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ARTICLE

Stress impacts corticoamygdalar connectivity in an age-dependent manner

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Stress is a socio-environmental risk factor for the development of psychiatric disorders, with the age of exposure potentially determining the outcome. Several brain regions mediate stress responsivity, with a prominent role of the medial prefrontal cortex (mPFC) and basolateral amygdala (BLA) and their reciprocal inhibitory connectivity. Here we investigated the impact of stress exposure during adolescence and adulthood on the activity of putative pyramidal neurons in the BLA and corticoamygdalar plasticity using in vivo electrophysiology. 155 male Sprague-Dawley rats were subjected to a combination of footshock/restraint stress in either adolescence (postnatal day 31–40) or adulthood (postnatal day 65–74). Both adolescent and adult stress increased the number of spontaneously active putative BLA pyramidal neurons 1–2 weeks, but not 5–6 weeks post stress. High-frequency stimulation (HFS) of BLA and mPFC depressed evoked spike probability in the mPFC and BLA, respectively, in adult but not adolescent rats. In contrast, an adult-like BLA HFS-induced decrease in spike probability of mPFC neurons was found 1–2 weeks post-adolescent stress. Changes in mPFC and BLA neuron discharge were found 1–2 weeks post-adult stress after BLA and mPFC HFS, respectively. All these changes were transient since they were not found 5–6 weeks post adolescent or adult stress. Our findings indicate that stress during adolescence may accelerate the development of BLA–PFC plasticity, probably due to BLA hyperactivity, which can also disrupt the reciprocal communication of BLA–mPFC after adult stress. Therefore, precocious BLA–mPFC connectivity alterations may represent an early adaptive stress response that ultimately may contribute to vulnerability to adult psychiatric disorders.

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INTRODUCTION

Stressful life events are known socio-environmental risk factors for the development of psychiatric disorders, including depression and schizophrenia [1–3]. The adversities can have a profound functional impact on brain areas and systems involved in the modulation of the stress response [4, 5]. Two pivotal brain structures involved in stress regulation are the medial prefrontal cortex (mPFC) and amygdala in humans and basolateral amygdala (BLA) in rodents [6–9]. The mPFC is known to play an inhibitory role in the regulation of stress responsivity by decreasing amygdala activity [10–13]. In addition, increased amygdala activity has been strongly associated with stress [8, 14]. The mPFC–BLA pathway has reciprocal inhibitory connections that control their activity [11, 15] and dysregulation in these brain areas is proposed to play a role in the pathophysiology of psychiatric disorders [14, 16–20].

Psychiatric disorders such as depression and schizophrenia share environmental and genetic risk factors [21, 22]. Moreover, evidence indicates that the timing of exposure to adversity may determine the outcome. We found that, in rodents, stress during adolescence led to long-term changes resembling schizophrenia at adulthood [23, 24], whereas the same stressor applied to adult rats induced short-term changes analogous to depression [23]. The impact of stress during neurodevelopment likely impacts maturational changes of BLA and PFC [25, 26].

The maturation of mPFC and BLA and their interconnectivity emerge mainly during the juvenile and adolescence periods [25, 27–31]. Thus, stress during this critical period of neurodevelopment can negatively impact the developmental trajectories of BLA and mPFC that may lead to the emergence of psychiatric disorders later in life [26, 32–35]. Moreover, studies show that early-life stress can accelerate the functional maturation of brain areas and some behavioral responses [36–38], which have been controversially associated with both better stress coping and higher susceptible to psychopathology [39]. Early-life stress can impact the development of depressive-like conditions at adulthood [40–42], and adversity during adolescence is garnering attention due to maturational refinement occurring in mPFC which represents one of the last brain areas to mature [43, 44]. Thus, the effect of stress on BLA and mPFC neurodevelopmental trajectories requires further investigation. Here we examined the short- and long-term impact of stress exposure during adolescence and adulthood on BLA activity and BLA–mPFC reciprocal connectivity.

MATERIALS AND METHODS

Animals

For the adolescent stress, 20 pregnant Sprague-Dawley rats at gestational day 14 were purchased from Envigo (Indianapolis, IN)

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and gave birth in our animal facility. On postnatal day (PD) 21, litters were weaned and housed in groups of 2–3 per cage. A total of 76 male offspring were used in this study. For the adult stress, 79 adult rats (PD60) were received from Envigo (Indianapolis, IN) and allowed to acclimate for 5 days before the stress regimen. Animal arrival and handing was similar to those previously employed by our group [16, 24] and was not found to impact behavioral and electrophysiology outcomes. All rats were housed in a temperature- and humidity-controlled room (22 ± 1 °C), with a 12 h/light–dark cycle (7 a.m. light on) and water/food available ad libidum. The stress protocol was carried out during the lights-on cycle. All procedures were performed in accordance with the NIH Guide for the Care and Use of Laboratory Animals and approved by the Institutional Animal Care and Use Committee of the University of Pittsburgh.

Stress protocol

Adolescent (PD 31–40) and adult (PD 67–76) rats were subjected to a stress protocol as previously described [23, 24]. Briefly, rats were subjected to a footshock (FS) session (25 FS, 1 mA/2 s, 20–60 s random interval) daily for 10 days and to three sessions of 1 h restraint stress (RS), in a Plexiglas cylindrical size-adjusted tube, with exposure occurring immediately following the FS session on days 1, 2, and 10 of FS exposure.

Electrophysiological recordings

Recordings were performed either 1–2 or 5–6 weeks post-adolescent or -adult stress. Rats received an intraperitoneal injection of chloral hydrate (400 mg/kg) anesthetic and in vivo extracellular recording was performed as described in the Supplementary Material.

In vivo extracellular recordings of spontaneously active putative pyramidal neurons in the BLA was performed by making 6–9 vertical tracks (Fig. 1A; all coordinates in Supplementary Material). Putative pyramidal neurons were identified based on action potential waveform and firing rate (Fig. 1B). Population activity (spontaneously active neurons) and firing rate were evaluated [45, 46].

