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Stress during critical periods of development and risk for schizophrenia

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Abstract

Schizophrenia is a neurodevelopmental disorder with genetic predisposition, and stress has long been linked to its etiology. While stress affects all stages of the illness, increasing evidence suggests that stress during critical periods of development may be particularly detrimental, increasing individual's vulnerability to psychosis. To thoroughly understand the potential causative role of stress, our group has been focusing on the prenatal methylazoxymethanol acetate (MAM) rodent model, and discovered that MAM offspring display abnormal stress reactivity and heightened anxiety prepubertally, prior to the manifestation of a hyperdopaminergic state. Furthermore, pharmacologically treating anxiety during prepuberty prevented the emergence of the dopamine dysfunction in adulthood. Interestingly, sufficiently strong stressors applied to normal rats selectively during early development can recapitulate multiple schizophrenia-related phenotypes of MAM rats, whereas the same stress paradigm during adulthood only produced short-term depression-related deficits. Altogether, the evidence is thus converging: developmental disruption (genetic or environmental) might render animals more susceptible to the deleterious effects of stress during critical time windows, during which unregulated stress can lead to the emergence of psychosis later in life. As an important region regulating the midbrain dopamine system, the ventral hippocampus is particularly vulnerable to stress, and the distinct maturational profile of its fast-spiking parvalbumin interneurons may largely underlie such vulnerability. In this review, by discussing emerging evidence spanning clinical and basic science studies, we propose developmental stress vulnerability as a novel link between early predispositions and environmental triggering events in the pathophysiology of schizophrenia. This promising line of research can potentially provide not only insights into the etiology, but also a "roadmap" for disease prevention.

Keywords

stress; psychosis; parvalbumin; perineuronal nets; critical period plasticity

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Conflict of interest

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Introduction

Schizophrenia is a chronic and severe psychiatric disorder that typically strikes individuals in late adolescence and early adulthood, impacting their ability to function effectively in society. For decades, research has centered on trying to better understand the cause of schizophrenia and to develop more effective treatments. One focus has been in identifying the genetic basis of schizophrenia, which has indicated that schizophrenia is polygenic in nature (Schizophrenia Working Group of the Psychiatric Genomics, 2014). However, almost all of the risk genes associated with the disorder confer only a small effect on the phenotype, and only a small percentage of genetic carriers transition to psychosis (Jagannath et al., 2017). Indeed, despite having an identical genetic background, the concordance rate of schizophrenia among identical twins is only about 50% (Cardno and Gottesman, 2000) and a substantial proportion of schizophrenia is idiopathic, without an identified family history. These evidences indicate that schizophrenia is not completely genetically determined. As a result, studies have also focused on how other risk factors could amplify the impact of genetic predisposition.

As with other major psychiatric disorders, schizophrenia is believed to arise from a combination of genetic predisposition and socio-environmental insults, such as exposure to victimization (physical abuse, sexual abuse, bullying by peers), urbanicity, social disadvantage, and others (Tsuang, 2000; van Os et al., 2010). Importantly, the impact of these socio-environmental factors is more pronounced during critical periods of development such as childhood and adolescence. Individuals with psychosis report experiencing more frequent and more severe childhood abuse than people without past or current psychiatric conditions (Mauritz et al., 2013). In addition, children and adolescents at-risk for schizophrenia, in which 20–40% will convert to the full-blown disorder (Fusar-Poli et al., 2012), experience abnormally high reactivity to stressful events (Pruessner et al., 2011) and are more likely to convert to psychosis if they show high anxiety and decreased tolerance to stress (Trotman et al., 2014; Yung et al., 2005). In fact, a multicenter study from the North American Prodrome Longitudinal Study (NAPLS) examining a large sample of adolescents at-risk found that cortisol levels, an index of stress, were significantly elevated among those who transitioned to psychosis (Walker et al., 2013).

