013)	5-day social defeat stress	Delayed alternating T-maze task	36 male, Sprague-Dawley rats PND35 at time of stressor PND60 at time of working memory paradigm	⇓ working memory
F.Zhang et al. (2016)	10 days of social defeat stress	Attentional Set-Shifting task	9–11 male, C57BL/6 J mice per group Experiment 1: PND28, PND38, or PND70 at the start of stress followed by isolation housing; half of mice in each group did behavioral tests 1 week after stress and half did behavioral tests 6 weeks after stress Experiment 2: PND28 at start of stress followed by social housing for 6 weeks	⇓ cognitive flexibility in adulthood for mice stressed in early adolescence

(continued on next page)

Table 1 (*continued*)

Reference	Stress paradigm	Cognitive paradigm	Sample	Effect on cognition
			until behavioral tests	
Y.Zhang et al. (2017)	Unpredictable chronic mild stress; 2–4 stressors every day for 2 weeks, including food/water deprivation, cage tilt, lighting disruptions, white noise, wet bedding, paired housing, hot/cold air	Attentional Set-Shifting task	18 male, Wistar rats (9 per group) PND28 – 41 stress paradigm PND66 – 72 for AST task	⇓ cognitive flexibility
Snyder et al. (2014)	5 days of social defeat stress	Operant strategy-shifting task	8 – 28 male, Sprague-Dawley rats PND28, PND 42, or PND 70 for start of stress paradigm Behavioral test either 6 days after stressor or in adulthood	⇓ cognitive flexibility in adulthood for rats stressed in mid-adolescence
Hyer et al. (2021)	2 weeks of mixed-modality stressors, including social isolation, social defeat, and restraint stress	Attentional Set-Shifting task	4 – 12 male & female Wistar Rats PND35 for start of stress paradigm PND85 for behavioral test	⇓ cognitive flexibility in female rats
Vassilev et al. (2021)	Accelerated social defeat stress (4 days, 2x per day)	Go/No-Go task	125 adolescent rats and 111 adults Male, C57BL/6 J mice PND25 for adolescents and PND65 at start of stress Tested on Go/No Go Task 40 days after stressor	⇓ inhibitory control in adult mice stressed in adolescence but not in mice stressed as adults
Chaby et al. (2015)	40 days of a mix of physical, social, and predation stress; each week rats encountered 6 stressors with each type 2x per week	Radial Arm Maze	24 male, Sprague-Dawley rats (12 per group) PND30 at start of stressor, PND 70 at end PND261–262 at time of working memory paradigm	More easily disrupted working memory
Lyons et al. (2000)	28 days of drinking cortisol-treated water	Line-of-sight task	16 young adult female squirrel monkeys (27 – 44 months old) 16 older adult female squirrel monkeys (116 – 171 months old)	⇓ inhibitory control in both young and older adult monkeys
Torregrossa et al. (2012)	20 days of drinking cortisol-treated water	Stop Signal Task	Male, Sprague-Dawley rats PND 30 – 50 cortisol treatment PND 60 inhibitory control task	⇑ inhibitory control

continue to exert other slow effects which may be involved in the boost in cognition after a delay period following acute stress (Joëls and Baram, 2009).

In a more naturalistic study design, adolescents and adults showed impaired inhibitory control as measured by the Go/No Go task following self-reported high stress conditions as compared to low stress conditions (Rahdar and Galván, 2014). Although both adolescents and adults showed impairment in a "high stress" state relative to a "low stress" state, the effect was more pronounced for adolescents than adults, in line with the proposal that adolescence may be a time of unique stress reactivity. Further, in adolescents, this effect was specifically accompanied by reduced dorsolateral PFC activation during the task, supporting a unique impact on PFC during adolescence. In this study, there was on average a 2-hour delay between daily stressor reporting and lab visit. Although this is seemingly in conflict with the previous studies that suggested that a delay between stressor and task could lead to enhancing effects on cognition, given that participants self-reported low and high stress states, the authors were not able to control for the level of stress experienced by the participant, which may have included high or chronic stress states. Therefore, it is possible that this effect supports the idea that stressors of a higher intensity have the potential to be impairing, as the "high stress" state self-reported by the participants may have been beyond the optimal, moderate level of arousal that can benefit cognition, an effect which may be even more enhanced for adolescents. In sum, acute stress may initially engage systems that could undermine cognitive processes, but following a recovery period, acute stress could actually enhance cognition, suggestive of a potentially adaptive process.

2.2. *Chronic stress*

A larger number of studies on animal models, predominantly rodents, have focused on examining the effects of chronic stress during adolescence on cognition (see Tables 1 and 3). Male rats that underwent a social defeat stress paradigm for 5 days starting at PND 35 exhibited worse working memory performance when tested as adults, that worsened with increased working memory demands (Novick et al., 2013). Similarly, multiple studies looking at the effect of chronic social defeat stress during adolescence found impairments in cognitive flexibility. In male mice that underwent 10 days of social defeat stress starting at PND 28, cognitive flexibility in adulthood was found to be deficient as compared to controls, specifically in the extra-dimensional set-shifting (EDS) stage of the Attentional Set-Shifting Task (AST) (Xu et al., 2021; F. Zhang et al., 2016). When adult mice experienced prolonged stress, cognitive deficits were immediately evident but they were transient, whereas mice stressed at PND28 had deficits that did not emerge until adulthood but persisted (F. Zhang et al., 2016). Similarly, male rats that underwent an unpredictable chronic mild stress paradigm starting at PND28 until PND 41 had persistently impaired cognitive flexibility in adulthood specific to the EDS stage (Y. Zhang et al., 2017). Finally, male rats that underwent 5 days of social defeat stress starting at PND 28 exhibited cognitive flexibility deficits as adults during the strategy-shifting phase of the Operant Set-Shifting Task (Snyder et al., 2014). In all of these tasks, the deficit occurred on the last stage of the task, which could be considered the most cognitively difficult, thus

suggesting that adolescent chronic stress could uniquely impact more difficult cognitive tasks rather than all of cognition. In comparison to the aforementioned studies that started stress paradigms earlier in adolescence, 3 weeks of social isolation starting at PND 38 led to deficits in both the reversal learning stage and the EDS stage of the AST (Lander et al., 2017). In rodent lesion studies, lesions of mPFC (medial prefrontal cortex) have been shown to specifically impair set-shifting, while OFC (orbitofrontal cortex) lesions were shown to impair reversal learning (Birrell and Brown, 2000; Liston et al., 2006; McAlonan and Brown, 2003). Therefore, it is possible that this effect could have been due to differences in the timing of stressors, where earlier stressor timing may have affected the maturation of mPFC and its related functionality more, while later timing may have affected OFC. Indeed, in rodents, medial PFC may reach adult volumes prior to OFC (van Eden and Uylings, 1985).

However, it should be noted that a study of both male and female rats using a 12-day chronic stress paradigm consisting of a combination of social isolation, social defeat, and restraint stress in mid-adolescence found that only adult female rats that had been stressed as adolescents had deficits in the cognitive flexibility task specific to the reversal learning stage of the AST, but not the EDS stage (Hyer et al., 2021). In Hyer et al. (2021), the deficit in female rats was attenuated following ovariectomy, suggesting a possible role of estradiol. This differing result could have been due to differences in the type of stress paradigms used. Given the conflicting results and limited literature including female animal models, more work is needed to further interrogate how different stress paradigms and their combinations could impact cognition, as well as sex differences within that.