For evaluation of either mPFC–BLA or BLA–mPFC connectivity, electrodes were lowered into mPFC or BLA. Concentric bipolar stimulation electrodes (NEX-100X; Rhodes Medical Instruments) targeted the BLA or mPFC for single-pulse and high-frequency stimulation (HFS; 20 Hz; 10 s at suprathreshold). A dual-output stimulator (S8800; Grass Technologies) was used to apply single-pulse stimulation to the BLA and mPFC (1 mA intensity/0.5 Hz frequency/0.25 ms pulse duration) to search for responsive neurons in the mPFC or BLA, respectively. After a responsive monosynaptically activated neuron was found, the current intensity was adjusted to evoke spikes at 50% probability. Monosynaptic connectivity was determined according to previous data [13, 47] including variability in latency to evoked spike discharge during the single-pulse stimulus baseline period and linear decrease in latency with increased stimulus strength. All neurons recorded exhibited spike durations >2 ms, characteristic of projection neurons [13]. The baseline spike probability was measured for 10 min. After HFS, neuron responsivity was measured for 30 min. Spike probability was calculated by dividing the number of spikes by the total number of single-pulse stimuli. Only one neuron in the mPFC or BLA was recorded per animal. At the end of the recordings, the brains were removed for histology verification (Supplementary Material).

Statistical analyses

Data are presented as mean ± SEM and analyzed using *t* test or two-way ANOVA, followed by Tukey's post hoc test. The condition and time or age were used as factors for the ANOVA analysis. $p < 0.05$ was considered significant.

RESULTS

Impact of adolescent and adult stress on BLA pyramidal neuron population activity

Adolescent and adult stress increased the number of spontaneously active putative pyramidal neurons in the BLA (electrode placement Fig. 2C) 1–2 weeks post stress. For adolescent stress, 2-way ANOVA indicated an effect of condition (naive or stressed; $F_{1,19} = 7.65$, $p < 0.05$), a trend for time of recording (1–2 or 5–6 weeks post stress; $F_{1,19} = 4.12$, $p = 0.06$), and no interaction ($p > 0.05$). Post hoc analyses showed that stressed animals exhibited greater population activity 1–2 weeks post-adolescent stress ($n = 6$ rats; 34 cells; 0.61 ± 0.06 cells/track) compared to naive rats ($n = 6$ rats; 22 cells; 0.92 ± 0.08 cells/track; Fig. 1D). This change was not persistent since population activity returned to control levels 5–6 weeks post stress (naïve: $n = 6$ rats; 20 cells;

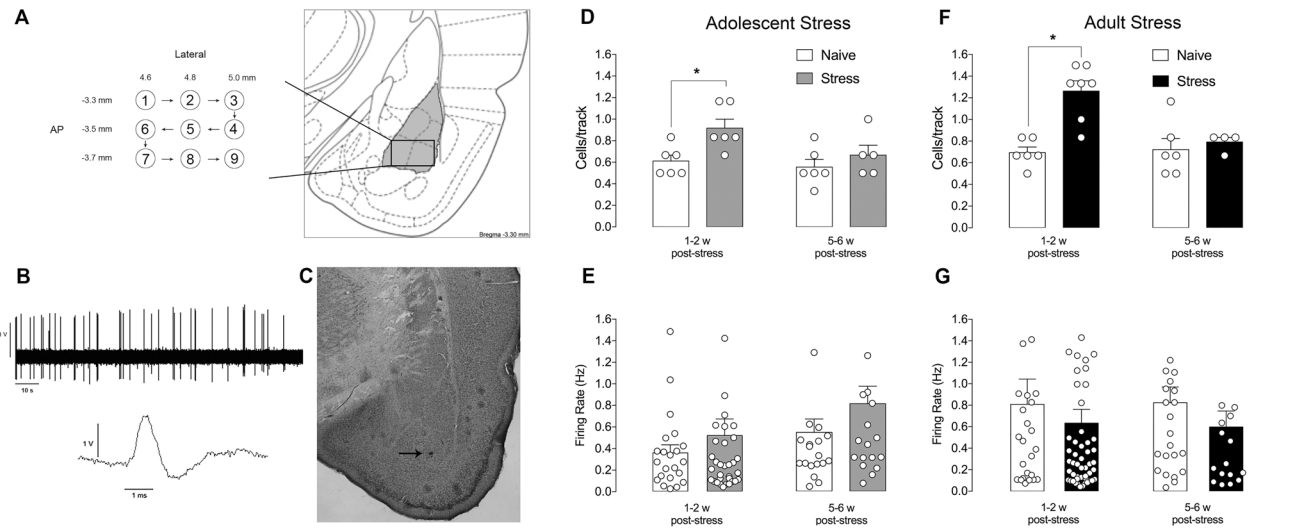
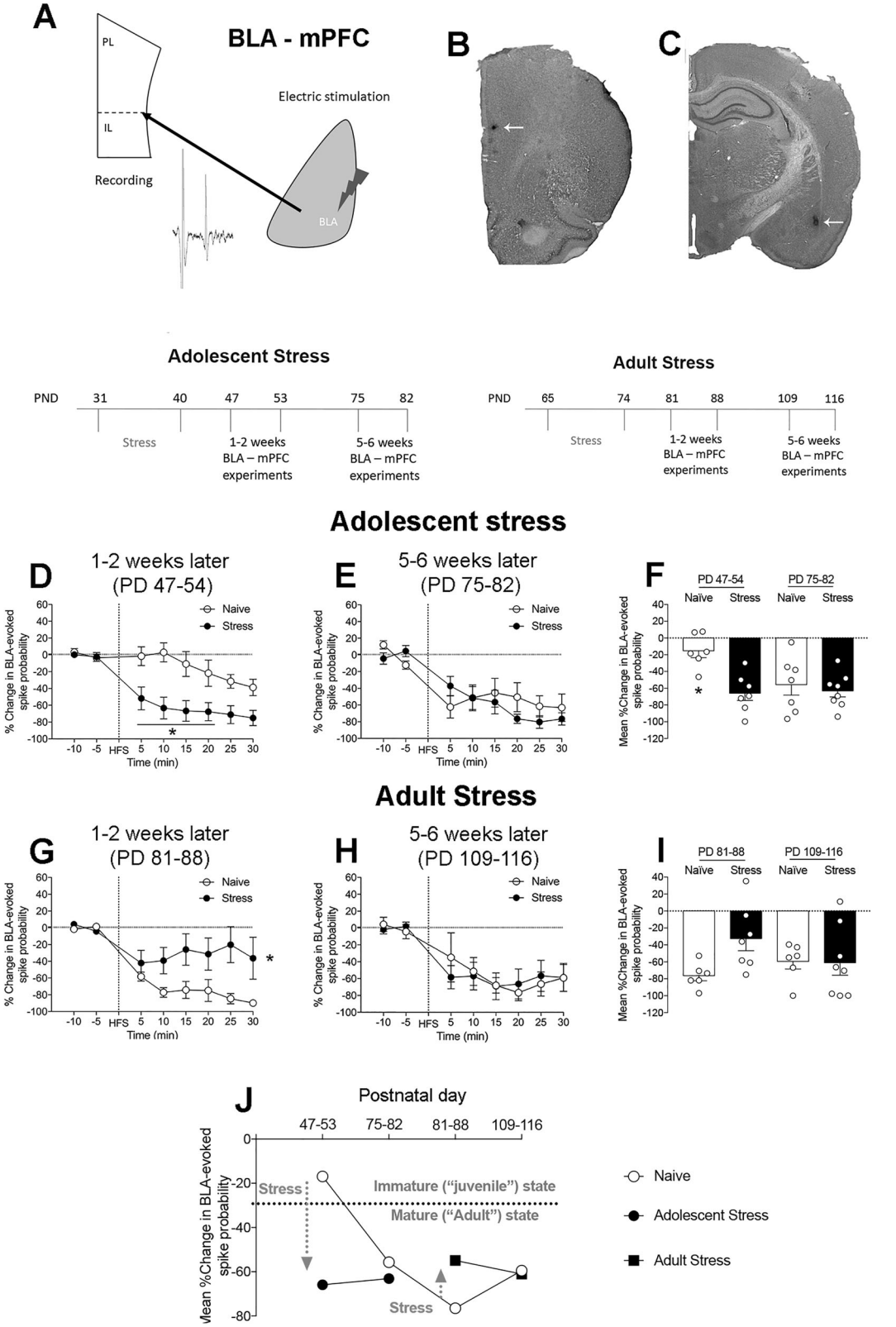