During childhood and adolescence, a large number of dynamic alterations in physiological processes and social dynamics occurs as the person learns to adapt to their environment (Sisk and Foster, 2004; Spear, 2000). These processes, when combined with genetically influenced developmental changes, shape the neurobiological features that underlie brain maturation. Notably, these dynamic changes also make the developing brain highly vulnerable to exposure to detrimental environmental factors that can lead to the emergence of psychiatric disorders. Indeed, adolescence is a period of peak onset for many common mental disorders, including schizophrenia (Kessler et al., 2007). The neurobiological substrate for this susceptibility is currently unknown. However, it has been proposed that an elevated stress reactivity and the ongoing maturational processes of the hypothalamic-pituitary-adrenal (HPA) axis (which is part of the stress response system) during this period, as well as immaturity of cortical regions that play a role in emotion regulation, may

contribute to this increased susceptibility (Gogtay et al., 2004; Romeo, 2017; Romeo and McEwen, 2006).

Given that elevated stress levels may be secondary to illness-related factors, most of the human studies are unable to discriminate true causation from association. Thus, animal studies, even with limitations, are crucial to capturing evidence to support a causative role for stress in the pathophysiology of brain development that can lead to susceptibility to psychiatric disorders, including schizophrenia. In this context, our group has been employing a neurodevelopmental disruption model that uses the mitotoxin methylazoxymethanol acetate (MAM) to garner insight into how genetic susceptibility interacts with environmental factors to lead to the pathology. Several brain regions are involved in the stress response, such as the medial prefrontal cortex, basolateral amygdala, ventral hippocampus, and ventral tegmental area. To a less neuro-inclined reader, a quick guide table summarizes the role of each of these regions in the stress response (Table 1).

Insights from the MAM model of schizophrenia

The MAM model consists of the administration of MAM, a mitotoxin that is a DNA alkylating agent, to pregnant rats at gestational day (GD) 17 and leads to abnormal DNA methylation in the offspring (Hoareau et al., 2006), which in turn leads to neurodevelopmental disruption. As a consequence, the MAM offspring mimic many of the features found in schizophrenia (Modinos et al., 2015), including behavioral impairments (i.e., sensory gating, reversal of response strategy, social interaction) and neuroanatomical changes (thinning of limbic cortices, increased cell packing density, loss of parvalbumin neurons), in addition to a dopamine (DA) system hyperresponsivity as indicated by enhanced locomotor response to psychotomimetic drugs (i.e., phencyclidine and amphetamine) and increased number of spontaneously active DA neurons in the ventral tegmental area (VTA) (Flagstad et al., 2004; Lodge and Grace, 2007; Moore et al., 2006). Consistent with what is observed in humans, most of the schizophrenia-like changes in the MAM model appears during late adolescence/early adulthood (Gomes et al., 2016).

Dysregulation of the stress response has been proposed as a potential etiological factor in the development of schizophrenia (Gomes and Grace, 2017a). As with individuals at risk for schizophrenia (Jones et al., 2016), MAM rats also exhibit increased stress reactivity and heightened anxiety during early adolescence. We recently found that MAM rats in the juvenile period [postnatal day (PD) 22] are more responsive to stress. In response to acute footshock, juvenile MAM emitted more ultrasonic vocalizations (USVs; 22 kHz), vocalized for a longer duration and spent more time in freezing behavior compared to controls and older MAM rats (Zimmerman et al., 2013). In addition, during the peripubertal period (PD31–40), corresponding to mid-to-late adolescence in humans, MAM rats displayed anxiety-like behavior (Du and Grace, 2013), which was associated with a hyperactivity of the basolateral amygdala (Du and Grace, 2016), and showed attenuated corticosterone response to acute footshock that, unlike controls, persisted for 10 days of repeated stress exposure (Zimmerman et al., 2013). Collectively, these findings are consistent with epidemiological studies of adolescents at high-risk for schizophrenia indicating that those

showing greater sensitivity to stress and increased anxiety tended to be the ones that convert to schizophrenia later in life (Devylder et al., 2013; Owens et al., 2005).

Similar to MAM rats, a blunted cortisol response to stress has also been reported in both established psychosis and individuals at-risk (Brenner et al., 2009; Pruessner et al., 2013). These findings suggest that adolescent MAM rats, as well as schizophrenia patients and individuals at-risk, may be unable to integrate appropriate responses to stress and, since a substantial cortisol/corticosterone response is necessary for homeostatic stress adaptation (McEwen and Gianaros, 2010), they also seem unable to adapt to repeated stress. It is worth mentioning that an attenuated cortisol response is thought to be a consequence of a prolonged period of hyperactivity of the HPA axis due to chronic stress (Fries et al., 2005; Pruessner et al., 2017).