Importantly, in studies that compared across developmental stage, cognitive deficits seen in animals stressed in adulthood were immediately present but generally transient whereas adolescent-stressed animals seemed to have no short-term cognitive deficits, but rather exhibited deficits that persisted and emerged in adulthood (Snyder et al., 2014; F. Zhang et al., 2016). In addition to the deficits in cognitive flexibility and working memory, inhibitory control was found to also exhibit this delayed effect from chronic stress in adolescence, wherein male mice stressed for 4 days starting at PND 25 and tested 40 days later as adults exhibited inhibitory control deficits but mice stressed as adults did not (Vassilev et al., 2021). Therefore, stress experienced during adolescence could have a differential impact to stress experienced during adulthood. This may be due to stress interacting with experience-dependent plasticity during adolescence that could begin the process of altering the trajectory of cognitive outcomes, even if the impact of that might only emerge over time once trajectories are more established (Andersen and Navalta, 2004; F. Zhang et al., 2016). In line with this are additional findings from the Zhang et al. (2016) study, demonstrating that social housing following early adolescent social defeat stress was able to reverse cognitive deficits in adulthood, thus highlighting the ability to harness ongoing plasticity during adolescence to ameliorate the impact of stressful life experiences. However, it should be noted these findings differed on whether stress during early or middle adolescence would have the most impact on later cognitive outcomes, possibly due to differences in the animal models used (mice vs rats), thus underscoring the importance of future studies examining this in humans.

Therefore, while the majority of studies find that chronic stress during adolescence leads to later cognitive deficits, some report somewhat counter findings. In male rats that underwent a chronic, unpredictable stress paradigm that started at PND 30 and consisted of a mix of physical, social, and predation stressors until PND 70, there were no differences observed between unstressed and adolescent-stressed rats in working memory performance when measured at PND 261 (Chaby et al., 2015). HoFwever, following exposure to a novel environment that was aimed to disrupt the memory for the original working memory task, adolescent-stressed rats' performance dropped to that of their first trial on the task, whereas control rats that were not stressed continued to linearly improve on the task, suggesting that adolescent-stressed rats may have more easily disrupted cognition. The observed differences between this study and the prior studies could be due to the different durations of stress during adolescence, the different type of stressors, or the measurement of working memory much later in adulthood. Further, two studies using cortisol-treated drinking water during adolescence as their stress paradigm as opposed to behavioral stress paradigms found either no difference in inhibitory control (Lyons et al., 2000) or enhanced inhibitory control (Torregrossa et al., 2012) in adulthood. It should be noted that given the complex relationship between glucocorticoids and chronic stress, it is not clear how keeping sustained, high glucocorticoids levels high would translate to naturalistic stress-responses and outcomes. Given the conflicting results as compared to behavioral stress paradigms, more work is needed to understand how cortisol levels over time would fluctuate as a result of chronic behavioral stressors.

In sum, acute stress appears to have the potential to produce cognitively enhancing effects across cognitive constructs under certain conditions. However, the severity and intensity of the acute stressor could determine whether or not the stressor is enhancing or whether the stressor becomes potentially impairing. In contrast, chronic stressors are generally found to have detrimental effects on cognition. This effect may be limited to more challenging cognitive tasks. Importantly, chronic stress in adulthood may be evident immediately and be more short lived following removal of the stressor, whereas in adolescence, cognitive effects emerge over time and persist into adulthood likely due to altered developmental trajectories.

3. Impact of stress during adolescence on cortical excitation

3.1. Acute Stress

As discussed previously, acute stress can have an enhancing effect on cognition. One mechanism underlying this adaptive effect might be the enhancement of excitatory glutamatergic activity, which is known to initiate many forms of synaptic potentiation and plasticity processes (Barnes et al., 2020). Yuen et al. (2009) examined the effect of a variety of physical acute stress paradigms on glutamatergic processes in the mPFC of PND 25–28 male rats (see Tables 2 and 3). These acute stress paradigms led to greater potentiation of excitatory neurons by up-regulating post-synaptic glutamate receptors, which may contribute to the aforementioned results showing enhanced working memory ability. These effects on excitation and cognition were mediated by corticosterone binding on glucocorticoid receptors on the surface of excitatory mPFC neurons (Yuen et al., 2009, 2011). Another study using a mild acute stressor in the form of a brief cage change in PND 56 male and female mice was shown to induce growth of spines in a region of mPFC, the prelimbic cortex, specifically mushroom spines (Barfield et al., 2020). These mushroom spines are a more mature, stable type of spine that can potentiate and stabilize synapses, providing for longer-term synaptic plasticity (Bourne and Harris, 2007). Finally, in human adolescents that developed Post-Traumatic Stress Disorder (PTSD) following the 2008 Wenchuan Earthquake, Magnetic Resonance Spectroscopy showed lower levels of glutamate in the anterior cingulate cortex as compared to healthy controls and participants in remission from PTSD (Yang et al., 2015). Although the earthquake stressor is acute in its duration, the intensity of the stressor may be more akin to the impact of a chronic stressor, which would dampen glutamatergic activity in PFC, as has been reported in animal studies of chronic stress which will be discussed shortly. Thus, the intensity of the stressor is an important dimension to consider, as stressors that are acute but very intense or traumatic likely impact the brain differently than milder acute stressors that can show potentially enhancing effects on glutamate and cognition (Abdallah et al., 2019).

Table 2
Summary of findings from studies of impact of stress on excitation and inhibition. Sample size for rodents reflects range used throughout experiments as group sizes varied between experiments. Sample size was reported with the information that was provided.