Fig. 1 Adolescent and adult stress increased the number of spontaneously active putative pyramidal neurons in the BLA. The pattern of tracks performed during BLA recording (**A**). Representative spontaneous activity tracing recorded over 1 min and pyramidal neuron waveform in the BLA (**B**). Photomicrograph of electrode placement in the BLA (**C**). The number of BLA putative pyramidal neurons per track (cells/tracks) after adolescent (**D**) and adult stress (**F**) are increased after 1–2 weeks, but not 5–6 weeks post stress. No statistical difference was found for the firing rate of recorded neurons after adolescent (**E**) or adult stress (**G**). *$p < 0.05$, ANOVA followed by Tukey's post hoc analysis.



0.56 ± 0.07 cells/track; stress: $n = 5$ rats; 20 cells; 0.67 ± 0.09 cells/track; Fig. 1D). For adult stress, 2-way ANOVA indicated an effect for condition (naive or stressed; $F_{1,19} = 13.34$, $p < 0.05$), time of recording (1–2 or 5–6 weeks post stress; $F_{1,19} = 6.44$, $p < 0.05$), and interaction (condition and time; $F_{1,19} = 8.16$, $p < 0.05$). Post hoc analyses showed that stressed animals showed greater putative BLA pyramidal neuron population activity 1–2 weeks post-adult stress ($n = 7$ rats; 53 cells; 1.26 ± 0.09 cells/track) compared to naïve rats ($n = 6$ rats; 25 cells; 0.69 ± 0.05 cells/track; Fig. 1F). Similar to the adolescent stress, this change was transient since no

Fig. 2 Adolescent stress induces adult-like inhibitory plasticity of BLA to PFC neurons whereas adult stress impairs it. The high-frequency stimulation (HFS) was delivered into the BLA and the activity of monosynaptically activated neurons in mPFC was recorded for 30 min (**A**). Representative photomicrographs of mPFC recording electrode (**B**) and BLA stimulation electrode (**C**) placement. Adolescent stress induces a long-term depression in BLA–mPFC plasticity 1–2 weeks post stress as indicated by a decrease in the magnitude of BLA-evoked mPFC spike probability (**D**, $*p < 0.05$, ANOVA). 5–6 weeks post stress, when animals had already reached adulthood, BLA HFS-induced a long-term depression in BLA–mPFC plasticity without any impact of stress as indicated by the time course of % change in BLA-evoked mPFC spike probability (**E**). Long-term depression after adolescent stress in the mean % change across the 30 min period (**F**, $*p < 0.05$, ANOVA). Adult stress impairs the % change in BLA-evoked mPFC spike probability (**G**, time course, $*p < 0.05$, ANOVA). 5–6 weeks post stress, no alterations were found in the % change of BLA-evoked mPFC spike probability (**H**, time course). The long-term depression of the BLA–mPFC pathway after adult stress in the mean % change across the 30 min period (**I**). Representative graph showing the acceleration of adult plasticity form 1–2 weeks post-adolescent stress and decreased depression of mPFC neuron activity 1–2 weeks post-adult stress (**J**).

Table 1. Latency to spike discharge, stimulus intensity, and spike probability values of neurons recording either in the mPFC or BLA during the baseline period (before HFS) of animals exposed to adolescent and adult stress.