Given that stress during developmental periods plays a role in schizophrenia, we proposed that alleviating anxiety and abnormal stress responsivity during these periods may prevent the emergence of the disease later in life. This idea was tested by treating MAM rats with daily administration of the anxiolytic drug diazepam during peripuberty (PD31–40) at a dose sufficient to normalize anxiety responses and amygdala activity (Du and Grace, 2013, 2016). As a result, peripubertal diazepam administration prevented the emergence of anxiety-like behavior and the higher neuronal firing rates within the BLA of MAM rats at adulthood (Du and Grace, 2016) as well as preventing the emergence of the hyperdopaminergic state observed in adult MAM rats (Du and Grace, 2013). These findings indicate that relieving stress in MAM rats around puberty circumvents the transition to the schizophrenia-like phenotype in the adult MAM rat. It is likely that other stress-relieving interventions will also be effective. Thus, these interventions applied to at-risk individuals may prevent the eventual transition to schizophrenia (Crush et al., 2018).

Deleterious effects of stress driving schizophrenia development

Based on our findings with the MAM model suggesting that stress drives the emergence of the schizophrenia phenotype and that it can be circumvented by relieving stress, we propose that maybe MAM does not “cause” schizophrenia but instead it may predispose to the emergence of pathology in the adult via increased sensitivity to environmental stressors. This is consistent with studies showing that of children at familial risk for schizophrenia, those that show heightened stress responsivity tend to convert to psychosis later in life (Owens et al., 2005). Therefore, we posit that MAM, and perhaps genetic risk factors in humans, cause the organism to show heightened susceptibility to the deleterious effects of stress during sensitive developmental periods, causing disruption to emerge later in life. Accordingly, if this model is accurate, one could predict that i) exposing normal rats to sufficiently strong stressors early in life would lead to pathophysiology in the adult that recapitulates that resulting from MAM treatment, and ii) interfering with structures that serve to limit the impact of stress exposure could mimic or exacerbate the impact of stress.

To test this, normal rats were exposed to different stressors during the same period that MAM rats were treated with diazepam (PD31–40). The stressors included either daily footshock for 10 days (PD31–40), 3 sessions of restraint stress (at PD31, 32 and 40), or the

combination of 3 sessions of restraint stress plus daily footshock. All stressors impaired weight gain and induced anxiety-like responses in adults (>PD65). Exposure to daily footshock or to the combination of stressors also disrupted cognitive function. Interestingly, only the combination of stressors induced changes in DA system activity reflected by an increase in the number of spontaneously active DA neurons in the VTA and an enhanced amphetamine-induced locomotor response (Gomes and Grace, 2017b). These findings suggest that the impact on the DA system seems to depend on multiple interacting factors. Human studies have also suggested a cumulative effect of stress, indicating that experiencing two or more different types of victimization during childhood and adolescence is associated with a higher risk of developing psychotic symptoms (Arseneault et al., 2011; Kelleher et al., 2013). Together, these observations indicate that it is the repeated nature of the stress that is important, rather than a single event.

The hyperdopaminergic state observed in animals exposed to the combination of stressors during adolescence is similar to that found in MAM rats (Lodge and Grace, 2007) and is highly consistent with clinical studies. Thus, schizophrenia patients show abnormally high amphetamine-induced DA release (measured by raclopride displacement) in the striatum (Kegeles et al., 2010), consistent with the increased locomotor response to amphetamine in normal adult animals exposed to the combination of stressors during adolescence as well as in MAM rats, and an increase in fluorodopa uptake (Egerton et al., 2013) indicative of an increased number of active terminals, consistent with an increased number of spontaneously active DA neurons in the VTA (Grace, 2016). Interestingly, the increased DA neuron population activity found in animals exposed peripubertally to the combined stressor was confined to the lateral aspects of the VTA (Gomes and Grace, 2017b), which project to associative striatal regions analogous to those found to be hyper-responsive in schizophrenia patients (Weinstein et al., 2017).