Reference	Stress paradigm	Sample	Effect on excitation and/or inhibition
Acute Stressor			
Yang et al. (2015)	2008 Wenchuan Earthquake	21 healthy controls (13 – 17 y.o., 11 F) 10 PTSD participants (mean age = 13 – 16 y.o., 6 F) 23 remitted participants (13 – 16 y.o., 13 F)	⇓ Glx/Cr in ACC of PTSD participants
Houtepen et al. (2017)	Trier Social Stress Test	30 male participants (18–40 y.o.)	No change in GABA/Cr Less correlated GABA and Glu
Hasler et al. (2010)	Threat of Shock	10 participants (19–49 y.o.; 4 F)	⇓ prefrontal GABA in threat of shock condition
Chronic Stressor			
Novick et al. (2016)	5 days of social defeat stress	20 male, Sprague-Dawley rats (10 per group) P35 for start of stress P56 for histology	⇓ NMDA receptors in mPFC
Leussis and Andersen (2008)	5 days of social isolation	5 – 8 male & female Sprague-Dawley rats P30 at start of stress P36 for histology	⇓ spinophilin, SVP in infralimbic and cingulate cortex, no sex differences
Leussis et al. (2008)	5 days of social isolation	48 male Sprague-Dawley rats (6 per group) P30 at start of stress Between P40 and P55 for MK-801 or Adinazolam P60 for histology	⇓ spinophilin, SVP in infralimbic and cingulate cortex Effects reversed by MK-801 and Adinazolam
Urban and Valentino (2017)	5 days of social defeat stress	4 – 5 male & Female Sprague-Dawley rats PND30, PND 42, or PND 69 for start of stress Histology done 24 h after stress	⇓ amplitude of post-synaptic currents in mPFC ⇓ excitability of mPFC neurons in mid-adolescence especially
H.Zhang et al. (2016)	14 days of social defeat stress	10 – 19 male Balb/c mice PND 28 for start of stress MRS the day after stress and 3 weeks after stress	⇓ Glx right after last session of stress which returned to control level 3 weeks later
Negrón-Oyarzo et al. (2014)	7 days of restraint stress	40 male Sprague-Dawley rats (20 per group) P42 at start of stress P50 or P71 for electrophysiology	⇓ EPSPs one day after stressor that returned to control levels in adulthood
Eiland et al. (2012)	21 days of restraint stress for 6 h per day	7–8 male & female Sprague-Dawley rats PND20 for start of stress	⇓ apical dendrite length, apical branch points for both males and females in prelimbic cortex
Breach et al. (2019)	15 days of social instability stress (SIS) for 1 h per day	24 male & female Sprague-Dawley rats (12 per group) PND30 for start of stress PND79 for histology	⇓ apical dendrite length and thin spine density in females after SIS in prelimbic cortex ⇓ basilar dendrite length in males after SIS in prelimbic cortex
Ng et al. (2018)	7 days of restraint stress for 6 h per day	4 – 6 C57BL/6 J mice PND30 at start of stress	⇓ new spine formation after 2 days ⇑ spine elimination after 2 days (mostly mushroom spines) ⇓ overall spines at 7 days ⇓ survival of new spines at 7 days
Barfield et al. (2020)	25 days of drinking corticosterone in water; cage change	4 – 9 male & female C57BL/6 mice PND31 for start of CORT drinking P56 cage change and/or histology	⇑ mushroom spine in prelimbic cortex of both control mice and CORT treated mice after acute stress ⇓ mushroom and thin spine densities in OFC but not prelimbic after chronic CORT drinking
Wei et al. (2014)	7 days restraint stress	4 – 14 male & female Sprague-Dawley rats P21–23 at start of stress Glutamate measured 1 day after stress	⇓ amplitude of mPFC layer V EPSCs in males but not females ⇓ post-synaptic AMPA and NMDA receptors
Page and Coutellier (2018)	2 weeks of daily unpredictable chronic mild stress presented randomly; daily exposure to 24 hr abscence of netting material, 6 hr of cage tilt, 8 hr absence of bedding in cage, 8 min of restraint stress in the dark, 4 min of restraint stress in bright light	3 – 5 male & female C57BL/6 J mice PND28 start of stress PND48 or PND 80–83 for histology	⇑ NR2B expression in male but not female mice ⇓ number of PV neurons in PL cortex of male but not female mice No change in PNN in PL cortex ⇑ PNN in IL cortex of female mice only
Bueno-Fernandez et al. (2021)	Mixed-modality physical and predation stressors took place for 7 days between PND28 and PND42	8 – 11 male and female THY1 and PV-tdT mice PND28 at start of stress P90 histology for male mice, P90–95 histology for female	All results in IL cortex ⇓ spine density in males ⇑ spine density in females No change in VGLUT puncta ⇑ VGAT puncta

(*continued on next page*)

Table 2 (*continued*)

Reference	Stress paradigm	Sample	Effect on excitation and/or inhibition
		mice (when reached diestrus phase)	in both sexes ⇓ VGLUT/VGAT ratio No change in number of PV neurons ⇑ dendritic arborization in females only No change in PNNs
Tzanoulinou et al. (2016)	7 days of exposure to synthetic fox odor and elevated platform in a 7 day period	6 – 16 male, Wistar rats PND28 start of stress PND95 at histology	⇓ GAD6 in prelimbic, infralimbic, and orbitofrontal cortex, but not cingulate cortex
Bicks et al. (2020)	2 weeks of social isolation	8 – 11 male, C57BL/6 or PV-Cre or PV-GFP mice P21 at start of stress	⇓ excitability of dmPFC PV neurons ⇓ excitatory drive onto dmPFC PV neurons
Perova et al. (2015)	2 days of learned helplessness induction followed by 1 day of testing	24 – 39 male C57BL/6 N mice PND35–42	⇓ amplitude of EPSCs onto layer V PV neurons in mPFC
Ueno et al. (2017)	5 weeks of social isolation	10 male C57BL/6 N mice (5 per group) P21 at start of stress P56 for histology	No change in number of PV neurons ⇓ PV expression in PL cortex ⇓ PNNs in PL cortex and dACC

3.2. Chronic stress

Overall, studies looking at the effect of chronic stress during adolescence have generally found decreases in aspects of excitation. Yuen et al. (2012) examined the impact of 7 days of either restraint stress or an unpredictable stress paradigm consisting of a variety of physical stressors starting at PND21 on excitatory processes in mPFC. In both the restraint stress and unpredictable stress groups, decreased levels of post-synaptic AMPA and NMDA glutamate receptors was observed. In addition, 7 days of stress was found to produce deficits on the Temporal Order Recognition Task, a task involving PFC in addition to temporal cortex and hippocampus. Importantly, when a glucocorticoid antagonist was administered, the impact of chronic stress was prevented, providing a mechanistic link between stress-response mediating glucocorticoids and excitatory processes. Similarly, male rats that underwent 5 days of social defeat stress starting at PND 35 had decreases in glutamate receptor expression, specifically NMDA receptors, at PND 56 in a region of mPFC, the infralimbic cortex (Novick et al., 2016). Both AMPA and NMDA receptors are critically involved in the induction of synaptic plasticity; thus, downregulating these receptors could result in dampening of plasticity. In line with this model are findings showing that isolation housing starting at PND 30 led to decreased amounts of synaptophisn, a protein marker of synaptic density, and spinophilin, a protein marker of dendritic structure and function, which could be reflective of mechanisms involved in plasticity, in infralimbic cortex and cingulate cortex immediately after the stressor that persisted into adulthood (Leussis et al., 2008; Leussis and Andersen, 2008). In addition, chronic stress during adolescence has been found to have an overall effect on excitatory activity and glutamate levels. In adolescent Sprague-Dawley rats, 5 days of social defeat stress (Urban and Valentino, 2017) and 7 days of restraint stress (Yuen et al., 2012) were both shown to lead to dampening of excitatory activity as a result of decreased post-synaptic responses in mPFC. Although social defeat stress dampened excitation immediately after the stressor in both adolescence and adulthood, stress during mid-adolescence (starting at PND 42) had additional unique impacts, leading to the dampening of intrinsic neuronal excitability in addition to the decreased post-synaptic response of excitatory neurons in mPFC in both male and female rats (Urban and Valentino, 2017). In addition to effects on neurons, social defeat stress was found to impact glutamate levels as well. After a 2-week long social defeat stress paradigm beginning at PND 28, male mice were found to have decreased mPFC glutamate levels one day after stress in mice stressed in adolescence as compared to unstressed mice (H. Zhang et al., 2016). Glutamate levels returned to control levels following three stress-free weeks. In addition, 7 days of restraint stress starting at PND 42 led to dampened excitatory activity in the prelimbic cortex of male rats measured one day after stressor, which similarly returned to control levels three weeks after cessation of stressor (Negrón-Oyarzo et al., 2014).