BLA–mPFC	Adolescent stress				Adult stress			
	1–2 w		5–6 w		1–2 w		5–6 w	
	Naive	Stress	Naive	Stress	Naive	Stress	Naive	Stress
Number of neurons recorded	6	7	7	8	6	7	6	8
Latency to spike discharge	18.92 ± 2.9	17.99 ± 3.32	17.14 ± 4.26	21.63 ± 4.05	17.83 ± 2.45	15.93 ± 1.88	14.5 ± 1.48	16.38 ± 1.50
Current intensity	1.09 ± 0.12	1.197 ± 0.08	1.17 ± 0.09	1.04 ± 0.09	0.99 ± 0.12	0.97 ± 0.09	1.01 ± 0.10	0.78 ± 0.09
Basal spike probability	0.66 ± 0.04	0.63 ± 0.04	0.71 ± 0.04	0.78 ± 0.06	0.70 ± 0.08	0.69 ± 0.06	0.65 ± 0.06	0.72 ± 0.05
mPFC–BLA	Adolescent stress				Adult stress			
	1–2 w		5–6 w		1–2 w		5–6 w	
	Naive	Stress	Naive	Stress	Naive	Stress	Naive	Stress
Number of neurons recorded	6	7	6	6	6	6	8	9
Latency to spike discharge	27.24 ± 2.60	17.59 ± 2.28*	20.43 ± 2.71	22.8 ± 2.19	19.85 ± 2.01	21.9 ± 3.30	18.61 ± 2.74	19.05 ± 1.26
Current intensity	1.08 ± 0.14	0.82 ± 0.12	0.91 ± 0.12	0.69 ± 0.13	0.68 ± 0.12	0.86 ± 0.12	0.69 ± 0.17	0.80 ± 0.08
Basal spike probability	0.47 ± 0.04	0.54 ± 0.04	0.66 ± 0.04	0.66 ± 0.05	0.66 ± 0.03	0.69 ± 0.04	0.57 ± 0.06	0.63 ± 0.04

1–2 w 1–2 weeks post stress, *5–6 w* 5–6 weeks post stress.
$*p < 0.05$ *t* test.

change was found 5–6 weeks post-adult stress (naive: $n = 6$ rats; 25 cells; 0.72 ± 0.1 cells/track; stress: $n = 4$ rats; 28 cells; 0.79 ± 0.04 cells/track; Fig. 1F). Moreover, neither adolescent nor adult stress impacted the average firing rate of putative pyramidal neurons in the BLA at the time-points studied (Fig. 1E, G).

Adolescent stress induces an adult-like BLA–mPFC connectivity

The effect of BLA HFS on mPFC monosynaptically-evoked spike discharge was assessed 1–2- and 5–6 weeks post-adolescent stress (Fig. 2A; BLA stimulation and mPFC recording sites shown in Fig. 2B, C). No difference was found for the mean latency, current intensity, and basal spike probability for the neurons recorded in the mPFC of naïve and stressed animals at PD47-54 (1–2 weeks post-adolescent stress) and naïve and stressed animals at PD75-82 (5–6 weeks post-adolescence stress; $p > 0.05$ in all parameters; *t* test; Table 1) at baseline. After BLA HFS, 2-way ANOVA indicated an effect for condition (naïve or stressed; $F_{1,11} = 14.71$, $p < 0.05$), time ($F_{7,77} = 12.29$, $p < 0.05$), and interaction between condition and time ($F_{7,77} = 3.89$, $p < 0.05$). Post hoc analyses showed that BLA HFS 1–2 weeks post-adolescent stress decreased the probability of evoking spikes in mPFC neurons; an effect that was not observed in naive animals (Fig. 2D). 5–6 weeks post-adolescent stress, when animals had reached adulthood (PD75-82), 2-way ANOVA indicated that HFS of the BLA decreased the probability to evoke spike discharge in mPFC neurons in both naïve and stressed animals (time, $F_{7,91} = 18.02$, $p < 0.05$; Fig. 2E), with no effect of condition ($p > 0.05$) and interaction ($p > 0.05$), indicating that BLA HFS in the adult induces long-term depression (LTD) in mPFC neurons as previously reported [48]. Moreover, 2-way ANOVA of the mean % change in BLA-evoked spike probability following HFS at all time-points indicated an effect of age (PD47-54 vs. PD75-82; $F_{1,24} = 4.6$, $p < 0.05$), condition (naive vs. stress; $F_{1,24} = 9.67$, $p < 0.05$) and interaction between the age and condition ($F_{1,24} = 6.02$, $p < 0.05$). Post hoc analysis indicated that the mean % change in BLA-evoked spike probability is lower in naïve animals at PD47-54 (adolescence) than in naïve animals at PD75-82 (adulthood; $p < 0.05$, Tukey). In addition, adolescent stress induced an adult-like response 1–2 weeks post stress (stressed animals at PD47-54 vs. naïve animals at PD75-82, $p > 0.05$ Tukey), when animals were still in adolescence (Fig. 2F). Overall, these findings indicate that the BLA–mPFC connectivity is not mature in adolescent animals (PD47-54) and that the LTD in mPFC induced by BLA stimulation found 1–2 weeks post-adolescent stress is similar to that found in adult naïve animals (Fig. 2J).

Adult stress induces transient changes in BLA–mPFC connectivity

The effect of BLA HFS on mPFC monosynaptically-evoked spike discharge was evaluated 1–2- and 5–6 weeks post-adult stress. No difference was found in the mean latency, current intensity, and basal spike probability for the neurons recorded in the mPFC of naïve and stressed animals at either PD81-88 (1–2 weeks post-adult stress) or at PD109-116 (5–6 weeks post-adult stress; $p > 0.05$ in all parameters; *t* test; Table 1) during the baseline period. 1–2 weeks after adult stress, 2-way ANOVA of the post-HFS period

indicated an effect of condition ($F_{1,11} = 7.05$, $p < 0.05$), time ($F_{7,77} = 9.88$, $p < 0.05$), and interaction between factors ($F_{7,77} = 23.03$, $p < 0.05$). Post hoc analyses showed that adult stress decreased the magnitude of BLA HFS-induced depression in the probability of evoking spikes in mPFC when the recordings were performed 1–2 weeks post stress (Fig. 2G). 5–6 weeks post-adult stress, 2-way ANOVA revealed an effect of time ($F_{7,84} = 11.15$, $p < 0.05$), but with no effect of condition ($p > 0.05$) or their interaction ($p > 0.05$). BLA HFS similarly decreased the probability to evoke spikes of mPFC neurons in adult naïve and stressed animals (Fig. 2H). 2-way ANOVA of the mean % change in BLA-evoked spike probability following HFS at all time-points did not reveal an effect of age (PD81-88 vs. PD109-116, $p > 0.05$) and condition (naive vs. stress, $p > 0.05$), but there was trend for interaction between age and condition ($F_{1,23} = 3.25$, $p = 0.08$; Fig. 2I). Altogether, these findings suggest a disrupted inhibitory control of BLA over mPFC neurons 1–2 weeks post-adult stress indicated by the altered % change in BLA-evoked spike probability after HFS, which was not present 5–6 weeks post stress (Fig. 2G, H, J).