What could make MAM rats or humans that are predisposed to schizophrenia have increased sensitivity to the disruptive effects of stress? Although stress is regulated by multiple brain regions, the medial prefrontal cortex (mPFC) is proposed as a primary integrator of the response to stress. In our earlier studies, we showed that the mPFC, specifically its prelimbic portion (plPFC), limited the impact of stress on activation of the BLA (Rosenkranz and Grace, 2001, 2002). Therefore, a dysfunction of the plPFC may impair the ability to respond appropriately to stress. Indeed, we found that plPFC lesions performed post-weaning (at PD25) caused the rats to show increased anxiety as adults (>PD65), and now footshock alone during PD31–40, which was inadequate to alter DA system responsivity, caused the rats to exhibit the hyperdopaminergic state in the adult (Gomes and Grace, 2017b). Also, an mPFC dysfunction in MAM animals was associated with a greater vulnerability to stress (Goto and Grace, 2006). A dysfunctional PFC has been extensively linked to the pathophysiology of schizophrenia and it can be present in the prodromal phase (Volk and Lewis, 2010). In fact, deficits in this region have been observed in the prodromal state of schizophrenia and subjects at ultra-high risk during tasks involving emotion regulation (Phillips and Seidman, 2008; van der Velde et al., 2015) as well as an abnormal connectivity between the amygdala and the PFC during emotion processing (Potvin et al., 2017). Thus, deficits in PFC function, which may be present in at-risk individuals, could limit the ability of this structure to regulate the impact of stress, increasing the vulnerability to the

deleterious effects of stress and contributing to the emergence of psychiatric disorders such as schizophrenia.

In addition to the mPFC and amygdala, the hippocampus (Hipp) also plays a crucial role in modulating stress responses (McEwen et al., 2016). However, repeated stress damages the Hipp. For example, maintained stress leads to a loss of parvalbumin-containing GABAergic interneurons (PVI) in the Hipp (Czeh et al., 2005). Importantly, in schizophrenia, a PVI loss in the anterior Hipp, a region homologous to the ventral Hipp (vHipp) in rodents, is thought to lead to a hippocampal hyperactivity which in turn drives the hyperdopaminergic state associated with psychotic symptoms (Grace and Gomes, 2018). Thus, an increased VTA DA system activity induced by the combined stressors could be associated with a loss of PVI in the vHipp. Moreover, seizure-mediated activation of the BLA, an area activated during stress, decreases the number of PVI in the Hipp (Berretta et al., 2004). Hence, abnormal stress responsivity secondary to plPFC dysfunctional regulation of BLA reactivity to stress could to lead to hippocampal dysfunction, contributing to the emergence of a hyperdopaminergic state (Figure 1). Importantly, structural and functional imaging studies show hippocampal abnormalities in the prodromal state of schizophrenia (Baglivo et al., 2018; Vargas et al., 2018; Nenadic et al., 2015).

Hippocampal PVI Dysfunction in Schizophrenia

Alterations in GABAergic circuits are proposed to be associated with numerous neurodevelopmental disorders, including schizophrenia. In fact, pathological changes in GABAergic circuits are widely reported in the PFC (Lewis et al., 2012; Volk and Lewis, 2010) and in the Hipp of schizophrenia patients (Benes et al., 2007; Konradi et al., 2011; Zhang and Reynolds, 2002). In the Hipp, GABAergic dysfunction seems to largely involve PVI, and a selective reduction in PVI density has been reported in post-mortem tissues (Konradi et al., 2011; Zhang and Reynolds, 2002). Functionally, PVIs are critical for maintaining regional excitatory-inhibitory (E/I) balance (Wöhr et al., 2015), and PVI dysregulation can potentially cause Hipp dysfunction (Pelkey et al., 2017) that is commonly associated with schizophrenia (Lieberman et al., 2018). In part, the selective vulnerability of the Hipp is attributable to its “fragile” E/I balance, and in fact the vast majority of Hipp neurons (approximately 90%) are excitatory pyramidal neurons (Freund and Buzsaki, 1996; Olbrich and Braak, 1985), which is markedly different from cortical regions where pyramidal cells and non-pyramidal cells are more balanced (Mouton, 2013). Such E/I imbalance in Hipp by default might explain its selective vulnerability to focal excitation.