Finally, chronic stress during adolescence has also been shown to lead to changes in neuronal structure in excitatory glutamatergic neurons. Shorter apical dendrites and fewer branch points in prelimbic cortex (but not infralimbic cortex) were found after 21 days of restraint stress in both male and female rats starting at PND 20 (Eiland et al., 2012). This contrasts with another study that showed that social instability stress starting at PND 30 in male and female rats led to shorter prelimbic cortex apical dendrite length and spine density in adult female rats, but shorter basilar dendrite length in adult male rats (Breach et al., 2019). These differences in what specific aspect of neuronal structure is impacted could be due to the timing of the stress paradigm, with later stress impacting the basilar dendrites, or the type of stress paradigm used. After 7 days of restraint stress starting at PND 30 in mice, there was an increase in mushroom spine elimination on dendrites of excitatory neurons as well as a decrease in new mushroom spine formation in frontal association cortex (Ng et al., 2018). This effect on mushroom spines was not able to be reversed by 5 stress-free days. Finally, one study examined the impact of drinking corticosterone treated water starting at P30 on spines measured at P56, and found no effect in the prelimbic cortex but fewer spine densities, specifically mushroom and thin type, in orbitofrontal cortex (Barfield et al., 2020). Therefore, it would appear that the majority of studies find that chronic stress during adolescence has the ability to impact neuronal structure in such a way that could limit plasticity (but see Lander et al., 2017 who saw either increases in markers of excitation).

Interestingly, there may be sex differences in the impact of stress on aspects of excitatory neurotransmission. Seven days of restraint stress starting at PND 21–23 replicated the decreased glutamate levels and dampened excitatory activity as previously shown in male rats, but female rats were unaffected (Wei et al., 2014). Estrogen injections were able to reverse the deficits in male rats, suggesting that estrogen may have a protective effect on the impact of stress on these changes in excitation (Wei et al., 2014). In addition, chronic stress starting at PND 42 led to less frequent excitatory firing in male mice but not female mice (Urban and Valentino, 2017). Further, sex differences were also found in NMDA receptors following 2 weeks of an unpredictable chronic mild stress (CMS) paradigm starting at PND 28 (Page and Coutellier, 2018). As a result of the CMS in adolescence, there was a significant increase in NR2B-type NMDA receptor subunit expression as compared to NR2A specifically in adult male mice stressed as adolescents, but not female mice. Changing the composition of NMDA receptors can have an impact on the firing patterns of excitatory neurons (Monaco et al., 2015). Indeed, this subunit composition changes normatively through adolescence, with a greater proportion of NR2B subunits during developmental periods transiently necessary to promote plasticity processes; however, NR2B levels typically reduce with the closing of the critical period

Table 3
Summary of findings from studies of impact of stress on cognition and excitation/inhibition. Sample size for rodents reflects range used throughout experiments as group sizes varied between experiments. Sample size was reported with the information that was provided.

Reference	Stress paradigm	Cognitive Task	Sample	Effect on excitation and/or inhibition	Effect on cognition
Acute Stressor					
Yuen et al. (2009)	Forced Swim, Restraint Stress, Elevated Platform	Delayed Alternation task	12 – 18 male, Sprague-Dawley rats Stress at PND25–28	⇑ post-synaptic glutamate receptors in layer V mPFC pyramidal neurons	⇑ working memory Effect gone 2 days after stressor
Chronic Stressor					
Xu et al. (2021)	10 days of social defeat stress followed by isolated housing	Attentional Set-Shifting task	7 – 9 male, C57BL/6 J mice PND28 – 37 social defeat stress, followed by isolation housing until PND70 which was the start of behavioral testing	⇓ inhibitory currents and GAD2 mRNA expression in mPFC	⇓ cognitive flexibility
Lander et al. (2017)	3 weeks of social isolation	Attentional Set-Shifting task	7 – 22 male, C57BL/6 J mice PND38 or PND60	⇑ mRNA expression of GLS1, EEAT1, vGlut1	⇓ cognitive flexibility, both reversal learning and extra-dimensional set-shifting
Yuen et al. (2012)	7-days of either restraint stress or unpredictable stress (2 stressors per day out of 6 different physical stressors)	Temporal order recognition task	5–9 male, Sprague-Dawley rats PND21 for start of stress PND29 for glutamate measurements and behavior	⇓ post-synaptic excitatory currents in layer V mPFC ⇓ post-synaptic glutamate receptors in mPFC	⇓ preference for novel object
Ueno et al. (2018)	8 days of physical stressors	Alternation task in a Y-Maze	20 male C57BL/6 N mice (10 per group) P21 or P71 at start of stress Histology done 10 days after start of stress	No change in number of PV neurons or number of PNNs ⇓ in fluorescence intensity of PNNs in dACC and IL cortex ⇓ soma area in dACC	No change in working memory ability
de de de Araújo Costa Folha et al. (2017)	Mixed physical stressors	Spontaneous Alternation task in an elevated plus maze	48 male Wistar rats (24 per group) P28 at start of stress Divided into 7, 15, or 35 days Histology done right after stressor & behavioral test	⇑ in PNNs in mPFC after 7 days of stress ⇓ in PNNs after 15 and 35 days of stress	⇑ working memory after 7 days ⇓ working memory after 15 and 35 days

(Larsen and Luna, 2018). Thus, an increase in NR2B subunits relative to what is expected developmentally could suggest a more immature neural circuitry (Page and Coutellier, 2018). Taken together, the literature suggests that males may be more vulnerable to the impact of chronic stress during adolescence on excitatory processes in frontal cortex. However, more work is needed on this subject as other studies did not find sex differences with regard to stress-induced dendritic remodeling (Eiland et al., 2012) and intrinsic neuronal excitability (Urban and Valentino, 2017). In addition, one study using a unique stress paradigm found decreased spine density in infralimbic cortex as a result of 7 days of mixed physical stressors in early adolescence, but actually found increased spine density in females (Bueno-Fernandez et al., 2021). Therefore, further research is needed to clarify sex differences, but some studies suggest that males may be more vulnerable, in addition to sex effects possibly being restricted to specific aspects of excitatory transmission.

In summary, the literature generally supports a biphasic model of stress with regard to its effects on excitatory, glutamatergic processes. During adolescence, acute lower-intensity stressors may have an enhancing effect on excitatory activity in frontal cortex and plasticity processes. Importantly, this may not be the case for more intense acute stressors, which may resemble chronic stressors. Chronic stressors during adolescence might decrease excitatory activity and plasticity in frontal cortex.

4. Impact of stress during adolescence on cortical inhibition

To the best of our knowledge, it appears that there are no studies examining the impact of *acute* stress on frontal GABA specifically limited to adolescents or comparing adolescents to other age groups. This is an important gap in the literature that future studies should aim to address. However, some studies have examined the effect of *chronic* stress during adolescence on GABAergic inhibition in frontal cortex.

After 10 days of social defeat stress starting at PND 28 followed by socially isolated housing until PND 70, there were fewer inhibitory currents and less GABA-synthesizing enzyme GAD65 (as indexed by less expression of GAD2 mRNA) in mPFC of male mice, in addition to impaired cognitive flexibility as measured by the AST and elaborated on previously (Xu et al., 2021) (see Tables 2 and 3). GAD2 is a gene that encodes for GAD65, an enzyme that specifically synthesizes GABA that is to be packaged into vesicles for release, whereas GAD1, which did not show any differences due to stress, is a gene that encodes another GABA synthesizing enzyme related to GABA used for other purposes, such as in metabolic pathways (Grone and Maruska, 2016). Further, adolescent rats exposed to 7 days of fox odor (predation) stressor and elevated platform stressor presented in a variable order starting at PND 28 showed reductions in the adult expression of GAD-6, an expression marker for GABA synthesizing enzymes, in the prelimbic, infralimbic, and orbital cortices, but not cingulate cortex (Tzanoulinou et al., 2016). Similarly, 2 weeks of social isolation starting at PND 21 found that stressed adolescent rats failed to exhibit developmentally normative increases in dmPFC PV neuron activity; rather, they showed decreased activity of PV neurons by way of lower excitatory drive onto PV neurons and decreased excitability of PV neurons themselves (Bicks et al., 2020). Similarly, in adolescent male mice that underwent the learned helplessness procedure at PND 35 for 3 days, inhibition was also found to be dampened in mice that were helpless, and this was found to be associated with decreased excitation of the inhibitory neurons in mPFC (Perova et al., 2015). Additionally, artificially suppressing PV neuron activity with pharmacogenetic approaches led to enhanced helpless behavior, supporting the link between dampened PV neuron activity in mPFC and helplessness behavior. Further, mice that experienced 5 weeks of social isolation beginning at PND 21 found no difference in the overall number of PV cells in the PFC, but did find a decrease in the