Adolescent stress did not affect mPFC–BLA connectivity

The influence of mPFC HFS on BLA monosynaptically-evoked spike discharge was investigated 1–2- and 5–6 weeks post-adolescent stress (Fig. 3A; placement of stimulating electrode in mPFC and recording electrode in BLA shown in Fig. 3B, C). At baseline, the current intensity and basal spike probability were not different between naïve and stress groups ($p > 0.05$; *t* test; Table 1) at either stress time point. The latency to evoke spike discharge decreased in the stress group ($t_{11} = 2.8$, $p < 0.05$, Table 1) only at 1–2 weeks post-adolescent stress. After mPFC HFS, 2-way ANOVA did not show effects for condition ($p > 0.05$), time ($p > 0.05$), or their interaction ($p > 0.05$) 1–2 weeks post-adolescent stress (Fig. 3D). 5–6 weeks post-adolescent stress, 2-way ANOVA revealed an effect of time ($F_{7,70} = 6.48$, $p < 0.05$), but not for condition ($p > 0.05$) or interaction ($p > 0.05$, Fig. 3E). 2-way ANOVA of the mean % change in mPFC-evoked spike probability following HFS at all time-points (Fig. 3F) did not indicate an effect of age (PD47-54 vs. PD75-82, $p > 0.05$), condition (naive vs. stress $p > 0.05$) or interaction between age and condition ($p > 0.05$), indicating that adolescent stress did not induce short- or long-term changes in the spike probability of BLA neurons after mPFC HFS (Fig. 3J).

Adult stress induces transitory changes in mPFC–BLA connectivity

The effect of mPFC HFS on BLA monosynaptically-evoked spike discharge was also evaluated 1–2- and 5–6 weeks post-adult stress. The mean latency, current intensity, and basal spike probability were not different between naïve and stressed animals at either time point ($p > 0.05$ in all parameters; *t* test, Table 1) during the baseline period. 1–2 weeks post-adult stress, 2-way ANOVA of the post-HFS indicated an effect of the condition ($F_{1,10} = 11.64$, $p < 0.05$), time ($F_{7,70} = 4.39$, $p < 0.05$), and interaction ($F_{7,70} = 4.88$, $p < 0.05$). Post hoc analyses showed that mPFC HFS 1–2 weeks post-adult stress did not induce depression in the probability of evoking spike discharge in the BLA normally observed in naïve rats (Fig. 3G). 5–6 weeks post-adult stress, 2-way ANOVA showed an effect of time ($F_{7,105} = 8.11$, $p < 0.05$), but not condition ($p > 0.05$) or their interaction ($p > 0.05$). mPFC HFS similarly decreased the probability to evoke spikes in BLA neurons in adult naïve and stressed animals at this time point (Fig. 3H). 2-way ANOVA of the mean % change in mPFC-evoked spike probability following HFS at all time-points did not reveal an effect of age (PD81-88 vs. PD109-116, $p > 0.05$), but there was an effect of condition (naive vs. stress; $F_{1,25} = 7.14$, $p < 0.05$) and interaction between age and condition ($F_{1,25} = 5.81$, $p < 0.05$). Post hoc analysis indicated that the mean % change in mPFC-evoked spike probability was lower in stressed animals 1–2 weeks post-adult stress than in naive animals ($p < 0.05$ vs. all groups, Tukey; Fig. 3I). No change was found 5–6 weeks post-adult stress (Fig. 3I). These data indicate that adult stress disrupts the inhibitory control of mPFC over BLA 1–2 weeks post-adult stress and this change is not persistent (Fig. 3J).