Adolescent stress vulnerability is a critical period – relevance to schizophrenia

PVI dysfunction has also been extensively studied in animal models of schizophrenia, including the MAM model (Modinos et al., 2015). In MAM rats, PV reduction has been reported in the mPFC and selectively throughout subregions of the vHipp but not in their dorsal counterparts (Gill and Grace, 2014), a pattern that parallels schizophrenia patients in whom hippocampal pathologies tend to accumulate in the anterior limbic portion (Lieberman et al., 2018). Of all the Hipp regions manifesting PV reduction and/or PVI loss,

the ventral subiculum (vSub) is of particular interest, as its local PVIs continue to mature until at least late adolescence (Caballero et al., 2013) and is highly susceptible to stress (O'Mara, 2005). This susceptibility may arise from their potent glutamatergic input from regions both intrinsically from hippocampal formation (e.g., CA1) and extrinsically from other brain structures (e.g., BLA, thalamus, and hypothalamus) (O'Mara, 2005). During early development, such glutamatergic input onto PVI are highly plastic as the organism adapts to the environment, potently altering regional E/I balance, and eventually triggering maturational and plasticity events termed the critical period (Hensch, 2004). However, it could remain a source of pathology if the heightened plasticity is not terminated properly, since excessive glutamatergic drive can lead to abnormal calcium accumulation in the fast-spiking PVI (Stanika et al., 2009), increased oxidative stress (Behrens et al., 2007), and increased metabolic demand (Do et al., 2009), all of which can lead to cell damage and even cell death (Berretta et al., 2001). This vulnerability continues until the closure of the critical period by the perineuronal nets (PNNs), a glycosaminoglycan matrix sheath that surrounds mainly PVI and stabilizes glutamatergic inputs to end the plastic phase, but also protect PVI from metabolic and oxidative damage (Cabungcal et al., 2013). PVIs mature at different rate across the brain, and since PNNs also form at different rates in a region-specific manner, neural system typically manifest sequential onset of diverse types of critical periods (Toyoizumi et al., 2013). Thus, we hypothesize that during early development, when PNNs are not yet fully formed, aberrant excitation onto PVIs in the vHipp, for example, could lead to cell damage, producing pathological changes related to schizophrenia (Figure 2). Furthermore, in adult animals, similar insults to the PVIs would not produce similar results, as hippocampal PVIs are largely mature and hence protected by the PNNs from damage.

To test this, we exposed normal rats to the aforementioned combination of stressors during adolescence (PD31–40) or adulthood (PD65–74), and compared the stress-induced short- and long-term changes in the DA system activity in the VTA. Our findings indicate that the timing of stress seems to be a critical determinant of the pathology that is present in the adult. Whereas adolescent stress led to a persistent schizophrenia-like hyperdopaminergic state, adult stress produced a short-term hypodopaminergic state (Gomes et al. 2018) that is more consistent with animal models of depression (Belujon and Grace, 2014; Chang and Grace, 2014; Moreines et al., 2017). To elucidate the structural basis for the distinct stress responses observed, we examined the maturational profile of PVIs in the Hipp of animals stressed during adolescence. Confirming a previous report (Caballero et al., 2013), we found in naïve animals PVIs in the vSub continue to increase during PD31–51, suggesting a relatively immature state of the region during the stress period (PD31–40) (Zhu et al., 2018). In animals exposed to adolescent stress, a persistent decrease in the number of PVIs selectively in the vSub (but not in the dSub) was observed, suggesting potential PVI loss in the region. Furthermore, the number of mature PVIs (i.e., PVIs enwrapped by PNNs) also decreased after adolescent stress exposure, whereas adult stress does not seem to alter these markers (Zhu et al., 2018). The reduction in the number of PVIs had functional consequences, as an increase in the firing rate of the pyramidal neurons in these regions was observed (Gomes et al., 2018), which is consistent with the abnormal hippocampal activation in schizophrenia patients (Malaspina et al., 1999; Medoff et al., 2001; Schobel et al., 2013). All together, these results suggest that vulnerability to adolescent stress might

indeed be a component of the critical period, and stress during this period produced distinct pathological profiles related to schizophrenia. It is noteworthy that the hippocampal PVI deficits produced by adolescent stress seemed to be region-specific, as dorsal Hipp (e.g., dorsal subiculum region) is relatively resilient to the stress effects. This is likely due to increased PNNs enwrapping in the dSub at an earlier time point.