levels of parvalbumin inside these neurons in prelimbic cortex of stressed mice (Ueno et al., 2017). A decrease in the levels of parvalbumin inside these neurons can impact inhibitory activity by leading to dampened inhibitory activity via less frequent firing of PV neurons and thus impairment of oscillatory activity (Volman et al., 2011). Similarly, in male and female mice that experienced 2 weeks of unpredictable, mild physical stressors starting at PND 28, adult male mice showed less parvalbumin in the prelimbic cortex (Page and Coutellier, 2018). However, this study did not distinguish between number of PV cells and levels of parvalbumin inside the cells, limiting our mechanistic understanding. Overall, chronic stress during adolescence was found to lead to less inhibitory activity and decreases in mechanisms of inhibition in frontal cortex (but see Lander et al., 2017 and Bueno-Fernandez et al., 2021 for different findings).

Given the important role of perineuronal nets (PNNs) in inhibitory processes and closing of plasticity, some studies looked at the impact of adolescent stress on PNNs surrounding PV neurons in frontal cortex. In male mice that underwent 5 weeks of social isolation starting at PND 21, a decrease in overall parvalbumin levels was found as aforementioned, in addition to fewer PNNs surrounding PV neurons in the prelimbic region of mPFC and the dACC as compared to unstressed mice (Ueno et al., 2017). In male rats that experienced an unpredictable mild stressor starting at PND 28 and lasting for either 7, 15, or 35 days, there was an increase in PNNs after 7 days, followed by a decline in PNNs at 15 and 35 days in the mPFC (de de de Araújo Costa Folha et al., 2017). In comparison, unstressed control animals linearly increased in PNN number, as expected through the normative course of development. In another study, following 8 days of variable physical stressors starting at PND 21, male mice were found to have decreased PNN fluorescence intensity in dACC and infralimbic cortex, which could suggest decreased concentration or structural changes in PNNs (Ueno et al., 2018). Thus, PNNs may be sensitive to the duration of stressor, and may not reduce in number until stressors are present for a longer amount of time. However, Ueno et al. (2018) did not systematically vary stress duration as de de de Araújo Costa Folha et al. (2017) did, and these two studies also did not use the same animal model. However, Bueno-Fernandez et al. (2021) found that male and female mice were found to have no change in PNNs in any region of mPFC following 7 days of stress starting at PND28. It should be noted that Bueno-Fernandez et al. (2021) quantified PNNs 48 days after the stressor, whereas de de de Araújo Costa Folha et al. (2017) quantified PNNs right after the stressor, and therefore, any changes in PNNs may have reversed by adulthood. In line with this idea, a mix of mild physical stressors for 2 weeks starting in early adolescence found more PNNs surrounding PV neurons in infralimbic cortex of adolescent female mice only that did not persist into adulthood, but, contrary to the other studies, found no change in male mice (Page and Coutellier, 2018). It is possible that due to these stressors being "milder" in nature, the effects may have been different than stronger chronic stressors, although it is unclear how the intensity of stressors were defined and quantified. Thus, more work is needed to understand the gradient along which the intensity of chronic stress differentially affects PNNs, what the consequences are of transient changes in PNNs during adolescence, and how stress-induced changes may or may not persist into adulthood.

In summary, more research is needed on the effects of acute stress during adolescence on PFC inhibitory activity. While more work is also needed on the effect of chronic stress, the research is generally more consistent. Overall, there appears to be a dampening of inhibitory activity and a destabilization of neural circuits (e.g., less PNNs) in PFC as a result of chronic adolescent stress, especially stress that is present for a longer duration. More research is needed to elucidate the mechanism underlying this threshold.

5. Discussion

The extant literature suggests that stress experienced during adolescence has differential effects on excitatory and inhibitory activity in frontal cortex and cognition depending on a variety of factors. First, the duration of the stressor (acute versus chronic) appears to have distinct impacts. Acute stressors have the potential to enhance cognition in certain contexts, potentially mechanistically driven by enhancement of excitatory, glutamatergic and plasticity processes. The enhancing cognitive effects of an acute stressor may not be immediate, and may involve slower-acting stress-response mediators. However, more work is needed on the underlying biological mechanisms of this effect. Further, the impact of acute stress experienced during adolescence on inhibitory GABAergic processes is under-studied. It would generally appear that there may be an increase in inhibitory activity in the PFC following an acute stressor in adult rodent models (Drouet et al., 2015; for review see Perez-Rando et al., 2022), but adolescent-specific work is needed. It is important to note that the literature suggests that not all acute stressors are enhancing; acute but intense stressors (e.g. natural disasters), whose negative effects persist, may have impairing effects on cognition, and thus may mechanistically resemble more chronic stressors.

Divergent effects on the impact of acute stress on PFC-dependent cognition have been reported, with some studies reporting impairing effects and other studies reporting enhancing effects (Arnsten, 2009; Sandi, 2013). The variability in this literature is likely due to factors such as intensity of the stressor, timing of administration of the stressor relative to the cognitive task, or individual appraisal of the stressor (Sandi, 2013; Shields, 2020), as discussed throughout this review. Additionally, individual differences such as variations in genetics may play a role in whether cognition is enhanced or impaired by acute stressors (Zareyan et al., 2020). When considering acute stress experienced during adolescence specifically, the literature in both animal models and humans fits with the broader literature, where acute stressors are able to enhance cognition under the right conditions. However, it is important to note that adolescents exhibit greater hormonal stress reactivity as compared to both children and adults (Foilb et al., 2011; Shirtcliff et al., 2012; Sumter et al., 2010), so the impact of acute stressors may be exaggerated in adolescence as suggested in Rahdar and Galván (2014), and therefore the window of enhancement could be different than in other age groups. Future studies should aim to directly measure this by comparing adolescence to other developmental age groups to better understand how unique adolescent stress reactivity could mechanistically modulate the outcomes of the stress response.

An emerging literature has implicated glutamate as a mechanism underlying acute stress-induced enhancement of cognitive function. Acute stress and acute administration of stress hormones in adolescence have been shown to exert rapid effects on excitatory activity and plasticity-related mechanisms both pre- and post-synaptically, with evidence for more glutamate release, more post-synaptic glutamate activation of receptors, as well as post-synaptic modifications of receptors that could enhance plasticity (Popoli et al., 2012; Sanacora et al., 2022). This is generally in line with the reviewed findings that examined acute stress in adolescence, with acute stress paradigms leading to post-synaptic modifications in excitatory neurons which boosted cognition. With regard to the biological mediators of this process, corticosterone binding to excitatory neurons was shown to be one mediator. However, more work is needed to replicate and extend these findings and to elucidate the impact of acute stress on inhibitory processes during adolescence that interact with these excitatory processes. Despite these unanswered questions, it appears that acute stressors have the potential to interact with ongoing developmental plasticity processes in enhancing or synergistic ways. Given the ubiquity of more acute small-scale stressors in daily life, these stressors are unlikely to drastically alter developmental processes or trajectories. Indeed, encountering these types of stressors may be a learning opportunity that can be adaptive, and can lead to greater resilience in the face of future stressors (Albrecht et al., 2017). However, it is important to note that a previous history of stress in early life could modify the way adolescents respond to acute stressors and how neurodevelopmental processes during adolescence unfold (Majcher-Maślanka et al., 2018).