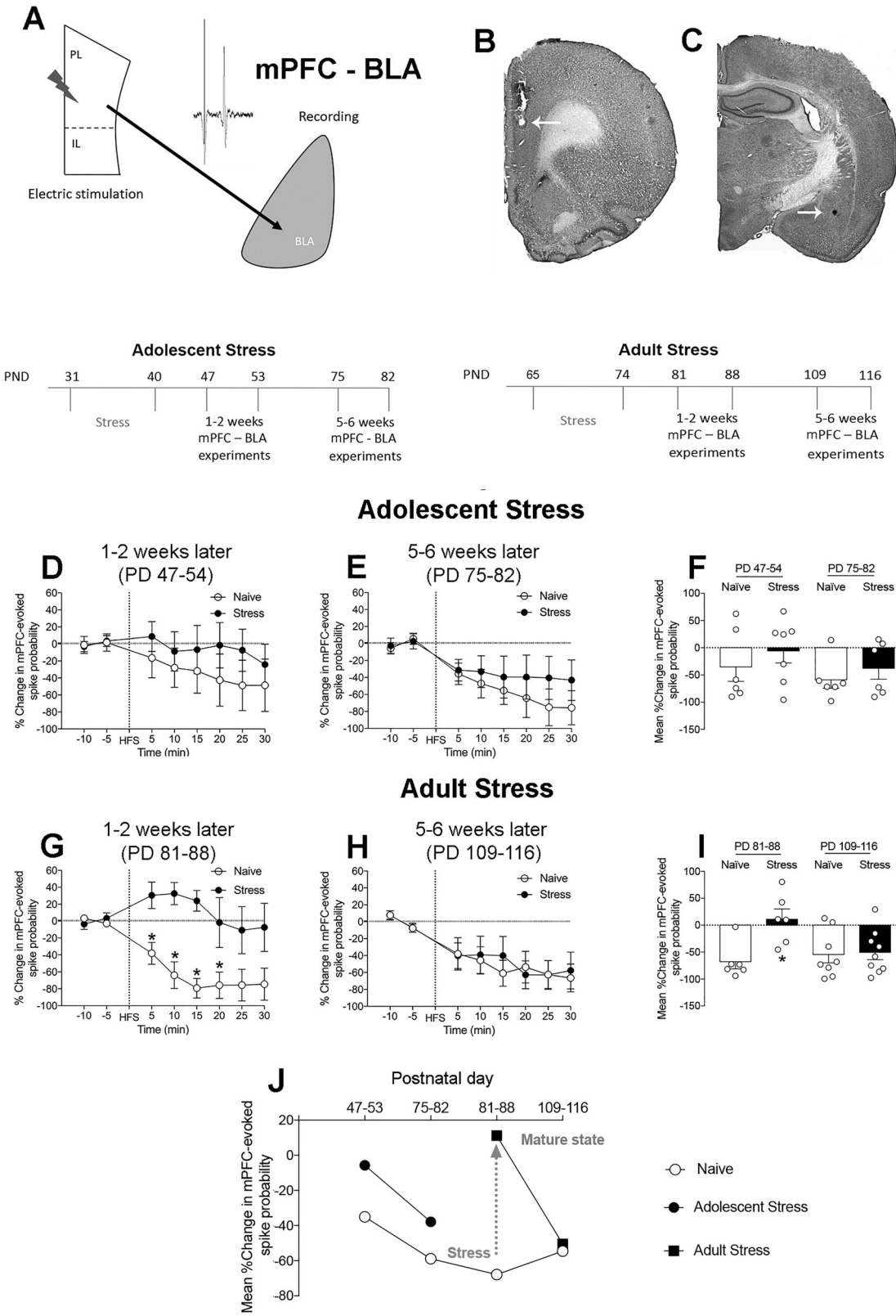
DISCUSSION

Our findings indicate a differential impact of stress exposure during adolescence and adulthood on corticoamygdalar connectivity, as exemplified in Fig. 4. We found previously that while the exposure of adolescent rats (PD31-40) to the combination of FS and RS led to long-lasting changes associated with schizophrenia, the same stressors applied to adult animals (PD65-74) resulted in a transient depression-like state [23, 24]. We now show that, although the timing of stress may be a critical factor in determining the outcome, the combination of FS and RS during either adolescence or adulthood led to short-term increased BLA activity. In addition, stress exposure impacted corticoamygdalar plasticity, but in an age-dependent manner. BLA HFS-induced LTD in mPFC neurons of adult but not adolescent rats. Interestingly, adolescent stress caused a precocious induction of an adult-like LTD in mPFC driven by BLA stimulation 1–2 weeks post stress, but with no impact on mPFC–BLA connectivity. In contrast, adult stress induced transient decreased LTD magnitude in both BLA–mPFC and mPFC–BLA connectivity. The age-dependent effect of stress on corticoamygdalar plasticity could represent a potential mechanism suggesting the timing of stress as a critical determinant of the outcome.

The mPFC is involved in the regulation of stress responses, in that it exerts control over amygdala responsivity to stress [10–13]. In addition, functional impairment of mPFC activity is associated with greater stress susceptibility and has been related to pathologic states [49, 50]. In rodents, disruption of mPFC during adolescence increased vulnerability to schizophrenia-like changes induced by exposure to adolescent stress that was subthreshold for inducing these changes in intact rats [24]. Also, adolescent mPFC disruption by itself increased the vulnerability of adult animals to learned helplessness [51]. We propose that this increased susceptibility to stress induced by mPFC disruption may be secondary to mPFC dysfunctional regulation of BLA reactivity to stress [16].

The BLA regulates stress responses mainly through excitatory projections to brain areas involved in emotional modulation, including the mPFC [8, 52, 53]. Increases in BLA activity have been reported after exposure to stressors [46, 54–56]. In humans, increased amygdala activity and connectivity changes were reported in depression and schizophrenia [57, 58], supporting its role in psychopathologies. We found that adolescent stress increased the number of spontaneously active putative pyramidal neurons in the BLA at 1–2, but not 5–6 weeks post-stress, which was similar to studies involving repeated adolescent stress with recordings performed 1–3 days post-stress [54–56]. However, in contrast to our results, these studies reported increased firing rate in neurons recorded after repeated adult stress. This is likely because in our study rats were recorded 1–2 weeks post stress, during which any acutely increased firing rate would have normalized. Moreover, the stress protocol applied in the current study potentially is more aversive, which in turn could drive the increased number of active neurons in the BLA. These changes in the BLA could suggest modifications of synaptic inputs, particularly from mPFC.

Inhibitory reciprocal connectivity between the mPFC and BLA is known to modulate behavioral responses and its dysfunction is implicated in psychiatric disorders [11, 12, 19, 20, 25, 48]. Thus, higher strength prefrontal–amygdala connectivity is related to lower levels of anxiety [59, 60] and stimulation of cortical areas in individuals with high trait anxiety decreases the amygdala reactivity to threat [61]. We observed in a previous study that HFS of BLA induces LTD in the mPFC [48]. Also, the prelimbic PFC



is reported to drive inhibition of BLA neurons [11]. Here, we found that, in adult naïve rats, HFS of the mPFC and BLA induced LTD in BLA and mPFC, respectively. Moreover, greater connectivity between the amygdala and PFC during emotional regulation increases with age [62], which suggests that the maturational state of these areas may affect the stress response. In fact, we found that connectivity is indeed in a different state in adolescence, a period when LTD formation is not present in the BLA–mPFC pathway. However, an adult-like form of LTD occurred prematurely in rats exposed to adolescent stress, suggesting that adolescent stress may accelerate the maturation of BLA–mPFC connectivity.