If vulnerability to adolescent stress is indeed a critical period, or at least a critical-period-like process, one exciting possibility would be that such plastic events might be regulated by common mechanisms shared by critical periods across different brain regions (Hensch and Bilimoria, 2012). In fact, overlapping mechanisms underlying the regulation of critical period plasticity have been established from visual system and fear learning systems (Nabel and Morishita, 2013). Collectively, mechanisms that are involved in limiting critical period plasticity in adulthood are terms as plasticity “brakes” (Bavelier et al., 2010), including structural “brakes” such as formation of PNNs, molecular “brakes” such as myelin-related inhibitory signaling, and functional “brakes” such as downregulation of histone acetylation, and altered E/I balance (Nabel and Morishita, 2013). Importantly, lifting these “brakes” has been shown to reopen various forms of critical period plasticity in adulthood, resulting in an adolescent-like state (Nabel and Morishita, 2013). Therefore, to further test whether the observed adolescent vulnerability to stress is truly a critical period, we applied an established compound known to reopen the critical period, sodium valproate (VPA), in the adult and measured short and long-term stress consequences. Our results indicated that reopening the critical period of normal animals caused them to regain adolescent-like stress vulnerability, evident from the findings that stress in reopened animals induces increased VTA DA neuron population activity, vHipp hyperactivity, and reduction in numbers of PV-positive neurons (Gomes et al., 2018).

VPA has multiple mechanisms of actions, including the potentiation of GABA neurotransmission to enhance inhibitory function and enduring effects on gene transcription as a pan-HDAC inhibitor (Monti et al., 2009). HDAC inhibition is more likely to be of relevance to the observed action of re-opening of the critical period. In fact, in the primary visual cortex, enhancement of intercortical inhibition does not trigger plasticity in adults (Fagiolini and Hensch, 2000), but HDAC inhibition does (Lennartsson et al., 2015). To further test the relevance of HDAC inhibition in reopening the critical period, we utilized another potent and more selective pan-HDAC inhibitor, SAHA. SAHA has no documented action on inhibitory neurotransmission when used at the dose known to enhance cortical plasticity (Baroncelli et al., 2016), and indeed, in our study, SAHA-treated adult rats also regained adolescent-like stress vulnerability (Gomes et al., 2018). Altogether, the findings cited above indicate that adolescence is a critical period for stress vulnerability that can be reinstated (at least by HDAC inhibition) in adults. Based on these data, we posit that the interaction between stress and stress vulnerability might be an integral part of the pathophysiology of schizophrenia. Whether the onset of stress vulnerability is truly associated specifically with the critical period requires further elucidation; however, as a recent report from Smith et al. (Smith et al., 2018) addresses, schizophrenia patients are likely to express aberrant level of critical period genes, highlighting the importance of adding age- and development-specificity into future studies.

Conclusion

Converging evidence from clinical and basic science studies suggest that schizophrenia is a disorder caused by multiple interacting factors. Central to these is stress occurring during vulnerable periods. Thus, during the prepubertal period, hippocampal PVI are in a vulnerable state, and sufficient stress can lead to pathological changes including cell death of these interneurons. For stress to have this impact, it either has to be severe in nature, or experienced as more severe possibly due to inadequate stress regulation. Principle among the areas involved in stress regulation is the prelimbic prefrontal cortex, which has been shown to attenuate stress responses of the BLA (Rosenkranz and Grace, 2001, 2002). Therefore, there appears to be a balance, in which stress vulnerability and presence of stressors produce an additive effect with respect to risk for schizophrenia. Depression, which has a vulnerability period in adulthood, also can be triggered by severe stressors. Interestingly, it is known that both schizophrenia and depression run in the same families (Cross-Disorder Group of the Psychiatric Genomics, 2013). It may be that the common factor in both disorders is a genetic vulnerability to stress, such that if one can “survive” the critical period prepubertally one may be more vulnerable to depression as adults. For example, prenatal MAM exposure in rats leads to a schizophrenia phenotype, but if conversion is prevented (by relieving stress during adolescence), the adult is more susceptible to affective disorders. This is in agreement with studies showing that ultra-high risk patients (i.e., those showing attenuated psychotic signs) that do not transition to schizophrenia often show affective disorders as adults (Lin et al., 2015). Therefore, genetic susceptibility may not be directly related to schizophrenia, but instead to a vulnerability to environmental factors that can be expressed as schizophrenia or affective disorders depending on the staging of the stress exposure.