With regards to chronic stress during adolescence, generally impairing effects on cognition have been noted across cognitive processes. At a neurobiological level, there appears to be a dampening of both excitatory glutamatergic activity and inhibitory GABAergic activity in frontal cortex in adolescence that could underlie the observed cognitive deficits. This is generally in line with the broader literature on the effects of chronic stress on cognition, with impairing effects of chronic stress evident across cognitive processes in both animal models and human work (Sandi, 2013). However, chronic stress experienced during adolescence may have different and more persistent effects on cognitive outcomes. The timing of the stressor may impact what regions are affected most due to their ongoing maturation, thus leading to differential cognitive outcomes. Further, chronic stressors experienced during adolescence may have more persistent effects on cognition that linger into adulthood as compared to stress effects in adulthood, which may be more transient and reversible. Finally, the effects of chronic stress on cognition may not be immediately evident in adolescence, but instead might emerge over time as the result of altered developmental trajectories.

Mechanistically, the impairing effect of chronic stress during adolescence on cognition could be driven by decreases in frontal cortex excitatory and inhibitory activity. Generally, chronic stress in adolescence appears to decrease excitatory activity in frontal cortex, decrease levels of glutamate, and decrease glutamate receptor expression. In addition, structural changes on excitatory neurons such as shorter dendrites and increased elimination of spines could further dampen plasticity. Chronic stress also appears to dampen inhibitory activity in frontal cortex, in addition to leading to fewer GABA synthesizing enzymes, and lower levels of parvalbumin, which could lead to less frequent inhibitory activity. The impact on inhibition could be a consequence of dampened excitatory drive onto inhibitory neurons, a critical mechanism driving critical period plasticity processes as well as the generation of neural oscillations. Indeed, preventing PV neuron activity during adolescence leads to persistent impairments in adult PFC network function and cognition, while suppressing PV neuron activity in adulthood does not lead to persistent deficits (Canetta et al., 2022). Importantly, much of this work has focused on PV neurons, which are important in the context of adolescent critical period plasticity, but stress may or may not affect other aspects of inhibition as well.

More broadly, various models have been proposed with regard to the impact of stress on PFC excitation and inhibition. While a large body of literature generally converges on PFC hypoactivity as a result of chronic stress (for review see Arnsten, 2015; Arnsten et al., 2015), there is some disagreement with regard to the mechanism underlying this hypoactivity as well as the outcomes. There is generally agreement on reductions in glutamatergic, excitatory signaling and plasticity (Negrón-Oyarzo et al., 2016), but the impacts on GABA are less well understood. Prior reviews looking at the impact of chronic stress on E/I balance in adulthood have found evidence for increased inhibitory function in the PFC following chronic stress (McKlveen et al., 2019; Page and Coutellier, 2019). However, findings of chronic stress on PFC inhibition in development are mixed (McKlveen et al., 2019). This discrepancy in findings may be due to collapsing across distinct developmental periods such as pre- and perinatal, infancy, childhood, and adolescent periods, which have their unique cortical maturation process.

5.1. A model of the impact of stress during the adolescent critical period

As outlined in this review, the primary literature looking at the impact of chronic stress restricted to the window of adolescence generally suggests a dampening of both excitatory and inhibitory processes across regions of frontal cortex. Therefore, stress experienced during adolescence has the potential to interact with ongoing critical period plasticity processes to alter the course of development (Fig. 1). As aforementioned, acute stressors could interact with critical period plasticity processes in potentially enhancing ways, provided that they are relatively mild in intensity and not long-lasting. During adolescence in PFC and during critical periods more broadly, there is enhanced excitatory input that triggers the start of the critical period, combined with increases in plasticity promoting mechanisms (Larsen and Luna, 2018). These plasticity processes appear similar to the mechanisms of acute stressors on excitation, such as enhancement of excitatory activity and up-regulation of post-synaptic glutamate receptors involved in synaptic potentiation. Therefore, facing acute stressors through development could lead to enhanced cognitive ability over time as the brain adapts and learns from these challenges. This could support experience-dependent learning and cognitive development through adolescence. However, this highlights the importance of cognitive appraisal of acute stressors in determining how enhancing they can be, a question which is under-studied in this literature due to the reliance on animal models.

Chronic stressors or acute stressors that pass beyond a certain biological threshold are likely detrimental to frontal cortex critical period plasticity processes. Evidence indicates that stress operates in an inverted U function where too little or, importantly, too much is suboptimal. Determining these thresholds, which could vary by age and at the individual level, should be a goal of future research. Here, we found that the majority of the literature supports that chronic stress appears to dampen the excitatory activity necessary to drive experience-driven plasticity, in addition to decreasing plasticity-promoting mechanisms like post-synaptic glutamate receptors necessary for long-term plasticity

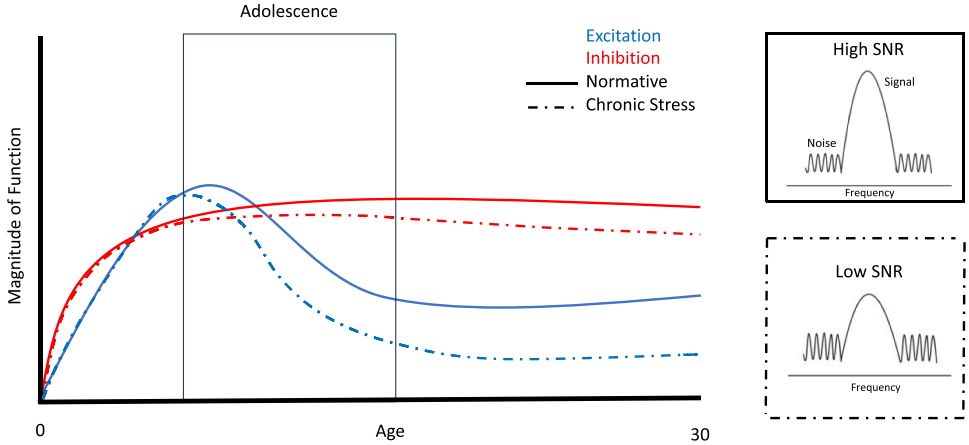

Fig. 1. A model of how stress impacts development of excitation and inhibition in frontal cortex during adolescence. During normative adolescent development, excitation decreases and inhibition increases, in line with a model of adolescence as a critical period for cognitive development. Chronic or very intense stressors experienced during adolescence dampen excitatory and inhibitory activity. This could have important functional consequences, such as leading to neural activity with a lower signal-to-noise ratio (SNR) and cognitive deficits. Curves are schematics meant to summarize findings from reviewed literature. Blue curve denotes excitatory function and red curve denotes inhibitory function. Solid curves indicate normative development, while dotted curves indicate trajectories impacted by stress. The gray box indicates the adolescent period. Figure created with BioRender.com.

as well as structural changes like the shortening of dendrites and decreases in new spine formation. Overall, this could potentially indicate that experiences may have less of an impact on frontal cortex organization and development during this time. If this is the case, it is possible that this could lead to a premature closing of the critical period window, which could potentially reopen if the chronic stressor was removed. Future studies directly investigating the impact of stressors on critical periods are needed to advance our understanding. These findings could also inform the extent literature reporting reduced PFC volumes. Decreases in glutamatergic function as a result of chronic stress could interact with ongoing, normative thinning of PFC and synaptic pruning, which involves pruning of primarily excitatory synapses (Giedd et al., 1999; Gogtay et al., 2004; Petanjek et al., 2011). Therefore, this could possibly lead to precocious maturation, in line with the Stress Acceleration Hypothesis, or over-pruning of synapses (Callaghan and Tottenham, 2016; Keshavan et al., 1994), which may also contribute to excessive thinning or premature critical period closing.