Fig. 3 Adult stress impairs the inhibitory plasticity in the mPFC to BLA neuron projection 1–2 weeks post stress. The high-frequency stimulation (HFS) was delivered into the mPFC and the activity of a monosynaptically activated BLA neuron was recorded for 30 min (**A**). Representative photomicrographs of mPFC stimulation site (**B**) and BLA recording electrode placement (**C**). Adolescent stress did not affect the mPFC–BLA plasticity 1–2 weeks post stress as indicated by the time course of % change in mPFC-evoked BLA spike probability (**D**). 5–6 weeks post stress, when animals had reached adulthood, mPFC HFS-induced long-term depression in mPFC–BLA plasticity without any effect of stress as observed by the time course of % change in mPFC-evoked BLA spike probability (**E**). The long-term depression of the mPFC–BLA pathway after adolescent stress in the mean % change across the 30 min period (**F**). Adult stress impairs the % change in mPFC-evoked BLA spike probability (**G**, time course, $*p < 0.05$, ANOVA). 5–6 weeks post stress, no alterations were found in the % change in mPFC-evoked BLA spike probability (**H**, time course). Changes in the long-term depression of the mPFC–BLA pathway after 1–2 weeks post-adult stress in the mean % change across the 30 min period (**I**). Representative graph showing changes in the inhibitory plasticity form of BLA neuron activity induce by mPFC HFS (**J**).

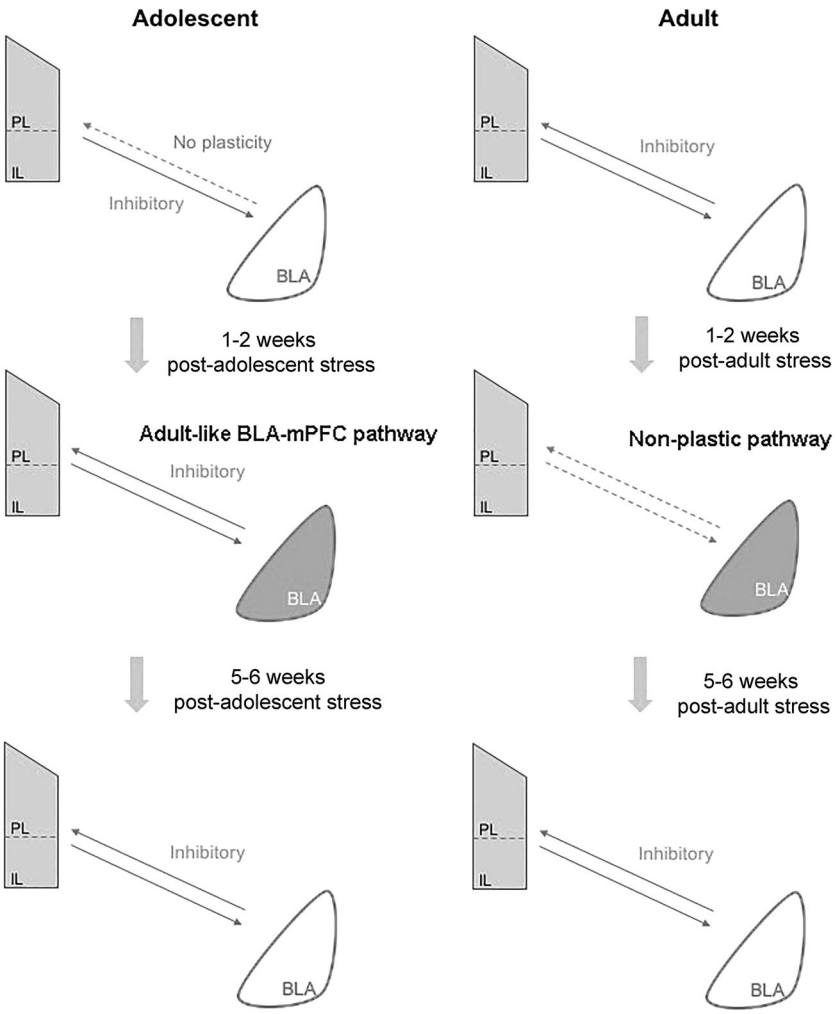


Fig. 4 A schematic representation of adolescent and adult stress impact on mPFC–BLA connectivity. Both adolescent and adult stress increases the BLA activity and produces short-term alterations over the BLA–mPFC plasticity 1–2 weeks post stress. The adolescent stress precipitates the inhibitory adult form of the BLA to mPFC projection 1–2 weeks post stress but did not affect the time course of mPFC to BLA plasticity. The adult stress impairs the inhibitory plasticity of both BLA–mPFC and mPFC–BLA pathways 1–2 weeks post stress, suggesting a nonplastic pathway. Changes induced by both adolescent and adult stress were present 5–6 weeks post stress. Overall, stress seems to have a different impact on brain circuits involved in stress regulation and it depends on the age of exposure which could contribute to different outcomes.

The acceleration of maturational states produced by stress has been described in rodents and humans [36, 38, 39] and may be implicated in psychiatric disorders. Dysregulated age-normative amygdala connectivity is observed in psychosis spectrum disorder with reduced amygdala connectivity in late childhood and adolescence typically found in healthy adults [58]. Our data showing an adult-like pattern in BLA–mPFC connectivity after adolescent stress we propose correlates with our previous data showing that the same stress protocol applied to adolescent rats produced behavioral and electrophysiological changes mimicking a schizophrenia-like phenotype at adulthood [23, 24]. Although our previous findings and the electrophysiological plasticity data are correlative in nature, the results are consistent with that reported in humans. Moreover, additional preclinical data indicate that early-life adversity induces precocious maturation of the BLA–PFC pathway [63]. In humans, maternal deprivation accelerates the connectivity between the amygdala and mPFC [38], and amygdala structural/functional alterations [64–67]. This accelerated maturation induced by early adversities may facilitate coping with immediate environmental insults [39, 68]. However, it may

result in the circuit being less efficient in stress regulation at adulthood [39]. Our findings suggest that adolescent stress may have induced an early albeit transient adaptation of the BLA–mPFC pathway 1–2 weeks post stress. However, the transient changes in BLA activity and BLA–mPFC alteration induced by adolescent stress may ultimately increase susceptibility for the development of psychopathologies later in life [16, 18]. In fact, changes in the normal trajectory of maturation of circuits during adolescence are believed to contribute to the emergence of psychiatric disorders [69].