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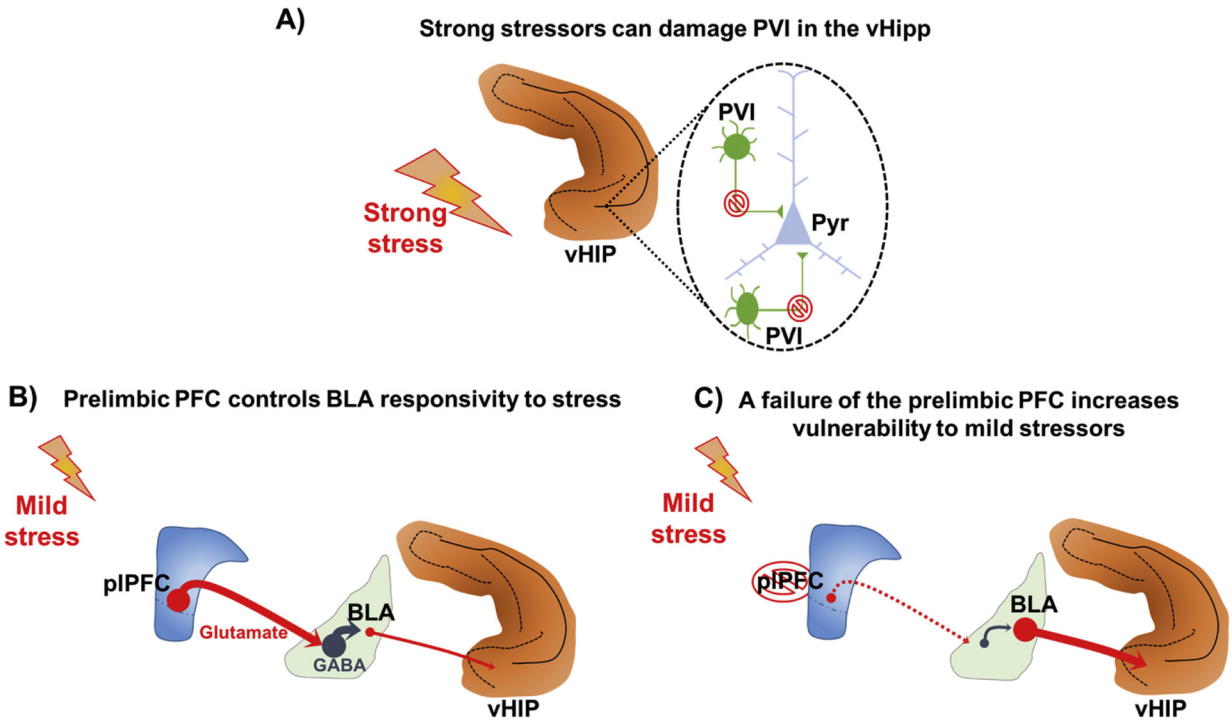

Figure 1 –.

Stress as a risk factor for schizophrenia development. **(A)** Strong stressors during critical periods impact the ventral hippocampus (vHip) leading to a dysfunction of parvalbunin interneurons (PVI), or even to a PVI cell loss, which in turn contributes to the hyperactivity of glutamatergic pyramidal neurons that will drive a midbrain hyperdopaminergic state that underlies the emergence of psychosis. Alternately, genetic or gestational factors can increase susceptibility to mild stressor. **(B)** The prelimbic portion of the medial prefrontal cortex (plPFC) has been shown to control basolateral amygdala (BLA) responsivity to stress. **(C)** A failure of the plPFC to regulate BLA reactivity to stress could lead to a BLA glutamatergic overdrive to the vHipp which could damage PVI, contributing to the emergence of a hyperdopaminergic state.