In line with the impacts on cortical thickness are damage to spines as a result of chronic stress, which was shown to be specific to mushroom spines in prelimbic cortex and both mushroom and thin spines in orbitofrontal cortex. As mentioned previously, mushroom spines are a more mature spine type that indicates more stable synapses. Interestingly, mushroom spines are preferentially created and selectively eliminated during normative synaptic pruning during adolescence (Dienel et al., 2022). Therefore, damage to more mature mushroom spines being created could suggest a stress-induced acceleration of a normative ongoing pruning process and a decrease in the creation of new mushroom spines, thus leading to over-pruning of mature synapses and therefore, creating a neural system resembling a more immature phenotype with fewer mushroom spines. In line with the idea of chronic stress leading to a more immature state are the impacts on NR2B receptors. NR2B receptors are expected to rise at the start of the critical period, but they also are expected to decline during the closing of the critical period in order to stabilize circuitry and limit further plasticity from occurring (Erisir and Harris, 2003). An elevation in NR2B receptors could suggest either a failure to limit plasticity in a developmentally normative way or an actual increase in these receptors, suggesting ongoing or even enhanced plasticity beyond the point that would be expected. This is also in line with some evidence suggesting that chronic stress could lead to fewer PNNs. As aforementioned, as a plasticity closing factor, PNNs are expected to slowly increase across adolescence as synapses and circuits stabilize. Thus, a decrease in PNNs could be the result of either a failure to increase or a degradation of PNNs. Decreases in PNNs is also suggestive of an immature, unstable network. This evidence could indicate a failure to reach maturity, or possibly even a compensatory mechanism by the brain to keep plasticity open, perhaps making up for the decreased excitatory drive by trying to prolong the plastic window. However, this renders the system vulnerable to ongoing environmental disturbance.

Finally, there seems to be less inhibitory activity as a result of chronic stress. Maturation of inhibitory GABAergic circuitry (specifically PV neurons) during critical periods is triggered by an over-abundance of excitatory activity. Increases in inhibition is one mechanism of critical period activity as it can act to compensate for the initial over-excitation, eventually bringing the system back into E/I balance. This shift in E/I balance across the critical period must occur in order for experience to drive plasticity, and neural circuitry to eventually stabilize. As aforementioned, this maturation of inhibitory circuitry is important in order to dampen spontaneous activity and allow evoked, environmentally-driven activity to be the primary driver of neural circuitry maturation, thus leading to high signal-to-noise ratio neural activity (Toyoizumi et al., 2013). In addition, PV neurons are involved in generating oscillatory activity, such as gamma oscillations, which arise as a result of tightly correlated excitatory and inhibitory activity (Uhlhaas & Singer, 2011). Gamma oscillations in PFC are thought to underlie complex prefrontal cognitive processes, notably working memory, and to develop through adolescence in PFC (Uhlhaas & Singer, 2011). Thus, the outcome of a critical period would ideally be stable, high signal-to-noise ratio, synchronous neural activity (Larsen and Luna, 2018). Resultingly, chronic stress experienced during adolescence may decrease excitatory activity, leading to a dampening of plasticity, and in turn, a decreased maturational drive for inhibitory circuitry. This effect may be specific to PV inhibitory neurons and not other GABAergic neuron subtypes, as PV neurons are thought to be increasing in number during adolescence in frontal cortex while other subclasses of inhibitory neurons mature earlier (Caballero et al., 2014; Lewis et al., 2004), although this does not appear to have been directly studied yet. Overall, this suggests that experiences may not sculpt circuitry as much as they would otherwise. These neurobiological changes could lead to a PFC that resembles a more immature state, with less stable and therefore more disruptable neural circuitry. Some possible outcomes of this could be neural signaling with a lower signal-to-noise ratio and more spontaneous activity relative to evoked than would be expected, and as a consequence, suboptimal cognition due to degraded processing. It is important to note that the observed impacts on cognition may not occur immediately following the stressor and alteration in E/I balance during adolescence but rather, might emerge over time as a result of disrupted trajectories that could lead to persistent deficits in adulthood.

The timing of stressors could play a critical role in what region is most impacted and therefore, what cognitive outcome is most affected. Based on structural studies in humans, dorsolateral PFC reaches adult volumes prior to OFC (Gogtay et al., 2004). In contrast, human white matter studies show that the cingulum, linking medial temporal regions to mPFC, dlPFC, and OFC, exhibits a protracted maturation into the early 20 s, while the uncinate fasciculus, which integrates OFC with amygdala and hippocampus to the OFC, continues to mature into the late 30 s (Simmonds et al., 2014). Thus, OFC white matter maturation, supporting integration of widely distributed circuity, may be more protracted than dlPFC and mPFC maturation, with earlier stressors potentially impacting mPFC and dlPFC and their related functionality (working memory, inhibitory control) more than OFC (valuation, cognitive flexibility, and decision making). Even more specifically than entire regions, cortical layers may have unique maturational timelines as synaptic pruning through adolescence has been found predominantly in PFC layer III (Hoftman et al., 2017; Hoftman & Lewis, 2011), which supports corticocortical integration, compared to layer V, which supports cortico-subcortical integration (Petanjek et al., 2011). Maturational patterns of changes in glutamate and GABA systems demonstrated in layer III have also been shown to not be pronounced in layer 6, thus suggesting that all cortical layers may not exhibit the same pattern of heightened plasticity, but rather, only specific layers (Hoftman et al., 2021). These initial results would suggest that corticocortical integration may be particularly vulnerable to stressors through adolescence. However, this has been under-studied in the literature reviewed here, as the studies that looked within layers of cortex (rodent mPFC) all looked within layer V only (Perova et al., 2015; Yuen et al., 2009, 2012), and therefore, conclusive layer-specific inferences cannot yet be made.

In this literature, the majority of studies have looked at males, but in studies that have looked at both males and females, results have been more pronounced in males. Males may exhibit greater physiological stress reactivity to acute stressors (Ordaz and Luna, 2012), which in combination with greater reactivity during adolescence, could compound stress effects. Additionally, estrogen appears to have a possibly protective effect against impacts on excitation and cognition. However, maturational timing could also explain the observed sex differences across many of the studies reviewed here, as females often reach puberty earlier and may reach adult gray matter volume earlier than males as well (J. Giedd et al., 1999; J. N. Giedd et al., 2012). Thus, stress in earlier life may predominantly affect females while stress later in adolescence may be particularly impactful in males (Goodwill et al., 2019). Indeed, males and females have different rates of stress-related psychopathology, with males having more substance-related disorders and females

having more anxiety and depressive disorders (Bangasser and Valentino, 2014). Further, in schizophrenia, which as aforementioned has been shown to be associated with stress, men tend to present with more negative symptoms, including cognitive deficits, while women tend to present with more affective symptoms. Thus, the underlying neurobiological mechanisms triggering these effects may be distinct across the sexes.