During the transition from childhood to adolescence, amygdala–prefrontal connectivity switches from positive to negative functional connectivity accompanied by a decrease in amygdala reactivity [64]. In rodents, BLA projections to the mPFC emerge earlier in development (around PD13-30) [29, 30, 70–72], which may indicate that BLA could be more sensitive to early environmental adversities. The BLA hyperexcitability found after adolescent stress may represent an important signal for the maturation of PFC connectivity. mPFC volumetric value reaches higher levels around PD24 (comparable to the juvenile period) [73], but it is only at PD45 that the mPFC–BLA connectivity achieves greater levels in relation to the number of mPFC-projecting neurons to BLA [31], suggesting a late development of this pathway. Functionally, activation of the mPFC input to the BLA produces a weaker response in adolescents (PD39) when compared to adults (PD72–75) [74]. We observed LTD in BLA activity after mPFC HFS in both naïve and stressed animals 1–2 weeks post-adolescent stress (PD47-54) that also tended to be weaker. We did observe substantial variability in spike probability changes after mPFC HFS in BLA neurons. Although this may represent a potential caveat, we propose that the complex nature of the connectivity, the individual variability, and the specific cell type could play a role in these events. Moreover, this characteristic was observed across all conditions and time-points studied, which we propose to be related to the nature of the connectivity instead of a stress and age effect over the mPFC–BLA pathway. Thus, it appears that stress did not change the maturational state of these projections, which is probably due to the late maturation of the mPFC itself even after the stress.

Alternately, adult stress impairs the reciprocal inhibitory plasticity of mPFC–BLA connectivity, which may imply that the areas are decoupling and not responding appropriately to stress. HFS of the mPFC and BLA in adult naive rats induced LTD in BLA and mPFC, respectively. However, adult stressed rats showed decreased magnitude of LTD in BLA and mPFC neurons after mPFC and BLA HFS 1–2 weeks later. An increased BLA activity after adult stress may drive the abnormal corticoamygdalar plasticity. These changes may also be associated with pathological states. Thus, a dysregulated connectivity between the amygdala and prefrontal cortex is found in depression patients [19, 57]; an alteration that normalizes with remission [75, 76]. Based on our findings, we propose that the initial dysregulated response to stress leads to maladaptive behavioral and dysfunctional amygdala and mPFC activity. Thus, the system seems to fail to communicate and consequently the animal fails to effectively respond to external information, which in turn may increase susceptibility to a pathological state.

Although we did not investigate a mechanism associated with the age-dependent effect of stress on corticoamygdalar plasticity, we posit that these changes are probably a consequence of a complex interaction between neurochemical changes in these areas. At the microcircuit level, these changes may involve a putative dysfunction of GABAergic interneurons. During adolescence, specific populations of GABAergic interneurons, such as those expressing parvalbumin (PV) and somatostatin (SOM), are still under development [43, 77–80], which may be impacted by adolescent stress. A functional loss of GABAergic interneurons has been related to stress, depression [81–85], and schizophrenia [86–88]. Furthermore, the inhibitory form of plasticity within mPFC seems to be mediated by SOM [89]. Thus, our findings regarding precocious LTD in the mPFC after BLA HFS in stressed adolescent rats may involve changes in SOM development. Further investigation will provide a better understanding of the potential involvement of PFC GABAergic dysfunction in abnormal corticoamygdalar plasticity elicited by adolescent and adult stress. In addition, it is likely that other brain areas could contribute to the neurodevelopmental plasticity disruption in the corticolimbic pathway, i.e., the hyperexcitability of the ventral hippocampus observed after adolescent stress [16, 23]. However, the involvement of other areas beyond the BLA–PFC connectivity after adolescent and adult stress requires further investigation.

A potential limitation of our study is the fact that animals subject to adolescent or adult stress had different life histories, in that animals subject to adolescent stress were born in our facility but animals subject to adult stress were shipped to our facility at PD60. However, during the standardization of our stress protocol, we observed that shipping did not affect behavioral responses and ventral tegmental area dopamine neuron activity of rats stressed during adulthood when arriving as adults or being born in our animal facility [23, 24]. In addition, we observed similar LTD for both pathways (BLA–mPFC and mPFC–BLA) in adult naive rats born at our facility or ordered as adult, suggesting that the plasticity is not affected. Another limitation of our study is that we only tested the impact of stress in males to match our prior studies [23, 24]. Contrary to males [23], we found that females exposed to the same combination of stressors during PD31-40 did not present either short or long-lasting behavioral and electrophysiological changes [90]. Thus, further studies are required to investigate if our findings in male would be found in females if exposed at a different time point as well and whether the time course of susceptibility correlates with postnatal age or pubertal stage.

In conclusion, our data suggest that an early increase in BLA activity after stressful life events could lead to a dysfunctional BLA–mPFC pathway and may represent an early marker of a maladaptive response to stress. The changes in corticoamygdalar connectivity and the dysregulated response to stress can drive alterations in other brain areas that mediate different behavioral outcomes observed after adolescent and adult stress. The results also point to adolescence as a sensitive period of vulnerability in which stress can affect the normal trajectories of neurodevelopment and accelerate the maturation of the BLA–mPFC pathway. Therefore, the timing of the adversity in life seems to be essential for the consequences at adulthood, as the adolescent stress causing a precocious adult corticoamygdalar pattern which may impact the later outcomes. In adulthood, where developmental compensations are not taking place, chronic stress induces short-term impairment in mPFC and BLA activity that ultimately could affect the responsivity to stress. Overall, changes in corticoamygdalar connectivity may represent an antecedent of a maladaptive response to stress which can lead to psychiatric disorders.

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AUTHOR CONTRIBUTIONS

DLU: conceptualization, methodology, data acquisition, formal analysis, interpretation, and writing—original draft. FVGs: conceptualization, methodology, data acquisition, interpretation, and writing—review and editing. AAG: conceptualization, resources, interpretation, writing—review and editing, supervision, and funding acquisition.

ADDITIONAL INFORMATION

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