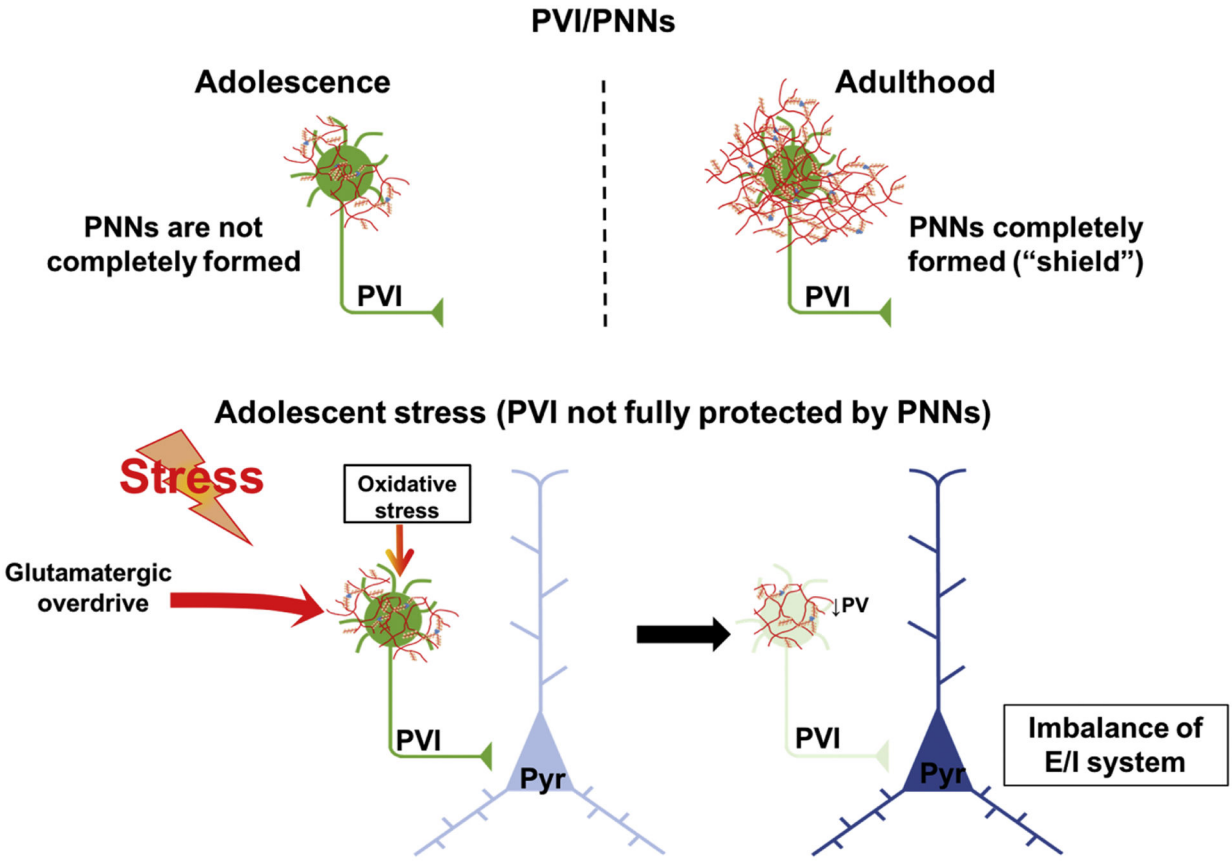

Figure 2 –.

During critical periods parvalbumin interneurons (PVI) are more vulnerable to stress. This vulnerability continues until the closure of the critical period by the perineuronal nets (PNNs), a glycosaminoglycan matrix sheath that surrounds PVI to end the plastic phase, but also protect PVI from metabolic and oxidative damage. Thus, during periods when PNNs are not yet fully formed, such as adolescence, the exposure to stress can increase the oxidative stress and cause aberrant excitation onto PVIs in the vHipp, for example, leading to PVI damage/loss. This in turn results in deficits in the excitatory/inhibitory (E/I) balance producing pathological changes related to schizophrenia. In adult animals, similar insults to the PVIs would not produce the same results, as PVIs are largely protected by the PNNs from damage.

Table 1 –

Main brain regions involved in the response to stress discussed in the present review.

Brain region	Acronym	Role in stress response
Medial prefrontal cortex	mPFC	control of subcortical stress responses
Basolateral amygdala	BLA	expression of anxiety
Ventral hippocampus/ventral subiculum	vHipp/vSub	limbic hippocampus involved in context
Ventral tegmental area	VTA	dopamine neurons modulating cortical/limbic regions