5.2. Limitations

This model reflects a scenario in which stressors are only experienced during adolescence, which is useful for isolating the effects of specific variables on specific developmental processes. This experience of minimal stress followed by a period of chronic stress may be true in the life of some adolescents, as in the case of a teenager who has to move to a new school and struggles to make friends, or a teenager who begins to be bullied in school regularly, or even teenagers that experienced isolation during the COVID-19 pandemic. However, there are limitations to generalizability. Many adolescents experience multiple stressors throughout their lives that often begin prior to adolescence. Indeed, epidemiology studies have confirmed that exposure to stress and trauma is not evenly distributed, and people who are most at-risk often experience multiple stressors and traumas throughout their lives (Benjet et al., 2016). This experience of multiple "hits" of stress throughout different developmental sensitive or critical periods may differentially impact later development of psychopathology as compared to stress experienced in only one period of life. Two-hit models of stress have posited that a first hit of stress experienced earlier in life may negatively impact later coping ability in response to the next set of stressors (Horovitz et al., 2012; Peña et al., 2017). Importantly, while some studies find that experiencing a stressor earlier in life may negatively impact coping skills leading to a compounding of the impact of stress experienced later on (Horovitz et al., 2012; Peña et al., 2017), other studies suggest that it is possible to develop resilience following a first hit of a stressor during a critical developmental window such as adolescence that could lead to more adaptive coping skills during the second hit (Mancini et al., 2021). In addition, studies have shown that stress experienced even prior to birth, such as stress experienced by the mother during gestation, could have possible downstream effects on later neurodevelopment (Glover, 2015). This underscores the importance of future work to specifically test how stress experienced during multiple specific developmental windows can interact to impact later development, and what factors increase risk for the development of maladaptive coping strategies and stress-related psychopathology as opposed to resilience. Thus, it would be valuable to compare the impact of stress on different developmental stages by systematically varying the timing of stress to occur in gestation, early in life, during adolescence, and in adulthood, and then comparing the impact on frontal excitatory and inhibitory processes and cognition.

Another important limitation of this literature is that the majority of this work, particularly on neurobiological mechanisms, is done in rodent models. Given the lack of a lateral cortex homologue in rodent models, the translatability of findings in rodent mPFC and cingulate cortex to the more expansive and complex human frontal cortex remains unknown. Additionally, the translational validity of many rodent stress paradigms to situations that are stressful to humans is still unknown. Rodent stress paradigms that include things like predation stress or restraint stress, which do not directly reflect situations commonly encountered by humans, could either share mechanisms to those seen in humans or could be mechanistically unique. Further, there is much heterogeneity across these studies in their design that makes it difficult to isolate the effect of variables within stress paradigms. The varying types of stressors, combinations of stressors, duration of stressors, timing of stressors and outcome measurements complicates efforts to get a clear understanding of how stressors of various types during different time periods through adolescence could have disparate effects on neurodevelopmental mechanisms and cognitive outcomes.

Further, more work is needed on understanding the biological mediators of the stress response that could be producing these changes in excitation, inhibition, and cognition. While glucocorticoids have been mechanistically linked and are likely involved in these processes, the relationship between glucocorticoid levels and the experience of stress is complex and may not entirely explain these effects. Thus, while glucocorticoids are likely to be involved, it is unclear what other stress-response mechanisms could also produce these effects, and what mechanisms might maintain these stress-induced changes, as these could be distinct. Other possible mechanisms that are involved in the stress response and have been linked to the effects of chronic stress on neural function include immune mechanisms as well as the endocannabinoid system (Abush and Akirav, 2013; Gururajan et al., 2019). Further, the mechanisms underlying the transition from acute, enhancing effects of stress to chronic or intense, detrimental effects of stress are not yet well understood.

Finally, a large amount of the work reviewed in this literature was done in male animals only, making the findings regarding sex differences difficult to interpret definitively. This problem is not unique to the literature reviewed here, but is a broader problem in animal model research. Further, different mouse strains may have sex effects that systematically vary across strains (Tabbaa et al., 2023), which complicates the translation of these findings to humans. Finally, the mechanistic link between actual sex hormones and the observed sex effects are unclear in many of these studies. This is particularly important given the important role of puberty during adolescent development in guiding critical period plasticity and cognitive development. Indeed, puberty may be a better predictor of some neurobiological and cognitive outcomes than age (Bramen et al., 2011; Ojha et al., 2022; Ravindranath et al., 2022). Future work should aim to measure sex hormones and examine the effect that pubertal hormones might have within this framework in order to delineate whether this is a true sex difference driven by differences in sex hormones or if this is a difference in pubertal timing, where females and males may have different windows of vulnerability to stress.

5.3. Implications and future directions

Aberrant excitatory and inhibitory activity development in PFC has been proposed as a transdiagnostic mechanism underlying cognitive symptoms across many psychiatric disorders (Uhlhaas and Singer, 2012). Schizophrenia and psychosis spectrum illnesses (and in particular the cognitive deficits associated with them) have been linked to disruptions in prefrontal plasticity and excitation/inhibition balance, and have been proposed to possibly arise as a result of disrupted prefrontal critical period plasticity processes (Dienel et al., 2022; Vinogradov et al., 2022). Studies from the schizophrenia literature suggest that symptoms of schizophrenia, including cognitive deficits, can arise from decreases in PV neuron activity, dis-coordinated neural activity, reduced signal-to-noise ratio of neural activity, and aberrant synaptic pruning of excitatory synapses (Hoftman et al., 2017; Vinogradov et al., 2022). Therefore, the model proposed could provide a mechanistic explanation for how stressful experiences during adolescence can drive or exacerbate some of the biological mechanisms seen in psychosis, as exposure to stressors is thought to be an environmental risk factor for the development of schizophrenia (Mittal and Walker, 2019).

Stress is also a risk factor for many other mental illnesses, such as depression and PTSD, although the role of disrupted E/I balance and plasticity has not been as thoroughly studied in these disorders. However, decreased glutamatergic activity in PFC has emerged in the literature as a possible factor in PTSD symptomatology (Averill et al., 2017), in line with the idea that acute but traumatic stressors may result in deficits more similar to chronic stressors. Further, a growing body of work has implicated deficient prefrontal GABAergic signaling in Major Depressive Disorder (Fogaça and Duman, 2019). Novel antidepressant

therapeutics for depression, such as ketamine, target E/I balance and are showing promise in treating these disorders.

However, of course, not all individuals will end up with psychopathology, aberrant E/I activity, and/or cognitive deficits following stressors in adolescence, even chronic ones. A variety of individual differences and protective factors, both environmental and genetic, should be noted that play a role in how stress will embed itself biologically (Rodman et al., 2019; Silk et al., 2007). Cognitive factors, such as appraisal of stressors, also have a significant impact on how stressors are experienced (Denson et al., 2009). Further, developmental timing is an important consideration; exposure to stressors prior to adolescence could have already changed maturational trajectories, such that prefrontal critical period plasticity could occur sooner, as per the Stress Acceleration Hypothesis, or proceed on a different trajectory altogether (Callaghan and Tottenham, 2016). This could be one factor determining the timing of when mental illness emergence or what mental illness emerges. Despite these moderating factors, this model provides a hypothesis for a mechanistic link between stress and E/I disruptions that could be broadly implicated across psychopathologies. Future work should aim to test this in humans, as novel, mechanistic targets for intervention could emerge.

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